World Health Strategy *eBook*

For Happier Longer Lives

Edited By Renata G. Bushko

Editor of *Strategy for the Future of Health*, *Future of Intelligent and Extelligent Health Environment* & *Future of Health Technology*

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Videos from the 20th Future of Health Technology Summit

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About 20th Anniversary Future of Health Technology Summit®

As we reflect upon the 20th Future of Health Technology Summit, many thanks to Professor Marvin Minsky, Dr. Gloria Rudisch, Dr. Danuta Glowacka, Professor Alex (Sandy) Pentland, Dr. Tracy Heibeck, Professor Rosalind Picard, Dr. Aubrey de Grey, Dr. Ray Kurzweil, Dr. Craig Feied, Dr. Gary Kreps, Dr. Joseph Kvedar, Dr. Michael McDonald, Glenn Fields, and Dr. Zbigniew Glowacki for their guidance in the development and their participation in Future of Health Technology Summits since 1996.

At FHTI 2016 we honored and remembered great scientist and mentor Marvin Minsky 1927-2016. Renata Bushko, Marvin Minsky's student, led a session "From Artificial Intelligence to Intelligent Health" on how to build upon his work while Henry Lieberman discussed the importance of Minsky's ideas to medicine. Ray Kurzweil, and panel with Aubrey de Grey, Michael McDonald, Glenn Fields and Joshua Feast remembered him as well.

Bringing together most prominent voices in the field of medicine and technology, 20th Future of Health Technology Summit examined the constantly changing horizon of ideas and technologies which must be addressed by decision makers involved in health-related investments. Future progress depends on the decisions to invest in research, development, education and strategic repositioning today

2016 FHTI Summit touched upon all aspects of the health system to provide direction for those making investment decisions. It addressed the unprecedented technological revolution in healthcare which is manifesting itself in the convergence of molecular biology, computer and medical science, electrical, mechanical, genetic and biomedical engineering. Health professionals look towards a future where caring machines will assist them in much of their work and consumers will diagnose and treat themselves with self-health tools, personalized designer drugs and automatic surgery bubbles. Such developments will lead to dramatic shift towards consumer-driven healthcare, cost reduction and happier, longer lives for all.

2016 FHTI Summit begun with the presentation of art works by photographic artist and Nobel Laureate Wally Gilbert, Christopher MacDonald and Jehan Said of New England Institute of Arts. Then Renata Bushko discussed New World Health Strategy shifting from supply-side to demand-based R&D and healthcare and the need for major R&D changes in US to keep up with accelerating and already dominating medical technology innovation in East and South Asia and Latin-America. Future of Health Technology Summit mobilizes to action and sets a new direction to international cooperation.

The opening talk on treating patients as valued customers was delivered by innovative co-founder of Prosperata LLC Sanjay Sarma who shared his expertise in customer-centric design helping healthcare organizations transform the patient experience and evolve patient

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transactions into enduring relationships. Then keynote by leading computational biologist and statistician Dr. Tom Chittenden of WuXi NextCODE Genomics uncoverd "Novel Strategies for Enhanced Predictive Modelling and Deep Learning in the Biosciences" – a scientific development of immense importance to the world health strategy.

Congratulations to Dr. Xiu-Min Li, honoree of the 2016 Future of Health Technology, for turning her love for traditional herbal remedies into science-based medicines. The title of her Award Lecture was "Can Chinese Herb-based Medicines Heal the Immune System and Cure Allergies?". Renown leader Barbara Winston of Bruce Winston Gem Corporation, familiar with Dr. Li's excellent clinical outcomes and patient care spoke at the Award Ceremony representing Dr. Li's patients and symbolizing patient empowerment era. The immensely important topic of herbal science was continued with insights from renown scientist Dr. Jing-Ke Weng of MIT and Whitehead Institute for Biomedical Research - "How can we harness healing power from plants?" and presentation by Rennna Bushko of Smith College on the important role of scientific herbal medicine in combatting inflammation.

Keynote by Sylvia Hobbs of Massachusetts Center for Health Information and Analysis, "Can Terabytes of new Data Deepen our Knowledge of the state of Health Care in the Commonwealth of Massachusetts?" opened a discussion on the role of BIG data in health. Most quoted computational scientist in the world, Professor Alex (Sandy) Pentland of MIT Media Lab, further explored Big Data and Health by looking into how it can help us in work and life. Creator of Wolfram Alpha, Dr. Stephen Wolfram spoke about the future of computation with Big Data. Healthcare innovator Shari Heath of Medalogix, provided an example of how Big Data can make a big difference in the end-of-life care.

An intriguing and far reaching question: "How to cure almost everything in brain disorder with light?" was asked by Dr. Newton Howard, Professor of Oxford University and it was the title of his distinguished lecture. The author of "Ending Aging" Dr. Aubrey de Grey of SENS Foundation uncovered secrets of staying young in addition to an update on his progressive longevity research while Dr. Lorraine Gudas of Weill Cornell Medical College and Sveikatal, Inc. unveiled new innovative offerings to the consumer in the cancer treatment area.

Doctor of the future debate started at FHTI 20 years ago by Renata Bushko was reignited by the paper by Dr. Urs-Vit Albrecht from Hannover Medical School who explained how we can build trustworthy, secure and transparent health-apps so essential in consumer empowerment and self-care movement. Leader of affective computing, Professor Rosalind Picard of MIT Media Lab and Affectiva Inc. introduced intelligent, affective applications by asking if "we can forecast changes in mood and mental health, like we forecast a storm". A theme of technological innovation in mental health was continued by Dr.

Skyler Place of Cogito Health who explained how our smartphones may know more about our mental health than our doctors.

That trend may continue into fashion so a session led by Renata Bushko on how high-tech fashion and wearable technology would impact consumers' health addressed high-tech fashion 5.8 billion market. Creative and artistic Dr. Katia Vega of MIT media Lab investigated Beauty Technology: "When Technology meets Cosmetics" presenting among other topics conductive makeup including eyelashes than can turn on the lights for disabled.

TI 2016. FutureofHealth.org

Innovative technologies may also help in reduction of fast growing opioid misuse among chronic pain patients according to Dr. Robert Jamison of Harvard Medical School who led session on that topic while Dr. Darin Correll of Brigham and Women's Hospital chaired the panel on the future of pain management and urgent need for more consumer education around the world with Dr. Daniell Carr of Tufts University School of Medicine and Dr. Navil Sethna of Harvard Medical School. Health communications expert, Shelagh Maloney of Canada Health Infoway presented on how we should communicate to the public about the health technology revolution to assure progress.

The path of this revolution was charted by prominent healthcare leader Dr. Gary Kreps of George Mason University and further described by Dr. Joe Kvedar of Partners HealthCare, Dr. Guergana Savova of Harvard Medical School and Dr. Robert Teague from Quorum Health Resources in a session on future of healthcare in 10-20 years. This Future of Care panel moderated by futurist and healthcare strategist Renata Bushko of FHTI included remarks by Dr. Xing Jijun, Counselor Consul for Science and Technology, Consulate General of P.R. China in New York focusing on the future of healthcare in China. Visionary talk by Dr. Nick van Terheyden of Dell – "Will healthcare be delivered by George Jetson in the future?" completed this topic. Critical importance of renewable energy distributed collectively through intelligent grids globally was explored by public health strategist, Dr. Michael McDonald, of Global Health Response and Resilience Alliance.

Nanomedicine revolution was be outlined by Dr. Guillermo Ulises Ruiz Esparza and Dr. Yu Shrike Zhang of Harvard-MIT Division of Health Sciences and Technology. They described what's next in the application of Nanotechnology-based Molecular Delivery Systems (Sr. Esparza) and how Google Glass can remotely integrate with microfluidic biosensors and actuators (Dr. Zhang).

Professor Hermano Igo Krebs of MIT unveiled methods to repair a broken brain with movement therapy while Professor Ernesto Rodriguez Leal of Tecnologico de Monterrey outlined strategy for building exoskeletal body support to avoid physical disparity and ten demonstrated his prototype.

Two essential financial questions (1) What are the new possible ways to fund basic bio-medical research? and (2) How can we accelerate formation and success of biotechnology startups? were discussed by the

group leading into strategic links between inventors and investors. Albert di Rienzo of Radicle Innovation LLC moderating a panel on ways to increase success of bio-tech startups was joined by two renown experts Dr. Eric Elenko of Pure Tech and Dr. Adam Greenspan of Business Incubation University City Science Center in Philadelphia.

New generation of talented researchers and students unveiled bold ideas leading to happier longer lives in the FHTI poster session. Dr. Agnes Stibe of MIT Media Labs Changing Places Group helped us imagine cities that feel, understand, and take care of our wellbeing. Dr. Brittany Seymour of Harvard School of Dental Medicine explained how network science can be applied for an expanded understanding of large online network information structures and behaviors to modernize public health communication strategies for improved health outcomes.

The future of depression prediction based on self-report diary via smartphone applications was discussed by Yoshihiko Suhara of MIT Media Lab. Psychology topic was continued by another amazing MIT Media Lab student Sooyeon Jeong presenting on the topic of: "How can we implement personalized positive psychology interventions in the form of interactive journaling?" Renna Bushko of Smith College and Research Intern at Ichan School of Medicine at Mount Sinai talked about the role of Arctigenin isolated from Arctium lappa L. in inhibiting IgE production and reducing inflammation, providing hope to treat IgE associated inflammatory diseases. "How can we reduce the economic burden of Type 2 Diabetes management through smartphone technology and Big Data?" was a question posed and discussed by Ian Pentland of Northeastern University and Dr. Todd Reid, of Massachusetts General Hospital and MIT Connection Science.

Dr. Luis Alonso Pastor of MIT Media Lab partnering with the team from Schepens Eye Research Institute and Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, discussed how 3-D printing can help with epithelial wound healing.

Talented dancer and choreographer, Maria Caruso of Bodiography and La Roche College of Performing Arts prepared original dance performance illustrating ideas in the summit. Renown Violinist, Yuan Mei Xing celebrated her 20th performance at the Future of Health Technology Institute's summits by playing with pianist, Steven Jackson Member of the orchestra, Boston Lyric Opera

20th FHTI Summit resulted in the World Health Strategy eBook (Ed.) Renata G. Bushko www.futureofhealth.org. Both chapters and video-lectures from the eBook provide an excellent roadmap to plan the future of healthcare globally.

50+ Luminaries Asking and Answering Most Pressing Questions of our Times:

The best way to progress with health investments to assure best outcomes for humanity. 2016 BIG Questions selected by FHTI are:

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1. **How can we honor and build upon Marvin Minsky's work?**
Aubrey de Grey, Joshua Feast, Glenn Fields, Renata Bushko, Mike McDonald

2. **What should the new world health strategy be? What fundamental changes and dramatic shifts do we need to prepare for?**
Renata Bushko

3. **How do we treat patients like valued customers?**
Sanjay Sarma, Rahul Ghate

4. **Can terabytes of new data deepen our knowledge of the state of health care in the Commonwealth of Massachusetts?**
Sylvia Hobbs

5. **What are novel strategies for enhanced predictive modelling and deep learning in the biosciences?**
Tom Chittenden

6. **How will health care look like in 20 years?**
Renata Bushko, Xing Jijun, Joseph Kvedar, Guergana Savova,

7. **How can Big Data help you in work and life?** Alex (Sandy) Pentland

8. **How to cure almost everything in brain disorder with light?** Newton Howard

9. **Can Chinese herb-based medicine heal the immune system and cure allergies?**
Xiu-Min Li

10. **Can we forecast changes in mood and mental health, like we forecast a storm?**
Rosalind Picard

11. **What is the healing story of Dr. Xiu-Min Li?**
Barbara Winston

12. **How should we remember Marvin Minsky?**
Ray Kurzweil

13. **How can we chart the future for digital health information systems?**
Gary Kreps

14.**What are seven secrets to staying young?**
Aubrey de Grey

15. **What is the future of pain management?**
Darin Correll

16. **What is the future of computation?** Stephen Wolfram

17. **Why Minsky's ideas are important for medicine?**
Henry Lieberman

18. **How can we reduce opioid misuse among chronic pain patients and what is the role of risk assessment and innovative technology?**
Robert Jamison

19. **Will healthcare be delivered by George Jetson in the future?**
Nick van Terheyden

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20. **What are new innovative offerings to the consumer in the cancer treatment area?**
Lorraine J. Gudas

21. **Are exoskeletons a solution to physical disparity?**
Ernesto Rodríguez Leal

22. **What would best catalyze 100% renewable energy distributed collectively through intelligent grids globally?**
Michael McDonald

23. **How can we harness healing power from plants?**
Jing-Ke Weng

24. **How should we communicate to the public about health technology?**
Shelagh Maloney

25. **Is hospital a place?**
Robert Teague

26. **What is the future of international cooperation in health research, development and commercialization?**
Renata Bushko

27. **Can art inspire?**
Wally Gilbert

28. **What is the best way to communicate ideas through graphic design and media arts?**
Christoper MacDonald, Jehan Said, Lauren Callahan, Dianna Cox, Tania Saade, Marisa Campbell, Andrew R Emery, Charles Searle

29. **What is the future of eHealth?** Claudia Pagliari

30. **How can we build trustworthy, secure and transparent health-apps?**
Urs-Vit Albrecht

31. **How will health care look like in 20 years?**
Renata Bushko, Guergana Savova, Joseph Kvedar

32. **What are the new possible ways to fund basic bio-medical research?**
Renata Bushko

33. **How can we accelerate formation and success of biotechnology startups?**
Eric Elenko, Albert Di Rienzo, Tanveer Patel, Adam Greenspan

34. **How can Big Data make a big difference in the end-of-life care?**
Dan Hogan

35. **Does your smartphone know more about your mental health than your doctor?**
Skyler Place

36. **Is violin music healing?**
Yuan Mei Xing

37. **What is the road from Artificial Intelligence to Intelligent Health?**
Renata Bushko

38. **Can we repair a broken brain with movement therapy approach? Hermao**
Igo Krebs

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39. **How can Google Glass remotely integrate with microfluidic biosensors and actuators?**
Yu Shrike Zhang

40. **What's next in the application of nanotechnology-based molecular delivery Systems?**
Guillermo Ulises Ruiz Esparza

41. **Can you imagine cities that feel, understand, and take care of your wellbeing? Agnis Stibe**

42. **How Can 3-D printing help with epithelial wound healing? Louis** Alonso Pastor

43. **Can Arctigenin reduce inflammation giving hope to treat igE related inflammatory diseases?**
Renna Bushko

44. **What is the future of depression prediction based on self-report diary via smartphone applications?**
Yoshihiko Suhara

45. **How can we reduce the economic burden of Type 2 Diabetes management through smartphone technology and Big Data?**
Todd Reid, Ian Pentland

46. **How can network science be applied for an expanded understanding of large online network information structures and behaviors to modernize public health communication strategies for improved health outcomes?**
Brittany Seymour

47. **How can we implement personalized positive psychology interventions in the form of interactive journaling?**
Sooyeon Jeong

48.**How will fashion industry change healthcare? How will high-tech fashion and wearable technology market impact consumers' health? Will garment be a new health app development platform?**
Renata Bushko

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Renata G. Bushko / From Artificial Intelligence to Intelligent Health in "World Health Strategy" eBook, (Ed.) Renata.G. Bushko FHTI, 2016. Futureofhealth.org

Chapter 3: From Artificial Intelligence to Intelligent Health

Renata G. Bushko
September 17, 1995
"If you understand something one way you do not understand it at all."
Marvin Minsky

In 1956, a meeting at Dartmouth initiated a new field of science, Artificial Intelligence. The goal of that meeting of the minds was to discover the unknown and mysterious machinery of the mind. We could consider this to be a model of leadership and innovation--skills that will surely be essential for dealing with the problems of the 21st century. How can we exploit that successful example to deal with the new complexities that lie ahead?

The world has changed in forty years since Marvin Minsky, John McCarthy, Allen Newell, Herbert Simon and other inquisitive minds met at Dartmouth to begin the field of Artificial Intelligence.

In the same forty years, the world of biology and medicine saw equally radical changes. Few workers had as much effect in that period as did Dr. C. Everett Koop, who pursued the goal of improving health. The 1996 Future of Health Technology meeting will address achievements of the last forty years in both those realms, and try to map out how those fields might come closer together in the future.

These fields could merge in several ways:

(1).Advancing Medical Technologies.

(2)The Health Information Infrastructure.

(3)Advancing Intellectual Leadership

(1) Advancing medical technologies.

Many advances in health services have come from technical innovations, such as:

*New Genetic knowledge.

*Non-invasive Visualization: CAT, PET, MRI, Ultrasound, etc.

*Virtual Reality

*Telemedicine

*Designer Drugs, Radiopharmaceuticals

*Intelligent Networks, Collaborative Work Environments

*Electronic Medical Records, and new methods of analysis.

*Transplants, prosthetics, artificial organs.
Etc.

A major problem is that we now see a widespread fear that these wonderful innovations are coming to have a dreadful side effect: relentlessly increasing costs. Most observers see that as inevitable. However, one of our goals should be to show how that

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could be stopped, and even reversed.

In the field of computers, we've seen just the opposite: the cost of computers has decreased exponentially! Why should not that be the case, as well, in the domain of health. Why can't we exploit the new techniques that will come in AI to make those procedures less costly? Perhaps it is merely a matter of vision and leadership.

(2) The Health Information Infrastructure.
According to Dr. C. Everett Koop two revolutions are taking place: (1) health systems transformation (2) global presence of intelligent networks. The Health Information Infrastructure (HII) lies at the "volatile intersection" of these two revolutions. HII has the potential for substantially improving health of Americans even within the next decade. How shall we proceed with its development, so that the developing countries are included?

(3) Advancing Intellectual Leadership.
Professor Minsky's book, The Society of Mind, provides a new agent-based model of the mind. There is a convergence between new ideas about minds and machines and the focus on adaptiveness in current research on leadership. The future merger between new ideas about technology, leadership, and science of the mind will make it possible to create intelligent health systems much faster.

September 17, 1995; Reviewed by Marvin Minsky 1/19/1996

Renata Bushko
Tel: 508-497-2577,
Fax: 508-497-2518

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Robert A. Freitas Jr./ Welcome to the Future of Medicine in "World Health Strategy" eBook, (Ed.) Renata G. Bushko, FHTI, 2016. Futureofhealth.org From Strategy for the Future of Health (Ed.) Renata G. Bushko, IOS Press 2009

Chapter 4: Welcome to the Future of Medicine

Robert A. Freitas Jr.
Senior Research Fellow, Institute for Molecular Manufacturing
Palo Alto, California USA

Abstract

This chapter describes the negative consequences of medical technology development and commercialization that is too slow, and makes the case for an immediate large scale investment in medical nanorobots to save 52 million lives a year. It also explains the essence of nanotechnology, its life-saving applications, the engineering challenges, and the possibility of 1000-fold improvement over our current human biological abilities. Every decade that we delay development and commercialization of medical nanorobotics, half a billion people perish who could have been saved.

Introduction

I never met my maternal grandfather, Irving Lincoln Smith. I understand he was a good man, a kind and loving father, a hard worker. He died in 1935, at the age of 39, when my mother was only 12.

Irving died of encephalitis, or "sleeping sickness." It is a horrible disease with many possible causes which has up to a 50% untreated mortality rate in some population subgroups. Encephalitis is an inflammation of the brain. Prolonged fevers over 106 Fahrenheit are not uncommon. There is a pounding headache, unending nausea, stiff muscles, then drowsiness, coma, and sometimes death.

Irving's passing was a great hardship on the family, which now consisted solely of my mother and grandmother. The Great Depression, you may recall, hit bottom in 1935, the year Irving died. My scrappy grandmother, who had never worked, managed to find a job and held on to the house. She and my mother burned player piano rolls in the fireplace that winter, to keep warm. The piano had been delivered just days before Irving fell ill. As a matter of fact, I still have that once-prized piano, and the last two surviving rolls, in my own house today.

What Irving's wife and daughter did not know, what none of Irving's doctors knew, what almost no one in the entire world knew, was that almost a decade earlier, in 1928, an obscure Scottish microbiologist named Alexander Fleming had first reported the antibacterial activity of a common blue-green mold. By 1929, Fleming had isolated the antibiotic substance and named it: "penicillin". Tests showed that penicillin was not toxic to humans.

But that was 1929. Irving died in 1935, six years later. Almost nothing was done to promote the use or production of penicillin until 1938.

That's when two British biochemists, Florey and Chain, began an intensive study to define the range of bacteria affected by penicillin. They discovered, among other things, that penicillin was an effective treatment for some bacterial forms of encephalitis.

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By 1941-44, in cooperation with American industry and the War Department, up to a ton of penicillin was being manufactured and distributed to Allied troops fighting in World War II. Penicillin, a true wonder in its day, saved millions of wounded soldiers from dying of gangrene and other common battlefield bacterial infections that just a few years earlier would have been fatal. But all this good news came a decade too late for Irving.

My grandfather may have died, not because the cure he needed had yet to be discovered, and not because the FDA had taken too long to approve a new drug, but simply because the development and commercialization of a new technology took too long. As a result, I never knew my grandfather, and my life has been forever impoverished as a result.

Each of us similarly has friends and loved ones we care deeply about – children, spouses, parents and friends. Two of them die every second, somewhere on Earth, totaling 52 million worldwide annually. But almost all of these deaths are, in principle, medically preventable – not by the methods of present-day medicine, but by a new form of medicine, called nanomedicine, that now lurks on the technological horizon.

1. What is Nanomedicine?

What is nanomedicine? The concept is fairly easy to understand. The only important difference between the carbon atoms in a plain lump of coal and the carbon atoms in a stunning crystal of diamond is their molecular arrangement, relative to each other. Future technology currently envisioned will allow us to rearrange all atoms exactly the way we want them, consistent with natural laws, thus permitting the manufacture of artificial objects of surpassing beauty and strength that are far more valuable than diamonds. This is the essence of nanotechnology: the control of the composition and structure of matter at the atomic level. The prefix "nano-" refers to the scale of these constructions. A nanometer is one-billionth of a meter, the width of about 5 carbon atoms nestled side by side. Nanomedicine is the application of nanotechnology to the field of medicine.

2. Nanorobotics

In decades to come, nanotechnologists will build nanoscale molecular parts like gears, bearings, and ratchets. Each nanopart may comprise a few thousand precisely placed atoms. These mechanical nanoparts will then be assembled into larger working machines such as nanopumps, nanocomputers, and even complete nanorobots. With medical nanorobots in hand, doctors will be able to quickly cure most diseases that hobble and kill people today, rapidly repair most physical injuries our bodies can suffer, and vastly extend the human healthspan. This application of nanotechnology to the improvement of human health is the most visionary branch of nanomedicine, called medical nanorobotics.

Microscale robots are already being investigated for *in vivo* medical use. In 2002, researchers at Tohoku

University tested magnetically-driven spinning screws intended to propel drug payloads through veins and into infected tissues, or even to burrow into tumors and destroy them with heat. In 2005 a team at the Swiss Federal Institute of Technology in Zurich fabricated a similarly-powered microrobot small enough to be injected into the body through a syringe. The team hopes their device might be used to deliver drugs or to perform minimally invasive eye surgery. Moving still smaller in scale, experimentalists have used a rapidly vibrating micropipette to slice individual dendrites from single neurons without damaging cell viability. Other researchers have wielded tightly focused femtosecond lasers as nano-scissors to perform nanosurgery on individual chromosomes inside a live cell nucleus, and have dissected the cell wall of a single bacterium, layer by layer, using an atomic force microscope.

Medical nanorobots would be even smaller and would be constructed entirely of atomically precise mechanical components. The first and most famous scientist to voice the possibility of nanorobots traveling through the body, searching out and clearing up diseases, was the late Nobel physicist Richard P. Feynman. In his remarkably prescient 1959 talk "There's Plenty of Room at the Bottom," Feynman proposed employing machine tools to make smaller machine tools, these to be used in turn to make still smaller machine tools, and so on all the way down to the atomic level, noting that this is "a development which I think cannot be avoided."

With these small machine tools in hand, small mechanical devices, including nanorobots, could be constructed. This technology, said Feynman, "suggests a very interesting possibility for relatively small machines. Although it is a very wild idea, it would be interesting in surgery if you could swallow the surgeon. You put the mechanical surgeon inside the blood vessel and it goes into the heart and looks around. (Of course the information has to be fed out.) It finds out which valve is the faulty one and takes a little knife and slices it out. ... [Imagine] that we can manufacture an object that maneuvers at that level!... Other small machines might be permanently incorporated in the body to assist some inadequately functioning organ."

What is a medical nanorobot? Like a regular robot, a nanorobot may be made of many thousands of mechanical parts such as bearings and gears composed of strong diamond-like material. A nanorobot will have motors to make things move, and perhaps manipulator arms or mechanical legs for mobility. It will have a power supply for energy, sensors to guide its actions, and an onboard computer to control its behavior. But unlike a regular robot, a nanorobot will be very small. A nanorobot that would travel through the bloodstream must be tiny enough to squeeze through even the narrowest capillaries in the human body. Such machines must be smaller than the red cells in our blood. A convenient measure of size is the micron, or one-millionth of a meter. A

red cell is about 7 microns wide. A bloodborne medical nanorobot will typically be no larger than 2-3 microns in its largest dimension. The mechanical parts that make up a nanorobot will be much smaller still, typically 1-10 nanometers in size.

3. Nanorobotics Revolution by 2020s

We cannot build such tiny robots today. But perhaps by the 2020s, we will. These future devices may be made of rigid diamondoid nanometer-scale parts and subsystems including onboard sensors, motors, manipulators, and molecular computers. They will be fabricated in a nanofactory via positional assembly: picking and placing nanoscale parts one by one, then moving them along controlled trajectories much like the robot arms that manufacture cars on automobile assembly lines. These steps will be repeated over and over with all the different parts until the final product, such as a medical nanorobot, is fully assembled.

The ability to build nanorobots cheaply and in therapeutically useful numbers will revolutionize the practice of medicine. Performance improvements up to 1000-fold over natural biological systems of similar function appear possible. For example, the respirocyte is an artificial mechanical red blood cell just 1 micron in diameter having 1/100th the volume of a natural red cell. Red cells carry oxygen to our tissues and remove carbon dioxide. Respirocytes do too, but would be made of much stronger diamond-like materials, not floppy lipids and proteins as we find in living cells. This allows respiratory gases to be safely stored within the respirocyte at tremendous pressures – up to 1000 atmospheres – and to be loaded or unloaded, molecule by molecule, using mechanical pumps on the device's surface. This simple nanorobot is regulated by onboard computers, powered by glucose fuel cells, and controlled by a physician who communicates with the device via ultrasound signals beamed into the body from outside. A therapeutic 5-cc injection of respirocytes, just 1/1000th of total blood volume, duplicates the oxygen-carrying ability of the entire human blood mass. Such a dose could instantly revive emergency victims of carbon monoxide poisoning at the scene of a fire.

Artificial mechanical white blood cell devices called microbivores are nanorobots that would seek and digest harmful bloodborne pathogens including bacteria, viruses, or fungi. The pathogens are completely digested into harmless sugars, amino acids and the like, which are the only effluents from this 3-micron nanorobot. No matter that a bacterium has acquired multiple drug resistance to antibiotics or to any other traditional treatment – the microbivore will eat it anyway. Microbivores would completely clear even the most severe bloodborne infections in hours or less, then be removed from the body. This is 1000 times faster than the weeks or months often needed for traditional antibiotic-based cures.

Related medical nanorobots with enhanced tissue mobility could similarly consume tumor cells with unmatched speed and surgical precision, eliminating cancer. Other

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devices could be programmed to remove circulatory obstructions in just minutes, quickly rescuing even the most compromised stroke victim from near-certain brain damage.

The most advanced types of nanomedical devices could perform surgery on your individual cells. In one procedure, a nanorobot called a chromallocyte, controlled by a physician, would extract existing chromosomes from a diseased tissue cell in a living patient, then insert fresh new ones in their place. This process is called chromosome replacement therapy. The replacement chromosomes would be manufactured earlier, outside of the patient's body, by a desktop nanofactory that includes a molecular assembly line, using the patient's individual genome as the blueprint. If the patient chooses, inherited defective genes could be replaced with nondefective base-pair sequences, permanently curing any genetic disease and permitting cancerous cells to be reprogrammed to a healthy state. Each chromallocyte is loaded with a single copy of the digitally-corrected chromosome set. After injection, each device travels to its target tissue cell, enters the nucleus, replaces old worn-out genes with new chromosome copies, then exits the cell and is removed from the body.

The implications for extension of healthy lifespan are profound. Perhaps most importantly, chromosome replacement therapy could be used to correct the accumulating genetic damage and mutations that leads to aging in every one of your cells. With annual checkups and cleanouts, and some occasional major cellular repairs, your biological age could be restored once a year to a more or less constant physiological age that you select. Nanomedicine thus may permit us first to arrest, and later to reverse, the biological effects of aging and most of the current medical causes of natural death, severing forever the link between calendar time and biological health.

This sounds almost miraculous, but getting there is primarily an engineering and R&D challenge. Building nanorobots requires the ability to fabricate strong, rigid, nanoscale diamond or diamond-like machine parts that are atomically precise, and then to assemble them into working machinery. Reminiscent of Alexander Fleming's early experiments with blue-green mold in 1928, an obscure Japanese research group led by Oscar Custance at Osaka University in Japan reported, in 2003, the first atomically precise bonding and unbonding of a single silicon atom, on a single spot on a silicon surface, using purely mechanical forces. This was the first laboratory demonstration of a mechanically-forced chemical reaction – called mechanosynthesis – in history. And mechanosynthesis is the key manufacturing technology that must be developed in order to build medical nanorobots, atom by atom.

Several years ago, Ralph Merkle and I founded the Nanofactory Collaboration to coordinate a combined experimental and theoretical R&D program to design and construct the first working diamondoid nanofactory, which could then build

medical nanorobots. This long-term effort must start by developing the initial technology of positionally controlled mechanosynthesis of diamondoid structures using engineered tooltips and simple molecular feedstock. Our Collaboration has led to continuing efforts involving direct collaborations among more than two dozen researchers at a dozen organizations in 5 countries – the U.S., U.K., Russia, Australia, and Belgium. A dozen peer-reviewed papers are published or in progress as of 2008.

Most recently, after working closely for three years with Philip Moriarty, one of the leading scanning probe microscopists in the U.K., in 2008 our international colleague received a five-year $3M grant to undertake direct experiments to build and validate several of our proposed mechanosynthesis tooltips in his laboratory. We're also preparing a separate research program proposal of our own to solicit additional funding from various U.S. public or private sources to support further mechanosynthesis-related experimental and theory work on a greatly accelerated schedule. We expect these efforts will ultimately lead to the design and manufacture of medical nanorobots for life extension, perhaps during the 2020s.

Conclusions

This new medical technology needs to be moved forward as quickly as possible. Every year we delay, 52 million of our fellow travelers on the river of life fall overboard and are lost forever to the rest of us. Every decade that we delay, half a billion people perish who could have been saved. The stupendous loss of knowledge and human capital is unquestionably the greatest catastrophe that humankind has ever faced. This catastrophe continues tormenting us year after year. We have a moral obligation to minimize the number of people who die unnecessarily between now and the day that nanorobotic medicine is first introduced for therapeutic purposes.

Let's not repeat the mistakes of the past. Let's not take too long to develop this important new medical technology. I'm sure – though I never had the pleasure of meeting him – that my grandfather Irving Smith would have heartily agreed.

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Bio on Freitas

Robert A. Freitas Jr. is Senior Research Fellow at the Institute for Molecular Manufacturing (IMM) in Palo Alto, California, and was a Research Scientist at Zyvex Corp. (Richardson, Texas), the first molecular nanotechnology company, during 2000-2004. He received B.S. degrees in Physics and Psychology from Harvey Mudd College in 1974 and a J.D. from University of Santa Clara in 1979. Freitas co-edited the 1980 NASA feasibility analysis of self-replicating space factories and in 1996 authored the first detailed technical design study of a medical nanorobot ever published in a peer-reviewed mainstream biomedical journal. Freitas is the author of Nanomedicine, the first book-length technical discussion of the potential medical applications of molecular nanotechnology and medical nanorobotics; the first two volumes of this 4-volume series were published in 1999 and 2003 by Landes Bioscience. His research interests include: nanomedicine, medical nanorobotics design, molecular machine systems, diamondoid mechanosynthesis (theory and experimental pathways), molecular assemblers and nanofactories, and self-replication in machine and factory systems. He has published 35 refereed journal publications and contributed book chapters, co-authored Kinematic Self-Replicating Machines (Landes Bioscience, 2004), and co-founded the Nanofactory Collaboration. His home page is at www.rfreitas.com.

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Chapter 5: A Strategy for Staying Young

Aubrey de Grey, Ph.D.
Department of Genetics, University of Cambridge, Cambridge, UK

Abstract

It may seem premature to be discussing approaches to the effective elimination of human aging as a cause of death at a time when essentially no progress has yet been made in even postponing it. However, two aspects of human aging combine to undermine this assessment. The first is that aging is happening to us throughout our lives but only results in appreciable functional decline after four or more decades of life: this shows that we can postpone aging arbitrarily well without knowing how to prevent it completely. The second is that the typical rate of refinement of dramatic technological breakthroughs is rather reliable (so long as public enthusiasm for them is abundant) and is fast enough to change such technologies (be they in medicine, transport, or computing) almost beyond recognition within a natural human lifespan. Here I explain, first, why it is reasonable to expect that (presuming adequate funding for the initial preclinical work) therapies that can add 30 healthy years to the remaining lifespan of healthy 55-year-olds will arrive within the next few decades, and, second, why those who benefit from those therapies will very probably continue to benefit from progressively improved therapies indefinitely and thus avoid debilitation or death from age-related causes at any age.

1. Introduction

The approach to postponing aging that I shall describe in this essay is one of maintenance and repair. Those who like to claim that aging is intrinsically immutable are often inclined to start by asserting, ex cathedra, that living organisms are qualitatively unlike machines and therefore cannot be maintained beyond their "warranty period" in the way that typical machines can. Even leaving aside the absence of any justification of the "therefore" in that assertion, there is a conspicuous fragility in the idea that organisms (even humans) are in any relevant way unlike machines. The property of living organisms that is most often suggested as distinguishing them from machines is their capacity for self-repair, and indeed that is undoubtedly something at which organisms are vastly superior to any machine currently in existence. But to consider it a qualitative difference is clearly incorrect: as a simple example one need only consider household robots that plug themselves into the mains when their batteries run low, or photocopiers that suspend operation to clean their wires when they automatically detect the need.

The pessimist often retorts that, even if this is not a qualitative difference, the difference of degree is so astronomical that the practical feasibility of maintaining an organism as one does a machine is far too distant to be worth considering. But here again we see a crass logical error, because the idea is to *augment*

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our natural maintenance systems: thus, the fact that they are so good already means that there is that much *less* for us to do to make them good enough to work indefinitely. There is much more to this question, as will emerge below, but the crux of the argument is as just stated.

In the next section I will describe in rather abstract terms the sort of maintenance that I believe we should be working towards in the quest to postpone aging as much as possible as soon as possible. In the following section I will go into more concrete biological detail, giving an overview of the specific types of maintenance and repair that humans need to do better in order to maintain our health and youth for a lot longer and the methods already under development to implement those required improvements. The concrete and detailed nature of those prospective interventions leads me to the view that we are potentially within only a decade of developing them all in laboratory mice, and that once we have done so we have perhaps a 50% chance of developing them in humans within only 15 years thereafter. Then, in the final section I will explain why this should be enough to put us beyond "life extension escape velocity" – the point at which we are improving these technologies faster than the remaining imperfections in them are catching up with us. Once we reach that point, and presuming we can stay there (which, I will argue, is virtually certain), no one need die of old age ever again, whatever age they attain.

2. The Lag Phase of Aging: Our Window of Opportunity

What is aging, actually? It is often suggested that aging is very hard to define. That is true if one requires a definition that suits all purposes, but when discussing interventions an altogether uncontroversial definition is easily found. A typical one is as follows:

> Aging is the set of side-effects of metabolism that alter the composition of our bodies over time to make it progressively less capable of self-maintenance and thereby, eventually, less functional.

This definition allows us to identify three very distinct strategies for postponing aging and thereby extending healthy and total lifespan. Curiously (at least in retrospect), only two of them have historically been pursued. They are depicted in figure 1, in which the flat-headed arrows are used in the conventional genetics sense to mean "inhibits".

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Figure 1. The two traditional approaches to postponing aging.

Putting Figure 1 into words: the gerontology approach is pre-emptive, seeking to diminish the side-effects of metabolism mentioned above and thereby to slow down the rate at which metabolism changes the composition of our bodies, whereas the geriatrics approach is reactive, seeking to delay the functional decline (i.e., pathology) that those changes in composition cause. The changes in composition themselves, in Figure 1, are simply denoted by the term "damage": they are no more nor less than the accumulation of that damage. It is important to stress that I will use the term "damage" in this very precise sense throughout this essay: for present purposes it is defined as the entire set of changes of bodily composition that (a) are side-effects of metabolism and (b) are eventually pathogenic. In particular, the reader should not infer any implication concerning how this damage is laid down, such as whether it could reasonably be called "wear and tear".

What is the prognosis for the gerontology and geriatrics approaches, in the foreseeable future? It is easy to see that the geriatrics approach is short-termist almost by definition: as damage accumulates, its natural pathological consequences become progressively harder to avert. Besides, even if we could in principle develop geriatric medicine so sophisticated that pathology was slowed, that would be a somewhat mixed blessing, as it would constitute an extension of the frail period of life.

The gerontology approach initially seems much more promising. If one can retard the rate at which metabolism lays down damage in the first place, one will certainly extend the healthy part of life, which would seem unambiguously desirable. (Possibly the frail part would be extended too, but probably less so.) However, it has two daunting shortcomings. Firstly, damage that has already

been laid down before the treatment begins will not be affected: hence, those who already have enough of it to be starting to suffer functional decline will not have that loss of function restored by such therapies. Secondly, the practicality of the gerontology approach is determined by the extent to which we understand metabolism, because altering the workings of a system that we understand only very poorly tends either to have no effect at all on its behaviour or to do more harm than good. And unfortunately, that is the case with metabolism: though we certainly understand far more about it than we did only a few decades ago, we are regularly reminded by the discoveries of fundamental new aspects of metabolism (such as RNA interference, discovered only a few years ago [1]) that in reality we have still hardly scratched the surface of its complexity. This bleak conclusion is reinforced by the failure of the rational but evidently over simplistic approaches to extending mammalian lifespan that gerontologists have attempted over the past 50 years: it remains the case that, apart from a scattering of reports that were never reliably reproduced, the only way to extend mammalian lifespan is to elicit a response that metabolism already has available to it, namely the intensification of repair and maintenance that results from moderate deprivation of nutrients [2]. (This is no longer the only way to elicit that response – genetic manipulation has done it too [3,4] – but it is still essentially the same response.)

If we wish to postpone aging any time soon, therefore, it seems clear that we must seek a third way – something radically different from the gerontology and geriatrics approaches. Just such an approach has been the focus of my work since 2000 and has become known as "Strategies for Engineered Negligible Senescence" or SENS [5,6]. It can best be explained by embellishing Figure 1, as shown in Figure 2.

Figure 2. How the engineering (SENS) approach to postponing aging relates to the two traditional approaches.

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The key feature of the SENS approach is that it intervenes early enough to avoid being a "losing battle" like the geriatrics approach, but at the same time it does not attempt to improve the already indescribably complex and well-honed machine that is our metabolism, but rather to clean up after it. In short, the SENS approach does not attempt to interfere in processes – neither the process whereby metabolism causes damage, nor that by which damage causes pathology. Rather, it seeks to remove the damage that metabolism lays down, at least as fast as it is laid down, and thereby to prevent it from ever translating into pathology at all.

The SENS approach relies on a frequently overlooked aspect of aging which is mentioned in the definition I gave earlier: that even though metabolism causes damage all the time, throughout our whole life, damage only eventually causes functional decline. If you live and eat essentially as your mother told you to, and if you are not particularly unlucky in terms of genetics, you will probably be able to run and think more or less as fast at the age of 40 as you could when you were 20. This tells us that there is a threshold level of damage beyond which trouble starts but below which metabolism copes without degradation of performance, rather as a roof carries on keeping the rain out if only a couple of isolated slates are dislodged, or as a car continues to work if it has acquired just the odd patch of rust. A machine is only as dependable as its weakest link, of course, so there may be a variety of types of damage, all of which must be kept below the threshold, but that does not alter the logic.

Perhaps the most obvious initial objection to the SENS approach, and certainly a common one heard from biogerontologists, is that it "must" be impossibly infeasible simply because it seeks to reverse age-related decline. The idea here is that reversing a process is intuitively far harder than slowing it down, and we have made precious little progress (even in mice, let alone humans) in slowing aging down. There are two main errors in this logic. The first is that reversing a process is only necessarily harder than retarding it if one restricts oneself to using the same methods for reversal as one would for retardation and doing them so well that the retardation outstrips the progression. In reality, there are other approaches to reversing a process that do not act in this "head-on" way. Consider the predicament of a person in a small rowing-boat in the centre of a large lake, which has sprung a leak. The person has two fundamentally different options for keeping afloat until rescue arrives: he can try to plug the leak, thereby retarding the rate at which water enters, or he can bail water over the side, counterbalancing the influx. The latter process constitutes a reversal of the accumulation of the problem, but by a method that (unlike forcing the water back through the hole!) is technologically no more challenging than plugging the leak.

The other error in the idea that reversal is inherently far harder than retardation is equally important. If one has few tools available, one may only

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be able to plug the leak rather imperfectly, so that some water continues to enter and one will prolong one's survival but not indefinitely. In the case of bailing, by contrast, a sufficient but finite rate of removal of water will suffice to keep one afloat for as long as may be required. This has especially profound implications in the longer term, as will be explained below.

3. From Boats to Biology: Is the Analogy Valid?

Analogies are all very well for showing that an idea makes sense in principle, but what about putting it into practice? In order to demonstrate that the SENS approach is truly foreseeable, it is necessary to describe in concrete terms what the "damage" is that SENS must repair, and also to propose specific biotechnological approaches to that repair for each type of such damage. Moreover, the proposed approaches must embody sufficient detail to give confidence that we can get there from here in a meaningfully predictable timeframe.

Without further ado, then, I offer in Table 1 what I claim is an adequately complete list of the types of side-effect of metabolism that can be considered to qualify as "damage" by the definition being employed in this essay – that is, changes that there is some reason to believe contribute to age-related pathologies of one sort or another. By "adequately complete" I mean that it includes all types of change in our molecular and cellular composition that may contribute to tissue dysfunction in a currently normal lifetime; I acknowledge that other types of such change, such as nuclear mutations that do not affect the cell cycle, may be pathogenic when we reach ages considerably exceeding our existing lifespan.

Table 1. The seven "deadly things": types of damage that SENS seeks to combat and the dates when they were first suggested by gerontologists to contribute to mammalian aging.

Type of age-related damage	*Suggested by, in*
Cell loss, cell atrophy	Brody, 1955 [7]
Senescent/toxic cells	Hayflick, 1965 [8]
Oncogenic nuclear mutations/ epimutations	Szilard, 1959 [9]; Cutler, 1982 [10]
Mitochondrial mutations	Harman, 1972 [11]
Intracellular aggregates	Strehler, 1959 [12]
Extracellular aggregates	Alzheimer, 1907 [13]
Extracellular crosslinks	Monnier and Cerami, 1981 [14]

The suggestion that this list is indeed adequately complete is a bold one and is routinely challenged. However, there are two strong arguments for this contention. The first concerns the dates noted in the right-hand column, the most recent of which is 1982. The analytical sophistication available to biologists has advanced very considerably since then, so the fact that this list has not been extended as a result constitutes a strong circumstantial argument that no "eighth sin" will be discovered in the future either (except, as noted above, in those who reach ages that

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the seven problems listed above currently prevent anyone from attaining).

The second argument that the above is a complete list is perhaps more attractive to the biologist: it is that the list can be derived from first principles by examining our biology systematically. The starting-point for doing this is to note (a) that the list is of types of damage, not of processes that cause that damage (which would be a much longer one – indeed, one that certainly could not be confidently completed with current knowledge) and (b) that, by definition, damage can only accumulate in long-lived structures. Intracellular proteins, for example, vary somewhat in half-life but never survive for more than a small fraction of the human lifespan: thus, any deleterious modifications that they suffer are eliminated when they are destroyed. With these two points in mind, we can then ask: what are we made of? The first-level answer is: cells and stuff between cells. Cells of a given type can become more or less numerous with age: when this is deleterious we have the first two of the seven types of aging listed in Table 1. Within cells there are only two types of long-lived molecule – DNA (which of course is long-lived in an unusual way, because it is synthesised by replication) and garbage, i.e. indigestible substances that are sequestered indefinitely, usually in the lysosome. That accounts for items 3, 4 and 5 in Table 1. In the extracellular space, similarly, there are just two types of long-lived molecule: complex proteinaceous structures such as the lens of the eye and the artery wall that can become chemically and thus physically modified over time (item 7), and garbage, again of different composition in different tissues but collectively termed amyloid (item 6).

So far, so good: we have a satisfactorily complete description of the problem. What about solutions? Table 2 summarises the current state of play as I see it.

Table 2. Foreseeable approaches to repair or obviation of the seven types of damage listed in Table 1.

Type of damage	*Proposed repair (or obviation)*
Cell loss, cell atrophy	Stem cells, growth factors, exercise [15]
Senescent/toxic cells	Ablation of unwanted cells [16]
Oncogenic nuclear mutations/ epimutations	"WILT" (Whole-body Interdiction of Lengthening of Telomeres) [17,18]
Mitochondrial mutations	Allotopic expression of 13 proteins [19]
Intracellular aggregates	Microbial hydrolases [20,21]
Extracellular aggregates	Immune-mediated phagocytosis [22]
Extracellular crosslinks	AGE-breaking molecules [23]

The first point to emphasise about Table 2 is that, of the seven therapies listed, two are not strictly repair strategies (reversing the accumulation of the specified type of damage) but rather obviation strategies that make the phenomenon no longer capable of causing pathology, and thus make it

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cease to classify as "damage". These are items 3 and 4 in the list, addressing nuclear and mitochondrial mutations respectively. For nuclear mutations, the proposal is a treatment for cancer that does not stop cells from accumulating the mutations that allow them to divide uncontrollably, but instead gives them a time-bomb – telomere shortening – which they cannot defuse even by the hypermutation that makes cancers so versatile in eluding all contemporary therapies. For mitochondrial mutations the suggested strategy is to make such mutations harmless by allotopic expression –introducing copies of the 13 protein-coding genes of the mitochondrial DNA into the nucleus, with modifications such that they will still encode the correct amino acid sequence when translated on cytosolic ribosomes and will then be targeted to and imported into mitochondria by the pathway already employed by the thousand-odd naturally nuclear-coded mitochondrial proteins. These proteins would maintain mitochondrial function in the presence of any mitochondrial mutation.

How far away are the therapies listed in Table 2? In order to answer that question one must ask it somewhat more precisely, by specifying two additional things: how well the therapies must work, and in what organism. Here we encounter an slightly paradoxical pair of comparisons: initial, relatively modest progress will certainly occur sooner in shorter-lived mammals (specifically mice) than in the relatively long-lived human, but longer-term and more dramatic advances will occur in humans first – indeed, they will quite probably never occur in mice. The latter will be the topic of the next section; in this section we consider more modest, more near-term advances.

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There are two main reasons why the first substantial steps in extending healthy lifespan with late-onset interventions will occur in mice sooner than in humans: firstly there is the biological reality that organisms with longer lifespans are already avoiding aging rather well and thus are harder to improve by copying ideas (genes, in particular) from even longer-lived species, and secondly there is the sociological reason that society mostly considers the deaths of rather large numbers of mice in the quest to perfect a therapy to be much more acceptable than the death of even one human in that quest. Neither is likely to change any time soon, so we first address the extension of mouse lifespan.

As noted, we must also specify a degree of progress that can be considered an appropriate milestone.

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The one that I have championed in recent years, with the moniker "Robust Mouse Rejuvenation" (RMR) [24], is to treble the remaining average lifespan of a cohort of naturally long-lived mice that are already 2/3 through their natural lifespan before any intervention (whether genetic, pharmacological or dietary) is begun. Long-lived mouse strains typically live to three years of age on average, so this means initiative a protocol on such mice at the age of two years and giving them an average age at death of five years.

So to the timeframe for interventions. The last two items in Table 2 are the ones in which we are furthest advanced at present. In 1996, a small molecule was revealed which restored elasticity of rat tail tendons to a remarkable degree [25]; subsequent work from the same group has demonstrated the restoration of youthful elasticity in a biomedically more significant tissue, the artery wall [23]. Likewise, in 1999, a mouse model of Alzheimer's disease was shown to exhibit a dramatic reversal of the accumulation of senile plaques, the main extracellular feature of the disease, in response to vaccination against their major constituent, the Abeta peptide [22]. Both these discoveries are only the start in developing comprehensive reversal of their respective "sins", but they are both promising enough to have progressed in only a few years to clinical trials. In both cases the main work remaining to be done in mice is to apply the same principles to other major types of (respectively) crosslink and amyloid than the ones which these pioneering therapies address, but in fact it may transpire that these initial treatments, though currently restricted to one category of crosslink and one amyloid-accumulating tissue, will address a sufficient proportion of their respective categories of damage to deliver RMR (so long, of course, as the therapies for the other five classes of damage are also up to scratch).

Compensation for cell loss is also going rather well. Many tissues that lose cells during normal aging or in the context of disease are the subject of intensive research into cell replacement using growth factors or stem cell therapy, some of which has also reached the clinic [26-28]. This work lags behind the two SENS strands just discussed only insofar as the differences between therapies for different tissues are probably more challenging, relying as they currently do (at least in the case of stem cell therapies) on rather precise *ex vivo* "pre-differentiation" of initially over-versatile stem cells that are otherwise prone to develop not only into the desired cell type but also into a variety of unwanted ones.

Elimination of supernumerary cells in rodents varies greatly in difficulty depending on the type of cell to be eliminated. The simplest is visceral fat, which can be surgically removed from the abdominal cavity of rats and results in the abrupt alleviation of previously advanced diabetes [16]. Potentially there is also the possibility of converting the cells in question to a benign form, but no systematic method to identify such an intervention is yet evident. There are two attractive options that do qualify as "rationally designed", however, both exploiting the identifiability of the problematic

cells by their excessive expression of particular genes. In the first method, "suicide" genes [29] are introduced by somatic gene therapy: these typically enter cells of many cell types, but the gene is placed under the promoter of the excessively-expressed gene so that it is only expressed in the cells that one wishes to eliminate. In the second approach, the undesired cells are removed by the immune system as a result of stimulation by appropriate vaccines and adjuvants [30]. However, none of these strategies has yet reached the clinical trial stage.

The remaining three SENS strands may be considered the "critical path" towards RMR, as they are all some way from implementation even in mice. Allotopic expression of the mitochondrial proteins from nuclear transgenes may be closer than it seems *in vitro*, as recent work gives considerable confidence that the only remaining requirement is to identify amino acid changes to these proteins' transmembrane domains which makes them a little less hydrophobic and thus more readily importable by the mitochondrial protein import apparatus [19,31]. The remaining issue for RMR in regard to mitochondrial mutations is delivery of these genes to affected cells, and the current state of somatic gene therapy in mice is such that this may be only moderately challenging, especially in view of the fact that introduction of these genes into mitochondrially healthy cells should be harmless

The runner-up in the difficulty stakes for RMR is probably the removal of intracellular aggregates. Indigestible material progressively impairs cell function, not least by impairing the degradation of other substances that the cell was hitherto able to process efficiently. An approach to this problem that I introduced in 2002 [20] and which has since enjoyed increasing interest [21] is to identify microbial enzymes that can break down such compounds (or convert them to ones that mammalian metabolism already handles). Exploration of the microbial ecology of contaminated environments has proven so extraordinarily successful in bioremediation that there is widespread optimism for the corresponding strategy in respect of material that accumulates in the environment of our bodies. However, the challenges that will arise in the later stages of implementing such a therapy – such as the avoidance of toxicity, the retention of function in the mammalian cell and the management of any immune response – mean that "lysosomal enhancement" is realistically up to a decade away even in mice.

Finally we come to nuclear mutations, and specifically those which promote cancer. The energy with which cancer has been fought by the biomedical research community over recent decades, especially since Nixon's initiation of the "War on Cancer" in 1971, is matched only by that effort's lack of success in coming close to the rate of progress predicted by many leading cancer specialists at that time. This sobering reality led me to introduce recently [17,18] a proposed anti-cancer strategy, termed WILT (Whole-body Interdiction of Lengthening of Telomeres) that is as ambitious as it is audacious: the use of

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both *ex vivo* and somatic gene therapy to delete the genes for telomerase and (as and when they are identified) ALT (Alternative Lengthening of Telomeres) from as many of our cells as possible. This will have deleterious side effects that are obvious and daunting: telomere shortening will irresistibly eliminate the stem cell pools that maintain all our continually-renewing tissues, such as the blood, the gut and the skin. My proposal is to avert these consequences by periodic replenishment of our stem cell pools with new cells that also lack genes for telomere elongation but have had their telomeres extended *ex vivo* to normal lengths with exogenous telomerase. This is a decidedly tall order, and is only even worthy of contemplation because it appears that the frequency of such replenishment may not need to exceed once a decade in humans. However, WILT is for many reasons exceptionally difficult to test in mice and may thus need to be developed in less convenient species. It is this, above all, that makes it the hardest SENS strand to develop. In a sense this could be argued to be irrelevant to RMR, because many of the anti-cancer therapies that have had such modest success in humans actually work extremely well in mice, quite possibly well enough to achieve the RMR milestone. However, ultimately the purpose of working towards RMR is to achieve the corresponding advance in humans thereafter, so there is a certain inadequacy in that line of reasoning.

4. Escape Velocity: When Humans Become Easier Than Mice

Once RMR is achieved, I am convinced that society's attitude to the postponement of human aging will become unrecognisable. I have therefore predicted that there is a 50% chance of our achieving a comparable advance in human life extension within 15 years after we achieve RMR. This human milestone, which I rather unimaginatively term "Robust Human Rejuvenation" or RHR, is not in my formulation precisely proportional to RMR: rather than a trebling of the remaining lifespan of people who are already 2/3 of the way to the prevailing average age at death, I define it as only a doubling. This means roughly 25-30 years of extra healthy life for people who are perhaps 55 when treatment begins.

Why have I chosen a relatively toned-down version of RMR to define as RHR? Simply, because 25-30 years is a familiar duration in the history of technology, and specifically in that part of the history of many technologies which, in respect of life extension, I will now discuss. How long does it take, following some fundamental technological breakthrough, for that technology to progress by incremental refinements to a stage beyond that which the architects of the original breakthrough could reasonably have contemplated? The answer seems rather reliably to be in the 20-30 year range. Lindbergh flew the Atlantic 24 years after the Wright brothers' first flight. Commercial jetliners first flew 22 years after that, and supersonic airliners 20 years after that. In computing, the personal computer arrived about 28 years after the first electronic computer and the first convenient laptops arrived about 20 years later. In medicine, the discovery

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of antibiotics followed the publicising of the germ theory by about 30 years and was in turn followed, after another 25 years, by the development of methods to manufacture vaccines specific for a particular disease.

The implications of this pattern for the lives of people who are in middle age or younger at the time that RHR is achieved is clear, but no less dramatic for that. Put simply, there is a very high probability that the 25-30 years of good health conferred on its recipients by the first-generation panel of rejuvenation therapies (defined as those which achieve RHR) will suffice for the development of much more thorough and comprehensive therapies, capable of delivering more like a century of extra life to those who are in relatively good health at the time those therapies arrive. This is where the longevity escape velocity (LEV) concept [24] arises. The recipients of the first-generation therapies – the ones that gave only around 30 years of extra healthy life – will, at least if sociopolitical pressures do not intervene, mostly also be among the beneficiaries of the second-generation ones, since they will be in the same degree of health at that time as they were when the first-generation therapies arrived. The same logic of course applies indefinitely into the future, just so long as the rate of progress in improving the comprehensiveness of the therapies continues to outstrip the rate at which the remaining imperfections in those therapies allow the accumulation of eventually pathogenic damage. It should now be clear why the correspondingly dramatic extension of mouse lifespan may in fact be much harder than for humans (indeed, maybe impossible) – since mice age so fast, new age-related problems will kill mice rather soon after they are discovered, too quickly for those problems to be addressed by scientific advances.

What does this add up to for lifespan? Clearly the life spans of those who live their entire lives in a period when progress is faster than LEV will be indefinite, since a given individual's risk of death at any adult age will be less than at earlier adult ages. What is less immediately clear is how to estimate the life spans of those already alive (and at various ages) at the time RHR arrives. My estimates are depicted (for actual numbers are too speculative to estimate) in Figure 3. To summarise: I estimate that 50-year-olds who are in average health at the arrival of RHR and who are, thereafter, able to benefit from the latest and best rejuvenation therapies, will have at least a 50/50 chance of reaching their own personal escape velocity – that is, of being restored to a truly youthful state with a very low mortality risk. Most of those who are only 30 at that time will never reach a state of age-related frailty. Moreover, elite individuals – those who would naturally live to 100 or more even in the absence of these therapies – will have that 50/50 chance even if they are already in their 70's when RHR arrives. A key corollary of the above considerations is that there will be a stunningly sharp "cusp" in the increase in life spans of those born in successive years. One way to quantify this is that the first 1000-year-old is probably only about ten years younger than the first 150-year-old. Another, possibly of more relevance to those who do not consider themselves

Figure 3. Plausible trajectories of "biological age" for typical individuals of the specified ages at the time RHR arrives, presuming access to the best therapies at any time.

inherently likely to live exceptionally long, is that a whole generation will be, in the words of the Australian writer Damian Broderick [32], the "last mortal generation" – a cohort who live roughly as long as those born in 1900, but whose offspring mostly live indefinitely and die only of causes unrelated to age. The sociopolitical implications are highly unpredictable but it seems inescapable that they will be unprecedentedly profound.

5. Conclusion: We know not what the future brings, but we must hasten it anyway.
I have attempted in this essay to outline the methods by which humanity will in due course defeat its greatest remaining scourge. Much of what I have written is plainly speculative in the extreme, yet I have stuck my neck out and given estimates of timeframes, with probabilities attached to them. Some feel that speculations of this sort are irresponsible, engendering unwarranted optimism about the rate of progress. I take the diametrically opposite view: I am convinced that it is irresponsible to remain silent on such matters, because doing so engenders unwarranted pessimism: the public are predisposed to presume that nothing can be done about aging and thus do not agitate for efforts to hasten progress, and that will only change if their sights are raised [33]. Accordingly, I have no compunction in setting out (here and elsewhere) a scenario that, after much consideration, I consider the most likely way in which, and rate at which, we will move to a post-aging world.

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Chapter 6: Defining Future of Health Technology

Renata G. Bushko, M.S.
Founder, Future of Health Technology Institute, Hopkinton, MA, US

Abstract

Future progress in healthcare and medicine depends on today's investment in research, development, and education. We cannot leave such urgent issues to determine themselves, but rather must actively collaborate to ensure a stable healthcare system. This chapter describes efforts made by leading experts in industry, government, and academia to better ascertain future healthcare management. Such collaboration has occurred during a series of Future Healthcare Technology Summits [1] helping in planning investments in health technology. Deliberating and reviewing plans before taking action will accelerate progress as it will (1) save costs, (2) encourage compliance, (3) improve clinical outcomes, and (4) ensure greater patient satisfaction [2]. What we must resolve is: How can we invest a couple billion dollars to save hundreds of billions and, most importantly, increase human health in the future. A new branch of science, Biomechatronics, with millions of Intelligent Caring Creatures– is the answer.

1. Introduction

In early 1990's I worked on national healthcare programs organized by Vice President Gore, Dr. C. Everett Koop, and former secretary of Health and Human Services Dr. Louis Sullivan. I advised on health technology investment issues in US, UK, Puerto Rico, Australia, New Zealand, and Poland. Through my experiences with these healthcare programs I realized that we needed to spend more time on long-term planning. We needed an independent agency to discuss and oversee long-term issues of health technology. This agency would prepare for a future society where computers might outsmart people, where we might be able to stop diseases before they begin, where Affective Intelligent Caring Creatures [3] will aid physicians in 90% of their work and individuals can diagnose and cure themselves with self-health tools and designer drugs. Such an agency would prepare the medical community and consumers for inevitable technological changes and advances.

2. Agency To Look At Long-Term Issues Of Health Technology

The Future of Health Technology Institute (FHTI) was founded in 1996 to address the long-term issues of health technology [4]. FHTI is a think-tank aimed at defining an agenda for health technology development and determining the most critical focus areas for health technology investment in the new century. Founded on the 40th anniversary of the field of Artificial Intelligence, FHTI found inspiration in the intellectual legacy of Professor Marvin Minsky. He is one of the founders of Artificial Intelligence and one of the most creative minds of our times. I became his student in 1985 when he was working on the Society of Mind theory.

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Since its foundation in 1996, FHTI has been doing what Professor Dertouzos describes as:
"Put in a salad bowl the wildest, most forward-thinking technological ideas that you can imagine. Then add your best sense of what will be useful to people. Start mixing the salad. Something will pop up that begins to qualify on both counts" [5]. Professor Dertouzos suggests that we should then "Grab it and run with it," which agrees with the paradigm that the best way to define the future is to invent it.

Unfortunately this optimistic model leaves a lot to random chance. The salad-bowl approach is a good start, but each idea should be attributed impact value and compared against alternative ideas. The ideas rely on both technological novelty and human usefulness. The process of comparing various ideas can be an efficient way to save time and money. FHTI proposes to manage the coordination of the most promising ideas in health technology using top-level experts from the industry, government and academia during Future of Health Technology Summits 1996-2001 [1]. The most investment-productive health technology areas are presented in this chapter (Tables 2-9).

3. Background: Thinking Model from the Field of Artificial Intelligence

In 1956 a diverse group of scientists consolidated various studies into a new field of science: Artificial Intelligence. They aimed to discover the unknown and mysterious machinery of the mind. Future of Health Technology Institute considers their efforts a model of leadership and innovation, representing skills essential in facing the problems of the 21st century.

How can we use this successful example to address emerging complexities that lie ahead? The world has changed in forty years since Marvin Minsky, John McCarthy, Allen Newell, Herbert Simon and other inquisitive minds met to design the field of Artificial Intelligence. In the same forty years the world of biology and medicine faced equally radical changes. FHTI summits address achievements of the last forty years in both medicine and medicine, trying to map out how those fields might come closer and merge in the future.

With the development of new technological innovations, people naturally fear that increased costs are inevitable. FHTI, however, believes that increased expenses can be stopped or even reversed. For example, while computer technology continues to expand, computer costs have decreased exponentially. Why should technological improvements in healthcare not follow the same progression? How can we take advantage of new technologies to improve the quality of life and simultaneously reduce procedure and treatment costs? Perhaps it is a matter of vision and leadership.

Specific goals of the Future of Health Technology Institute are:

1.Develop a vision of future health care supported by current and future health technologies.

2. Define distinct promising health technology research areas.

3. Demonstrate that technology driven cost increases in healthcare can be stopped and possibly reversed by a new allocation of research and development resources.

4.Define productive areas for research and development that will have potential impact on healthcare.

5.Identify new technologies that are practical
and necessary in health and wellness maintenance.

6.Identify research and development needed to meet future health challenges.

7.Identify current products best for preparing 21st century healthcare.

4. Health Challenges – Need for Common Sense

4.1 Dare to Guess – Dealing with Hard Problems

Defining the future of health technology is difficult and requires both common sense and intuition. "Common sense is an immense society of hard earned practical ideas – of multitudes of life-learned rules and exceptions, dispositions and tendencies, balances and checks."[6] These balances and checks are especially useful when performing estimation tasks, where we deal with incomplete information. "For a hard problem, it may be almost as difficult to recognize progress as to solve the problem itself". [6] "A problem is hard if it requires common sense knowledge in addition to specialized knowledge and a set of non-obvious to the non-expert heuristics in order to be solved effectively and accurately. A body of knowledge required to solve a hard problem is not algorithmical but it is not totally intuitional either" [7]. A difficult (hard) problem manifests itself by the following facts:

(1)There exist experts that can solve that problem better (significantly faster, with better accuracy) than an average human

(2)Providing solution involves some symbolic reasoning and some common sense reasoning that is perceived as intuition

(3)Training humans to solve this kind of problem is a long-lasting, difficult, and not always successful process

(4)Even single experts accuracy leaves some space for improvement

Hard problems require making educated guesses and then verifying that hypothesis. We do not know the algorithm generating the solution but we can verify the positive solution once a guess is provided [7]. The best way to make some progress in defining the future of health technology is to work with a group of experts in related fields and also reach out to other industries to transfer relevant

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knowledge and know-how (e.g. hotel industry's customer satisfaction model at FHT99) [7, 8].

4.2 Define Health Challenges

The first step is to define challenges ahead of us. A group of experts was asked to define health challenges of the 21st. Century using survey method. The results are listed in Table 1. Experts were energized and inspired to action by the approaching Future of Health Technology Summit.

Table 1. Health challenges of the new century. Order does not reflect importance.

1	Poverty
2	Hunger
3	Escalating costs of drugs
4	Escalating costs of technology
5	Engaging people to be responsible for their health and their family's health
6	Empowering consumers with better information and self help tools
7	Expanding & improving access to quality services including advanced diagnostic/ therapeutic technologies while maintaining or reducing costs
8	Improving medical informatics literacy among medical staff
9	Reengineering the medical visit
10	Establishing Internet electronic medical record
11	Better monitoring and treatment of chronically ill patients away from the hospital
12	Finding cure for cancer and heart disease
13	Finding cure for paralysis
14	Coordination of services, transfer of information between providers and provider /patients
15	Effective Knowledge management
16	Providing relevant health information to the people who most need it
17	Creating happy environment for being sick
18	Emotional aspects of getting over healthcare problem and death
19	Assuring medical data integration
20	Improving healthcare workflow
21	Patient-omic data management and analysis (patient genomic, proteomics, physiomics) and patient cross-comparisons
22	Expanding use of body-pervasive monitoring devices
23	Personalized drug design
24	Improved gene repair
25	Providing high quality health care services to all people, regardless of where they reside, what their socioeconomic status is, or what their cultural characteristics is
26	Reducing healthcare disparity
27	Maintaining high levels of health services (with tight budgets)
28	Inter-disciplinary issues related to the human element, not technology
29	Aging population explosion
30	Healthcare access, especially preventive care, for the large number of the uninsured
31	Shortage of nurses
32	Appropriate selection and use of healthcare resources by clients, self-care, and healthy habits through the dissemination of quality health information
33	Establishing cost-conscious evidence-based practice
34	Stop rising cost of healthcare
35	Increasing expenses and demand for services with decreasing reimbursement
36	Eliminating medical errors (estimated 40,000-98,000 inpatient deaths annually in US[1])
37	Extending human lifespan

[1] Institute of Medicine report released on November 29, 1999

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4.3 Most Promising Health Technologies – Brainstorming Method

In order to approximate seven most promising health technology areas, the list of most promising health technologies generated by the before-summit survey, was presented to experts for prioritization. Then, seven most promising areas were selected during the brainstorming session. Results are presented in Table 2.

Table 2. Seven most promising health technology areas. Brainstorming method. Summarized by Dr. Gary Kreps [9].

1	Instant Medical Data Collection and Knowledge Dissemination Technologies and Standards
2	Decision Making and Support Technology (personal and point of care)
3	Individualized Diagnosis and Treatment (e.g. real time protein synthesis, real time genetic testing)
4	Health Systems Methodologies
5	High Tech Intervention (e.g. Robotic Surgery, Sensors, Teleconsultations)
6	Information Access and Feedback Technologies
7	New Technologies Evaluation Methodologies

4.4 Most Promising Health Technologies – Survey Method

Seven technology areas listed in Table 3 were selected as most promising using the survey method. None of these lists or any other lists should be taken as the only lead to follow. They are only useful to attune our common sense and to turn into the right direction in the specific technology investment process.

Table 3. Seven most promising health technology areas selected by experts. Survey method.

1	(A) Tissue Bioengineering & (B) Nanotherapeutic Technologies
2	Knowledge Management Technologies (including decision support and data mining)
3	Electronic Health Record in a Standard Format with Unique Patient Identifier
4	(A) Powerful yet easy to use Self-diagnostic Technologies & (B) Vaccine Biology
5	Affordable information system access with decision support for healthcare professional
6	Internet-driven Technologies
7	Voice Recognition, (B) Psychological Aids & (C) Artificial Intelligence & (D) Controlled Medical Vocabularies

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4.5 Seven Health Technology Areas with Highest ROI

As the last step, experts were asked to prioritize technologies given that "most promising" meant technology producing the highest impact with the lowest investment (technologies with highest return on investment - ROI). ROI was evaluated intuitively based on the diverse knowledge of the experts involved. FHTI's graphical Common Sense Squares Method was used in the ranking process.

Table 4. Seven health technology areas with the highest return on investment. Survey method and FHTI's "Common Sense Squares Method" method.

1	Internet-driven Technologies
2	Electronic Health Record in a Standard Format with Unique Patient Identifier
3	Psychological Aids
4	Vaccine Biology
5	Powerful yet easy to use Self-diagnostic Technologies
6	Intelligent Agents (Intelligent Caring Creatures)
7	Affordable information system access with decision support for healthcare professional & patient

4. 6 Most Promising Health Technology Research Areas - Insight

To balance group thinking (Table 3 and 4) FHTI asked one of the leading thinkers, Professor Alice Pentland, to propose a separate list of seven most promising health technology research areas [10]. This list was generated independently from the lists obtained from survey and brainstorming method but all experts involved in prioritization heard a detailed explanation of Professor Pentland's selection just before their brainstorming session.

Table 5. Seven most promising health technology research areas as defined by Professor Alice Pentland.

1	Memory Assistance Aids
2	Tissue Bioengineering and Gene Therapy
3	Perceptual Prostheses
4	Vaccine Biology
5	Rapid Diagnosis
6	3D Mapping
7	Psychological Aids

5. Rapid and Cost-effective Technology Impact Assessment

Technology impact study is an important next step after selection of most promising health technologies. An example of a cost-effective impact study is presented in the chapter "Impact of Voice and Knowledge-enabled Clinical Reporting – US Example" in this book. It uses Unified Quality Framework [2, 11, 12] that helps to examine technology impact on quality of healthcare using four qualitative and quantitative dimensions:

1)Process Quality as measured by cost

2)Organizational Quality as measured by compliance

3)Clinical Quality as measured by clinical outcomes

4)Service Quality as measured by patient and staff satisfaction

It is important that we try to maximize the use of Unified Quality Framework and FHTI's common sense methodology to evaluate quality impact of various technologies. The goal is to generate studies that are not expensive and comparable with each other. We could learn a lot faster if health technology assessment studies, performed by 160 different nations were easily comparable. We would be much closer to the goal of making the process of investment in new technologies less of a random chance. Then one might say – let's leave it all to the market forces. May be it would be a good idea? But then, let's ask ourselves what would have happen if we invested in nanotechnology 20 years ago when Dr. Eric Drexler and others uncovered its potential. How many lives and how much human suffering could we spear? Maybe cancer would be a history by now.

Figure 1. National quality cube in the Unified Quality Framework. Example of a component of the Unified Quality Framework. Top corners illustrate types of quality and bottom corners show the measure of quality.

6. Important Challenges and Technologies in Genetics and Bioengineering

Because of the importance of genetic engineering, a survey regarding most important health challenges and technologies was conducted on a focused group of experts with genetics background. The results are listed in Table 6 and Table 7. Table 8 shows a list of most promising bioengineering areas as defined by the American Medical Association for comparison [13].

Table 6. Health challenges in the beginning of the new millennium. Survey method used on experts with background in genetics.

1	Understanding the genetics of complex traits
2	Curing and preventing disease onset
3	Preventing healthcare and insurance discrimination
4	Delivering mental health focused care (major consumer of healthcare in 2010)
5	Shifting paradigm from reactive to proactive

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6	Constraining technology lacking sufficient positive predictive value for treatment/diagnosis
7	Food delivery
8	Preventing cost increase in national healthcare systems
9	Working out disease pathways
10	Development of disease phenotype
11	Establishing interaction of environment and genetics as causes of cancer, diabetes and heart diseases
12	Individualized medicine
13	Lifestyle awareness
14	Wider variety and less expensive drugs
15	Understanding complex molecular networks involved in human diseases
16	Extending medical advances to developing countries
17	Global minimum standards for health
18	Conquering bacterial resistance towards antibiotics
19	Developing cost-effective cures for TB, Malaria, AIDS
20	Deconvolution of clinical disease in terms of genes and function
21	Developing of therapeutics through knowledge of genes and proteins involved
22	Personalized genetic diagnosis and treatment
23	Predictive diagnostic technologies
24	Predictive therapeutic technologies
25	True connectivity for medical professionals and consumers
26	Antibiotic-resistant microorganisms
27	Auto-immune diseases
28	Allergic variations in CYT-P4O (different individuals respond differently to the same drug)
29	Protein folding – function

Table 7. Technologies that can meet health challenges listed in Table 6. Order does not reflect importance

1	Genetic mapping: Genome-wide SNP association studies
2	Diagnostic SNP chips
3	Gene Therapy
4	New antigen delivery systems (molecular biology of peptide expression on cell surfaces)
5	Genome analysis/Genomics
6	Structural genomics
7	Cost-effectiveness analysis technology
8	Bioinformatics
9	Structural biology and drug design
10	Pharmacogenomics
11	Gene/Protein chips
12	Genomic profiling
13	Accurate annotation of genes and prediction of functions

It is also important to keep track of advances in biomedical engineering, especially in the seven areas listed in Table 8.

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Table 8. Important areas of biomedical engineering; Order does not reflect importance

1	Molecular Engineering
2	Cell Engineering
3	Tissue Engineering
4	BioMEMS and Microfluidics
5	Virtual Surgery and Nanoinstrumentation
6	Imaging
7	Bioinformatics

7. Technology Areas Important for All Sectors of Economy Including Healthcare

We should never treat healthcare as a separate island, isolated from other parts of the economy. Thus, it is important to keep track of technologies that will change entire economy. Emerging Technology Areas that will soon have a profound impact on the entire economy including healthcare sector are listed in Table 9.

Table 9. Emerging technology areas that will soon have a profound impact on the entire economy including healthcare sector. Order does not reflect importance.

I	**Human-Machine Interaction - Requesting Things from Machines**
	Hybrid Brain-Machine Interfaces (HBMI) – Thought to Computer Communication
	Natural Language Processing
	Automatic Voice Recognition
	Mobile, wireless, wearable, and textile computing
	Computer Implants (connected to tagged smart environment)
	Haptics
II	**Machine Intelligence**
	Processing Requests
	Data Mining
	Common Sense Reasoning
	Reasoning by Analogy
	Flexible Transistors (e.g. on plastic)
	Responding to Requests
	Organic Light Emitting Displays (data glasses, e-paper, smart windows)
	Speech Generation
	Affective Computing (emotional communication)
	Visualization of Data
	Automatic Summarization / Abstracting
	Triggering Action
	Decision Triggers
	Biomechatronic Interfaces (to cells and biomechanical devices)
	Electronic Skin (e.g. triggering payment transaction on the way out of supermarket with no cashiers)
III	**Preservation of Individuality and Security**
	Digital Rights Management
	Biometrics (Face, Voice, DNA, finger print, behavioral pattern recognition)
	Biometronics Ethics and Law
IV	**Human-Machine Global Network**
	Microphotonics (all optical Internet with super high bandwidth)
	High-temperature Superconductivity (inexpensive power quality devices SMES[2])
	Infinite High-density Data Storage

[2]Superconducting Magnetic Energy Storage

	Restructuring Code (Software Engineering)
V	**Intelligent Creatures**
	Mobile Mechanical Machines
	Nanorobots (Microfluidics)
	Humanoids (Cyborgs)
	Machine Vision
	Machine Learning
	Robot Design
VI	**Sources of Energy**
	Body-heat Batteries
	Chemical Molecular Energy (e.g. ATP)
	Earth tides (Geothermal Energy)
	Solar Energy
	Superconductive Generators

8. Defining the Future by Vision Statements, Insights and Scenarios

Another way to uncover the future is to envision it and create scenarios. Most of chapter authors whom I invited to focus on specific issues in this book did just that brilliantly. The most convincing vision will have an impact on decision makers and thus on resource allocation decisions today. Selection of topics covered in the book is a result of five years of research by the Future of Health Technology Institute to define health technology agenda for the new century.

8.1 Integrative Vision from Future of Health Technology Summits

8.1.1 Weight-Power Perspective - From 1946 to 2050

In 1946 – ENIAK – the first electronic computer weighted 30 tons and had less computing power than a digital watch; In 2010 one computer could have the same power as all computers on earth in 1999 and it will be printed on plastic with flexible organic light emitting display so we can roll it like a piece of old-fashioned paper. It will be small enough to work inside our bodies powered by molecular chemical reactions (E.g., ATP) or on our bodies as sensors powered by our body-heat. In 2020 computers will be smarter than people and we'll have a choice to augment ourselves to extend our cognition or not. By 2050 most of us will become cyborgs with implanted computers that extend our cognitive powers and give us extra senses (e.g., ultrasonic sense).

8.1.2 Light-Flexibility Perspective – From 1880 to 2006

Electric light, one of the most visible inventions of the 20th Century, was first featured on a steam ship Columbia that traveled from port to port, making headlines by showing the light of 150 light bulbs produced by four generators. The new Millennium has started with a similar story: In May 2000, Quinn Mary in Long Beach California became the showing place for what will become one of the most visible technologies of the 21st Century – technology that will allow flexible, paper-thin, bendable computer and video displays. Future of Health Technology Institute's Cruise to the Future™ planned for the year 2006 will continue Columbia's and Quinn

Mary's tradition with specific focus on health technologies.

Organic light emitting diodes combined with polymer transistors will evolve into electronic paper, personalized hardware that one can print at home, personalized disposable computers woven into textiles, wallpaper that is also a control center of a hospital or electronic skin that is able to respond mechanically to changing conditions. This means that making healthcare paperless does not make sense anymore and that there is hope for rapid computerization of medicine because the biggest obstacle to computerization – computer itself (the way it looks in early 2001) – will change dramatically.

8.1.3 From Electronic Care to Smart Care

We should reformulate "electronic health record" goal in order to make faster progress in technology introduction to healthcare. Framing this problem as "electronic patient record" suggests that the only thing that we are striving for is moving information about patient and care from paper to electronic format. This is not our primary goal. We do not want electronic care – we want smarter and more sensitive care (high tech combined with high touch).

8.1.4 From Electronic Health Record to Intelligent Health Environment

We should use a term:"Intelligent Health Environment" instead of "Electronic Health Record" to embrace the generative aspect of modern computer technology. Health record in an Intelligent Health Environment will also include not only a mere record of human interactions and health metrics but also machine-generated knowledge (facts and relationships). Machines involved will be both software agents (ICCs) and robots. Intelligent Health Environment will utilize biosensors and machine learning techniques. With time it will lead to the Affective Intelligent Caring System embracing other aspects of our lives like childcare, homes, relationships, finance, shopping, work and pleasure activities.

8.1.5 From Knowledge Management to Self-Health Tools

Intelligent Health Environment will involve wearable, wireless and implantable self-health tools based on personal genomic information and linked to tags and geographic positioning system for ongoing monitoring of people's vital signs and location. Fast progress in microphotonics leading to all optical Internet with huge bandwidth will allow real time video links to every home, school and workplace making telemedicine and telepresence a common place.

8.1.6 From Doctor, Nurse and Pharmacists to Affective Intelligent Caring Creature

In an Intelligent Health Environment each person will have a personal distributed Affective Intelligent Caring Creature (ICC) – a hybrid physician/nurse/pharmacist that processes all the data from biosensors, genomic data sources, medical science and other ICCs. Affective Intelligent Caring Creature has many helpers embedded

in our homes and also in our bodies, showers, cars, beds, toothbrushes, and kitchen counters. ICCs use Inter-ICC language that allows them to communicate effectively, interlink facts and predict emergency situations that will reduce to the minimum need to have emergency rooms as they are today.

Some helpers are embedded in robots equipped with computer vision and natural language understanding for remote presence. For example, your ICC embedded in a robot may go through the house of your elderly mother to check on her when you are away. Since you can navigate the robot through the Internet you will be able to see her and talk to her.

Yet, another ICC may specialize in monitoring products on international markets that may have impact on your health and well-being. This ICC – health purchasing agent – may suggest that you buy a car that uses video cameras to eliminate the blind spot and that automatically adjusts car seat for your 5-year old child, when the car turns into an airplane. It may then call your financial ICC to prepare savings strategy to buy that "healthy car" resulting in the cancellation of your virtual trip to Mars in 2058.

8.1.7 From Robotic Surgery to Nanosurgery

We will also have private tele-surgery bubble as a mobile attachment to our homes and cars. Intelligent Caring Creature will schedule surgery for us with the surgeon or a surgical robot most experienced with our particular condition. Telesurgeon will see the operating field through virtual retinal display goggles. With rapid progress in hybrid-brain-machine interfaces (HBMI) in the year 2070 we will have direct brain-surgical-tools interface where surgeon operates using her/his thoughts not hands. Thought operated surgical equipment will be as common as thought operated cars for disabled (eventually we will all want to use them).

We will not use surgery bubble a lot though because nanorobots will do most of the surgical jobs for us – starting before our birth. Chromosome replacement and nanocytosurgery will save us from surgeries that are currently necessary. Nanorobots will voyage through our bodies to repair damage, treat tumors, attack viruses, repair cell walls, deliver drugs, and remove blockages. The first nanotweezers and rotating, chemically powered nanomotors were successfully built in 1999. The year 2000 brought the first molecular switches – a great step towards nanocomputers.

8.1.8 From Pharmaceutical Lab to Cellular Drug Invention and Distribution

By 2020 personalized drug design and production in Intelligent Caring Centers will be a common place. Mergers between pharmaceutical companies, health information systems vendors, and providers will be long forgotten by then.

By 2050 we will have nanopharmacies – tiny cellular pharmacies that produce a drug, store it, and release it when needed inside our bodies. They will replace drug

prescriptions, lengthy lab design, clinical trials and eventually mixing procedures. Drugs produced by nanopharmacies and designed by Intelligent Caring Creatures will be personalized to a single individual avoiding any adverse reactions and delivered directly to locations in our bodies that need them. As a new form of entertainment we'll watch on VRDs how cancer cells are eliminated because nonorobots will have tiny video transmitters.

8.2 Closer Look at the Doctor of the Future – Affective Intelligent Caring Creature

In 2057 your personal pharmacists/nurse/physician - Dr. Zuzu - will not be a human but an ICC, a distributed Intelligent Caring Creature, with the knowledge of 1000 best physicians, pharmacists, and nurses from different specialties, traditional medicine from 50 cultures and an office in the Cyberspace.

All Dr. Zuzu's patients will be equipped with computers in their homes and cars in the form of data glasses, windows, mirrors and e-wallpaper. In addition, they will have on-body sensors and nanocomputers inside their bodies allowing continuous screening, monitoring and data collection about their physical and emotional state (e.g. EKG, GSR). They will also have bathroom MRI machines, shower skin mole detectors, toothbrush protein analyzers, smart beds monitoring sleep pattern, and sensors equivalent to a hospital pathology lab, checking daily basic lab results.

Their on and in-body sensors will be able to report pain or any unusual physical or emotional state directly to Dr. Zuzu. They could also do it via a voice-enabled telehealth tool at any time since Dr. Zuzu understands 105 human languages and 1005 machine languages. Another communication option will be hybrid brain-machine interface allowing a patient to send a request to Dr, Zuzu just by thinking about requesting an extraordinary pleasant virtual experience such as petting a rabbit on the skyglide to ULURU, or getting rid of terrible nightmares about spiders.

It is important to note that Dr. Zuzu will be prepared to respond to many requests related to maximizing joy and pleasures of life not reducing pain because most of the diseases were eliminated and probability of the rest of them was minimized in the neonatal phase through chromosome replacement. Effective preventors (stress reducers) helping ICCs also contributed to low-sickness levels.

Dr. Zuzu will always listen to all its patients (no limit on amount) and will process their vital signs and test results, relating all the findings and looking for unusual patterns. Dr. Zuzu will be able to warn patients about incoming health problem (e.g., pain) using its case-based and memory-based predictive engine: for example, it could warn you "Please, call your surgery robots before leaving for work, to remove a splinter that will cause pain in 3 hour and 15 min – just when you have to change plains in Denver, Colorado."

Dr. Zuzu's will have a rich library of health stories extracted from life-long medical data. These stories will be

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parsed and represented in the knowledge base for further retrieval and then turned into video scripts out of which context-specific educational health movies will be assembled for other patients in need.

To facilitate ease of patient-physician communication, Dr. Zuzu will have multiple personalities, sex, age, voice and cognitive style depending on the situation and the patient. This includes the ability to become a humanoid version of the best friend from high school in order to maximize its convincing power and emotional closeness. This way Dr. Zuzu will be able to relate well to emotional states of its young and elderly patients in a close and friendly manner.

What if Dr. Zuzu gets sick itself? Dr. Zuzu will use self-treatment through knowledge injections. Another option is to call on other Intelligent Caring Creatures and get a byte of support. Most of the time Dr. Zuzu is in perfect shape – never tired like its human predesesors, never competitive or jealous, never anxious or annoyed.

Based on the genetic profile of each patient Dr. Zuzu will develop a long-term educational and care plan based on personalized interactive movies, illustrating major behavioral points that should be reinforced to maximize life's capacity, length, and pleasure. Dr. Zuzu's ability to annotate and retrieve from image and video libraries allows a just-in-time health education or compliance program. Dr. Zuzu will also be able to prescribe and then develop (in its virtual R&D lab) personalized drugs just for its patient.

Dr. Zuzu will help its patients not only to maintain good health but also deal with bad health in a compassionate and emotional way. With Dr. Zuzu you will have a happy environment when you are ill. It will have millions of stories of other people going through a given condition including:

() Encoded mental states

() Most common thoughts they thought and

() Activities and words that helped them to make it through the rough experience.

Dr. Zuzu's collective common sense knowledge will allow it to always say the right thing or to produce a right virtual companion, that you can interact with through direct retinal projection, in difficult cases.

Dr. Zuzu will charge its patients per knowledge injection and per successful interaction that will be automatically recorded based on your positive response recorded in your data stream. The payment will be expected also in the form of knowledge – your permission to use your data to further improve Dr. Zuzu's common sense and medical knowledge. This way your personal ICC will revitalize its curing and educational ability.

8.3 The Integrating Power of Insight – Biomechatronics

Future of Health Technology Summit thinking sessions generate knowledge waves present long after the event. 6th Summit, FHT2001, confirmed that an unprecedented revolution is taking place: molecular biology, computer and medical science, electrical, mechanical, genetic and biomedical engineering, are merging into one field best described as Biomechatronics.

To make progress we need to have not only manageable models of the future but also of the science and technology behind it. Biomechatronics brings together tissue engineering, robot design, information technologies, knowledge management, pharmacogenomics, biometrics, nanotechnology, and bioinformatics.

One reason that back in 1996 I focused on health technology in the era of booming healthcare informatics was an observation that health-related information comes from and is embedded in biological, electronic and mechanical artifacts – it is an integral part of Biomechatronics not an independent island. On-going symbolic reasoning on health data and tools helping humans or cyborgs to make sense out of the multi-layered biomedical, organizational and mechanical processes is an important goal. Creating meaning out of petabytes of personal information requires the same common sense capabilities as generating smart medical advice.

9. Defining the Future of Health Technology as a Dynamic Learning Process

According to Allan Newell, knowledge can only be created dynamically in time [14]. "It is generated by an observer, relative to his point of view, in the process of making sense (modeling)" [15]. It is the same with knowledge in health technology – it should be an adaptive, dynamic process not a one-time event or publication. Current rate of innovation and product creation makes the process of defining what to invest in similar to seating on a raft on a fast, infinite, mountain river trying to decide where to stop. "Knowledge about [healthcare] cannot be captured in a finite structure" [14] – it has to be an ongoing dialog. Results of that dialog could be used by decision makers in different situations and different places on earth as hints and general direction in their own problem solving processes.

More than forty years of research on learning, problem solving, and intelligence conducted by the field of Artificial Intelligence brings hope of making that process more effective. Realizing that information becomes knowledge when it starts guiding decision making, makes it even more obvious that defining future of health technology involves on-going, adaptive dynamic learning by industry, governments and academia.

Seven Strategies to Leadership [2] based on forty years of knowledge science provide a guiding structure.

1. Sustained Renewal & Growth

Treat Sustained Growth as a final goal;You do not want to be successful only once -
you want to be continuously successful

2. Situated Adaptability
Change your organization in a specific situation and problem solving context; 21st Century requires ongoing situated adaptability

3. Sociotechnological Responsibility
Learn and use new technologies and do not delegate it to others - "I am non-technical" syndrome; Think about your goal in a context of sociotechnological process; technology and organizations cannot be separated

4. Strategic Repositioning
Look outside your organization and ahead in time; Use Unified Quality Framework

5. Simplification
Avoid bureaucracy and look for unconventional shortcuts

6. Self-Reinventing
Keep learning and developing leadership and innovation skills

7. Strength, Savings, Satisfaction
Spend time absorbing results of work; Bring back child-like joy and celebration spirit

10. Conclusions
Future progress in healthcare and medicine depends on the investments in research, development and education made today. Defining most promising health technology areas by the group of experts from industry, government and academia may help in planning investments in health technology. The answer to the question of how to invest a couple of billion dollars to save hundreds of billions and increase human health in the future is an ongoing effort to point in the right direction. According to opinions gathered at Future of Health Technology Summits (1) Instant Medical Data Collection and Knowledge Dissemination Technologies, (2) Tissue Bioengineering & Nanotherapeutic Technologies, (3) Internet-driven Technologies and (4) Brain-Machine Interfaces are the key investment areas for the next 10 –20 years. Unprecedented technological revolution manifests itself in convergence of molecular biology, computer and medical science, electrical, mechanical, genetic and biomedical engineering (including cell, molecular and tissue engineering) into biomechatronics. It will play an integrative role in the future of health technology accelerating the speed of discoveries leading to dramatic cost reduction. It is necessary to maintain an ongoing watch of new technologies and revisit the issue of resource allocation periodically with different groups of experts. We have a unique chance to define the future not to observe it; to say what should happen instead of saying what will happen if we do not change anything.

Edited by: **Renata G. Bushko** - bushko@fhti.org
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Chapter 7: Indistinguishable From Magic: Health and Wellness in a Future of Sufficiently Advanced Technology

Craig F. Feied, M.D.
Health Strategy Officer, Microsoft Health Solutions Group and Professor of Emergency Medicine at Georgetown University
Jonathan A. Handler, M.D.
Chief Deployment Architect, Microsoft HSG and Clinical Associate Professor of Emergency Medicine at Northwestern University
Michael Gillam, M.D.
Director, Advanced Development Lab, Microsoft HSG and Clinical Associate Professor of Emergency Medicine at Northwestern University.
Mark S. Smith, M.D.
Professor & Chair of Emergency Medicine at MedStar Health and Georgetown University

Abstract

We describe a future in which health and wellness are transformed by (1) the availability of definitive and unambiguous tests to prove or disprove each diagnosis, (2) new methods based in systems biology to help unravel the web of messages transmitted across cellular and subcellular networks, and (3) universal access to data that has been freed from data silos to produce true data liquidity for a constellation of purposes ranging from personal health management to population health research. We believe the resulting "connected health" environment will have a profound impact on every aspect of modern life.

1 Imagining the future

Clarke's Third Law states that "Any sufficiently advanced technology is indistinguishable from magic" [1] and in truth it is relatively easy to imagine a future in which health technology is so advanced that we can't even begin to understand it; a future in which everybody is automatically well, all the time, and everybody lives forever, or as long as they want to. Some sort of incomprehensible machine repairs us when necessary – or perhaps billions of tiny machines live inside our bodies and spend all their time repairing us from the inside out. The resulting population problem is resolved in some ingenious manner – perhaps through an arrangement whereby having children requires giving up your own opportunity to "live forever."

A more difficult problem is how to imagine a series of futures leading up to that one; a series in which the technologies in use are sufficiently advanced to make a real difference in health, but not so advanced that they become indistinguishable from magic.

We believe five identifiable forces will shape a future of healthcare that is quite different from that of today.

1. True data liquidity – bringing together all existing data and allowing it to be combined and queried in real time and in ways that were never before possible.

2. Truly definitive tests for an increasingly large percentage of known ailments, through positive identification of pathogens on the basis of their genomic makeup and proteomic activity.

3. Systems biology approaches to unravel the complexity of biological interactions and identify patterns of gene activation in a variety of disease states and altered states of wellness.

4. Improved imaging techniques and the fusion of image and non-image data.

5.Human clinicians abandoning a flawed dependence on clinical judgment and adopting diagnostic and therapeutic methodologies that are based in fact and anchored by definitive tests.

A host of other technological advances will also help to establish a world in which we have very different expectations about health and sickness, and very different approaches to our daily lives.

2 Fundamental problems in healthcare

Envisioning the future does not require us to think mechanistically about what is wrong today and how to fix it, yet there is value in recognizing the underlying gaps that prevent us from enjoying a life of health and wellness today. Although this begins with human failings, in the end it is viewed as a pure technology problem. It has nothing to do with politics, or economics, nor is it brought about or perpetuated by any payor system or system of incentives. In our view healthcare is not worse because some cabal has elected to place profit over people, nor because clinicians systematically deny their patients life-saving treatments in order to navigate some system of incentives. Healthcare is worse than it should be because true knowledge is scant or absent, the underlying concepts are wrong or incomplete, and the tools used to investigate are insufficient to the need. Healthcare is flawed because people have flawed ways of thinking about the underlying problems and no readily available mechanism by which to improve this. In some sense, healthcare is not better because people are incapable of making it better within the current technology framework.

Fundamental problems in healthcare include lack of knowledge, information hiding, poor management of existing data, inadequate analysis, self-deception, over-reliance on flawed clinical judgment, failure to compensate for cognitive bias, lack of sufficient context to permit informed decision-making, and a near-universal emphasis on localized short-term gain rather than optimization against a set of larger imperatives.

2.1 Hidden knowledge: Physicians bury their mistakes

That physicians bury their mistakes is both literally and figuratively true, and it is one of the fundamental problems that must be addressed. The problem comes in two parts.

2.1.1 Cause of death

The first half of the problem is that we often do not know why a patient really died. Hospital records and death certificates are notoriously incorrect when it comes to cause of death. [2] Even with the patient's dead body in front of us we often

can't make a definitive and unambiguous diagnosis: autopsy studies routinely identify discordance between clinical and autopsy diagnoses in the range of 40%. [3] Some autopsy studies have found that half of cancer diagnoses were missed during the patient's life, while half of the cancer diagnoses that were made were wrong. [4] A review of more than 120,000 published autopsy cases shows that when patients die from pulmonary thromboembolism – blood clots that occlude the lungs and stop the heart – the diagnosis had been unsuspected in 80% of cases. If it requires an autopsy to even *suspect* the correct diagnosis in patients who die, how can we begin to expect proper diagnoses in patients who are alive?

Historically, autopsy was both an essential part of medical training and a routine opportunity to confirm or disprove clinical diagnoses, with roughly half of all deaths going to autopsy. Unfortunately the autopsy rate has been dropping for decades: today fewer than 6% of non-forensic deaths proceed to autopsy, [5] and more than half of all hospitals in a recent study had performed no autopsies during the prior year. [6] In fact, in the absence of a suspected crime, there is absolutely no rigor associated with any assertion as to the cause of death: when patients die, the vast majority do not undergo any sort of post-mortem examination whatsoever. How can we draw any conclusions about the efficacy of our treatments when we can't even tell what kind of cancer a patient has, or recognize when a person is dying because their heart and lungs are full of blood clots? How can we expect to make better diagnoses if there is no possibility of any feedback loop telling us whether we have got it wrong?

Part of the reason autopsy rates have been declining is the fact that many people find the notion of an autopsy abhorrent, whether due to religious convictions or personal squeamishness. However, it is now possible to acquire post-mortem 3-D radiographic images of precision sufficient to permit a virtual autopsy [7; 8] that presumably will not violate most sensibilities. Add to that a detailed analysis to detect pathogens and a proteomic sweep to identify patterns of gene activation, and we will be well on our way to confirming a positive cause of death in each case so evaluated.

Whether autopsy is virtual or physical, there would be transformative power in a unified database of detailed post mortem examinations on every person who dies while undergoing medical care. Rather than abstracting only a few data points of general interest, banked data should include everything that can be determined about the cause and mechanism of death, in as much detail as science will permit at the time.

2.1.2 Hiding data

The second half of the problem relates to data hiding. In a situation bizarrely similar to that faced by the United Nations nuclear weapons inspectors, hospitals and clinicians spend a significant amount of time and energy attempting to hide information about the care they provide and to keep out inspectors who would like to sunshine

the data. [9; 10; 11] Patients also participate in this data-hiding exercise, fearing that a breach of privacy will bring them personal harm. Vendors exacerbate the problem with business models based on keeping data captive in silos often referred to as "data jails."

This state of affairs has often been contrasted to the situation in the aviation industry, where it is universally recognized that information-hiding cannot lead to better outcomes. So long as vendors, clinicians, departments, hospitals, payors, and entire countries believe that restricting the flow of information is a path to success over their competitors, we can never achieve the clarity of understanding we need. The path to value involves making all data and metadata about every case constantly and automatically available both for clinical care and for cross-institutional research. Some of this could be accomplished with a policy shift to require that if hospital care is subsidized in any way by federal dollars, pseudo-anonymized data from that hospital must be shared for the common good. Some of it depends on enterprise adoption of a new class of data management systems designed from the ground up to facilitate data liquidity.

2.2 The Data Explosion

In addition to the challenges of sunshining previously hidden information and liberating data from data silos, medical decision-makers must also somehow cope with explosive growth in the number and kind of clinically relevant data sources, and in the volumes of data being produced by each one. The past few decades have seen a massive increase in the number, size, and complexity of dataflows, with no sign that the rate of increase will slacken. In addition to growth in traditional clinical and operational data sources (radiology, EKG, labs, meds, monitoring, MD notes, nurse observations, and billing) many new sources have become available, including such things as:

- Real-time biosensors in more and different clinical situations
- Continuous location tracking of every person and thing in a health setting
- Constant vital signs monitoring
- Transcutaneous monitoring of glucose, ETOH, etc.
- Testing to maintain wellness, rather than only in response to sickness
- Image utilization for new purposes
- Genomics and proteomics
- Personalized pharmacy

New data sources emerge with alarming frequency, and new sources can produce data of new types that cannot easily be accommodated by most current data stores. The volume of new data alone can be a problem, and the full integration of medical images adds a special challenge due to the extremely large size of current images.

Medical imaging still is in its infancy, with most of its growth ahead of it, yet the explosion is already underway. Utilization of existing modalities is increasing rapidly, and new imaging modalities already demonstrate applicability for disease states that previously did not benefit from imaging. 3D rendering and fusion of different image types are just beginning to become widely available, and the medical imaging landscape will continue to grow and diversify for the foreseeable future, improving diagnostic accuracy and elucidating disease entities in ways that were never before possible. At the same time, the challenges of acquiring, transforming, transporting, storing, analyzing, fusing, and displaying such massive image datasets will require new techniques in health data management.

Future analytical methods will need to take into account a lot more data of more diverse types, aggregated and sliced in many more different ways than ever before possible. Systems will need to work with bigger aggregates as data is rolled up across departments, hospitals, enterprises, regions, and entire countries. Clinicians will also need to work with smaller atomic slices, drilling down from summary data to individual events that can be combined in many different ways. And all of this needs to make sense in the context of traditional belief, newly published information, and emerging best practices. Traditional clinical data management systems are wholly inadequate to the challenge.

2.3 Definitions of disease

The primary value of data is to aid in the diagnosis and treatment of a disease, yet more often than not the diagnostic and treatment approach for a disease are not based on much valid data at all. Some of this is due to fuzziness in our definitions of disease.

For example, we often are told that a drug or treatment "is effective in 15% of cases," but it seems unlikely that we should ever have accepted this concept of sporadic or occasional efficacy. Of course what's really happening is that the drug or treatment works in 100% of patients who actually have the disease for which the treatment is effective – taking the patient's internal milieu as part of the "disease" definition. What we have today is a stewpot of diseases with similar signs and symptoms, all stirred together in a common diagnosis. Penicillin works in 5% of patients with pneumonia – but in 100% of patients with pneumococcal pneumonia of a serotype sensitive to penicillin.

With increasing clinical availability of genomic and proteomic testing (of both patients and pathogens) we are beginning to make progress in separating out false disease cognates[i], or "bucket" diagnoses that conflate distinct medical conditions simply because they share a common presentation and common clinical

[i] False cognates in linguistics are pairs or groups of words that are similar in form and meaning but have completely different linguistic roots. We use the term false disease cognates to refer to diseases or syndromes that appear to be the same and may share a common diagnosis, but have completely different pathogenic roots.

findings. Just as the nineteenth century false disease cognate "consumption" has been resolved into a group of distinct diagnoses (including tuberculosis, cancer, viral illness, anorexia, and a variety of degenerative diseases) we are now on the verge of making definitive sense of these and many other conditions that may represent false disease cognates. Among the common diagnostic entities that stand ready to be transformed, we may find:

- Chronic fatigue syndrome (chronic viral infections of various types, along with adrenal and pituitary malfunctions from a variety of etiologies)
- Cancer (etiologic and subtype diagnosis based on cell surface proteins and receptors; many viral etiologies)
- Flu (multiple disease entities, mostly not influenza)
- Gastroenteritis (multiple viral, bacterial, toxic, and parasitic etiologies)
- Obesity (many different etiologies)
- Coronary artery disease (many subtypes, including infectious and hereditary versions)
- Arthritis (various infectious and immune-mediated etiologies)
- All "idiopathic" diseases (mostly unrecognized infectious etiologies)
- Dementia of all types (injury, infection, prion disease)
- Gulf War Syndrome and many related ailments (infectious disease, toxic exposures, psychological illness)

2.4 Diverse treatment approaches for imprecise diagnoses

The bluntness of our instruments is reflected in the medical adage used to guide treatment of dermatologic problems by those outside the specialty: "If it's wet, dry it; if it's dry, wet it; if neither approach works then apply steroids." That may sound like a joke, but it is a recipe that quite accurately describes the approach to treatment of lesions about whose diagnosis a clinician hasn't a clue. Part of the challenge is in sunshining the data needed to identify best practices and decide among different approaches to the same problem.

Ten orthopedic surgeons perform knee surgery in ten different ways. They have different preferences for equipment, prostheses, surgical approach, sequence of steps, and so forth. They take different amounts of time and have different amounts of standard blood loss, which they cope with in different ways. Their patients have different lengths of hospital stay, different rehabilitation courses, different complication rates, and different overall outcomes. They cannot all be correct – yet we defend the heterogeneity as necessary and unavoidable, citing "surgeon's preference" and other intangibles. In fact – in medicine as in surgery – it seems increasingly clear that when the disease is fully characterized, one

treatment approach must be demonstrably superior to the others, and we should be able to identify that superiority through analysis of the data.

Certainly there are situations so complex that predicting the outcome of an intervention is impossible – yet in the vast majority of situations, we don't even try to use existing data or available tests to fully characterize the starting point and to define the planned intervention. We start from a position so impoverished of data that our predictive and analytic capacity is severely constrained, and we act as if the resulting uncertainty is somehow a fundamental law of the universe.

2.5 Miracle cures and bad diagnoses

Simply getting the diagnosis right on a consistent basis may be sufficient to underwrite a transformation of our entire healthcare system, because most of what we have taken for expensive variability in the natural history of disease and variable human response to treatment (requiring human judgment to navigate the protean pathways of disease management) is actually simply a problem with diagnostic ability. There are no miracle cures, there are only bad diagnoses.

2.5.1 Clinical judgment and other forms of guesswork

Absent a definitive test, most diagnoses are incorrect, yet most diagnoses are made without any definitive test ever being performed. [12; 13; 14; 15; 16] The problem is not that we have a ineffectual method for escalating the diagnostic process for unusual problems – it's that we routinely, every day, manage patients without even trying to make a definitive diagnosis. The vast majority of the time we choose to operate by inference and guesswork even when a definitive diagnostic test does exist. The problem is not confined to rare or subtle diagnoses: tests exist that can reliably detect or rule out appendicitis, yet the initial diagnosis is missed in up to 57% of children and nearly 100% of infants with the disease, leading to significant morbidity and mortality. [17] Test avoidance often is encouraged in an effort to secure cost savings; this is a false economy but a seductive one: the costs of diagnostic testing are immediate, explicit, and isolated to a single payer, while the true costs of incorrect diagnosis, although massive, are hidden, spread over time, and often spread over multiple payers.

Medicine today is not so advanced that we can afford to optimize for false savings or individual profits at the expense of universal knowledge. The cost of being wrong in each individual diagnosis may be a raindrop, but the aggregate downstream flood is strong enough to wash away the very foundations of our medical system. Simply put, we are chronically underinvested in diagnosis.

2.5.2 Knowledge gaps

Medicine enjoys a long history of technological advances that completely transform our understanding of a disease and its diagnosis and treatment. For most of the past century, even the best

clinicians could not come to agreement in distinguishing between pairs of common clinical perturbations, simply because there was no readily available or convenient method by which to test their clinical observations. A number of these confounding pairs are listed below, together with the technological advance that ultimately resolves the confusion.

- Does the patient have pneumonia? (chest x-ray)
- Is the patient hyperglycemic, euglycemic, or hypoglycemic? (blood sugar measurement)
- Are the oxygen or carbon dioxide low, normal, or high? (blood gas measurement)
- Is the patient euthyroid, hypothyroid, or hyperthyroid? (thyroid function tests)
- Is the sodium or potassium high, low, or normal? (serum electrolytes)
- Is the spleen or liver enlarged? (ultrasound; CT scan)
- Are the kidneys normal, large, small or is one absent? (ultrasound; CT scan)
- Is the patient acidotic or alkalotic? (blood gases and serum electrolytes)
- Does the patient have seizures, or are they pseudo seizures? (EEG)
- Has the patient had a myocardial infarction? (EKG, enzymes, echocardiogram)
- Is the patient in shock due to cardiogenic or septic causes? (Swan-Ganz catheterization)

At one time these were considered to be disputed diagnoses, but they were never actually diagnoses in the sense of carrying any understanding of causation. These were really just arguments about simple observations at a time when the observations could not be made directly, but were imputed from indirect effects and subtle findings. In each case a simple application of technology is sufficient to resolve a century of disputation.

Pride in the advanced state of our medical system notwithstanding, the same situation holds today for the majority of situations in which a patient is not well. Excepting trauma and proven infectious disease, most current “diagnoses” do not imply any real understanding of causation, nor do they necessarily imply the kind of understanding that would lead to a definitive or even normative approach to treatment. We perceive merely the shadows of reality, and not reality itself. It remains for us to create the technology that will resolve this century’s dogmatic and diagnostic disputes.

If we are to make progress it is essential that we be clear about what it means to make a definitive diagnosis and explicit about our (statistically defensible) level of confidence in each unproven diagnosis. With that clarity and transparency, we may confidently set forth a series of best practices against

which to drive iterative improvement in our diagnostic and therapeutic processes.

2.5.3 Diagnostic testing and reasoning through uncertainty

The first branches of traditional diagnostic decision-making depend on time-tested (i.e. primitive) approaches based on our five senses – focusing on the patient's description of his or her subjective experience and combining it with findings on inspection, palpation, auscultation, olfaction, and even gustation. At the next layer we add a series of crude tests intended to confirm or deny our initial guesses through the detection of non-specific changes in the body. For example, the white blood count is generally elevated to fight disease or in response to a variety of stresses; we attempt to use this finding in an attempt to verify or deny the existence of a disease as specific as appendicitis.

Although tests of this kind are necessary for many diagnoses today, the discriminative power of most tests is very low for any specific disease, and much of the diagnostic decision remains bound up in what we refer to as "prior probability" – essentially the weighted sum of our guesses before we add in the results of the test. This leads to an odd reality in which a test interpretation changes depending not on whether a specific patient actually has the disease, but rather on how common the disease is in the population.

Imagine a test that reliably detects 99% of cases of a disease (missing 1% of those who really have the disease) and that also reliably screens out 99% of those who do not have the disease (giving both a false-positive rate and a false-negative rate of 1%). In a population of 1 million people where the true incidence of the disease is 1 in 100 (10,000 people have the disease and 990,000 do not) the test will detect 9,900 of those with the disease, but will also be falsely positive in 9,900 of those who do not have the disease – so only half of those with a positive test actually have the disease, and the other half do not. Yet in a different community where half the people carry the disease, 99% of those with a positive test do have the disease, and 99% of those with a negative test do not.[ii]

For tests of this kind, "prior probability" dominates the equation so much as to make the test very difficult to apply rationally in practical situations. Many currently available tests are of this sort when used to help diagnose a specific disease. They give evidence that can support or weigh against an inference, but they cannot prove or disprove a specific diagnosis.

For all its uncertainties, current diagnostic evaluation at least follows a deterministic branching path that does not require any bizarre creative leaps to achieve its goals. Although our concept of a gold standard is soft,

[ii] 500,000 people do have the disease. The test detects 99%, or 495,000 of those with the disease, and gives false negatives to 1%, or 5000 people. The other 500,000 people do not have the disease. The test gives a true negative in 99%, or 495,000 people, and gives a false positive result to 1%, or 5000 people. Of all the people who had a positive test result, 495,000 are true positives and 5000 (1%) are false positives. The same ratio holds for those with a negative test.

being rooted in a historical dependence on expert opinion, it is nonetheless possible to model current diagnostic approaches effectively in software. Where this has been done it has often been possible to exceed the diagnostic accuracy and consistency of human clinicians. [18]

Fortunately, another class of diagnostic tests exists that is capable of proving or disproving specific diagnoses within the limits of certainty, and it is growth in this class of test that will help reduce the overall uncertainty in medical diagnosis over time. The ability to positively identify the genetic material of a pathogen is one such test that has already made a dramatic difference in our approach to certain diseases. The positive identification of specific molecular receptors in biopsy specimens is another example of a test that has transformed our approach to certain types of cancer.

2.5.4 Diagnostic certainty and new care models

When it becomes possible to have a correct diagnosis 100% of the time, and when complete data aggregation and constant analysis produce data and understanding to underlie all treatment protocols, the interaction between patients and the medical system may be completely different from today's limited set of offerings. For one thing, the traditional role of a primary care clinician may be subsumed into the system as a whole. After all, there will be no ambiguity about whether a patient needs to see a specialist: an absolutely definitive diagnosis will either respond to a specific pharmaceutical regimen, or it will require some other intervention, in which case a specialist will be required. With a new generation of unified intelligence systems managing all data, every clinician will have the same universal view of the patient's data. With no data gaps and no ambiguity about the diagnosis, there will be nothing to fall through the cracks and no cracks for it to fall through. When we know the exact pathogen and the biochemical behavior of the host, we will know whether a given drug is going to work or not, without guessing. When we know the exact anatomy of the patient and the precise motions of the robotic surgeon, we will know whether the surgery is going to work without guessing. There will be very little room remaining for what today is called clinical judgment.

2.6 Information overload

Many people believe that the root of our collective diagnostic incompetence is somehow associated with the phenomenon of information overload, and that "there's just too much to know." The problem of information overload is often regarded as a modern phenomenon. After all, one hundred years ago, a physician could reasonably expect to learn everything that was believed to be true in the field of medicine. As it happens, most of what was then believed has since been proven false – yet we cannot help but imagine how much happier a clinician must have been in an era when it was still possible to "know everything," even if it was all wrong. Today a primary care

doctor is expected to somehow stay abreast of approximately 10,000 named diseases and syndromes, 3,000 medications, and 1,100 laboratory tests. We can only speculate as to how much of this will later be proven false.

It is true that the biomedical literature now contains more than 18 million indexed articles, that more than 800,000 new articles are published each year, and that the rate of growth is doubling every 20 years. Clearly no individual can read and digest all the new raw information created each year even within their own area of specialization. Research librarians have estimated that a physician may need to spend 21 hours of study per day in order to remain current. [19] Of course this is impossible, and clinicians invariably fall behind.

In fact, the sense of information overload in medicine has been present for many years. Henry D. Noyes, the great oculist of the 19th century, opined in 1865 that "... medical men strive...to keep up their knowledge...*but* the preparatory work in the study of medicine is so great *that* if adequately done...few can spare time...".

2.6.1 Distilling knowledge for wayfinding

It is not surprising that clinicians are inadequately prepared to navigate a formless sea of information, and that current medical systems are incapable of aiding in that navigation, because we have defined the problem at entirely the wrong scale. A flood is indisputably made up of a trillion raindrops, but nobody thinks it essential to track all the raindrops in order to manage the flow of water. Keeping up does not require each clinician to understand all the minutiae of every disease entity and to bring all that detail together in order to exercise clinical judgment in every case. When a diagnosis can be made unambiguously, keeping up may only require each clinician to have some reliable mechanism by which to always find and use a valid approach for making each definitive diagnosis, and then to follow the most current accepted treatment protocol for each proven disease state.

The poet Edna St. Vincent Millay [20] captured this sense most beautifully in 1938, writing:

> Upon this age, that never speaks its mind,
> This furtive age, this age endowed with power
> To wake the moon with footsteps, fit an oar
> Into the rowlocks of the wind, and find
> What swims before his prow, what swirls behind ---
> Upon this gifted age, in its dark hour,
> Rains from the sky a meteoric shower
> Of facts . . . they lie unquestioned, uncombined.
> Wisdom enough to leech us of our ill
> Is daily spun; but there exists no loom
> To weave it into fabric; undefiled
> Proceeds pure Science, and has her say; but still
> Upon this world from the collective womb
> Is spewed all day the red triumphant child.

As Millay correctly perceived, the problem is not so much an overload of information as it is a need for knowledge synthesis – the weaving of facts into a fabric of knowledge. Why worry about information overload in the midst of a shortfall of understanding? Information is merely a distraction if it cannot lead to deterministic solutions to practical problems. Even if it were possible for clinicians somehow to keep up with the rapid pace of new developments

in their own narrow fields, the simple reality is that relying on the judgment of a small number of hyper-educated human clinicians is not a viable long-term basis for achieving widespread excellence in healthcare. There is too much to know in too many areas, and the raw knowledge grows and changes too quickly for humans to keep up.

2.6.2 Translational science and medicine

Yet even as it swamps an individual clinician, the increasing rate of growth of information in the biomedical literature seems to be associated with an overall increasing rate of adoption of the medical breakthroughs described in that literature.

It's difficult to predict breakthroughs in terms of content -- most real breakthroughs arise from the recognition of an unexpected occurrence or happy accident, making it unlikely that we can project the world of tomorrow simply by tracing the vectors of today. However, if we cannot tell what the future will hold, we can at least tell when it is likely to arrive; the pace of innovation has been increasing at a predictable rate for many centuries, in a sort of "Moore's law" of medical innovation. Gillam et al. [21] have remarked on the increasing pace with which new medical knowledge becomes adopted, from the 2500 years needed to bring knowledge of cardiac angina into common clinical care to the mere decades required for adoption of antibiotics in the treatment of helicobacter pylori, the recently-discovered etiologic agent for gastric and duodenal ulcers. Figures [1] and [2] graph the pace of adoption for longer-term and shorter-term time scales (reprinted by permission).

Based on these trends, the decade after

Figure 1: Time to widespread adoption of new medical knowledge - 2500 years.

Figure 2: Time to widespread adoption of new medical knowledge - 150 years.

2030 has been proposed as ripe for a "healthcare singularity" in which the instantaneity of adoption of new knowledge causes the entire class of medical technologies to undergo a fundamental shift to a simpler form. A post-singularity health era would imply a world where health discovery and practice are seamlessly meshed in a virtuous cycle of ever-accelerating improvement. Not coincidentally, Ray Kurzweil has identified the year 2040 as a potential time of "Technologic Singularity" [22] during which computers become able to recursively improve themselves in an explosion of intelligence that could transform every aspect of human culture and technology.

2.7 Cognitive gaps and bias

Our healthcare challenge is a daunting one: we begin with a fuzzy and incomplete concept of disease,

add an abridged and inconsistent approach to making any diagnosis, stir in a vast and increasing number of facts embedded in a clinical literature that is overwhelming in its volume, and layer on a vast and increasing amount of clinical data and an increasingly complex and detailed set of images. Finally we attempt to glue all this together with the human mind, relying on clinical judgment, experience, and intuition to bridge any gaps in knowledge and evidence. Unfortunately, the human mind appears to be hard-wired for susceptibility to a series of cognitive biases, blind spots, and logical fallacies. This susceptibility renders human clinicians uniquely unsuited to make unaided diagnoses or to design treatment plans under any but the least complicated of scenarios.

Researchers have identified more than a hundred common and replicable ways in which human judgment and decision-making differ from what we would predict on the basis of rational choice. [23] For example, the availability heuristic causes us to consider things more likely if they are more readily available in memory, resulting in a bias toward vivid or emotionally charged examples. The confirmation bias leads us to have greater confidence in evidence that supports a previously made decision than in evidence that contradicts it. The self-serving bias allows us to feel responsible for desirable outcomes but not for undesirable ones, and intervention bias causes us to feel responsible for bad outcomes following an active intervention but not for bad outcomes following a willful withholding of treatment. Wishful thinking causes us to prefer decisions that lead to a less likely but more pleasing outcome, rather than making decisions based on evidence and rational thought. Each of these leads to flawed decision-making in real-world clinical settings, and in some cases it is possible to count the bodies of those who have died after decisions driven by some of the more common cognitive biases.

2.7.1 Logical fallacies and cognitive blind spots

Many logical fallacies, cognitive biases, and blind spots seem to be based in mental heuristics that represent shortcuts in problem-solving; some are so deeply-rooted that it can be extremely difficult to think about them clearly, even after they have been exposed and elucidated. One of the best-known examples is a veridical paradox known as the "Monty Hall Paradox," given here as it was understood by readers when it appeared in Parade magazine a few years ago:

> Suppose you're on a game show, and you're given the choice of three doors: Behind one door is a car; behind the others, goats. You pick a door, say No. 1, and the host, who knows what's behind the doors, is compelled to open one of the remaining doors and show you a goat (if both remaining doors contained goats he will choose one at random). Say he opens door No. 3 and shows you a goat. He then must say to you, "I'll give you the option to switch your choice from door No. 1 to door No. 2." Is it to your advantage to switch your choice?

Obviously the open door contained a goat, and one of the two remaining unopened doors also contains a goat while the other contains a car. Since the assignment of goats and car was random, most people assume that each of the remaining doors has an equal probability (50/50) of containing the car. In fact, although it seems counter-intuitive, the door originally chosen by the contestant has only a 1/3 chance of containing the car, while the door being offered as an option now has a 2/3 chance of containing the car. Switching your choice doubles the probability of winning.[iii]

The paradox has been known for many years, but when the problem and solution appeared in Marilyn Vos Savant's column in Parade, some 10,000 readers (reportedly 1,000 claimed to have PhD degrees) wrote to the magazine insisting the published solution was wrong. Professors of mathematics declaimed their credentials and publicly staked their reputations on the true probability distribution being 50-50. This is a common response: even in the face of a wholly unambiguous problem statement offered with complete explanations and mathematical proofs, by an authoritative source, many people still refuse to believe the correct answer.

There are many ways of demonstrating the correct solution – from simulation to actually working through a number of trials with playing cards, to traditional probabilistic and even Bayesian arguments. With a little effort it is reasonably straightforward to convince oneself of the correctness of the true answer – yet this paradox has the peculiar quality that when re-introduced at another time, the result is so counter-intuitive that it is very difficult to remember or re-derive the understanding that was previously attained.

This cognitive shortfall seems to be associated with a predisposition for evenly distributed probabilities, and many other problems with uneven probability distributions can command the same sort of logical errors. For example, if a patient is equally likely to have any of three combinations of health markers A and B (AA, BB, or AB) and a test detects that our patient has at least one A marker, what is the likelihood that the other marker is also A (for a combination of AA)? Most people reason that the patient cannot have BB, so must have either AA or AB, thus has a 50% likelihood of having AA – however, that answer is incorrect.[iv]

In many settings it's merely amusing to note that humans are heavily predisposed to get this sort of thing wrong, and even more amusing to watch them defend their wrongness with their credentials as a shield. However, getting even this one simple thing wrong in a medical setting can lead to a significantly increased risk of

[iii] One way of thinking about this is to consider that when first choosing a door, we have a 1/3 chance of getting the car, but a 2/3 chance of having selected a goat. When Monty later shows us a goat and offers us the remaining closed door, he really is offering us the opportunity to swap our single door for both of the doors not originally chosen. Our original door has a 2/3 chance of having a goat, and the other two doors (together) had a 2/3 chance of having the car. Together, they still have that 2/3 chance of having had the car – even though one of the doors is open (showing a goat) and the other remains closed. If offered, take the switch.

[iv] In reality, there are three A markers in the mix and only one of them is opposite a B – so our patient has a 2/3 chance of being AA and only a 1/3 chance of being AB.

death, and it's a more serious problem if the clinician not only can't perceive the correct answer, but refuses to believe it even when it is pointed out. There are hundreds of examples of this sort of logical fallacy, probability conundrum, and cognitive bias. These problems are not just the stuff of riddles and game researchers. They are real and pervasive and affect thousands of medical decisions each day.

According to Crosskerry [24], in order to make progress in managing cognitive bias, "medical decision makers and educators have to do three things: (1) appreciate the full impact of diagnostic errors in medicine and the contribution of cognitive errors in particular; (2) refute the inevitability of cognitive diagnostic errors; and (3) dismiss the pessimism that surrounds approaches for lessening cognitive bias."

3 Solutions for the future

From this sea of challenges and change emerge a few trends that seem to offer hope as solutions for our most pressing problems. Some of these relate to new and better types of data that can help reduce the uncertainty in today's system. Others relate to new and better ways to aggregate, share, analyze, and present information, with an emphasis on data re-use and on new computational techniques that can augment or replace human effort, particularly where we are at our weakest.

3.1 Genomics and proteomics

The opportunity to definitively identify a pathogen through detection of its genome offers an incredible opportunity to reduce the overall level of uncertainty in medical diagnosis and to provide a therapy to which the pathogen can be guaranteed to be susceptible. Similarly, the opportunity to distinguish different biochemical and metabolic pathways in different patients allows us to adjust medication dosing in such a way as to ensure that each patient gets therapeutic levels of the drug prescribed. These new approaches are just beginning to be available to clinicians, and the impact on our understanding of disease is already enormous.

3.2 Systems Biology

Today's best candidate for a completely transformative approach to diagnostics may lie in the area of systems biology, a new and rapidly advancing field that attempts to understand complex biological and physiological phenomena through a mesh of empirical, mathematical and computational techniques. Systems biology explicitly addresses the fact that hundreds of distinct proteins are involved in information exchange even for a single cellular process, and that even minor defects in this web of information exchange can result in chronic illnesses such as diabetes mellitus, or in the development of certain types of cancer.

Traditional tools in the biological sciences can only focus on the activities of a single cell or a single biochemical pathway, and cannot capture or represent the mesh of interactions that exists in real life. Treatments designed by changing a single path within this mesh of

interactions carry a high likelihood of unintended consequences and a high likelihood that a disease will escape the treatment by following alternate biochemical pathways – problems that bedevil disease research and the new drug development process today.

Systems biology attempts to produce detailed route maps of the subcellular and extracellular networks that are activated in a particular state of the system (either in health or in a disease state) in order to allow perturbations to be modeled in a way that reflects the real biological world . Early results suggest that when sufficient quantitative data is available, even simple mathematical models can produce results of immediate practical use.

Systems biology implicitly recognizes a fundamental reality: that the human body is a complex adaptive system in which a very large number of inputs obey a large number of rules in a system with a high dependence on initial conditions and a high degree of nonlinearity, with feedback loops passing through many levels. In a complex adaptive system our ability to deterministically predict the results of a perturbation may be fundamentally limited by emergent behaviors. However, it is not necessary to predict all aspects of system behavior to exert control; many complex adaptive systems can be effectively (if not deterministically) controlled so long as the right subsystem can be identified and controlled. Furthermore, just as a few simple rules and a small number of variables can create a complex adaptive system, small reductions in the number of variables and rules can have dramatic and nonlinear impact in reducing the complexity of a system. Small technological advances that create simplification and shorten feedback loops in a complex adaptive system can have dramatic effects on the overall behavior of the system.

Systems biology also recognizes the need to capture information along many different axes in order to characterize the state of a system in terms of its envelope and its network of interactions. With this approach it is possible to examine, for example, the patterns of protein expression over time in order to determine which human and pathogen genes have been activated in a specific disease state. Laboratories today have successfully used this approach – using proteins circulating in the blood to track the activation of many different genes in brain tissue – to differentiate such things as prion disease and Alzheimer's disease from other causes of dementia that previously could be distinguished only through brain biopsy or (worse) only at autopsy. [25; 26]

3.3 Data Liquidity and re-use

Traditionally, healthcare data is created within a data silo, used for a single purpose, and discarded or archived when that purpose is complete. However, in an organization that has invested in data liquidity, data from all sources is brought together in one place and made available for a wide variety of current and future purposes. Data is stored with an extensive list of attributes and metadata so it can be repurposed

easily. All types of data are made "instantly and ubiquitously" available through multiple cycles of creation, capture, storage, purposing, and presentation. This kind of data re-use can bring a tremendous amount of new value at low cost.

One source of value comes from using data from multiple sources to drive predictive analysis both at the operational level and at the personal health level. The analogy is to an "air-traffic control system" for health in which a "flight plan" may be filed and deviations from a normal course detected early enough to permit course correction. Such predictive systems will be highly dependent on the constant availability of rich real-time datasets, forcing a gradual migration away from an environment in which data is highly restricted and hard to obtain, and towards an environment in which data is highly mobilized and readily available where needed ("data liquidity").

In traditional environments (dominated by hard-coded point solutions for a small number of old, known problems) it can be difficult even to perceive newly emerging problems, let alone to solve them. The future depends upon a data-centric environment in which many points of view (many purposes) are equally enabled through late binding of structured displays and functional modules, all using a unified data resource to create enterprise intelligence.

Just as tools like Visicalc and Excel wiped out legacy approaches to centralized reporting and analysis by empowering individual workers in unprecedented ways, legacy approaches to information hoarding are being challenged by new systems that can deliver unprecedented universal access to all existing data across an entire enterprise. Today this can be readily achieved across the medical enterprise and even across a region. Ultimately it will lead to pertinent information being instantly and ubiquitously available throughout the entire life of any individual.

3.3.1 Connected Health

With the advent of true data liquidity we are beginning to move from a world of data fragmentation towards a world of Connected Health, in which health information from any source can become part of a personal health data asset that is available wherever and whenever needed. Connected Health moves data freely from enterprise to consumer and from datacenter to desktop, with solutions for trust, authentication, identity, encryption, security, transmission, presentation, delivery, rights management, and other utility functions.

3.3.2 Decision support

New approaches are challenging the perception that a doctor's art is always better than the computer's algorithm. In many areas, even simple computer-aided decision-making approaches have been shown to be better and more consistent than an unaided clinician. Newer decision support offerings are based on Bayesian and multiple regression approaches, expert systems using rule-driven approaches, and more exotic methods

such as evolutionary algorithmic design and fuzzy logic.

3.3.3 Creating Context for Health Data

Context matters. For example, the current weight taken in isolation is all but meaningless for the management of a patient with congestive heart failure. However, with the added context of the patient's baseline dry weight, the current weight becomes the single strongest predictive factor for fluid overload and impending cardiovascular collapse. The same requirement for context will be true for hundreds of different measures that can and will be tracked on a regular basis, at home – and not just for disease entities that we can name and diagnose today.

In many cases, the meaning of medical data depends not only on historical context about that data element itself, but also on a systems context – on all the data about other things that are going on in the person's body and life. A blunted morning cortisol surge after a 30-hour plane ride means jet lag, and the balance is restored by restoring a normal sleep cycle for some period of time. However, a blunted morning cortisol surge that arises out of the blue may mean pituitary or adrenal dysfunction, and the balance is restored in quite a different way.

It's also likely that the context for understanding individual daily health data will also include some population and cohort data. If a patient feels terrible and has a fever during the flu season when 20% of people in the community also feel terrible and have fevers, the implications may be quite different from a scenario where only one person feels bad and has a fever.

Technological solutions already exist to provide significant benefits through improved management of clinical data and shared knowledge. For example, clinicians today choose an antibiotic from handbooks listing drugs-of-choice for presumed and proven infectious diseases. These handbooks are published via traditional methods and do not reflect the situation or condition of a specific hospital or a specific patient. Such recommendations could and should be made by clinical systems capable of drawing upon all known data about the situation. At a minimum, initial treatment recommendations may be based upon recent trends in antibiotic susceptibility in the local population, and with genomic characterization of pathogens there is no reason why there should be any ambiguity whatsoever in the optimum therapeutic regimen.

There are many other examples of ways in which existing data can be mobilized to provide guidance that is sorely needed. One that has obvious appeal involves the creation of a government-sponsored exhaustive list of diagnoses together with current recognized best practices for ruling in/ruling out each disease, along with some uniform mechanism by which to communicate our statistical confidence in a diagnosis, based on how the diagnosis was made.

4 Health and the spectrum of wellness

Over time, health data of various types

will play an ever-increasing role in daily life, initially by improving our ability to reduce sickness and manage chronic conditions, and later by improving our ability to enhance wellness. Over time, the false separation between wellness and sickness will become blurred and eventually forgotten.

4.1 Reducing sickness

Worldwide, 170 million people have diabetes, and the number is expected to double by the year 2030. Today, most diabetics in developed countries perform a blood test on themselves multiple times daily. They use the data in a crude way to guide their diet and activity, and in a more direct way to make specific metabolic adjustments, calculating how much of a medication is needed to maintain the balance of a single substance – glucose - within their body. Today, the data most often is used as a snapshot and then discarded; it is difficult or impossible to perceive patterns or trends for a single patient or across a population of patients. Tomorrow a snapshot approach will be unthinkable.

Today, a few people take hormone replacements – thyroid, testosterone, estrogen – to restore a natural homeostatic balance that has been lost through illness, accident, or aging. Dosing is static, based on a small number of crude tests that may be performed a single time or may be repeated annually. However, the hormonal ecology of the human body is extremely dynamic and tremendously complex, and hormonal requirements can change significantly on a daily basis in response to diet, activity, and other environmental factors. For this reason, patients on a standard regimen invariably have hormone levels that are at times too high, and at other times too low: real balance cannot be achieved through such crude "one size fits all" manipulations. For many of these deficiency states, tests are now available that can be performed by the patient at home – and as more frequent and more granular data elements become the norm, health data management needs will continue to develop in interesting ways.

4.2 Enhancing wellness

How many people now think about their health every day? Hint: it's not just people who are sick. How many people do something on a regular basis to deliberately adjust their physiology and biochemistry? Hint: it's not just those taking medication for a chronic disease. In actuality, most people already take actions to optimize some aspect of their health every single day, and this will only increase in the future.

How many people have a scale and step on it regularly? How many adjust their fitness regimen based on a target heart rate? How many people count calories or follow a diet of any kind? How many read the ingredients on food labels in order to avoid something they don't wish to ingest? How many know their waist size, height, and other body measurements, and use that data to guide clothing purchases?

How many have performed a home pregnancy test or an ovulatory cycle

test? How many have used a home test for occult blood in the stool? How many have checked their own blood pressure? These kinds of diagnostic activities once required a visit to a doctor's office. Today they are self-provisioning activities that affect personal decision-making, and leave a data trail that has value when integrated into a longitudinal record – or when aggregated across entire populations.

How many people drink coffee? How many take a vitamin? These are biochemical manipulations based on sensory feedback (coffee) or global beliefs about metabolic needs (vitamins), rather than based on measurements and calculations of personal needs at a specific time. Today there is no rational basis for customizing a vitamin regimen, yet many people have developed closely-held beliefs about their own specific vitamin needs, and an entire industry has arisen to help people select specific combinations of vitamins and other dietary supplements. Today those selections are based solely upon belief, but tomorrow they will be based on data from personal testing. In the future, each person will adjust their own biochemistry periodically based on personal health data-points and complex calculations involving many sources of data.

How many people use a cleanser, antibiotic, or other treatment for acne or other skin problems? Today these are generic approaches to the health of a specific organ system – the skin. It's already possible to do DNA analysis on the bacteria that colonize your skin, and feasible to adjust the mix with antibiotics and probiotics that are tailored to your own specific needs as they evolve over time.

How many people use mouthwash or brush their teeth with a cavity-preventing formulation? Today, those measures are moderately effective, but it's already possible to analyze the flora of the mouth environment, and people will regularly adjust their biochemistry (and that of their bacterial colonies) to eliminate such things as bad breath and tooth decay completely.

How many "healthy" people take regular medications of any kind? Oral contraceptives? Allergy medications? Headache remedies? Bone density formulations?

These are all activities that involve gathering health-related biometric and bio-environmental data and using it to affect decision-making and modify daily activities. These activities involve people engaging with their own health data to try to improve their *wellness* in some way. Today the data is crude and episodic, and isn't integrated with other data sources – it is used in snapshot form and then discarded – but when specific tests with sufficient granularity can make the *spectrum of wellness* a reality, the entire population will be engaged with their personal longitudinal health datastore in a meaningful way, every day.

Even sophisticated test-based adjustment of essential hormonal and metabolic systems may not remain confined to people who today have a recognized chronic deficiency state: there are biochemical reasons why people sometimes wake up feeling great, and other times wake up

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feeling rotten, and it may soon be possible to measure and correct those problems just as we're able to measure and correct blood sugar or blood pressure today. At some future time – probably not far off – each person will have the opportunity to assess his or her metabolic balance and make daily or even continuous adjustments on not one, but multiple different axes. Naturally these aren't going to be single-factor tests that exist at a single point in time – they will be systems biology data elements that will connect to a live mesh of health data to give them meaning.

Today we think health means "getting treated," "avoiding illness," or "managing chronic disease." Tomorrow we will use quantitative measures of the full spectrum of wellness, and will make data-based decisions about health that will affect every part of our lives. In a very fundamental way, the future of health is the future of beauty, fitness, and happiness.

4.3 Spectrum of wellness

Dynamic change along a functional continuum is the normal human condition; against that background there are periods of time when a person has clearly recognizable problems due to injury or illness, and there are also times when a person has some level of dysfunction that doesn't meet the current threshold of what's called illness or injury. Eventually our concept of wellness will converge with our concept of sickness, so that not only can we use health data to manage daily activities for enhanced wellness, but we can also manage our trajectory into a future that includes overt illness at some future time, in ways that simply are not possible today.

A clinician today applies a relatively crude set of screening capabilities to try to diagnose why a patient does not feel well. Even if tests are ordered, the tests themselves can only detect a small number of conditions that have been labeled as disease states. If a patient meets the criteria for a named illness, he or she most often is classified into one of a series of false disease cognates. Even when two people with similar findings do have exactly the same disease, they may not respond to treatment in the same way because of differences in genes, lifestyle, diet, or concomitant illness. And for those who do not meet the criteria for a named diagnosis, there is little to offer. Patients are told "there is nothing wrong with you," or "there is something wrong with you, but we don't know what to do about it."

The house of medicine today has very little to offer people who are "not sick" – yet are not as well as they used to be, not as well as they want to be, and not as well as they could be. However, a multi-billion dollar neutraceutical industry thinks it has something to offer, and a large number of fringe and quack offerings have arisen to address the problems of those who are not well, yet not sick with an identifiable disease. Fortunately, new advances in genomics, proteomics, metabolomics, and systems biology combine with advances in data management to improve the granular detail of our data, the level of complexity with which we can reason, and our

ability to make definitive diagnoses. As we progressively redefine the baseline of wellness, we will soon find ourselves able to define exactly what pathogens are active in a patient's body – and exactly what they are doing at any moment. In the case of an injury we will be able to measure what the body is doing to repair the injury, because we will know which genes are turned on and what proteins are being elaborated. When a patient doesn't feel well, more often than not we will be able to see and understand that process in terms of biochemical activities and a pattern of genomic activation and proteomic expression, making a definitive diagnosis where today we cannot even identify a patient as "sick."

When we can routinely measure these kinds of things, the clear threshold between "well" and "sick" will simply vanish, and we will see each individual very clearly positioned somewhere along a very broad spectrum of wellness that extends from "perfectly well" all the way to "very sick," with a granularity as fine as we care to make it.

Today we are just at the point where we can make not only a statistical argument, but a direct personal argument that a person who is going to work every day and generally feeling well – but has a slowly rising serum creatinine – actually is on a trajectory to end up with renal failure. We can show that if we intervene immediately, in many cases we can prevent that patient from ever progressing to need dialysis. We can imagine that with the right data and the right modeling tools, we may soon be able to say the same kind of thing about a vast number of health situations. When we have the tools to help us see and understand exactly how an early health disturbance today will lead to a bad outcome ten years later, we will have much better arguments to support investing in an individual today to achieve better outcomes later in life. Most importantly, instead of top-down population arguments, these will be real individual arguments with real biochemistry for a specific person behind each one – and in the aggregate they will add up to the population argument.

5 Conclusions

To be directionally correct in our headlong rush to the future requires from us only a small number of positive actions. We must stop hiding information and begin to share data widely, even if this requires changes in health data policy. We must embrace data liquidity and make all existing data available for clinical care and for subsequent analysis using systems approaches. We should establish definitive clearinghouses for each disease entity that is under study. Important progress may result simply from placing a strong emphasis on making a definitive and unambiguous diagnosis, and clearly distinguishing those cases where the diagnosis is suspect so we do not continue to contaminate our reasoning with data from false disease cognates. Genomic, proteomic, and systems biology approaches should be encouraged and supported. We must assiduously apply the best available

analytical tools to the data at hand. And finally, we must empower the individual as a full partner in his or her health and wellness, with unfettered access to the data necessary to make informed health decisions. Thus, we begin, in the greenish twilight of the past.

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Chapter 8: Strategy for the Future of Health

Renata G. Bushko, M.S.*
Founder, Future of Health Technology Institute, Hopkinton, MA, US

Abstract

This article shows the importance of goal setting in strategy development and presents the Future of Health Technology Institute's www.fhti.org goals as an example of goals that have transformative power. It also provides synthesis and developmental history of the "Strategy for the Future of Health" book while examining collective book design as a strategy development tool. It emphasizes unprecedented technological revolution manifesting itself in the convergence of molecular biology, computer and medical science, electrical, mechanical, genetic and biomedical engineering (including cell, molecular and tissue engineering) resulting in the merger of information technology (IT) with medicine and the formation of "ITicine".

1. Introduction

I have spent last twenty years running an independent agency – Future of Health Technology Institute (FHTI) www.fhti.org – to oversee long-term issues of health technology and to strategize and set goals for the future. This agency prepares for a future society where computers might outsmart people, where we might be able to stop diseases before they begin, where caring machines will aid physicians in 90% of their work and connected caring consumers will diagnose and cure themselves with self-health tools, personalized designer drugs, and automatic surgery bubbles. FHTI is a think-tank aimed at defining strategy for health technology development and determining the most critical focus areas for health technology investment in the new century. FHTI shares Schrodinger's optimism expressed in his seminal paper "What is Life":

> How can the events in space and time which take place within spacial boundary of living organism be accounted for by physics and chemistry?[...] The obvious inability of present-day physics and chemistry to account for such events is no reason at all for doubting that they can be accounted for by these sciences.
>
> Erwin Schrodinger, 1944

We will be able to watch, to explain and to control not only events in space and time in a living organism but also events that connect this organism to a multitude of other organisms. In order to successfully achieve this, however, but we need to outline a concrete strategy.

*Please send correspondence to Bushko@fhti.org

2. Strategy Development

Defining strategy for the future of health involves on-going, adaptive dynamic learning by industry, government, and academia. This involves ultimate goal setting and the definition of strategy equations.

2.1 Setting High Level Goals

The most important part of strategy development is goal setting. High-level goals provide distinct direction and sense of purpose and can assist large groups of people in creating a coordinated effort. Without these high level goals international, national and organizational operational strategic plans often fail because of lack of stamina and perseverance. Future of Health Technology Institute's goals listed below provide direction and inspiration to search for and develop a better future:

FHTI's Strategic Goals:

- Stop disease before it even begins
- Stop suffering before tears occur
- Stop symptoms before they hurt
- Stop medical errors before they kill
- Stop cyborgs before they control us
- Stop aging before it disables us

On the operational level these goals mean:

- Beginning to seriously think about and invest in long-term solutions
- Beginning to manage and organize the unpredictability of the technology creation and adoption process
- Beginning to address health crisis situations as national and international emergencies

It also means that we have to:

- Develop a vision of future health care supported by current and future health technologies.
- Define distinct promising health technology research areas.
- Demonstrate that technology driven cost increases in healthcare can be stopped and possibly reversed by a new allocation of research and development resources.
- Define productive areas for research and development that will have potential impact on healthcare.
- Identify new technologies that are practical and necessary in health and wellness maintenance.
- Identify research and development needed to meet future health challenges
.
- Identify current products that will best prepare for 21st century healthcare.

Figure 1. The Future of Health Technology Award (© 2006-9 FHTI) - a sculpture of Pegasus with crystal eyes, and a third eye (for seeing the future) created from a nano-made diamond. It is a symbol of inspiration to save lives, reduce suffering and enhance human potential with technolog. Winners include Marvin Minsky, Lorraine Gudas, Gary Kreps, Eric Dishman, Michael McDonald, Kevin Warwick, Xiu-Min Li, Craig Feied, Danuta Glowacka, Ray Kurzweil, Barry Robson, Benjamin Miller.

In this book we will touch upon all aspects of healthcare system (Figure 2) and the underlying science and technology that will inspire healthcare leaders responsible for resource allocation to make decisions that best serve both their immediate goals, as well as the human race as a whole. Future progress in healthcare and medicine depends on the investments in research, development and education made today.

Figure 2. National quality cube in the Unified Quality Framework (©FHTI 2002). Top corners illustrate types of quality and bottom corners show the measure of quality.

2.2 Simple Strategy Equation

Unprecedented technological revolution manifests itself in the convergence of molecular biology, computer and medical science, electrical, mechanical, genetic and biomedical engineering (including cell, molecular and tissue engineering). This convergence will led to new life forms and human-machine merger.

Simple Strategy Equation:
Life Science + Computer Science = New Synthetic Life Form

Another version of the above simple strategy equation, shown below, demonstrates complete conversion of health information technology with medicine resulting in a new field that could be called ITicine. This reflects the conversion of old-fashoned medicine with human doctor in the center to IT-centered medicine with caring machine or healthmatician as a main delivery vehicle.

Information Technology(IT) + Medicine = ITicine

3. Book Design as a Strategy Development Tool

In 2002, thirty-two experts contributed to the "Future of Health Technology", and in 2005, thirty-three experts expressed their thoughts in the second book "Future of Intelligent and Extelligent Health Environment". As editor, I have named the third volume produced in 2009, "Strategy for the Future of Health" to provide an inspiration to "think big", to build upon strategic nature of two previous volumes, and to provide a link between IT, medicine, and nanotechnology communities. The idea of developing high level goals, an underlying theme in all three volumes is similar to that expressed by Thomas Edison: "My philosophy of life is work – bringing out the secrets of nature and applying them for the happiness of man. I know of no better service to render during the short time we are in this world."

All three volumes segment health technology in different ways to assure that we capture multiple and constantly developing dimensions of the subject matter as presented below.

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3.1 Future of Health Technology - Book #1 2002

In the first Future of Health Technology book the following four areas of advancement were considered as strategic:

1. Looking into the Future
2. Advancing Medical Technologies
3. Advancing Intellectual Leadership
4. Advancing Global Health Information Infrastructure

Health technology becomes the center of healthcare systems' strategic planning process. Developing a clear vision of the future of health technology and smart investment in technology are the critical success factors. Healthcare leaders need to develop a vision of future health technology to lead effectively in the new century. The social and economic issues surrounding health care will be inextricably linked to the technological aspects of medicine in the next century. Given rapid progress in nanomedicine, the pressure towards detailed outcomes analysis, growing use of Internet, robotic surgery, genetic therapy, telemedicine, on-line consumer education, and bioinformatics health technology becomes the key to intelligent health care. To embrace technology is the only way health systems can assimilate with the technologically advanced society. On-going massive medical data collection, instantaneous analysis, affective computing with emotional intelligence, and nanosurgery will be possible soon.

Last century took us from the first electric switch back in 1880s to the first nanomotor's switch in the year 2000; from 30 ton computer to polymer transistors on a plastic that one can print at home; from electric light to electronic paper, windows, mirrors and wallpaper.
In the next century most current diseases will be history and medicine will be focused on maximizing joy and pleasures of long lives of humans augmented with biomechatronics. Most healthcare cost will be shifted from end-of-life to prenatal care. Since everybody will be augmented with biomechartonics, the word "disabled" will not exist anymore – we will all have the same chance to be truly human.

The "Future of Health Technology" book provides a comprehensive vision of the future ofhealth technology by looking at the ways to advance (1) medical technologies, (2) health information infrastructure, and (3) intellectual leadership. It also explores new technology creation and adoption processes including the impact of rapidly evolving technologies. People discover and respond to the future as much as they plan it. Health systems and societies with the clear vision of future health technology will have a better chance of reducing human suffering.

3.2 Future of Intelligent and Extelligent Environment – Book #2 2005

In the "Future of Intelligent and Extelligent Environment" book there are eight strategic areas selected as outlined below:

- Goals and Unsolved Problems

- Consumers Era - Sociotechnological Environment
- Healthons Era – Technology On our Body, in our Body and All Around Us
- Cyborgs Era – Implants, Merging of Men and Machine & Caring Machines
- Long Life Era - Extending Human Life-span and Future of Caring for Elders
- Hi-Tech Cure and Care Era – Examples: Future of Cancer and Addiction Control
- Global Healthcare Era - Enhancing Healthcare with Soft Technologies
- Adaptive and Errorless Era - Adaptive Healthcare Process Management

The cover design of this edition reflects the unsurpassed drive to understand health on the molecular level as well as a conviction that this is the only way to hope to eradicate major diseases and have control over mental health. It also reflects the need to connect traditional IT with Life sciences, and especially, with nanomedicine. In 1996, I focused on health technology in the era of booming healthcare informatics due to my observation that health-related information comes from and is embedded in biological, electronic and mechanical artifacts – it is an integral part of Medicine and does not exist as an independent and isolated island.

"The Future of Intelligent and Extelligent Health Environment " book brings you closer to the world where technology on our body, in our body and all around us enhances our health and wellbeing from conception to death. This environment is emerging now with intelligent caring machines, cyborgs, wireless embedded continuous computing, healthwear, sensors, healthons, nanomedicine, adaptive process control, mathematical modeling, and common sense systems.

Human body and the world in which it functions is a continuously changing complex adaptive system. We are able to collect more and more data about it (wearable body monitors will be soon in each household just like toothbrushes) but the real challenge is to infer local dynamics from that data. Intelligent Caring Biomechatronic Creatures and Healthmaticians (mathematicians serving human health) have a better chance of inferring the dynamics that needs to be understood than human physicians.

Humans can only process comfortably three dimensions (max 22) while computers can see infinite number of dimensions. Will we enjoy doing medical science if computers become better at it than us? We will need to trust the distributed network of healthons, Intelligent Caring Creatures, and NURSES (New Unified Resource System Engineers) - designers who inbuilt medical intelligence in our external environment - creating Health Extelligence (ubiquitous computing).

At Future of Health Technology Summit™ 2003 Space Elevator

example was used to show how seemingly impossible conceptual designs could become real. Celestial hospitals and errorless healthcare are possible. We may need to use bionic arms and extended cognition to do that but if we spend as much time designing our preferred future as we do researching the past we can get there in no time.

Developments like robo-docs, robo-cats, and space elevators are not just exotic; they are a reaffirmation that with creative thinking we can go a long way to the discoveries that will allow us to fix our healthcare system and set it on a high road for the future.

The dream of an intelligent caring machine is closer to reality considering that Timothy Bickmore's relational agent can help you with your fitness training, Yulun Wang's robotic doctor can help you even from a remote location (remote presence); BodyBug™ can collect your lifestyle data and tell you what to eat and how much to sleep. We are closer and closer to the world with healthons on your body, in your body and all around you; where not a doctor but your primary care healthmatician warns you about an approaching headache; and where NURSE programs your intelligent caring machines so they can talk to your cells and stop disease in its tracks.

Figure 3. Original picture of a "background neuron" (© 2002, FHTI) from the cover of "Future of Intelligent and Extelligent Health Environment" book taken by Danuta Glowacka Ph.D. during her research on morphological differentiation of PC12 Cells; Journal of Neuroscience Research 25:453-462 (1990).

Figure 4. Connecting Neurons. Cover illustration of Future of Intelligent and Extelligent Health Environment, Ed. R. Bushko, IOS Press 2005. Image (©2005, R. Bushko,) based on pictures of neurons grown by Danuta Glowacka Ph.D. 1990.

4. "Strategy for the Future of Health" and "World Health Syrategy" – Book #3 2009 and eBook #4 2016 - Book Synthesis

"Among the noblest aspirations of humanity are the development of advanced technologies for the conquest of aging and medically preventable causes of death, and the launching of a new era of personal choice in medicine. Strategy for the Future of Health gives us a solid push in the right direction."

Robert A. Freitas Jr., Author of "Nanomedicine"

Defining the future of health is difficult and requires both common sense and intuition. Attempts to find solutions for difficult problems require educated guesses and subsequent efforts to verify any hypothesis that is made. The best way to strategize for the future is to collaborate with experts in diverse fields and to then employ their collective knowledge and common sense to dare to guess.

Figure 5. Original picture of a "background neuron" (© 2009, FHTI) from the cover of "Strategy for the Future of Health" book taken by Danuta Glowacka Ph.D. during her research on morphological differentiation of PC12 Cells; Journal of Neuroscience Research 25:453-462 (1990).

Figure 6. Cover page illustration of the "Strategy for the Future of Health" book by Egg Design www.egg-design.com (© Renata Bushko, 2008-9) based on the above neuron picture by Danuta Glowacka Ph.D. shows future of medicine where we communicate with our nanorobots (artist's conception) to stop disease before it even produces any symptoms.

4.1 Health Care Strategy for the Future - General Directions

The most important part of strategy development is goal setting. High-level goals provide direction and sense of purpose. Without these high level goals international, national and organizational operational strategic plans often fail because of lack of stamina and perseverance. "Health Care Strategy for the Future - General Directions" segment describes the environment in which technology will be functioning, as well as its broader

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social ramifications in an attempt to create errorless healthcare.

As described by David Gruber, the American health care system is in crisis. Gruber begins to address the economic problems enveloping the field, describing a future environment where professionals, providers and policy experts holistically care for their patients, where technology plays an enormous role in increasing engagement, the personalization of healthcare, the sharing of experiences, and increase convenience as well as better choice making and where a cost effective primary care navigator becomes the central component of public policy. Robert Greenes echoes the concerns of Gruber regarding the current state of the American healthcare delivery, discussing issues of availability, access, quality and cost that afflict current models of health care delivery.

Craig Feied et al, in their visionary paper, "Indistinguishable From Magic: Health and Wellness in a Future of Sufficiently Advanced Technology", assert that the role of informatics is to act as a "key enabler" to address these problems through the availability of definitive and unambiguous tests, new methods of analyzing messages from cellular and subcellular networks and universal access to data in order to create "connected health" and to improve all aspects of health and modern life.

Gianfranco Zaccai adds to the discussion regarding a better future by suggesting the use of a holistic design process in order to address the multifaceted problems that affect our healthcare system, boldly asserting his goal in creating an ideal customer experience where science and technology have brought healthcare closer to an ideal form and where design can even further progress the field. Such design issues can be examined in the context of pilot projects, such as that described by Julia Royall in her chapter that examines the progress of the employment of a malaria electronic tutorial in Mifumi village, the use of a mental health electron tutorial in northern Uganda and the development of a health management system in Tororo Hospital. Through IT and medical informatics, these pilot projects demonstrate the possibilities that exist, in an African setting, when interdisciplinary teams employ health informatics to enhance community collaboration and overall health.
As it may be seen, the first step to strategizing about the future is to envision a holistic picture regarding the social environment of health care. Next, specific examples may be explored in order to understand what may be possible.

4.2 Strategy for Future of e-Health: Technologically Connected Consumers & Machines

In this segment, experts describe various concrete examples of technologies and currently available prototypes that will have great transformative power on healthcare and the progression towards errorless and perhaps, eventually, doctorless healthcare.

Klaus Peter Adlassnig et al. describe the first of these

technologies in a paper regarding the use of Artificial Intelligence to control hospital-based (nosocomial) infections, a system that will expand upon the computerization of patient records. They describe fuzzy and knowledge based systems of identification and monitoring employing medical knowledge packages (MKPs) in a system named Moni that may be incorporated into preexisting medical information systems leading to unparalleled nosicomial infection surveillance. One can imagine the wide variety of uses such technology could be used for.

In " Innovations in Connected Health," Kanwaljit Singh and Joseph Kvedar assert that recent technological advances make new innovations that lead to the concept of Connected Health feasible. Like Gruber and Greenes in Section 1, Singh and Kvedar remark that the crisis status of the current health care system provides a unique opportunity and avenue for reform in using technology to increase quality and access while simultaneously decreasing cost with hardware and software technology innovations.

In the paper "Can Consumers Cure Themselves?" Renata Bushko examines the future of e-Health within the context of a newly evolved field of "ITicine" which equally merges the more traditional medical discipline with Information Technology (IT) in order to improve medical diagnosis. This field would employ the use of caring machines as well as a sophisticated expert system by consumers themselves in order to analyze and reason with physiological and molecular data. These technologies will drastically reduce errors in medicine. John Moore and Henry Lieberman suggest another alternative to the traditional patient-health care provider relationship in which a system, named "I'm Listening" can work in conjunction with a human doctor to more efficiently and effectively conduct triage care to best take advantage of time and resources, as well as to reduce errors in communication and diagnosis.

James DelloStritto introduces innovative concept of "spontaneous interoperability" with his chapter on adaptive information networks in health. Creating a model based upon biological frameworks, DelloStritto describes memory maps that facilitate adaptability and interoperability with the transference of evolutionary history and meta-data associated with information. Despite challenges, this system will allow for greater availability of information which will lead to better prevention of disease, patient outcomes and fewer medical errors.

Rather than a holistic system reform, Alex Pentland et al. suggest that current technologies and their transaction "breadcrumbs" be used to fuel Reality Mining, which has the capability to use statistical analysis and machine learning methods to provide individually and collectively comprehensive pictures of our lives. Employed in fields of diagnosis, patient treatment and monitoring, health service planning, surveillance of disease and risk factors, and public health investigation and disease control, Reality Mining will use raw

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data provided by everyday devices such as mobile phones, cars and security cameras. Pentland et al., address the potential legal and privacy ramifications, yet clearly demonstrate the value of such technology.

As these various technologies are developed, we must stop to consider the retributions of inventing and using such technology with a large segment of the population, as described in Section I of this book. Barry Robson addresses just this, exploring issues of privacy, security, bandwidth and computational power that require roaming agents of analysis that send only conclusions rather than full reports of primary data. He suggests the use of best practice in inference and the future necessity for a universal agreement regarding the treatment of probabilistic higher order logic. According to Robson, quantum mechanics may provide such a system, one with emergent properties that might allow for understanding of the nature of thought, an issue he addresses in Chapter 18 in as well.

4.3 Life Extension Strategy: Longer Lives and New Life Forms

This segment delves into the current efforts towards the extension of human life and the maintenance of high quality throughout life. It examines ways in which existing human life may be extended, as well as how new or artificial life may be used in field such as organ regeneration in order to further improve existing and future human life. Issues of new machines and subsequent machine-human interactions and relations are also addressed

In Chapter 14, Raymond Kurzweil and Terry Grossman demonstrate the progression towards immortality and that eliminating human aging is becoming a reality through what they refer to as "Fantastic Voyage." This Program includes the aggressive application of current knowledge, the use of biotechnologies such as gene technologies and the use of nanotechnology to rebuild bodies and brains in order to slow aging and disease process. Aubrey deGrey addresses aging in terms of molecular and cellular decay, a process that can incrementally be defeated. He predicts a threshold on the succession of advances deemed "Methuselarity" that will follow a decreased rate of improvement in anti-aging technologies required as we age. He compares and contrasts this to the concept of "singularity," and makes interesting predictions regarding the future of this field.

In his chapter titled "Of Mice and Men," Kevin Warwick provides a concrete link between biology and technology in reference to the brain. Examining a laboratory cultured brain linked to and controlling a physical robot, Warwick explains his interesting insight regarding fundamental features of neural disease and the mechanisms of neural signal transfer. Examining a similar technology-biology link, S. Adam Hacking et al. explore the issue of tissue regeneration of artificial organs. They address the limits to such technological progression but also the emerging approaches that may be brought about in the near future

regarding control of stem cell differentiation, microscale control of local tissue and the generation of organs that contain multiple cell types.

In Chapter 18, Robson again investigates the connection between quantum mechanics (QM) and thought, suggesting ways in which QM can be used to decipher patterns of human thought and to aid in the communication between humans and machines. These papers provide but a simple snapshot of current ideas and despite the absence of a comprehensive picture, it can be surmised that we are well on our way to a different and better future. The next section furthers this conclusion, addressing the extension of human health and life with the use of nanotechnologies.

4.4 Nano-Strategy: Extending Human Potential with Nanomedicine

This segment focuses on current technology designed on a nanoscale to extend human life and to reduce suffering through non-invasive interventions, a technology that will vastly revolutionize the way we think about healthcare delivery and the acceptable levels of human suffering inflicted by surgery. In order to better understand the implications of nanomedicine, one can consider the use of nanotechnology to be as significant as the invention of anesthesia, an analogy that may be extended to understand the subsequent drastic reduction in suffering. This is an idea that must be kept in mind when considering the implications of the technologies related in the following chapters.

Welcoming us to the future of medicine, Robert A. Freitas Jr. begins the section with a discussion regarding the consequence of slow technology development, demonstrating the vast effects that an immediate and large-scale investment in nanorobots could make. Renata Bushko expands on the importance of recent technological events, describing chromallocyte, designed by Freitas. This nanorobot, capable of *in vivo* chromosome replacement, would reverse the effects of genetic disease and damage, preventing infirmity and aging. She also stresses the importance of timely investment and delivery. Rob Burgess addresses the medical applications of nanoparticles and nanomaterials and the current limitations of diagnostics and therapeutics that function without such technologies. He argues that in order to improve the sensitivity and efficacy of health care interventions, a new generation of technology will be required.

In Chapter 21, Robert Linares et al discuss the recent advances made in diamond technologies as well as the various ways in which diamonds, as a bio-compatible material, may be used, including quantum computing, molecular imaging and perhaps even eventually diamond nano-bots. The chapter asserts that a new generation of diamond based bio-electronic devices could usher in a paradigm shift for medical science. Benjamin Miller explores other revolutions in healthcare, examining the streamlining and simplification of detection and quantification capabilities regarding

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molecules of biomedical relevance. Tod Hogg looks how molecular electronics and nanoscale chemical sensors will be able to detect chemical pattern as they flow in a passive solution, demonstrating how information acquired from a large number of sources will allow for precise drug delivery as well as the increased speed and accuracy of microsurgery. Each of these chapters demonstrate an example of a branch of nanotechnology that when combined, will revolutionize modern healthcare.

4.5 Strategy for Wellness: Emotional and Physical Fitness

This section of the book introduces the concept of soft technology and a more qualitative improvement of human life. It describes examples of current technologies used for mental health applications as well the training of emotions, as described by Jason Kahn et al. Their chapter presents a computer-based intervention called RAGE (Regulate And Gain Emotional Control) which employs the paradigm of biofeedback and requires relaxation during a quick reactive pulse in order to train children to focus, react, inhibit impulses and control their own heart rate during stressful circumstances in order to increase emotional control.

James Drane et al. and Raffi Rembrand focus more upon learning disabilities and autism, respectively. Drane et al. examine the profound effects of technology on quality of life improvement for children with disabilities, looking at the benefits of robotics in eduation and rehabilitation. Rembrand looks towards technology as more of a diagnostic tool, particularly for autism. Rather than a diagnosis based upon behavioral measures, Rembrand demonstrates technologies that can diagnose and treat those with autism on the basis of Otoacoustic Emissions (OAE) and Attention Shift Delay (ASD) to improve quality of life.

Cindy Mason et al. discuss another field of soft medicine: haptic medicine. As healthcare based on the effects of loving touch on disease prevention, haptic medicine has been shown to have positive outcomes on over forty health conditions. Mason et al. describe two web-based education and media projects that will expand the field of haptic medicine, thus improving and extending human life.

As a concluding chapter, Caroline M. Apovian and Rosane Ness-Abramof's "Future of the Fight with Obesity" addresses a modern epidemic and the ways in which soft technology may be used to alleviate its consequences on both individual health and the health of society as a whole.

As it may be seen, technology, both hard and soft, provides us with the tools for an unimaginable number of solutions for issues in healthcare ranging from aging to obesity, diagnosing and treating learning disabilities and autism to unraveling the secrets of thought employing quantum mechanics. By discussing and outlining strategies in e-health, life extension, nanomedicine, and general wellness, we can begin to address the crisis of the current healthcare system as well as the endless possibilities for our future.

5. Conclusions

Goal setting is the most important part of strategy development. The Future of Health Technology Institute's www.fhti.org goals are an example of goals that have transformative power: (1) stop disease before it even begins, (2) stop suffering before tears occur, (3) stop symptoms before they hurt, (4) stop medical errors before they kill, (5) stop cyborgs before they control us, and stop aging before it disables us.

These goals can be realized because of unprecedented technological revolution manifesting itself in the convergence of molecular biology, computer and medical science, electrical, mechanical, genetic and biomedical engineering (including cell, molecular and tissue engineering). Resulting merger of information technology (IT) with medicine and the formation of "ITicine" is a major strategic development. It will play an integrative role in the future of health technology, accelerating the speed of discoveries leading to dramatic cost reduction and eventually to errorless healthcare. According to Aubrey de Grey, author of "Ending Aging", like all technology, health technology can only proceed so far by small incremental steps; every so often it needs vision, lateral thinking, the willingness to step back and consider radical new approaches. Renata Bushko's (Bushko@fhti.org) annual conference and associated books are a tremendous focus for this crucial long-term thinking." We have a unique chance to define the future rather than to simply observe it, and we must take absolute advantage of this opportunity. "Strategy for the future of Health" book is the nano-step in that direction. Most of the work is ahead of us and it will continue at annual Future of health technology summits: FHT2010 9/26-27/2010 and FHT2011 9/27-28/2011.

Appendix

Table 1. Future of Health Technology Book Ed. Renata G. Bushko, IOS Press 2002

Part I: Looking into the Future
• Defining the Future of Health Technology – Biomechatronics • Inventing the Future - Tools for Self-health
Part II: Advancing Medical Technologies
• Future of Medical Knowledge Management and Decision Support • Future of Nanofabrication and Molecular Scale Devices in Nanomedicine • Thought to Computer Communication • Affective Medicine: Technology with Emotional Intelligence • Future of Medical Computing • Intelligent Agent Software in Medicine • Speech and Language Technologies, Intelligent Content Management and Intelligent • Assistants
Part III: Advancing Global Health Information Infrastructure

- Developing the Health Information Infrastructure in the United States
- Future of Telemedicine
- Advanced Technology Program: Information Infrastructure for Health Focused Program
- Quality Enhancing Conceptual Tools for Medical Decision Making
- The Future of Highly Personalized Health Care
- Developing E-Commerce and Improving Resource Management
- The Future of Information Technology for Health in Developing Countries

Part IV: Advancing Intellectual Leadership

- What is Digital Medicine?
- Evaluating New Health Information Technologies: Expanding the Frontiers of Health Care Delivery
- Future of Security and Privacy in Medical Information
- Future of Health Technology to Augment Patient Care in the Hospitals
- Your Wealth Your Health – Bellweather Industries for Decision Tools and Symbiotic Stewardship
- Impact of Voice-enabled Clinical Reporting – US Example

Table 2. Future of Intelligent and Extelligent Health Environment Ed. Renata G. Bushko, IOS Press 2005

Goals and Unsolved Problems

- Healthons: Errorless Healthcare with Bionic Hugs and no Need for Quality Control

Consumers Era - Sociotechnological Environment

- The Prospects for Medical Technology in the Next Decade
- Innovation in Telehealth and the Role of the Government
- Present and Future Challenges in Medical Data Management: Economics, Ethics, and the Law

Healthons Era – Technology On our Body, in our Body and All Around Us

- Healthwear: Medical Technology Becomes Wearable
- Interfacing Biology and Computing for Health: The Future of Home Diagnostics
- Designing and Evaluating Home-based, Just-in-Time Supportive Technology
- Health. Care. Anywhere. Today.
- How Do We Get The Medical Intelligence Out?

Edited by: **Renata G. Bushko** - bushko@fhti.org
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Cyborgs Era – Implants, Merging of Men and Machine & Caring Machines

- Future of Computer Implant Technology and Intelligent Human-Machine Systems
- Future of Caring Machines
- Cyber-anthropology: A New Study on Human and Technological Co-evolution

Hi-Tech Cure and Care Era – Examples: Future of Cancer and Addiction Control

- Harnessing the Power of an Intelligent Health Environment in Cancer Control
- Future of Anti-addiction Vaccines
- Automating Addiction Treatment:Enhancing the Human Experience and Creating a Fix for the Future

Long Life Era - Extending Human Life-span and Future of Caring for Elders

- A Strategy for Postponing Aging Indefinitely
- Future of Caring For An Aging Population:Trends, Technology, and Caregiving
- Promoting Safe and Comfortable Driving for Elders

Global Healthcare Era - Enhancing Healthcare with Soft Technologies

- Global Medicine Technology
- Shaping a Healthy Future: Megabyte, Not Mega bite!
- Digital Literacy in a Landscape of Data: A Plea for a Broader Definition for Citizens and Patients

Adaptive and Errorless Era - Adaptive Healthcare Process Management

- Situated, Strategic and AI-enhanced Introduction of Technology to Health Care
- Towards an Intelligent Hospital Environment: Operating Room of the Future
- Framework for Measuring Adaptive Knowledge-Rich Systems Performance

Table 3. Strategy for the Future of Health, Ed. Renata G. Bushko, IOS Press 2009

Goals and Synthesis
• Strategy for the Future of Health – Goal Formation & ITicine
Health Care Strategy for the Future - General Directions
• Indistinguishable From Magic: Health and Wellness in a Future of Sufficiently Advanced Technology • Informatics and a Health Care Strategy for the Future - General Directions • Designing the Future of Healthcare • Can Consumers Cure Healthcare? • Strategies for Positive Outcomes: Can Information Technology Make a Difference in Health in Africa?
Strategy for Future of e-Health: Technologically Connected Consumers & Machines
• Using Reality Mining to Improve Public Health and Medicine • Artificial-Intelligence-Based Hospital-Acquired Infection Control • Adaptive Information Networks in Healthcare: Spontaneous Interoperability • Innovations in Connected Health • Talking About Painful Subjects: Flexibility and Constraints in Patient Interviews • Towards Intelligent Internet-Roaming Agents for Mining and Inference from Medical Data • Can Consumers Cure Themselves?

Life Extension Strategy – Longer, Happier Lives and New Life Forms
• Fantastic Voyage: Live Long Enough to Live Forever – The Science Behind Radical Life Extension • The Singularity and the Methuselarity: Similarities and Differences • Of Mice and Men • Future Approaches to Organ Regeneration: Microscale Environments, Stem Cell Engineering, and Self-assembly of Living Tissues • Links Between Quantum Physics and Thought
Nano-Strategy - Extending Human Potential with Nanomedicine
• Welcome to the Future of Medicine • Medical Applications of Nanoparticles and Nanomaterials • Diamond: A Bioelectronics Platform • Diagnostics for a Personalized Medical Future: Extending our Senses to the Molecular Scale • Maintaining Your Health from Within: Controls for Nanorobot Swarms in Fluids • Fight for Chromallocyte
Strategy for General Wellness - Emotional and Physical Fitness
• RAGE Control: Regulate And Gain Emotional Control • Therapeutic Robot for Children with Disabilities: Case Study • Sound of Hug • Haptic Medicine • Future of Obesity Prevention and Treatment

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Chapter 9: Present and Future Challenges in Medical Data Management: Economics, Ethics, and the Law

Salil H. Patel
Johns Hopkins School of Medicine
Departments of Urology and Radiology
The Johns Hopkins Hospital, Baltimore, MD, USA

Abstract

Electronically-linked knowledge plays an increasingly central role in the delivery of health services worldwide. Medical data collection, archival, and analysis are all increasing in both rate and volume; large, cohesive collections of personal health information are emerging rapidly. Factors driving this integration include value-added methods of diagnosis and therapy, interest in evidence-based practices, safety concerns, and increased consumer demand for personalized, comprehensive medical services. Practitioners, businesses, patients, and the public at large would be well-served to develop and sustain a dialogue addressing these phenomena, including assessments their of economic, ethical, legal implications.

1. Introduction

Since Watson and Crick's elucidation of the structure of DNA in 1953, a revolutionary tide has swept across the fields of biology and chemistry, profoundly affecting the practice of clinical medical care. The era of the 1990's marked the inception of a second major shift in the practice of medicine: the informatics wave. Seminal developments in the domains of data collection, manipulation, and distribution have potentiated the spread of novel modalities for practice, treatment, and payment. Concomitantly, the pervasive adoption of an Internet infrastructure, underpinned by a host of standardized open protocols (e.g., TCP/IP, SSL, DICOM, and VPN), served as a means for convergence of these technologies. Electronic medicine generates economic activity on the order of hundreds of millions each year, at levels ranging from individual private practices to comprehensive provider networks. According to the 2002 American Medical Association Study on Physicians' Use of the World Wide Web, nearly 80% of American physicians use the Web as part of their practice. One-third of surveyed doctors are affiliated with a website for promotional or public-education purposes. The era of information has indeed altered the behaviors of individual consumers of medical goods and services, with nearly one-half of all adults in America using the Web as a source of healthcare information [1]. On larger scales, companies such as Healtheon have already begun to offer commercial solutions for patient data, prescription, and claims management [2]. The implementation of electronic patient record systems such as Siemens SIENET's MagicWeb, which claims a user-base of 25,000 clinicians, has increased the degree of enterprise-wide data aggregation and communication among care providers, diagnostic facilities, and insurers. Greater centralization of health information in databases, according to

industry commentator Lawrence Gostin, is "already under way" and carries with it "an aura of inevitability." Although a monolithic, cross-industry and nationwide system might maximize the level of aggregation, it is perhaps more feasible that existing databases and information streams will interoperate by leveraging the current reach of open standards and Internet technologies. In light of these dramatic changes, it is possible to envision that the storage and manipulation of personal data such as medical histories, genetic profiles, and treatment delivery in novel paradigms, facilitated by information technology, may occur within a comprehensive electronic network established within our lifetimes. Such integration must proceed with careful consideration of issues such as economics, public health, and civil rights.

2. Economic Considerations

Linked information technology systems potentially bear a major impact upon the medical field in the realm of costs. Although the initial adoption of any new system entails some investment, in the long term, the savings to the health care system over a prolonged deployment period may be significant. In terms of startup expenditures, the major areas for investment will include software and hardware development and installation, as well as the creation of a robust services model to exploit fully the capabilities of the new system. The latter may entail changes in medical and consumer education methods, as well as training of librarians and data custodians to assist in data manipulation and storage. As Jones, et al. note, "Services are the most important factor in meeting organizational needs for knowledge-based information" [3]. The advantage of this early investment is a large projected return in terms of economic efficiency and effectiveness.

Inefficiencies in administration may be reduced through improved consistency in billing and data transfer practices. Such savings have already been demonstrated in the northeastern U.S., where the establishment of the New England Healthcare Electronic Data Interchange Network is currently reducing costs to care providers due to reduced administrative overhead and is forecasted to lead to annual savings on the order of 66 million dollars [4]. Furthermore, it is conceivable that an information-systems facilitated reduction in preventable medical errors, to be addressed shortly, and the employment of intelligent decision support systems may reduce exposure to malpractice suits, which have been partly responsible for dramatic increases in physician insurance premiums since 1999 [5]. In addition, the establishment of a "computerized decision support model" which analyzes care efficacy and alerts providers to treatment alternatives has been demonstrated empirically to reduce total expenditures and to decrease the length of hospital stays [6]. Even these models, however, must account for changes in the final "product" of quality of care delivered, as initial parameters of the treatment process are altered. Witness the

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enactment of an 80 hour work-week limitations for residents in accredited training programs at U.S. hospitals, a response to claims that fatigued residents are more likely to commit errors. One consequence of these regulations is that the care of a patient may be passed among several separate care teams within an initial span of 24-48 hours; the demands of multiple transfers of recent patient information may lead to altered content, granularity, and quality of these findings, and unintentionally compromised quality of care. Retrospective studies and randomized controlled trials are especially indicated in order to assess the response of the healthcare delivery system to such perturbations.

Tele-health services, involving remote diagnosis and supervision of care, may facilitate cost savings by increasing access and decreasing utilization of inpatient services [7]. The potential of using the nascent Internet II, with its high-bandwidth infrastructure, combined Quality of Service assurances and high network availability, for orthopaedic and cardiac telesurgery, promises to improve care efficiency even further [8]. Although cost-effectiveness for telemedicine has yet to be established [9], associated shifts in resource allocation may still improve overall efficiency of healthcare delivery in selected settings, such as rural areas [10] and public schools [11]. It has been proposed that a reimbursable-time or "billable hours" model, similar to that used by the legal profession, might be used to encourage physicians and allied health care professionals to incorporate electronic resources into busy clinical practices [12]. Finally, implications for cost reduction may reach across domestic borders and encourage developing countries to make use of a "leapfrog" model of healthcare development – i.e., the directed and proactive integration of current information technology in nascent public health systems. This same leapfrogging process has already been demonstrated in the telephony sector in countries such as China, India, and the former Soviet Republics, where high-capacity wireless cellular services in some areas are being deployed in lieu of traditional land-lines [13]. Thus, cost savings issues may provide an impetus for the adoption of electronic medicine internationally.

3. Ensuring Public Health

The convergence of personal data and delivery systems presents myriad potential boons and challenges to the health of both the individual and population levels. Hospitals are already recognizing the utility of electronic systems for preventing iatrogenic injury [14], in domains ranging from drug dispensation, dosage errors, and interactions, to the prevention of idiosyncratic allergic reactions and dose-related toxicity. Online medical information empowers patients to become more informed and engaged in their treatment process, and may encourage utilization of preventative educational services. In fact, 95% of patients in a representative clinical study "strongly preferred" electronic education pre-operatively over the conventional physician-mediated consent process;

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this was attributed in part to reduced patient levels of anxiety and intimidation [15]. In the realm of prescription drugs, the World Wide Web is increasingly being used by pharmaceutical companies to provide marketing materials and prescription information directly to physicians and consumers. At the same time, independent organizations are releasing cost-effectiveness data and clinical practice guidelines as part of publicly-accessible therapeutics databases. Medical indices and journals are widely available online though public systems sponsored by the National Library of Medicine. Other types of medical data are now accessible to the public as well, including the release of physician malpractice and disciplinary records by state boards of certification, as well as morbidity and mortality results for practicing individuals, albeit in limited cases [16]. Electronic mail, bulletin boards, and directed broadcast systems may be vital facets of future coordinated responses of care providers during times of medical emergencies. Enthusiasm of such widespread dissemination of medical information must be tempered with caution, however. With the flood of drug data available online, the reports of "off-label" uses by patient group websites, and the increase in direct-to-consumer marketing, inefficient utilization patterns may quickly emerge [17]. Even more significantly, judicious audits have revealed a wide range in the accuracy and completeness of online databases, presenting the potential for public confusion and misinformation [18;19]. In response to these challenges, Stone, et al. suggest the following standards in particular for all websites which profile physicians: disclosure statements about data sources and compensation, explanations for blank or missing records, reports of database size and scope, and an indication of the timeliness of each data field [16].

In the domain of public health, informatics may play a key role in the evaluation of populations as well as the prevention and treatment of disease. For instance, under an electronic system liked to established health authorities, the dissemination of reportable disease information may become rapid, accurate, and automatic (privacy concerns notwithstanding). For instance, Dr. John Bartlett, chief of Division of Infectious Diseases at the Johns Hopkins School of Medicine, established an e-mail broadcast system in response to the anthrax attacks of October 2001, with an estimated 18 thousand subscribers to the service one year later. Commercially, Oracle Corp. is marketing its Lightweight Epidemiology Advanced Detection and Emergency Response System for centralized outbreak monitoring and coordinated resource allocation.

Clinical measures studies of large databases will allow for greater efficacy assessment across a wide population, help to identify dangerous interactions or reactions to prescription pharmaceuticals post-FDA-approval, and aid public health planners in identifying populations with the greatest disease burden using objective and quantifiable metrics. The European Effective Health Care

Bulletins and systematic reviews of the international Cochrane Collaboration, all available online, attempt to synthesize the current state of medical care and compare relative treatment efficacies in an attempt to promote evidence-based, cost-aware healthcare practices. In the U.S., the Federal Agency for Healthcare Research and Quality has sponsored studies correlating clinical practices and outcomes for several years [20], although current limitations in dataset size and structure still are significant. Variable granularity, or specificity of information fields, is a limiting characteristic of current records, making cross-datatype and cross-database comparisons difficult. Implementation of methods gleaned from the disciplines of knowledge engineering, complex systems, nonlinear analysis, biostatistics, and predictive analytics will all be necessary in order to fully exploit a large and accessible database of health measures and outcomes. Research teams at IBM [21] and SAS [22] have proposed a methodology grounded in these premises, termed Unstructured Data Mining, that may be particularly well-suited to the task of sifting through arrays of disparate patient datasets. In fact, many retail corporations already use data mining techniques in sales trends analysis and consumer profiling [23].

Regardless of the power of sampling methods, it is still a daunting task to extract information about poorly-characterized or multifactorial disease syndromes with the current predominance of relatively decentralized or disconnected independent patient records. One controversial solution to this problem has been pursued by deCODE Genetics, a private entity contracting with the government of Iceland. The company has managed to secure full and proprietary access to the health and family history of all Icelandic citizens [24]. In less than two years, the company has reportedly identified putative genes for susceptibility to complex conditions such as late-onset Parkinson's Disease, Alzheimer's Disease, Type II diabetes, and obesity [25;26]. The products of basic research, such as gene sequence and homology, as well as related clinical and pathophysiological data, are also correlated using open-access initiatives such as Online Mendelian Inheritance in Man.

4. Health Databases and Issues of Rights

4.1 Assessments of Personal Liberty

In addition to the above considerations, convergence of the Internet and medical practice has itself occurred at the nexus of practical implementation and the boundaries of civil liberties. Is privacy a moral imperative? Regardless, there are implicit constitutional protections, as outlined by the classical "penumbra" established within the U.S. Bill of Rights, which protect reasonable expectations of personal privacy; comments Supreme Court Justice William Brennan (1977):

> "The central storage and easy accessibility of computerized data vastly increase the potential for abuse of that information, and I am not prepared to say that future development will not demonstrate the necessity of some curb on such technology." [27]

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One unanswered and contentious issue cannot be ignored: who actually owns increasingly commoditized patient data? In most local jurisdictions, it is actually the creator of the record, not the patient, who has primacy over the use of database, although individual privacy rights in fact supercede authorship rights in selected instances [28]. When databases span states and even countries, which nations' laws apply and in what circumstances? When data becomes stripped of specific individual identifiers, dis-aggregated, completely de-identified, or compounded, at what point do individuals whose data is part of this new set abrogate their rights to the derivative work? Furthermore, in what circumstances does the government justify the appropriation of personal health data for the public interest? One may view tension between public health and individual autonomy as delineating the boundaries of personal liberty. The U.S. Supreme Court, in Jacobson v. Massachusetts (1905), ruled that mandatory vaccination is justified to protect public welfare, notes that "The Constitution of the United States...does not import an absolute right in each person to be, at all times and in all circumstances, wholly freed from restraint. There are manifold restraints to which every person is necessarily subject for the common good." These emerging issues, clearly beyond the scope of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA), will soon demand legislative attention and the establishment of common standards for privacy. In the case of deCODE Genetics, for instance, individuals may opt-out of the private database if desired, although the process is cumbersome [1]. In some countries, such as the Republic of Singapore, a system of unique medical identifiers is already in place nationwide.

I would like to propose the application of the assessment of the ethical validity of the use of personal data in research, using archetypical, universal, and simple criteria outlined such as those by Emanuel, Wendler, and Grady, summarized in Table 1 [29]. Adherence to models such as these should be given consideration as integral components of any comprehensive medical data management infrastructure.

Table 1. Requirements for assessing the ethics of research on human subjects.

1	Social and scientific value of protocol
2	Scientific validity
3	Unbiased subject selection
4	Clear risk-to-benefit proposition
5	Independent review of protocol and reasoning
6	Informed consent of participants
7	Respect for autonomy and welfare of subjects

Emanuel, et al. (1999)

4.2 Government and Corporations

To what extent may a republic exercise powers of "eminent domain" over public health data? Collated and mined datasets bear heightened utility in times of crisis such as a looming threat of bioterror. In such an environment, how is the appropriation of personal information justified? It may be useful to consider three concerns regarding decisions made by leadership bodies in times of crisis: first, such decisions, by necessity, are rapidly made; second, is the opportunity and danger of over-generalization; third, discrimination and judgment may defer to "herd mentality" and hysteria. The most natural counterbalance to each of these tendencies is strong policy, formulated well in advance of a crisis, that is both flexible and powerful, and granted legitimacy by support from both the government and the populace.

In addition, significant pitfalls emerge from the research process. Before research may be conducted,

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to what extent may informed consent be a part of the process? Despite the relaxing of some draft provisions of HIPAA pertaining to data access allowed to providers and researchers [30], HIPAA still incorporates the Security Final Rule as well as privacy provisions, and as electronic informed consent systems are under rapid development [15], their use will soon be a practical necessity.

Finally, where do the rights of corporate entities intersect with those of individuals in a world of highly connected data-flow? For instance, under present law, the Learned Intermediary Rule shields drug marketing companies from direct civil litigation, since information is often funneled first through physicians. How will the increasing popularity of direct marketing, facilitated by the Internet and other electronic media, change this balance of power between individuals, corporations, and providers? Furthermore, which groups and individuals, specifically, should have access to personal health information? Will access-licensure boards be required to grant and review privileges? These issues are becoming increasing relevant with the rise of "computational medicine," which correlates drug reactions and efficacy with specific patient populations. Using data from patient records and clinical trials, Compugen Corp. has contracted with HMOs to obtain access to millions of patient records for the purpose of such data mining [31].

4.3 Safeguards

In the realm of individual electronic patient records, how will patients be able to audit and ensure the accuracy of their personal data? Perhaps, in a "clearinghouse" model similar to that used by credit agencies, consumers can be afforded legal protections to view their files and contest inaccuracies. The provisions of HIPAA allow for consumers to request changes to their personal health records if they believe that an error is extant, with the responsible provider having a maximum of 90 days to review the request. Given the complexity and possible subjective nature of some elements of the health history, the effectiveness of the clearinghouse approach is yet untested.

Also, in legal malpractice cases, will lawyers be given access to records during the evidence discovery process? Cost/benefit analysis may also be conducted from the springboard of the precautionary principle, as proposed by David Kreibel; namely, that one must take preventative action in uncertain times, that the proponents of an activity bear the burden of proof, that alternative actions must be explored, and that public participation is key in the decision-making process [32]. This model is particularly germane to both clinical research and public health research contexts.

In addressing issues of privacy protections, the nature of implementation of disclosure policies for large-scale databases is a key

issue. One consideration is the method of software and hardware development. As sound security infrastructure is required in order to safeguard civil liberties, the first major task to be addressed is a complete assessment of the scope of the problem (Table 2). What levels of protection are necessary? Is version control and tracking of records required? What degree of data archival and access logging is desired? In many situations, rapid deployment can begin by enabling secure, peer-reviewed technologies such as public key cryptography, redundancy, distributed systems, relational and regenerative databases that have been previously deployed in other service industries.

Table 2. Goals for a comprehensive electronic patient record andorder-entry system

	Primary objective: Archival of patient personal health data
1	Histories and summary dictati
2	Diagnostic imaging requisitions and reports
3	Laboratory and pathology results
4	Treatments administered and problem list
5	Follow-up reports
	Specific Endpoints:
1	Facilitation of fault-tolerant, highly-available datastreams
2	Electronic prescription and impatient ordering capability
3	Assured data integrity through hashing and checksums
4	Physical security safeguards to access and modification
5	Crytographically-secure delivery of datastreams
6	Access auditing
7	Integration with billing processes and insurance claims
8	Dynamic assessment of eligibility for clinical trial enrollment and provision of value-added services
9	Links to external references (drug formularies, patient education literature, best-practice guidelines, and literature reviews)
10	Record of patient consent and support for electronic signature capture
11	Support for telemedicine (health care worker present at point-of-service) and cybermedicine (without end-location physician) providers
12	Incorporation of intelligent models to highlight gathering epidemics and nosocomial outbreaks

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5. Complexity and Information Security

For collections of individual records assembled in databases, which themselves are linked in various ways, the topology of the network formed at each level attains particular importance. Yook, et al. have modeled the structure of Internet connections, and proposed that such a network may be classified as scale-free [33]; namely, a relatively small number of central nodes are responsible for a disproportionate level of the connectivity within the system [34]. The implications of identifying such a structure are important for several reasons: first, they offer an insight into the underlying communications load that various elements of the system must bear. Second, the central nodes are those which generally subserve critical functions (i.e., house data which is of particular utility). The random failure of such a node may be a rare event, but a coordinated attack upon several nodes may be catastrophic for the system [35]. A given health-care network, much like the Internet, is a system with connectivity directed by human parsing, that relies heavily upon centralized data-centers for specific information such as patient identification numbers, allergies, and prior history. This implies that, to ensure robustness of a health care network, the most important nodes should be identified and the majority of available resources should be directed towards protecting these centers against failure.

Routine audits of software are key in maintaining effectiveness and security [36]. As software is developed, linking existing database structures into an interoperable continuum, secure practices should be a key element of design and implementation. This might be facilitated through freely-viewable source code to be inspected by the community at large. This transparency will allow for the implementers to be confident in the integrity of the middleware code – cf. the Unix community's experience with the OpenBSD operating system, which emphasizes security through open source development and open audits. Through the use of continuous auditing processes [36], and the payment of reward bounties for reported security exploits, both the private and public sector may be able to cooperate in developing a secure and reliable data services infrastructure for medical practice, education, and research. Finally, as the criminal assault on personal data grows [37], the development of hardware and software must be paralleled by legal protections against cybercrime and electronic terrorism. The potential for theft and abuse by legitimate providers will only rise as perceived value of personal medical records increases.

6. Issues for Future Consideration

Despite the aforementioned hazards, several positive ethical ramifications of records and treatment computerization should be noted. The Institute of Medicine (IOM), in a highly-publicized report entitled "Unequal Medicine," documented racial disparities in the administration of American mental health services, medication dispensation, and surgical procedures. One path to closing the divide, the

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IOM recommends, is the careful correlation of patient and doctor racial and ethnic demography in order to identify the roots and possible solutions to the problem [38]. Even this pathway is not without controversy, however, as racial profiling and correlation may itself be a violation of individual human rights. Furthermore, information reform may be one possible path to tort reform, as changes in data storage, diagnosis, and treatment modalities may force a re-thinking of liability assessment strategies [39]. For instance, as doctors from multiple regions all collaborate to treat a patient, and as doctors, managed care organizations, and pharmacists build closer relationships, previous protections and delineations of accountability become blurred and new models must be developed for quality control, restitution, and risk assessment in medical practice [20]. In this way, the Internet revolution may perhaps provide a basis for moving toward a more egalitarian, patient-centered, "no-fault" model of medical practice. Finally, the establishment of a broader records-based system may open a door for cross-sector and even trans-national coordination and cooperation in terms of deployment and maintenance of records systems, while preventing an imbalance in favor of governmental or corporate interests. Lessons gleaned from the governance mechanism of the World Wide Web itself, namely the non-governmental Internet Corp. for Assigned Names and Numbers, show that private officials, elected at large to represent a diverse community, have the capability to set strong standards, in concert with industry groups. It is precisely this adoption of open and consensus-based standards that has allowed the Web to flourish as an economic and academic entity, and perhaps this model can be reprised by the creation of a "health board," charged with the responsibility of establishing consistent guidelines for technological interoperability and access across all medical data networks.

Thus, the potential for a bright future for public health and the public welfare is indeed promising, but only in the context of pro-active engagement by government entities, health-care providers, industry leaders, scientists, and the citizenry at large.

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Chapter 10: Big Data and Health

Alex P. Pentland, Ph.D.
Massachusetts Institute of Technology, Cambridge, MA, USA
Todd G. Reid, Sc.D., MBA, MPH
Massachusetts General Hospital / MIT Connection Science, Boston/Cambridge, MA, USA
Tracy H. Heibeck, Ph.D
Author

Abstract

Everyday devices such as cell phones now provide us with an enormous stream of data about human life and behavior. Combined with existing health data the behavioral data obtainable from these devices may greatly enhance opportunities to predict long-term health conditions and identify non-traditional intervention points, as well as to design better diagnostics tools, prevent diseases, and increase access to – and reduce the costs of – healthcare. Significant application areas include: chronic and infectious diseases, mental health, environmental health, nutrition, and social health. While there is enormous promise, there are also dangers to be avoided in terms of data privacy and ownership issues. Both regulation and technology must continue to evolve in order to provide us with the potential benefits while not exposing citizens to the dangers of exploitative companies or unreasonable government oversight. To this end, we discuss a taxonomy framed in terms of data control, including: open data commons; personal and proprietary data; and government data. To better support the emerging medical and health science based on the use of big data, we present several recommendations, including: (1) how to ensure data access; (2) how to allow for open data; (3) how to promote big data health science; (4) how to encourage public-private partnerships; and (5) how to accelerate big data health practices.

1. Introduction

Since the beginning of time most people have been isolated, without information about or access to the best health practices. But in just the last decade this has changed completely – through the spread of cell phone networks, the vast majority of humanity now has a two- way digital connection that can send voice, text, and most recently, images and digital sensor data. Healthcare is suddenly something that is potentially available to everyone; all across the world we are beginning to see healthcare workers collecting health information and delivering telemedicine consultations in even the most remote areas.

This new digital nervous system is also driving a more subtle and potentially even more profound change known popularly as `big data'. The proliferation of wireless devices such as cell phones provides an enormous stream of data about human life and behavior. Linking these petabytes of raw information to health records, demographic data and genetic information offers novel opportunities to uncover population health patterns, predict long-term

conditions and identify non-traditional intervention points. Improved disease prevention, better diagnostic tools as well as increased access to – and reduced cost of – health care are achievable. We are now beginning to be able to see the health conditions for all of humanity with unprecedented clarity.

This enhanced view of human health and behavior will enable important advances in medical science. The use of big data in health is a new and exciting field, full of promising case examples, but there are also practical problems to be worked out, such as data privacy and ownership issues. There are also dangers to be avoided such as the risks of misuse of personal data and new types of medical error. This chapter aims to give a view into the future of big data in health and to map out concrete steps that will help ensure that we can realize its full potential.

2. Scope of the Discussion

In this chapter, we will provide a framework to inform discussion about the role of big data, summarize existing best practices, highlight the remaining barriers, and develop policy recommendations to overcome the barriers in the intersection of big data, health, and medicine. We will focus our discussion outside of the complex hospital systems of developed nations because: (1) the transformative potential for big data seems greatest where there is currently the least data; (2) the vast majority of humans do not have access to advanced hospital systems; and (3) many of the challenges of using big data within hospitals concern entrenched financial interests and legacy legal barriers. Hence, they require detailed, specific discussion outside the scope of this paper.

While use of big data has enormous promise for improving health systems there are also dangers that must be avoided. There is scientific risk, because the unfamiliar, correlational nature of big data raises the possibility of misinterpretation that can cause serious harm. Consequently, we must devise new procedures for developing health systems that incorporate big data. There is also risk of misuse, which comes from the danger of putting so much personal data in the hands of either companies or governments. Therefore, we will discuss how new approaches to regulation and technology have been developed that can help protect personal privacy from exploitation and can mitigate the problem of government overreach as well.

3. The Role of Big Data in Health

The potential uses of big data extend far beyond enabling more efficient healthcare systems. So far, these uses have mostly remained theoretical possibilities due to a number of barriers including privacy and data ownership issues. There are emerging best practice examples, however, which demonstrate the potential of these largely untapped health and behavioral data.

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3.1 Chronic Diseases

The overwhelming majority of chronic diseases in humans arise as a consequence of a complex web of causes that act over years before the disease is manifested. The mission and challenge of epidemiologic research is to unravel these causes as a prerequisite for prevention. The Achilles' heel of such research is to accommodate the complexity of the data and adequately ascertain information about causes. In this regard, the new technologies that help collect, analyze, and correlate large volumes of personal health data might offer entirely new opportunities. Indeed, interactive prevention via such accessible technologies could be used to reach segments of the population that cannot access medical care otherwise.

Much information that we have now about preventing chronic, non-communicable diseases (NCDs) has come from traditional longitudinal studies. For instance, studies based in North America and Europe have heavily influenced preventive health policy such as dietary standards for schools and restaurants, laws regulating smoking, and air quality standards. [1] In some ways, these studies could be considered the progenitors of big data in that they typically enroll thousands of people and assess them periodically, usually by questionnaire. These questionnaires can be web-based, mailed, or in-person or telephone interview. For the most intensive of such studies the frequency of assessment is typically every 6 months to 2 years. The data from these research instruments, however, are limited to supplying only data about what individuals have said (or think) that they have done. With reality mining innovation, that is, using big data to measure what individuals have *actually* done, researchers can gain important new insights. [2]

Rapidly developing countries face the challenge of replicating such research suitable for their context given obstacles to dissemination of questionnaires such as limited mail and land-line telephone service, and access to Internet by their populations. Big data and reality mining techniques give scientists in these countries the opportunity to "leapfrog" over these obstacles, collect better and more information than before, and dramatically improve health data at the same time.

Behavioral data also offer intriguing possibilities in other areas of chronic disease. For example, research suggests that some chronic health-related conditions and behaviors are "contagious" in the sense that individual-level outcomes are linked to other individuals with whom one shares social connections. For example, both smoking behavior and obesity have been shown to spread within social networks. Smoking and obesity likely serve as good models for other health related behaviors such as diet, exercise, general hygiene, sexual habits, and so on. As such, reality mining might yield specific points of leverage for effective health interventions. That is, if certain behaviors are indeed contagious, then targeting individuals in key parts of the social network

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could result in more powerful approaches to intervention and more effective ways to promote behavior modification. Of course, privacy issues are paramount here (see Managing Big Data discussion).

3.2 Infectious Diseases

As the world becomes increasingly interconnected through the movement of people and goods, the potential for global pandemics of infectious disease rises as well. In recent years, outbreaks of SARS and other serious infectious diseases in widely separated but socially linked communities highlight the need for fundamental research on disease transmission and effective prevention and control strategies. In developed countries, health officials typically investigate cases of serious infectious disease (e.g., tuberculosis, SARS, malaria, etc.) to identify the source of infections and other cases of disease and to prevent further transmission.

In any of these scenarios, investigations are difficult and time consuming, while transmission continues unabated. Moreover, people often forget all the locations they have visited, even for recent periods. Similarly, they might not know many of the people to whom they were exposed or might have exposed themselves. All of these difficulties underline the potential value of systematically analyzing location and social behavioral data, both readily obtained from cell phones, for disease control. Logs of location tracking data from cases' cell phones can be examined to identify places where cases might have acquired or transmitted infection, thereby facilitating the investigation. Recently this approach has demonstrated its effectiveness in transmission of malaria [3] and food poisoning. [4]

Reality mining tools could also assist in the detection of outbreaks of such temporarily disabling disease. For instance, acute illnesses such as influenza that cause sufferers to reduce their physical activity and mobility patterns (even confining them to bed) or change their communication behavior, are identifiable in several types of reality monitoring data streams. [5] At the population level, fluctuations in digital traces of these behaviors may indicate outbreaks of temporarily disabling infectious diseases. At the individual level, examination of data about an individual's exposure summary as part of an emergency room or clinical intake process could indicate if the person ate or spent significant amounts of time near known outbreak areas, information that might not have been otherwise captured through self-report. In the future such tools could offer a formidable defense against pandemics: a recent pilot study has demonstrated the potential for real time tracking of flu propagation on an individual-to-individual using only behavioral data collected from smart phones. [6]

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Figure 1: Map of the MIT campus showing risk of contracting infectious disease at the current time, obtained from analysis of cell phone mobility patterns and short cell phone health surveys of selected individuals.

3.3 Diagnosis, Treatment and Follow-up of Human Disease

Big data obtained from the continuous monitoring of motor activity, metabolism, and so on can be extremely effective in tailoring medications/treatments for individuals. Once a course of treatment (behavioral, pharmaceutical, or otherwise) has been chosen, it is important for a clinician to monitor the patient's response to treatment. The same types of big data used for diagnosis can also be relevant for monitoring a patient's compliance, response and side-effects to treatment especially when such data on the patient are available for a period before diagnosis and can serve as a baseline for comparison. Even when these data streams are not relevant for diagnosis, they can be useful in assessing side effects of treatment, such as reduced mobility, activity, and communicative behavior. Because these data can be collected in real-time, a clinician would be able to adjust treatment according to the patient's response, perhaps leading to more effective treatment and preventing more costly office visits.

Currently, doctors prescribe medications based on population averages rather than individual characteristics. They assess patients for the appropriateness of the medication levels only occasionally – and expensively. With such a data-poor system, it is not surprising that medication doses are frequently over- or underestimated and that unforeseen drug interactions account for a sizable proportion of hospitalizations, notably among the elderly. Going further, correlating a continuous, rich source of behavioral data to prescription medication use for millions of people could make drug therapies more effective and help medical professionals detect new drug interactions more quickly. [7]

3.4 Mental Health

Mental diseases rank among the top health problems worldwide in their cost to society. Major depression, for instance, is the leading cause of disability in established market economies. Diagnoses of psychiatric disorders are overwhelmingly based on reporting by the patient, a teacher, family member, or neighbor. Many symptoms of psychiatric disorders concern patterns of physical movement, activity and communication – all things that can be measured by cell phone data. Accelerometers can reveal fidgeting, pacing, and abrupt or frenetic motions. Location tracking can reveal changes in places visited and routes taken as well as the overall extent of physical mobility. The frequency and pattern of individuals'

communications with others and the content and manner or their speech can also reflect key signs of several psychiatric disorders. [2, 8]

The ability to use inexpensive, pervasive computational platforms such as cell phones to monitor these sensitive indicators of psychological state offers the dramatic possibility of early detection of disorders such as depression, attention deficit hyperactivity disorder, bipolar disorder, agoraphobia, and others. [9] In addition, because these data streams provide direct, continuous and long-term assessment of patterns and behaviors, new avenues of treatment monitoring and assessment in mental health can be developed.

3.5 Environmental Health

Epidemiologic investigations of the links between various health conditions and individuals' exposures to airborne pollutants (e.g., particulate matter, carbon monoxide, nitric oxide) have relied on a variety of exposure measurement methods. To date, most studies of this type have been based on comparisons of aggregates of persons (e.g., residents of particular neighborhoods or cities, or students at specific schools) with exposure measurements applying to all individuals in a given group. Air pollution levels, however, can vary dramatically over short distances and time scales in urban and other environments. Hence, environmental health experts have called for more precise and dynamic measures of time-activity patterns in relation to exposures. Location tracking data generated by cell phones, when coupled with measurements of ambient air pollutions at numerous places in a community (gathered from existing air quality monitoring stations and/or inferred from vehicle traffic patterns and locations of industrial facilities), may offer just the kind of exposure measurement needed. [10]

3.6 Nutrition

Nutrition epidemiology may also be revolutionized by big data driven innovations. Long a major challenge in health research, dietary record keeping is often riddled with bias from the inaccurate recall of what people have eaten over the course of a week, month, or year. Because it is now possible to track dietary intake at almost every point of consumption, previous inaccuracies in recording can be minimized markedly. For example, GPS enabled cell phone applications could track whether individuals frequented fast-food restaurants or farmer's markets, or even the produce aisle versus the snack-food aisle in a community's grocery store. Detailed consumer purchase streams will serve not only as enormous, data-rich sources for dietary record keeping, but they will also offer unprecedented opportunities to track and analyze important correlated behavioral data associated with nutrition health outcomes. In addition, food security and availability can be improved to ensure more steady and adequate supplies of nutrition on a population level.

3.7 Social Health

Despite compelling evidence, most efforts to encourage healthy behavior and medical compliance continue to

be organized around conscious, individual decision making only, neglecting the social dimension almost entirely. Using big data to better understand social conditions, we will be able to achieve more in terms of behavioral modification, a major key to health advancements. For example, big data can be used to provide the social pressure needed to establish new, healthy behavior norms. Online `friend networks' have successfully been used to promote higher physical activity levels and to increase prosocial behaviors such as voting and energy conservation. [11, 12]

The Data for Development (D4D) initiative [13] highlighted in Figure 2 is another good example of using big data to address social health issues[1]. In this collaborative effort, ninety research organizations from around the world reported hundreds of results from their analyses of cell phone data. These data described the mobility and call patterns of the citizens of the entire African country of Ivory Coast, a country struggling with poverty and the aftermath of a recent civil war. Together with more traditional sources of information, these data were used to provide ubiquitous, up-to-the-minute mapping of poverty and ethnic boundaries within the entire country of Ivory Coast, two significant social health issues.

Figure 2: This example from the D4D initiative shows a map derived from a method for mapping poverty from the diversity of cell phone usage. As people have more disposable income, their patterns of movement and patterns of phone calls become increasingly diverse. Another example of using the D4D data for social health is the development of a method for mapping of ethnic boundaries. This method relies on the fact that ethnic and language groups communicate far more within their own group than they communicate with others. Mapping social boundaries is important because, while we know that ethic violence often erupts along such boundaries, the government and aid agencies are usually uncertain about the geography of these social fault zones.

4. Managing Big Data

Reality mining of big data for behavioral information is still in its infancy. Today, smartphones monitor physical activity, social interactions, sleep patterns, and routine behavior. These new tools, with their view of life in all its complexity, may well be the future of medical science and public health policy. There is risk in

[1] The D4D data were donated by the mobile carrier Orange, and the research initiative was organized with help from the University of Louvain (Belgium) and the MIT Human Dynamics Lab (United States), along with collaboration from Bouake University (Ivory Coast), the United Nation's Global Pulse, the World Economic Forum, and the GSMA (which is the mobile carriers' international trade association). The D4D program was led by Nicolas De Cordes (Orange), Vincent Blondel (Louvain), Alex Pentland (MIT), Robert Kirkpatrick (UN Global Pulse), and Bill Hoffman (World Economic Forum).

deploying this sort of data driven health system, however, because of the danger of putting so much personal data in the hands of either companies or governments. Both regulation and technology must continue to evolve in order to provide more scientific, real-time public policy without exposing citizens to the dangers of exploitative companies or governments. This section will outline the current best practices in this area.

Figure 3: This big data taxonomy is comprised of: (1) open data commons, including geolocated and time stamped statistics about aggregate costs, health outcomes and behaviors (e.g., mobility, smoking, drinking, crime, accidents); (2) personal data, including digital breadcrumbs (mobility, call, and purchasing patterns, etc), personal annotations about eating, subjective variables, and standard health data (temperature, glucose, genomic, etc); and (3) government data, including detailed healthcare system costs, individual performance ratings, fine-grain outcome data. Overlapping regions require trust networks for data sharing.

It is probably hopeless to provide a detailed taxonomy of data types and uses because the technology is progressing so quickly. But it is possible to provide a broad taxonomy framed in terms of control. The three main divisions within the spectrum of data control are: (1) data commons, which are available to all, with at most minor limitations on use; (2) personal or proprietary data, typically controlled by individuals or companies, for which there needs to be legal and technology infrastructure that provides strict control and auditing of use; and (3) the secret data of governments which typically have less direct public oversight and more stringent controls. The issues with data commons will be addressed first, followed by personal and proprietary data, and then government secret data.

4.1 Open Data Commons

The first entry in the data taxonomy is the data commons. A key insight is that our data are worth more when shared because they can inform improvements in systems such as health, transportation, and government. Using a “digital data commons” can potentially give us unprecedented instrumentation of how our policies are performing so we can know when to take action to quickly and effectively address the situation.

We already have many data commons available: maps, census data, and financial indices. With the advent of big data we can potentially develop many more types of data commons. These commons can be both ‘real time’ and far more detailed than previous examples because they depend mostly on data that are already produced as a side-effect of ongoing daily life (e.g., digital transaction records, cell phone location fixes, road toll records, etc.). That is, they can be produced automatically by computers without human intervention.

One major concern with such a data commons is that they can endanger personal privacy. Another secondary concern involves the tension between commercial or personal interests: these proprietary interests might tend to reduce the richness of such a commons, and diminish the ability of such a data commons to enable significant public goods.
To explore the viability of a big data commons, what is perhaps the world's first true 'big data' commons was created for the Data for Development (D4D) initiative, and included data describing the mobility and call patterns of the citizens of the entire African country of Ivory Coast as well as more traditional data sources. [1]

The work of the ninety research groups involved in D4D suggests that many of the privacy fears associated with the release of data about human behavior may be generally misunderstood. In this data commons, the data were processed by advanced computer algorithms (e.g., sophisticated sampling and use of aggregated indicators). Hence, it was unlikely that any individual could be re-identified. In fact, no path to re-identification was discovered, even by several of the research groups that studied this specific question.

In addition, while the data were freely available for any legitimate research that a group was interested in, the data were distributed under a legal contract that specified that the data could only be used for the purpose proposed and only by the specific people making the proposal. A similar technology-legal framework is used in trust networks described in the next section. The use of both advanced computer algorithms and contract law to specify and audit how personal data may be used and shared is the goal of new privacy regulations in the E.U., the United States, and elsewhere.

4.2 Personal and Proprietary Data

The second category in the data taxonomy is personal and proprietary data, typically controlled by individuals or companies, for which there needs to be legal and technology infrastructure that provides strict control and auditing of use. The current best practice is a system of data sharing called trust networks. [14] Trust networks are a combination of a computer network that keeps track of user permissions for each piece of personal data, with a legal contract that specifies both what can and cannot be done with the data and what happens if there is a violation of the permissions. This is the model of personal data management that is most frequently proposed within the World Economic Forum Personal Data Initiative. [15]

In such a system, all personal data have attached labels specifying what the data can, and cannot, be used for. These labels are exactly matched by terms in a legal contract between all the participants stating penalties for not obeying the permission labels and giving the right to audit the use of the data. Having permissions, including the provenance of the data, allows automatic auditing of data use and allows individuals to change their permissions and withdraw data.

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Today, there are long-standing versions of trust networks proven to be both secure and robust. The best known example is the SWIFT network, reliably handling trillions of dollars per day for inter-bank money transfer. Its most distinguishing feature is that it has never been hacked. Until recently such systems were only for the 'big guys'. To give individuals a similarly safe method of managing personal data, researchers have built open-source software systems such as openmhealth and openPDS (open Personal Data Store), and are now testing these systems with a variety of industry and government partners. [16, 17]

4.3 Government Secret Data

The third category in the taxonomy is secret government data, typically including tax data, detailed census data, detailed expenditures, and social health factors. The advent of big data health systems may dramatically expand the depth and breadth of these secret government data to include all types of individual behavior data.

A major risk of deploying data driven policies and regulations comes from the danger of putting so much personal data in the hands of governments. But how can it happen that governments choose to limit the data they keep? The answer is that unlimited access to data about citizens' behavior is a great danger to the government as well as the citizenry. Consider the NSA's response to the recent Snowden leaks in the United States:

"This failure originated from two practices that we need to reverse," Ashton B. Carter, the deputy secretary of defense, said recently. "There was an enormous amount of information concentrated in one place," he said. "That's a mistake." And second, no individual should be given the kind of access Mr. Snowden had, Mr. Carter said.

http://www.nytimes.com/2013/08/04/sunday-review

That is, the government must organize big data resources in a distributed manner, with each different type of data separated and dispersed among many locations, using many different types of computer systems and encryption. Similarly, human resources should be organized into cells of access and permission that are localized both spatially and by data type. Both computer and human resources should always be redundant and fragmented in order to avoid overly-powerful central actors.

The logic behind this observation is that physically and logically distributed databases which also have heterogeneous computer and encryption systems are hard to attack, both physically as well as through cyber attack. This is because any single exploit is likely to gain access to only a limited part of the whole database. Similarly, the resilience of organizations with a heterogeneous cell-like human and permissions structure is familiar from intelligence and terrorist organizations.[2]

[2] This architecture can help prevent the use of big data to trample individual freedoms. The key insight is that for these types of data systems, each type of data analysis operation has a characteristic pattern of communication between different databases and human operators. As a consequence, it is possible to monitor the functioning of the data analysis process without access to, or endangerment of, the analysis content. In short, one can use 'metadata about big data' in order to monitor the use of big data, and with some reasonable confidence ensure that only 'normal' analysis operations are being conducted without reference to specific content. Governments that structure their data resources in this manner can more easily monitor attacks and misuse of all sorts.

Edited by: **Renata G. Bushko** - bushko@fhti.org
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5. Recommendations

A medical and health science based on the use of big data is emerging. This new science leverages the capacity to collect and analyze data with a breadth and depth that was previously inconceivable. How can we best support the development of big data health systems? We have five key recommendations:

1. Ensure data access: Some of the thorniest challenges posed by our new digital capabilities revolve around data access and sharing. Robust models of collaboration and data sharing, between government, industry and the academy need to be developed; guarding both the privacy of consumers as well as corporations' legitimate competitive interests are vital here. Privacy and data ownership policies should be updated to ensure that data are accessible by patients and their healthcare providers, and that trust network technology is required in order to provide safe data sharing.

2. Allow for open data: Current data in healthcare, particularly those stemming from pharmaceutical and medical R&D, clinical settings, patient behavior, and payer activity are highly fragmented and not generally accessible by the health researchers or even patients themselves. The creation of broad, open data commons that support research is critical. The ability to pool unrestricted government data and non-proprietary private data in an open data commons would promote the development of a 'big data' health ecosystem. We suggest that there needs to be an international Charter for Open Data Sharing, which specifies best practice and commits nations to sharing health data for their mutual benefit.

3. Promote big data health science: The academic community needs to train more computational social scientists and develop big data experimental methodologies such as living laboratories and rich open data repositories. In addition, the availability of easy-to-use tools would greatly accelerate a big data health science. Just as mass-market computer assisted design software revolutionized the engineering world decades ago, common analysis tools and data sharing protocols will lead to significant advances. We suggest development of a 'best practice kit' that lowers the barrier to entry for interested countries.

4. Encourage public-private partnerships: Big data health systems require some investment in data handling infrastructure, but are not as intrinsically expensive as many civil systems. On the other hand, they require a continuous partnership between the healthcare system and private companies, private individuals, and healthcare professionals, since all of these are required to obtain the necessary data. Public-private partnerships can serve to underwrite costs and accelerate deployment; financial entities such as special-purpose banks that underwrite the required capital investment at low interest rates are likely to prove especially useful in promoting a big data health ecosystem.

5. Accelerate big data health practices: Significant potential health solutions are likely to be those developed in partnership with more inquisitive front-line physicians, who best understand the problems to be solved, who are interested in applying new approaches and piloting promising ideas, and who, most importantly, are committed to the iterative development of new solutions. After all, most technological success arises through a rapid, iterative process with motivated early adopters. The combination of pioneering physicians and behavioral scientists with experimental platforms such as living laboratories which support rapid innovation, is central to the rapid development of successful big data health practices.

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Chapter 11: Using Reality Mining to Improve Public Health and Medicine

Alex Pentland, Ph.D.
Massachusetts Institute of Technology
David Lazer, Ph.D.
Harvard University
Devon Brewer, Ph.D.
Interdisciplinary Scientific Research
Tracy Heibeck, Ph.D.
Author

Abstract

We live our lives in digital networks. We wake up in the morning, check our e-mail, make a quick phone call, commute to work, buy lunch. Many of these transactions leave digital breadcrumbs – tiny records of our daily experiences. Reality mining, which pulls together these crumbs using statistical analysis and machine learning methods, offers an increasingly comprehensive picture of our lives, both individually and collectively, with the potential of transforming our understanding of ourselves, our organizations, and our society in a fashion that was barely conceivable just a few years ago. It is for this reason that reality mining was recently identified by *Technology Review* as one of "10 emerging technologies that could change the world" [1].

Many everyday devices provide the raw database upon which reality mining builds; sensors in mobile phones, cars, security cameras, RFID ('smart card') readers, and others, all allow for the measurement of human physical and social activity. Computational models based on such data have the potential to dramatically transform the arenas of both individual and community health. Reality mining can provide new opportunities with respect to diagnosis, patient and treatment monitoring, health services planning, surveillance of disease and risk factors, and public health investigation and disease control.

Currently, the single most important source of reality mining data is the ubiquitous mobile phone. Every time a person uses a mobile phone, a few bits of information are left behind. The phone pings the nearest mobile-phone towers, revealing its location. The mobile phone service provider records the duration of the call and the number dialed.

In the near future, mobile phones and other technologies will collect even more information about their users, recording everything from their physical activity to their conversational cadences. While such data pose a potential threat to individual privacy, they also offer great potential value both to individuals and communities. With the aid of data-mining algorithms, these data could shed light on individual patterns of behavior and even on the well-being of communities, creating new ways to improve public health and medicine.

To illustrate, consider two examples of how reality mining may benefit individual health care. By taking advantage of special sensors in mobile phones, such as the microphone or the accelerometers built into newer devices such as Apple's iPhone, important diagnostic data can be captured. Clinical pilot

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data demonstrate that it may be possible to diagnose depression from the way a person talks – a depressed person tends to speak more slowly, a change that speech analysis software on a phone might recognize more readily than friends or family do. Similarly, monitoring a phone's motion sensors can also reveal small changes in gait, which could be an early indicator of ailments such as Parkinson's disease.

Within the next few years reality mining will become more common, thanks in part to the proliferation and increasing sophistication of mobile phones. Many handheld devices now have the processing power of low-end desktop computers, and they can also collect more varied data, due to components such as GPS chips that track location. The Chief Technology Officer of EMC, a large digital storage company, estimates that this sort of personal sensor data will balloon from 10% of all stored information to 90% within the next decade.

While the promise of reality mining is great, the idea of collecting so much personal information naturally raises many questions about privacy. It is crucial that behavior-logging technology not be forced on anyone. But legal statutes are lagging behind data collection capabilities, making it particularly important to begin discussing how the technology will and should be used. Therefore, an additional focus of this chapter will be the development of a legal and ethical framework concerning the data used by reality mining techniques.

1. Capabilities of reality mining

To date, the vast majority of research on the human condition has relied on single-shot, self-report data: a yearly census, public polls, focus groups, and the like. Reality mining offers a remarkable, second-by-second picture of both individual and group interactions over extended periods of time, providing dynamic, structural information and rich content.

1.1 Assessment of individual health

The basic functionality of mobile phones consists of the digital signal processing and transmission of the human voice. Advanced mobile phones also have accelerometers, so that they can measure the body movement of their users, and geolocation hardware (both GPS and other methods), so that they can report their users' locations. As a consequence, when users carry around and use their mobile phones they produce a rich characterization of their behavior.

Reality mining of these behavior signals may be correlated to the function of some major brain systems. This statistical behavior analysis therefore provides capabilities that can be thought of as a sort of low-resolution brain scanning technology. Figure 1 illustrates the relationship between brain state and observable behaviors for four types of behavior:

- Arousal of the autonomic nervous system produces changes in activity levels. These changes can be measured by audio or motion sensors, and have been successfully used to screen for depression [2,3,4]

- Tight time-coupling between people's speech or movement (called 'influence') is an indication of attention, since such tight coupling cannot be achieved without attending to and modeling the other person. This 'influence' measure has been successfully used for more than 30 years as a screen for language development problems in pre-verbal infants [5].

- Unconscious mimicry between people (e.g., reciprocated head nods, posture changes, etc.) is mediated by cortical mirror neurons and is very highly correlated with feelings of empathy and trust. Measurements of mimicry are thus considered to be reliable predictors of trust and empathy [6], and mimicry has been manipulated to dramatically improve compliance [7].

- Consistency or fluidity of movement or speech production is a well-known measure of cognitive load: novel physical activities or those 'loaded' by other mental activity have greater entropy (randomness) than activities that are highly practiced and performed with a singular focus. This relationship has long been used for diagnosis in both psychiatry [8] and neurology [9].

Figure 1: Reality mining has shown that statistical analysis of behavior can be related to the function of some major brain systems, providing capabilities that can be thought of as a sort of low-resolution brain scanning technology.

These qualitative measurements of brain function have been shown to be powerful, predictive measures of human behavior [10]. They play an important role in human social interactions, serving as 'honest signals' that provide social cues to dominance, empathy, attention, and trust, and may offer new methods of diagnosis, treatment monitoring, and population health assessments.

1.2 Mapping social networks

One of the most important applications of reality mining may be the automatic mapping of social networks [11]. In Figure 2(a), you see a smart phone that is programmed to sense and report continuously on its user's location, who else is nearby, the user's call and SMS patterns, and (with phones that have accelerometers) how the user is moving. One hundred of these phones were deployed to students at MIT during the 2004-2005 academic year.

Careful analysis of these data shows different patterns of behavior depending upon the social relationship between people. Figure 2(c) shows the pattern of proximity during one week, and it can be seen that self-reported reciprocal friends (both persons report the other as a friend), non-reciprocal friends (only one of a pair reports the other as a friend), and reciprocal non-friends (neither of a pair reports the other as a friend) exhibit very different patterns [12]. By using more sophisticated statistical analysis, we can map each participant's social network of friends

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and co-workers with an average accuracy of 96% [13].

Reality mining's capability for automatic social network mapping is now being used in a variety of research applications. As an example, a current research project underway at MIT is aimed at understanding health-related behaviors and infectious disease propagation. At this time, we have above 80% participation of students in a MIT dormitory that includes freshmen and upperclassmen, and are beginning to compare the behavior and health changes that freshmen normally experience with the changes in their various social networks. This experiment should help to disentangle causal pathways about how social networks influence obesity and other health-related behaviors, as well as provide unprecedented detail for modeling the spread of infectious disease.

1.3 Beyond demographics to behavior patterns

Most government health services rely on demographic data to guide service delivery. Demographic characteristics, however, are a relatively poor predictor of individual behavior, and it is behavior – not wealth, age, or place of residence – that is the major determinant of many health outcomes. Reality mining provides a way to characterize behavior, and thus provides a classification framework that is more directly relevant to health outcomes [10].

Figure 2: Mapping social networks from mobile phone location/proximity data. 2(a) shows a 'smart phone' programmed to sense other people using Bluetooth, 2(b) shows the pattern of proximity between people during one day, and 2(c) shows that different social relationships are associated with different patterns of proximity.

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The pattern of movement between the places a person lives, eats, works, and hangs out are known as a *behavior pattern*. Reality mining research has shown that most people have only a small repertoire of these behavior patterns, and that this small set of behavior patterns accounts for the vast majority of an individual's activity [14].

The fact that all mobile phones constantly measure their position (either through GPS or by finding the nearest cell tower) means that we can use reality mining of mobile phone location data to directly characterize an individual's set of behavior patterns. We can also cluster together people with similar behavior patterns in order to discover the independent subgroups within a population.

Figure 3(a) shows movement patterns with popular 'hang outs' color coded by the different subpopulations that populate these destinations, where the subpopulations are defined by both their demographics and, more importantly, by their behaviors. Figure 3(b) shows that the mixing between these different behavior subpopulations is surprisingly small.

Understanding the behavior patterns of different subpopulations and the mixing between them is critical to the delivery of public health services, because different subpopulations have different risk profiles and different attitudes about health-related choices. The use of reality mining to discover these behavior patterns can potentially provide great improvements in health education efforts and behavioral interventions.

Figure 3: Analysis of travel patterns allows discovery of largely independent subpopulations within a city. Movement patterns (a), measured from GPS mobile phones, allow (b) segmentation of the population into subpopulations with differing behavior patterns, and measurement of the 'mixing' between those groups [15].

2. The future potential of reality mining

In the previous section, we discussed how reality mining has the potential to assess individual health, to map social networks automatically and to discover subpopulations with different behavior patterns. In this section, we will explore how these capabilities may facilitate research and public health delivery in areas ranging from encouraging healthy behaviors to monitoring of medical treatments.

2.1 Health behaviors

Despite compelling evidence, most efforts to encourage healthy behavior and medical compliance continue to be focused on conscious decision making, neglecting the social dimension almost entirely. By understanding how to leverage social networks, we may achieve more in terms of behavioral change.

For example, research suggests that some chronic health-related conditions/behaviors are "contagious,"

in the sense that individual-level outcomes are linked to other individuals with whom one shares social connections. Both smoking behavior [16] and obesity [17] seem to spread within social networks. Smoking and obesity likely serve as good models for other health related behaviors, such as diet, exercise, general hygiene, and so on.

These findings, however, beg for an examination of the causal mechanism – an essential step if interventions are to be designed to improve public health. For example, is the diffusion of these behaviors and conditions driven by the emergence of norms within the network – e.g., smoking is cool; one should exercise frequently, etc.? Alternatively, is the diffusion driven directly by the social component of the relevant behaviors – e.g., smoking, eating, or exercising with one's friends? Or might the apparent spread of these behaviors reflect individuals seeking out others with similar inclinations? The type of data needed to understand the causal mechanism is exactly the fine granularity data that reality mining can provide.

Further, once the causal mechanisms are better understood, reality mining might yield specific points of leverage for effective interventions. For example, if certain behaviors are indeed contagious, this would suggest that targeting individuals in key parts of the network could prove useful (although privacy issues are relevant here; see privacy discussion). Taking this a step further, one could imagine using reality mining to evaluate particular public health interventions. Ideally, program evaluations should test not only whether an intervention was effective, but also the theory underlying the intervention. Consider, for example, an intervention based on targeting particular individuals and changing their behaviors. In an attempt to create an avalanche of change, it would be good to know if a given intervention failed because the targeting failed, or because the avalanche failed to materialize despite successful targeting.

2.2 Infectious disease

As the world becomes increasingly interconnected through the movement of people and goods, the potential for global pandemics of infectious disease rises as well. In recent years, outbreaks of SARS and other serious infectious diseases in widely separated but socially linked communities highlight the need for fundamental research on disease transmission and effective prevention and control strategies.

With GPS and related technologies, it is increasingly easy to track the movements of people [18, 11]. Logs of location tracking data from cell phones could prove invaluable to public health officials when investigating cases of serious infectious disease (e.g., tuberculosis, SARS, anthrax, measles, Legionnaires' disease, etc.) to help identify the source of infections and prevent further transmission. People often forget all the locations they have visited, even for recent periods, and similarly might not know many of the people to whom they were exposed or might have exposed themselves, all of which underlines the potential

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value of systematically analyzing such records for disease control.

2.3 Mental health

Even though they are treatable, mental diseases rank among the top health problems worldwide in terms of cost to society. Major depression, for example, is the leading cause of disability in established market economies [19]. Reality mining technology might assist in the early detection of psychiatric disorders such as depression, attention deficit hyperactivity disorder (ADHD), bipolar disorder, and agoraphobia.

Many signs and symptoms of these types of psychiatric disorders explicitly or implicitly relate to an individual's physical movement and activity patterns and communicative behavior, usually with reference to particular temporal periods or cycles. Data streams from reality mining allow direct, continuous, and long term assessment of these behavior patterns. Accelerometers in mobile phones might reveal fidgeting, pacing, abrupt or frenetic motions, and other small physical movements. Location tracking functions reveal individuals' spatial and geographic ranges, variation in locations visited, and the overall extent of physical mobility. The frequency and pattern of individuals' communications with others and the content and manner of speech might also reflect key signs of several psychiatric disorders.

For a more specific example of the potential power of reality mining technology in aiding diagnosis, consider the data presented in Figure 4. Researchers have long known that speech activity can be affected in pathological states such as depression or mania. Thus, they have used audio features such as fundamental frequency, amplitude modulation, formant structure, and power distribution to distinguish between the speech of normal, depressed, and schizophrenic subjects [2,4]. Similarly, movement velocity, range, and frequency have been shown to correlate with depressed mood [8]. Today, common cell phones have the computational power needed to monitor these sensitive indicators of psychological state, offering the possibility of early detection of mental problems.

Figure 4: (a) Voice analysis to extract activity, influence, mimicry, and consistency measures. (b) As estimates of depression level, there is a correlation of r=0.79 between these telephone-based measures and the Hamilton Depression Index.

2.4 Treatment monitoring

Once a course of treatment (whether behavioral, pharmaceutical, or otherwise) has been chosen, it is important for a clinician to monitor the patient's response to treatment. The same types of reality mining data used for diagnosis would also be relevant for monitoring patient response to treatment, especially when such data on the patient are available for a period before diagnosis and can serve as a baseline for comparison. Changes in mobility,

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activity, and communicative behavior could be collected in real-time, allowing clinicians to adjust treatment according to the patient's response, perhaps leading to more effective treatment and preventing more costly medical visits.

Self-report data can also be collected to complement the unobtrusive, automatically-generated and –collected reality mining data streams. In many cases, the outcomes of interest in medicine and public health (e.g., some kinds of symptoms) can only be measured through self-report. By gathering self-reported data in tandem with other reality mining data streams, memory errors can be reduced and dynamic aspects of health phenomena more fully revealed.

As a more specific example, consider the medication needs of Parkinson's patients. To function at their best, Parkinson's patients' medications must be optimally adjusted to the diurnal variation of symptoms. For this to occur, the managing clinician must have an accurate picture of how each patient's combined lack of normal movement (hypokinesia) and disruptive movements (dyskinesia) fluctuates throughout the day.

To achieve this, we combined movement data from wearable accelerometers with standard statistical algorithms to classify the movement states of Parkinson's patients and provide a timeline of how those movements fluctuate.

Two pilot studies were performed, consisting of seven patients, with the goal of assessing the ability to classify hypokinesia, dyskinesia, and bradykinesia (slow movement) based on accelerometer data, clinical observation, and videotaping. Using the patient's diary as the gold standard, the result was high accurate identification of bradykinesia and hypokinesia. In addition, the studies classified the two most important problems – predicting when the patient "feels off" or is about to experience troublesome dyskinesia – perfectly [9]. This type of fine-grained information, key to monitoring patients' treatment, is a strong endorsement of the value of reality mining techniques.

3. Reality mining and the new deal on data

Reality mining of behavior data is just beginning. In the near future it may be common for smart phones to continuously monitor a person's motor activity, social interactions, sleep patterns, and other health indicators. The system's software can use these data to build a personalized profile of an individual's physical performance and nervous system activation throughout the entire day. If these rich data streams were combined with self-reports and personal health records, including medical tests and taken and the medicines prescribed, there is the possibility of dramatic improvements in health care.

Creating such an information architecture, however, requires safeguards to maintain individual privacy. One approach to this problem is to place control and ownership of as much personal information as possible in the hands of the individual user, a proposal that is central to most proposals for creating personal medical records.

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We suggest that a similar approach, a 'new deal' for privacy and data ownership, be taken for data collected using reality mining: individuals own their own data. The simplest approach to defining what it means to 'own your own data' is to go back to Old English Common Law for the three basic tenets of ownership: the rights of possession, use, and disposal.

1. You have a right to possess your data. Companies should adopt the role of a Swiss bank account for your data, enabling you to check your data out whenever you'd like.

2. You, the data owner, must have full control over the use of your data. If you're not happy with the way your data are being used, you can remove them.

3. You have a right to dispose or distribute your data. If you want to destroy them or remove them and redeploy them elsewhere, it's your decision.

Social network mapping and the resulting subpopulation information inherently involves other people. As a consequence, some of the thorniest challenges posed by reality mining's ability to sense of the pulse of humanity concern data access and sharing. There are enormous risks to both individuals and corporations in the sharing of data about individuals. Robust models of collaboration and data sharing, between government, industry, and the academy need to be developed; guarding both the privacy of consumers as well as corporations' legitimate competitive interests are vital here.

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Clearly, our notions of privacy and ownership of data need to evolve in order to adapt to these new challenges.

4. Summary

Reality mining, although still in its infancy, is poised to quickly become more common, due in large part to the rapid proliferation and increasing sophistication of mobile phones. Many mobile phones and other technologies already collect a great deal of information about their users – data such as physical activity and conversational cadences – and this will only increase. Computational models based on such data could dramatically transform many areas of human life. Here, we have focused on improvements that could be realized in individual and community health. Reality mining can provide new opportunities with respect to

diagnosis, patient and treatment monitoring, health services planning, surveillance of disease and risk factors, and public health investigation and disease control, and doubtless others, yet unexplored.

In many respects, one of the most important applications of reality mining may be the automatic mapping of social networks. Reality mining's capability for automatic social network mapping is now being used in a variety of research applications and has clear implications for work in infectious disease, health behaviors, mental health, and treatment monitoring. While such data pose a potential threat to individual privacy, they also offer great potential value both to individuals and communities. Current legal statutes are lagging far behind our data collection capabilities, making it particularly important to begin discussing how this technology will and should be used.

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Renata G. Bushko, 45+ Big Questions at 20th Future of Health Technology Summit in "World Health Strategy", Renata G. Bushko (Ed.) eBook FHTI 2016. www.FutureofHealth.org

Chapter 12: 45+ Big Questions of the 20th FHTI Summit

Renata G. Bushko, bushko@fhti.org
Founder, Future of Health Technology Institute, Happier Longer Lives ® and Chair, 2016 FHTI Summit @futureofhealth #FHTI

20th FHTI Summit resulted in the World Health Strategy eBook (Ed.) Renata G. Bushko www.futureofhealth.org. Both chapters and video-lectures from the eBook provide an excellent roadmap to plan the future of healthcare globally by answering Big Questions listed below 50+ Luminaries Asking and Answering Most Pressing Questions of our Times: **The best way to progress with health investments to assure best outcomes for humanity. 2016 BIG Questions selected by FHTI are:**

1. How can we honor and build upon Marvin Minsky's work? *Aubrey de Grey, Joshua Feast, Glenn Fields, Renata Bushko, Mike McDonald*

2. What should the new world health strategy be? What fundamental changes and dramatic shifts do we need to prepare for? *Renata Bushko*

3. How do we treat patients like valued customers? *Sanjay Sarma*

4. Can terabytes of new data deepen our knowledge of the state of health care in the Commonwealth of Massachusetts? *Sylvia Hobbs*

5. What are novel strategies for enhanced predictive modelling and deep learning in the biosciences? *Tom Chittenden*

6. How will health care look like in 20 years? *Renata Bushko, Xing Jijun, Joseph Kvedar, Guergana Savova,*

7. How can Big Data help you in work and life? Alex (Sandy) Pentland

8. How to cure almost everything in brain disorder with light? *Newton Howard*

9. Can Chinese herb-based medicine heal the immune system and cure allergies? *Xiu-Min Li*

10. Can we forecast changes in mood and mental health, like we forecast a storm? *Rosalind Picard*

11. What is the healing story of Dr. Xiu-Min Li? *Barbara Winston*

12. How should we remember Marvin Minsky? *Ray Kurzweil*

13. How can we chart the future for digital health information systems? *Gary Kreps*

14. What are seven secrets to staying young? *Aubrey de Grey*

15. What is the future of pain management? *Darin Correll*

16. What is the future of computation? *Stephen Wolfram*

17. Why Minsky's ideas are important for medicine? *Henry Lieberman*

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18. How can we reduce opioid misuse among chronic pain patients and what is the role of risk assessment and innovative technology? *Robert Jamison*
19. Will healthcare be delivered by George Jetson in the future? *Nick van Terheyden*
20. What are new innovative offerings to the consumer in the cancer treatment area? *Lorraine J. Gudas*
21. Are exoskeletons a solution to physical disparity? *Ernesto Rodríguez Leal*
22. What would best catalyze 100% renewable energy distributed collectively through intelligent grids globally? *Michael McDonald*
23. How can we harness healing power from plants? *Jing-Ke Weng*
24. How should we communicate to the public about health technology? *Shelagh Maloney*
25. Is hospital a place? *Robert Teague*
26. What is the future of international cooperation in health research, development and commercialization? *Renata Bushko*
27. Can art inspire? *Wally Gilbert*
28. What is the best way to communicate ideas through graphic design and media arts?*Christoper MacDonald, Jehan Said, Lauren Callahan, Dianna Cox, Tania Saade, Marisa Campbell, Andrew R Emery, Charles Searle*
29. What is the future of eHealth? *Claudia Pagliari*
30. How can we build trustworthy, secure and transparent health-apps? *Urs-Vit Albrecht*
31. How will health care look like in 20 years? *Renata Bushko, Guergana Savova, Joseph Kvedar*
32. What are the new possible ways to fund basic bio-medical research? *Renata Bushko*
33. How can we accelerate formation and success of biotechnology startups? *Eric Elenko, Albert Di Rienzo, Tanveer Patel, Adam Greenspan*
34. How can Big Data make a big difference in the end-of-life care? *Dan Hogan*
35. Does your smartphone know more about your mental health than your doctor? *Skyler Place*
36. Is violin music healing? *Yuan Mei Xing*
37. What is the road from Artificial Intelligence to Intelligent Health? *Renata Bushko*
38. Can we repair a broken brain with movement therapy approach? *Hermao Igo Krebs*
39. How can Google Glass remotely integrate with microfluidic biosensors and actuators? *Yu Shrike Zhang*
40. What's next in the application of nanotechnology-based molecular delivery Systems? *Guillermo Ulises Ruiz Esparza*

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41. Can you imagine cities that feel, understand, and take care of your wellbeing? *Agnis Stibe*
42. How Can 3-D printing help with epithelial wound healing? *Louis Alonso-Pastor*
43. Can Arctigenin reduce inflammation giving hope to treat igE related inflammatory diseases? *Renna Bushko*
44. What is the future of depression prediction based on self-report diary via smartphone applications? *Yoshihiko Suhara*
45. How can we reduce the economic burden of Type 2 Diabetes management through smartphone technology and Big Data? *Todd Reid, Ian Pentland*
46. How can network science be applied for an expanded understanding of large online network information structures and behaviors to modernize public health communication strategies for improved health outcomes? *Brittany Seymour*
47. How can we implement personalized positive psychology interventions in the form of interactive journaling? *Sooyeon Jeong*
48. How will fashion industry change healthcare? How will high-tech fashion and wearable technology market impact consumers' health? Will garment be a new health app development platform? *Renata Bushko*
49. What is the future of brain's health? Is prevention of neural inflammation with Traditional Chinese Herbal Medicine possible? *Renna Bushko, Changda Liu, Beth Powell, Xiu-Min Li*

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Renata G. Bushko / Technology Map in World Health Strategy" eBook, www.Futureofhealth.org (Ed.) Renata G. Bushko, FHTI, 2016. In Future of Health Technology, Ed. R. Bushko, IOS Press 2002, Chapter 1: Defining Future of Health Technology – Biomechatronics - Renata G. Bushko

Chapter 13: Emerging technology areas that will have a profound impact on the entire economy including healthcare sector. *Order does not reflect importance.*

I	**Human-Machine Interaction - Requesting Things from Machines**
	Hybrid Brain-Machine Interfaces (HBMI) – Thought to Computer Communication
	Natural Language Processing
	Automatic Voice Recognition
	Mobile, wireless, wearable, and textile computing
	Computer Implants (connected to tagged smart environment)
	Haptics
II	**Machine Intelligence**
	Processing Requests
	Data Mining
	Common Sense Reasoning
	Reasoning by Analogy
	Flexible Transistors (e.g. on plastic)
	Responding to Requests
	Organic Light Emitting Displays (data glasses, e-paper, smart windows)
	Speech Generation
	Affective Computing (emotional communication)
	Visualization of Data
	Automatic Summarization /Abstracting
	Triggering Action
	Decision Triggers
	Biomechatronic Interfaces (to cells and biomechanical devices)
	Electronic Skin (e.g. triggering payment transaction on the way out of supermarket with no cashiers)
III	**Preservation of Individuality and Security**
	Digital Rights Management
	Biometrics (Face, Voice, DNA, finger print, behavioral pattern recognition)
	Biometronics Ethics and Law
IV	**Human-Machine Global Network**
	Microphotonics (all optical Internet with super high bandwidth)
	High-temperature Superconductivity (inexpensive power quality devices SMES^{0})

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	Infinite High-density Data Storage
	Restructuring Code (Software Engineering)
V	**Intelligent Machines**
	Mobile Mechanical Machines
	Nanorobots (Microfluidics)
	Humanoids (Cyborgs)
	Machine Vision – Vision Genome
	Machine Learning
	Deep Learning
VI	**Sources of Energy**
	Body-heat Batteries
	Chemical Molecular Energy (e.g. ATP)
	Earth tides (Geothermal Energy)
	Solar Energy
	Superconductive Generators

[1] Superconducting Magnetic Energy Storage

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Chapter 14: Unsolved Health Problems

Healthons: Errorless Healthcare with Bionic Hugs [...]
in Future of Intelligent and Extelligent Environment, IOS Press 2005

Renata G. Bushko
Director, Future of Health Technology Institute, Bushko@fhti.org

By analogy to mathematics where there is always a list of unsolved problems to guide the young generation of mathematicians, Future of Health Technology Institute conducted an "unsolved health problems" survey in 2003-5. The results are listed in the table below. Solving these problems will get us closer to happier, longer lives for all.

Table 1. Unsolved Health Problems – Based on FHTI's Unsolved Problems Survey 2003-5

Unsolved Problem	What will we gain if we solve this problem?	What will we lose if we do not solve this problem?
Lack of clean water in much of developing world.	Reduced (especially child) mortality rates.	Lives
Lack of drugs resulting from human genome.	Cures for previously untreatable, fatal illnesses.	Funding for genetic research
Really effective interfaces with human users.	Efficiency	Usability
Significant (in magnitude) replacement of human professionals by machines.	Enormous increase in efficacy/ productivity and better "results"/ outcomes.	Status quo
Translation from the Laboratory to the Bedside: many innovations seem to never to get past the "proof of concept demo" phase.	We may see more of these projects make a difference in clinical treatment.	We will waste a lot of our intellectual capital on projects that don't make it to the bedside.

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Unsolved Problem	What will we gain if we solve this problem?	What will we lose if we do not solve this problem?
Lack of tools to build causal models that integrate all pieces of medical and process information; information systems that can help us to integrate all information into causal models, test the models against available information, and help us do thought experiments to devise new hypothesis to test.	If we are able to overcome the problems of how to build, interpret and validate what will often be massively underspecified models of physiological systems, then we will be able to accelerate the process of discovery.	We will continue to build an increasingly fragmented knowledge base and many important discoveries will not get translated into useful understanding.
Independent nanorobots with smart software controls.	Stop disease before it develops.	Lives.
Anticipating human and system failures so that processes can be devised to prevent these failures.	We will be better able to optimize the care we can give with the clinical advances we have in hand.	Medical errors will continue to limit our ability to give the best care possible with the current clinical knowledge.
Structured capture of clinical data (history, physical examination, progress notes, procedure reports, discharge summaries.	Increased formal encoding of phenotype information to enable research, clinical care, decision support, etc.	We will continue the present process of having this information unavailable. Some could be captured through natural language processing techniques, but structured data capture also encourages more discipline and thoroughness in recording, and provides more opportunity for timely decision support.
Personal longitudinal integrated health record.	This will foster improved continuity of care, access to relevant information to care providers, better decision making, decreased errors (e.g., overlooking an allergy or ordering of a medication conflicting with another), and the ability to track a patient's care over time, issue reminders, recommendations for improved health, etc.	We will continue the present process of fragmented, incomplete, inefficient management of episodes of care without ever having a complete picture of the health status of a patient.
Comprehensive structured population health data bases.	This will provide the ability to do analyses of screening tests, genome-phenotype correlation, outcomes analyses, technology assessments, and clinical prediction/prognosis.	Continued current state of limited comparability and size of datasets.

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Unsolved Problem	What will we gain if we solve this problem?	What will we lose if we do not solve this problem?
Application of cutting edge technologies for Primary Prevention i.e. implanted calorie counter/blood sugar monitor with beeper or such for weight loss, nicotine or drug aversion implants etc to give ongoing feedback and stimulus for behavior change. The simple low cost pedometer is a good example, but perhaps taken to a higher level or personalized monitoring.	Decrease in incidence of chronic illness and money spend for chronic illness, care and improved quality of life.	Individual quality of life and economic stability in health care costs as current population ages with chronic illnesses due to behavior factors.
Cost benefit ratio analysis of health technologies.	Truly beneficial and cost effective health technology applications.	Increasing personal and 3rd party costs for marginal efficacy - "technology for technology sake".
Inadequate distribution of current technologies, based on geography, income etc.	Equity in world health.	Continued Inequitable distribution which may eventually be the death of us all i.e. SARS AIDS etc. spreading world wide without available monitoring and prevention measure
Lack of coordination. This problem crosses all applications of technology, whether business, aerospace, or medical. In medicine, the cost of mistakes is already too high.	A specific example of positive coordination among medical systems includes the sharing of patient information among pharmaceutical and patient records so that errors in prescriptions, both in hospital and out of hospital are reduced, if not eliminated. But also that same mechanism of sharing, can provide a uniform source of information across many platforms, many software systems, so that validation and cross checking among the different systems may be simplified and when errors are detected, more easily tracked.	If we do not attack the problem of coordination, we risk additional sources of error, loss of our ability to track errors, and loss of time, not to mention increases in medical error and possible law suits.

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Unsolved Problem	What will we gain if we solve this problem?	What will we lose if we do not solve this problem?
Lack of recognition that not all medical problems can be solved with "more technology"... sometimes, "LO TECH", is a more cost effective and patient friendly. E.g., providing access to meditation classes can reduce the cost of medication for chronic medical conditions such as high blood pressure and pain management.	Reduce patient load, empower patients, create first steps in the cultural shift to one where patients begin to take an ACTIVE rather than PASSIVE role in their own health.	Continuing on the path we are on is no longer an option. Health insurance costs are not going down. Not only are Americans uninsured they are also underinsured.
Effective use of media such as TV and the internet to raise awareness and engage the average consumer into healthcare. Make being healthy "trendy"; make it "attractive". This requires administrators to make this a line item in the budgets, a non-technical issue, but implementation is technical.	It will take time to help consumers reach for self care in their medicine cabinets rather than pills, but eventually we can hope to see an improvement in the overall health of human race reducing the costs of chronic conditions and the incidence of health problems.	We will continue to see the deterioration of health status. The cost of insurance, and the cost of Hi-tech healthcare need to be offset by low tech, such as dietary habits, practice of meditation, and so on.
Regenerative Medicine: ability to apply stem cells to address regenerative medicine.	Find cures for millions that suffer and sometimes die prematurely from degenerative illnesses.	Billions of dollars spent on unpromising therapy as well as incalculable human misery.
Background noise in biological agent detection system.	Ability to rapidly detect pathogens to isolate populations from further exposure.	Millions of lives lost to infectious disease epidemics that may be able to be curbed with early detection.
Growing new Telomeres from stem cells.	Potentially slow down the aging process.	Immortality
100% Electronic infrastructure for medical records.	Greater portability of data, greater collation of data for research, longitudinal tracking of health information, and potential reduction in medical errors.	Privacy lapses, consumer apprehension.
Wide-spread mobile computing in medical care.	Instant access to reference and clinical information, greater evidence-based healthcare.	Fragmentation of technological application in well-funded vs. poorly-funded settings; physician resistance and lack of acceptance of new computing technology.

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Unsolved Problem	What will we gain if we solve this problem?	What will we lose if we do not solve this problem?
Personal understanding of preventative health lifestyles.	Lower heath costs and better quality of life.	Lost market pressure for improved health care costs with monies being extracted for drugs and procedures no care and health.
Adequate pricing of health care	Reduction of serious ethical problems in health care pricing.	220,000 unnecessary inpatients deaths and millions of outpatient deaths and disabilities. About $500 Billion in unnecessary healthcare costs.
Inpatient medical error as the third leading cause of death. Medication error is the largest subcomponent and by itself is the fourth leading cause of death. 60% of medication error is caused by physician ordering and 30% is caused by nurse administration.	Eliminate of a substantial portion of 220,000 unnecessary inpatient deaths per year and millions of persons maimed or incapacitated in some way. Elimination of a portion of about 1M unnecessary outpatient deaths. Elimination of about half of patient visits and hospitalization by proper disease management.	See Above
Outpatient medical error (even higher than inpatient error, perhaps by an order of magnitude)	Human Lives	See Above
Disease management errors - the iceberg of which medical error is the visible tip. E.g., many unnecessary amputations on diabetics performed every year in the U.S., caused by improper follow-up.	Human Lives	Slow progress
Bringing the bio-med hypothesis builders and the tech developers closer (educational challenge).	Fast progress and better penetration of innovations into practice.	Lack of individualized biochemistry understanding and treatment.

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Unsolved Problem	What will we gain if we solve this problem?	What will we lose if we do not solve this problem?
A reliable protein/proteomics database for NORMAL human serum. (Surprisingly, from the many decades doctors have looked for signs of disease in the blood, the normal constituents--proteins-in blood are very poorly known, both qualitatively and quantitatively. Before we can exploit nanotech & high throughput methods, we really must get a handle on what the range of normal proteins is in peripheral blood).	Human Lives – Reduction in unnecessary anxiety about "symptoms" that are part of normal variation not a sign of disease.	Wasted human effort.
Expediting tech transfer from lab to clinic (administrative, governmental challenge).	Reduction in suffering.	We will fail to give people longer healthy life spans and reverse aging in order to reverse aging comprehensively enough to keep people alive and healthy for a few decades more than now, which will be enough to let us improve the therapies further and keep us alive indefinitely.
Finding the genetic basis of the telomerase-independent telomere extension seen in about 10% of human cancers.	We'll be able to control telomerase-independent cancers (including half of all sarcomas, for example) by gene therapy in the same way that we will be able to control telomerase-dependent cancers by gene therapy against the telomerase genes.	We will fail to give people longer healthy life spans. See Above
Making the 13 protein-coding mitochondrial genes work when placed in the nucleus.	We'll be able to ignore the accumulation of mitochondrial mutations during aging, because they will be harmless -- the proteins that are made from the mitochondrial DNA will be made from nuclear copies of the genes so the mitochondria will still work.	We will fail to give people longer healthy life spans. See Above.

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Unsolved Problem	What will we gain if we solve this problem?	What will we lose if we do not solve this problem?
Finding microbial enzymes to break down the cholesterol analogues that cause atherosclerosis and maybe Alzheimer's disease.	We'll be able to treat all major diseases that are caused by the accumulation of garbage inside cells. That includes atherosclerosis, macular degeneration and probably most types of neurodegeneration.	We will fail to give people longer healthy life spans. See Above.
Lack of machines with common sense that could take care of us	Well cared for population. Increased health status of the population.	Worldwide healthcare crisis due to lack of care givers. Unnecessary suffering.
Lack of comprehensive working easy to use framework for performance evaluation of adaptive complex systems.	Faster progress towards errorless healthcare.	Slow progress towards errorless healthcare.
Maintaining long-term engagement between users and health dialog systems (caring machines), especially crucial for chronic disease management systems in which we need people to use the system regularly for the rest of their lives.	Increased speed of acceptance of caring machines.	No good communication between people and caring machines.
Encoding of behavioral medicine concepts and theories into shareable computational ontologies, to support information sharing and re-use.	Exponential growth of the use and utilization of the caring machines.	Limited use of caring machines.

Conclusions

Utilizing Intelligent Caring Creatures (ICCs) to achieve errorless healthcare requires departure from thinking that the only entity that can justify a medical action is an un-aided human being. Once we are ready to delegate management of our health to ICCs we need to make sure that they are able and willing to explain their multidimensional reasoning. Compiling a list of “unsolved problems” helps moving towards errorless healthcare. It would be useful to have awards system for solving currently unsolved healthcare problems to make healthcare errorless, invisible, infrastructure-free and continuous sooner.

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Alice P. Pentland, Alex P. Pentland / Inventing the Future- Tools for Self-Health in "World Health Strategy" eBook, (Ed.) Renata.G. Bushko FHTI, 2016. Futureofhealth.org, From Future of Health Technology (Ed.) Renata G. Bushko, IOS Press 2002

Chapter 15: Inventing the Future – Tools for Self Health

Alice P. Pentland M.D.
Co-Director, Center for Future Health and Professor and Chair, Department of Dermatology, School of Medicine and Dentistry, University of Rochester, NY, US
Alex P. Pentland Ph.D.
Academic Head, MIT Media Laboratory, Cambridge, MA, US

Throughout the history of medicine, technology has produced radical changes in our understanding of human disease, the therapies that we use to treat it, and how we provide care. A useful example of the potential for technology to transform our approach to health and disease is the invention of the microscope. Prior to its invention, we had little understanding of the existence of microorganisms or the cellular structure of the human body. However, once this tool became available, the groundwork was laid so that it was possible to propose the germ theory of disease. We could also understand the cellular structure underlying human anatomy, and so begin to understand the fine processes of organ function. Medicine was revolutionized as a result.

Currently, we are in the midst of a new technology revolution, illustrated by the many chapters included in this book. The effects produced by this newest wave of technology have already begun to change medicine, and are likely to alter our health care system in the next century as much as it was transformed during the last one. The impact is likely to reshape the processes and tools through which we interact with health professionals, and ultimately how we think about caring for ourselves.

It is very important to visualize how future health technology can affect us, as the editor, Renata Bushko, and contributors to this book have done. For the full potential of new health technologies to be realized, we must collectively try to rationalize and discuss the best ways to capture the opportunities technology provides to serve our needs in health, in disease, as individuals and as a community. This task may prove difficult since our individual needs can be in conflict with those of our communities, necessitating careful implementation of public policy to balance them. Because of the complexity of the issues influencing these decisions, the positive as well as negative effects of technical advances on the state of medicine over the last century are therefore worth examining. We must also consider and test different technology evaluation methodologies, as well as methodologies estimating technology impact as discussed in chapters by Gary Kreps and Renata Bushko. These may help us to understand what goals we may want to set and how we may achieve them in the next hundred years.

Since 1900, the introduction of new technology has had a profound impact on the field of medicine. An example of this is the creation of the Pediatric Intensive Care Unit. Who would believe at the turn of the last century, that a child born at 26 weeks gestation would have a chance at a normal healthy life? We see this with some

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regularity today. Large machines, ventilators, constant monitoring of heart rate, respiration, pulse, and temperature along with the ability to give tiny increments of fluid in proportion to a tiny infant's size permit us to maintain these fragile beings. Now they can be supported until they are able to prosper in the world outside of the womb and live a long life.

Similarly, we have also seen our understanding of human cellular function permit us to design highly specific new drugs. Our understanding of intracellular mediators and cell receptors have allowed the creation of new "designer" pharmaceuticals. These chemicals can block cellular regulatory pathways, stimulating them to delicately tickle the balance of our blood flow, heart function or kidney excretion and battle such killers as diabetes, and heart disease at their root. The result of all of this success has been a wonderful and dramatic increase in the length of the human life span. People born in the United States can now count on an average life span into the late 70's and the number of centenarians is rising dramatically [1]. This is an increase in average life expectancy of nearly 30 years! These benefits have come at a cost, however. Many people recall great satisfaction with the human aspects of health care delivery in the middle decades of the century. For the most part, the doctor came to visit the sick at their bedside in their own home. People were born at home and died at home. The cycle of human life was part of the cycle of family life in an integral and community centered way. This integration of health care into the daily activities of the family can have a strengthening effect on families and communities that the modern hospital and clinic-based model does not provide.

However, it has not been possible to provide the advanced medical care that we have invented in a home setting. To treat prematurity, the baby currently must live in an isolette, and perhaps also be on a ventilator for weeks on end. This equipment is very expensive, and its proper use requires a great deal of training. Because of the complex knowledge and expense required to take proper care of such infants, it is currently necessary to centralize where such care is provided. The highly specialized physicians, nurses and other caretakers needed to care for the infant must be available near the equipment that contains their tiny patient. There must also be a library, so that these health professionals can take full advantage of the body of knowledge needed to keep these delicate infants alive. Centralization also allows the equipment to be regularly used, lessening its cost. A medical center environment also supports the large complex of machines needed to perform the array of tests that are necessary in order to monitor changes in the infant's health status. So the technology that created the opportunity to keep the premature infant (or the auto accident victim) alive has enlarged the complexity, expense and centralization of health care. In the process, we find ourselves feeling disconnected from our doctors, and perhaps more importantly, our sick relatives. Health care is too expensive,

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too tightly focused on care of disease and too separate from our daily lives. Ideally, the changes that are coming should work to reverse this trend without diminishing the benefits to our health we have already achieved through technical innovation.

Until recently, there has been very little success in attempting to extend health care into the home environment, yet there clearly is a huge demand for this. Americans currently spend 27 billion dollars on health care outside of the health care establishment [2] because they find it so difficult to access, expensive, and painful. A clear demand for better integration of the home into the health environment exists. No only that, but a dramatic shift in the composition of our population makes it absolutely necessary to develop such distributed systems.

In the year 1970, there were 25 caregivers for each disabled person [3]. However, the success of our health care system is such that the ratio of caregivers for the at-home disabled is going to be 6:1in the year 2030. How will those six people care for that seventh disabled person? Certainly we cannot have a centralized system of visiting nurses that travel to their homes to take care of them because we will not have enough individuals left working in the economy to support it. Thus, a more highly distributed system is not only something that we desire but it is an absolutely necessary change that must take place. Some efforts to alleviate the problem have been introduced with the advent of telemedicine as discussed in the chapter by Meg Wilson. Visiting nurses have recently begun to make house calls via telemedicine connections. In addition, a small industry is springing up around monitoring of key parameters in those with chronic illnesses such as emphysema, diabetes and congestive heart failure. The Physio Chair by Commwell and Lifeshirt by Vivometrics are examples. These new tools are just beginning to be adopted as reimbursement strategies are created which make them profitable.

In addition to extending the activities of health professionals into the home, optimal health care in the future will require the creation of new tools that extend the capacity of the individual to assess and maintain their own health. The technology required to implement this vision must be user friendly, intuitive, and have the user's trust. The technology will need to help an individual to maintain their normal health profile, allowing detailed information and measurements to be collected so that the earliest signs of disease can be detected. In contrast to the current state of information - measuring one's values against those of entire populations, having knowledge of one's own individual variations should better enable individuals to better determine when they need to seek health care, before they actually feel ill. Armed with his or her own personal information, the individual is also greatly empowered in the doctor's office. The visit can become a discussion between individual and doctor, and more time can be spent discussing the implications of such changes and providing personal support, rather than trying to determine whether or not

changes have occurred.

In the current system, a patient visits the doctor at intervals, and health information/ data is collected through obtrusive or invasive means. For future health technology to be something that individuals at home will use readily, the ongoing collection of personal information must occur in an unobtrusive and cost-effective manner.

What sorts of devices could be created to help an individual stay well? Collectively, they can be thought of as a "personal medical advisor", which could also be adapted to function in remote areas of the world as a local clinic. Where the health care system is well developed, they can help keep the aging population functional longer, guide parents more successfully through the difficulties of childrearing, and help those with chronic diseases function at their best. Some of the possibilities fulfilling this vision being explored currently are:

- "Memory Assistance" glasses in which the glass contains an extremely small and lightweight computer monitor readable by the wearer, and cameras which can interact with a tiny wearable computer to help an elderly person maintain their independence and social circle. As an example, this device could identify a person whose name has been forgotten or offer reminders regarding such tasks as taking medication or paying bills.

- Sensate Liner Garments such as shorts or socks for people who have lost sensation in their skin due to diabetes or neurologic injury, to monitor skin integrity and "warn" the wearer that their skin is developing a pressure sore.

- The "Smart Bandage" to measure the bacteria or virus in an injury and let the user know whether antibiotic treatment is needed and which antibiotic to use. Such a device can be easily adapted to monitoring food or water supplies, or identifying allergens in the environment.

- The "Smart Bed" to monitor a person's weight, temperature, electrocardiogram, or even electroencephalogram to identify sleep disorders, early stages of depression, and generally act as a central health data repository in the home.

- "Skin Surface Mapping" imaging devices that collect images of an individual's skin surface, then notes any change over time. This could allow very early detection of skin cancer such as melanoma, greatly increasing survival.

We will see many more such helpful innovations over the next several decades, as we understand better when individuals can effectively act to help themselves, and when assistance from a health professional is needed.

In this volume, there are contributions from an array of experts describing in detail how their particular expertise can reshape aspects of the way we approach

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health care in the future. To make effective changes, these technical advances must be integrated with new institutional strategies for health care delivery that address the needs of individuals for privacy, but still provide the benefit to communities of shared information resources. Public policy discussions must bring balance to these sometimes contradictory needs and points of view. These discussions are already underway with the new Health Insurance Portability and Accountability Act (HIPAA) legislation [4,5], but more work is needed.

The work presented here is therefore offered in the spirit of advancing this thoughtful debate. We hope that these discussions will not only unlock the tremendous opportunities that new health technology presents for treatment of acute illness and injury, but will also emphasize the potential of the advances being made to remedy the problems caused by the last wave of technical advancement and make preventive health care a reality.

The general areas in which new technology will be integrated to advance health care are information infrastructure, health technology interfaces, advances in the understanding and treatment of disease, and tools for understanding and assisting behavior change. The area of disease understanding and treatment is huge, and the complexity has been greatly expanded by the recent complete sequencing of the human genome [6,7].

One promising aspect of having sequenced the human genome will be the opportunity to understand the impact of one's genetic makeup to prevent episodes of disease. Inexpensive nanoscale sensor technology may allow us to prevent health problems in ways that were previously impossible, as envisioned by Barry Robson. Inexpensive rapid tests that determine an individual's susceptibility to disease or predict the likely side effects of medication may spring from such nanoscale creations. Genetic information combined with inexpensive sensors may allow a person to test themselves at home to ask questions such as "Do I have the susceptibility gene for penicillin allergy?" or "what pollen is triggering my runny nose today?" and help them make decisions about being exposed to drugs before they become allergic, or selectively avoid triggers for allergy in ways that were not possible without these tools. In the case of seasonal allergy, such tools could be used by consumers without the need for a medical consultation – only knowledge and antihistamines (already available over the counter) are needed for the average sufferer. Much new information about the causes of drug allergy and the markers of it must be collected before such a test is possible, but with microsensor arrays and knowledge of the human genome, the ability is in our hands for the first time.

Similarly, such nanoscale sensors can have a huge impact on traditional hospital-based medicine, where they be used to improve the rapid diagnostic tests available in clinical laboratories to increase speed and sensitivity while reducing cost. Nanorobots as surgical assistants will

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make possible selective surgery with greatly reduced risk and higher success rates. These new approaches will have the same pervasive impact that microsurgery has had over the past two decades. As nanotechnology is advanced, we can take the opportunity to change the large machines we currently employ to make them radically smaller. Devices such as those envisioned by Robert Freitas utilizing nanofabrication and constructed on a molecular scale, can potentially be made cheaply enough that they can be more widely available. Ideally, such sensors could be cheap enough to be placed in the home, for self-assessment and health maintenance purposes. This change will make it so the afflicted would only need to travel to hospitals and clinics when catastrophic illness strikes, or the desire for the support and sympathy that can be provided by interaction with a health professional is needed. Such nanoscale technology could also be used for creation of implantable devices to supplement inadequate organ function – for instance, it could be utilized to assist in the creation of an artificial pancreas for those with diabetes. We have already seen the earliest form of such a device with the creation of the personal insulin pump[8]. As the scale of the technology needed to support the acutely ill becomes smaller, perhaps the hospital will seem a less threatening place in which to be ill.

The information delivery requirements of the existing centralized architecture will need to change radically as we are better able to move and store information, as discussed by Blackford Middleton, Richard Spivack and others included here. Implementing and making interactive the currently available tools is already a formidable task, and one that is consuming large amounts of effort in health care systems and numerous corporations. Clear advantages in the quality of health care and cost of providing care are evident when the new infrastructure is successfully implemented as shown in the chapter by Mary Jo Deering.

Because of the complexity of health information, and the many needs that health information serves, organizing the architecture to serve the needs of all likely users is an active and fruitful area of research as discussed in the chapter by Gio Wiederhold. Communications between physicians, their patients and their insurers will all be subject to systemization over the next few years. We must be strong advocates for patient ease of use, access and privacy protection as these technologies unfold.

The ideal system will provide access to doctors and medical personnel when appropriate, and will also serve public health and research needs while privacy protection is adequately maintained. While systems providing health care are strongly motivated to reduce costs by moving information freely, this may not be in the best interest of the patient. HIPAA rules now under discussion address this set of issues, but clearly cannot deal with all eventualities. Giving patients better access to their own record may help apply pressure

to health systems to create systems that serve patients well. Some health systems are already exploring the role of the patient's personal medical record, and assessing how it should be integrated with the records kept by hospital systems. Soon we will be able to use internet applications for routine interactions with the doctor, nurse or pharmacist.

Intelligent agent software and decision support tools will be crucial to this process, as discussed here for use in health care by Henry Lieberman and Robert Greenes. In a distributed system that is personalized, updates of new knowledge to individual users will be crucial to keeping care optimal, and new strategies are likely to be needed regularly as the complexity of the information we require to keep us healthy increases. Information will be pushed to us (hopefully with our permission) about therapies that may be helpful to us. More important will be the direct delivery of warnings as side effects become known – such as the cardiac risk of taking Fen-Phen[9], or notification that flu has broken out in your neighborhood. Intelligent agents will also be available to help us as we ask questions about our health, identifying information sources that are most useful to our health.

Intelligent agents will also be helpful in guiding individuals choices about their medical care. People will be able to look to see whether or not the health care system they are working with provides quality services. Hospitals and physicians will have a report card given regularly - whether they cooperate with the process by which such report cards are generated or not! People will be able to know more about the quality of care that is being provided in their doctor's offices and in their communities. This will actually push doctors to provide better care and improve everyone's health.

Better organization of the information infrastructure in medicine, and use of intelligent agents gives us the opportunity to consider a more distributed health care system without losing the quality we currently have. Those tasks that are less complicated and which people might perform better if they felt they had ownership of them should be put into the home. The new technologies in testing and decision support will permit a redistribution of the kinds of care that occur in a clinic and in a doctor's office. The doctor's office will acquire more of the functions of a laboratory space where tests can be done quickly without having to send the patient off to a central facility at a hospital for testing. Hospitalizations will really be reserved for those times when a person needs to have an intervention such as a surgery and the big tools are absolutely required for health maintenance. Transfer between hospitals will be guided by the type and availability of services needed by the individual, rather than standard policy, maximizing the ability for patients to be treated nearer their homes when they are hospitalized.

The LINCOS project (little intelligent communities) is an experiment in how this kind of redistribution of care using low-cost high, tech interfaces impacts the

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health of rural communities in the third world. These "digital town centers" built in recycled shipping containers and powered by generator with a satellite uplink if needed, contain the basic equipment for business access to the web, education and telemedicine. By bundling the health care needs of a community with its education and business needs, LINCOS allows the creation of a relatively inexpensive high tech "town center" which can be placed in very remote settings to give individuals and communities who have been cut off from the mainstream the access they need to take action to improve their quality of life and health. Several containers have been placed in Costa Rica and in the Dominican Republic, and 60 more are planned. New strategies for assessing community needs prior to placement of the containers and new technologies for placement in these stand-alone city centers are underway [10]. The information gained can provide a roadmap for how decision support, sensors, telemedicine and health information architecture need to be constructed to optimize a distributed model of health care.

Despite advances in the medical infrastructure, sensors, disease understanding and treatments, a crucial aspect for success of health technology in the future will be the interface between the technology and the person using it, as explored in the chapters by Graziella Tonfoni and Jo Lernout.. Failed implementations of technology are frequent, and are often due to problems in understanding the complexity of the problem - or lack of understanding of the users needs. Bulky, slow and non-intuitive interfaces hamper the adoption of technology, both by health care consumers, providers and administrators. The new capabilities of natural language based interfaces will make it far more likely that future systems will be easily used, and may help to address the problem of technical literacy as well. Because health is everyone's problem, solutions for providing care must be readily usable by EVERYONE who needs care. Keyboards, monitors, wires and multistep instructions are an insurmountable barrier to many people – even in the current environment communication problems regularly precipitate emergency room visits.

The authors included here are addressing the problem of the interface with technology in a variety of ways. Natural language recognition, to avoid training needed for current voice recognition applications is a key goal for the future. Integrating this with affective computing as discussed by Rosalind Picard, will make the interaction with new health technology be more intuitive, and thus more useable. In the more distant future, thought to computer communication as discussed by Kevin Warwick, may be the method of choice – particularly for the handicapped, who have difficulty with manipulating any interface. Preliminary work combining implants with brain-wave operated controls has been promising [11].

Clearly the future of health technology is a bright one, with many opportunities to enhance the quality of our lives. By working to personalize, distribute, and cheapen state of the art disease care – perhaps we may even succeed at emphasizing prevention and health! Shouldn't health care focus on health, after all?

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S.S. Sarma / How Do We Treat Patients like Valued Customers? in "World Health Strategy" eBook, (Ed.) Renata.G. Bushko FHTI, 2016. Futureofhealth.org

Chapter 16: How Do We Treat Patients Like Valued Customers?

Sanjay S. Sarma
Co-Founder, Prosperata, LLC, Vienna VA, USA

Abstract

The notion of treating patients like valued customers in healthcare involves

• A fundamental transformation of healthcare from episodic, reactive care to a highly advanced system that leverages genetic, psycho-behavioral, social, clinical and environmental data and insights through advanced analysis, predictive algorithmic applications, and artificial intelligence

• That, combined with the support of health system and healthcare payer leadership, organizational and cultural transformations

• Creates a new futuristic system that predicts and prevents disease while providing necessary care
• By empowering patients with engaging experiences that motivate and inspire dynamic collaboration across the healthcare ecosystem

• That dramatically improve individual and societal health outcomes affordably and equitably.

• The responsibility is shared equally between patients and consumers, providers and health insurers, policy makers and technology vendors.

First, providers and payers must collaborate effectively to unify the experience for patients. Providers must share data from EMRs and other relevant applications to inform payers of the health status of their members. Payers must also share data on coverages levels, care approvals, and expected reimbursements, bonuses and penalties.

Second, EMR and other companies that store patient-level data must provide open APIs to facilitate data sharing and collaboration. Appropriate incentive structures and regulations must be in place to make this happen.

Most importantly, patients must take charge by demanding access to the information and resources that will inspire them towards healthy behaviors and wellness.
We are currently at a critical convergence point of forces in healthcare that is driven by rapid advancements in data sciences and technology, massive economic challenges to the system and a combination of individual and societal forces. The time to make this vision a reality is now, and the opportunity has never been greater.

1. Introduction - What does it mean to treat patients like valued customers?

To understand what this all means, first we must break this down into elements and understand: What is a patient? Etymologically speaking, the word "patient" comes from the Latin verb patere "to suffer." In today's system, this definition holds true. The

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patient is merely a conduit for disease or sickness, suffering as health care still remains focused on transactions. Doctors, hospitals, and health systems are paid for treating sickness and symptoms, not for treating patients as individuals or, for that matter, as valued customers.

Then what's a customer? I thought about this for a while and decided to look at a variety of definitions. According to Shakespeare's Othello, a customer was in fact a prostitute. Shakespeare's poetic license is quite obvious here! According to business dictionaries, a customer is an individual who consumes a product or service and has choice over what he buys. This sounds reasonable, but what does it mean to be a valued customer? To understand what it means, let us refer to what the great Mahatma Gandhi said many years ago: "A customer is the most important visitor on our premises. He is not dependent on us. We are dependent on him. He is not an interruption of our work. He is the purpose of it. He is not an outsider of our business. He is part of it. We are not doing him a favour by serving him. He is doing us a favour by giving us the opportunity to do so." This became the source of my inspiration for where healthcare needs to go.

2. What can we learn from other industries?

Many other industries have already figured this out. The financial services, retail, and entertainment industries have made major strides in ensuring that customer experiences are personalized, and each has a system that learns about their customers more and more which helps them to constantly innovate. Financial advisors now serve as a central hub that connect consumers to a variety of insurance, loans, and legal products that are based on the needs and preferences of the clients they serve. Amazon is already famous for its product recommendations, product education, ordering at a single click and many other features that encourage people to use their website and services. It has also taken ownership of the entire delivery process with same-day delivery and drones, displacing the Post Office and UPS as the last step. Disney has evolved its brand well beyond individual customer interactions and started to capture additional areas of the customer journey — they've moved from cartoons to parks to hotels and beyond.

3. What are the current state dynamics?

So why can't health care learn from these other industries? Why is healthcare always the last industry to learn from these experiences? Why haven't the same great minds that have been able to solve the customer experience problem for other industries failed in health care or simply avoided it altogether? The answer is that healthcare is not a traditional market, it is unlike any other industry.

Today, healthcare is triangulated in incentives. For the majority of Americans, over 60%, healthcare is paid for by their employer and they

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rarely feel the cost of healthcare. Those costs are paid as premiums to health insurers. When a patient visits the doctor or hospital, the provider does not view the patient as a customer. Their customer is in fact the health insurer, who determines how much will be paid to the provider based on the claims they submit. Patients are viewed as a third party. Let's assume the patient was paying for each test that a hospital conducted, such as EKGs, labs, and blood tests. Would the provider order the same tests as they do today? That is doubtful, as consumers would be put in an extremely challenging position of making decisions based on personal finances against healthcare quality and safety protocols. Therefore, we rely on the bureaucracy of payers to determine our coverage levels and providers to make our healthcare decisions.

Then who does view the patient as a customer? Since customers pay for health care through premiums, shouldn't health insurers view them as their customers? While this may seem like common sense, health insurers today view employers and H.R. departments as their primary customers. According to Ingrid Lindberg, a noted healthcare customer experience expert, "Health insurance is the only business that requires its customers to get permission to use services they've already paid for. If they get approval for a costly procedure, service, or medication after going through the mother-may-I process, customers then likely have to pay again for their share of the cost of this 'approved' care," she adds. In some ways patients are treated like children by parents who fly in their private jets, as health insurers now spend in excess of $1.7 trillion annually more than is spent in 32 industrialized nations. It's safe to say that the current triangulation between patients, providers, and payers puts patients in a difficult position and is, frankly, undemocratic.

4. What are the future trends and how do they impact?

Speaking of politics, the good news is that the Affordable Care Act makes reasonable attempts to address the triangulation. The ACA, as we all know, contains the controversial mandate for consumers to purchase their own plans and established the state-based health insurance marketplace. It also fostered the new model of accountable care that provides financial incentives for hospitals and health systems to keep people healthier. In some of these new "value-based" models, providers are reimbursed on claims based on the positive health outcomes of patients. In other more integrated and involved "accountable care" models, provider systems are being paid a fixed amount of dollars per patient on a monthly basis. They must keep the patient healthy and out of the hospital and are at financial risk if they fail to do so. These models are incenting patients to experiment with their payers and providers, which makes the customer experience important.

Providers also now have specific financial incentives tied to their HCAHPS scores. The HCAHPS (Hospital Consumer Assessment of Healthcare Providers and Systems)

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survey is the first national, standardized, publicly reported survey of patients' perspectives of hospital care. HCAHPS, also known as the CAHPS Hospital Survey, is a survey instrument and data collection methodology for measuring patients' perceptions of their hospital experience. While many hospitals have collected information on patient satisfaction for their own internal use, until HCAHPS there was no national standard for collecting and publicly reporting information about patient experience of care that allowed valid comparisons to be made across hospitals locally, regionally and nationally.
Moreover, in 2015 CMS eliminated financial bonuses for Medicare Advantage health plans that didn't have star ratings of four or five (on a five-point scale). Previously, any health plan with a star rating of three or higher was would receive a bonus. The star ratings now have a component entirely around patient satisfaction, which many health plans have failed to achieve. One health plan calculated the loss from getting no star ratings bonus at about $1.2 million. CMS now calls it patient experience while health plans favor "customer experience." Regardless of the label, the point is clear: Hospitals and health plans now have incentives tied to the quality of their customers' experience, whether that experience is a trip to the emergency room, an inpatient hospital stay, or the enrollment in a health plan. In summary, healthcare payers and providers are realizing that patients are customers, and healthcare services should be marketed and tailored to their specific needs at each turn in their patient journey.

5. Why is the transition proving to be so difficult?

While the incentives may be a starting point, the initial results on these new models have been mixed. Many of the major provider-payer organizations that were part of CMS's initial Pioneer ACO program either lost money due to the financial incentives and/or dropped out of the program altogether for the same reason. Why is this transition so difficult? There are two sides needed to make this possible: first patients must be empowered and engaged in their own health, while at the same time providers and payers must work collaboratively within their own systems and develop modern, efficient processes and IT systems to ensure that patients are provided with a positive experience. At the same time providers must remain focused on the ultimate responsibility of providing safe and effective care. This is all much easier said than done, of course.

Today, over 25% of patients are considering switching or have already switched either their health plan. Patients are demanding the same level of conveniences and customization that they have been afforded in other industries. The Millennial generation is a prime example of that. A recent study by the consulting firm Accenture found that some segments of patients switch providers simply due to poor digital experiences.

Moreover, to engage patients and to create positive experiences health systems must also show empathy and provide positive motivation to keep

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patients healthy. This is in addition to the numerous initiatives that need to take place to ensure that clinical, operational and financial processes are designed and optimized with a customer focus.

6. What do patients want?

Patients are seeking more fee-for-value features like concierge health, membership, and a breadth of services—online, telehealth, mobile. They want to do as much as they can for themselves and their families, and they want to get care and support when they need or want it. They are looking for more engagement with their providers, the health system, and others like themselves. In this model, health coaching, shared decision making, personalized health education, and support groups will continue to grow.

Customers will come back when we make things easier, more personalized, and convenient—not simply making the hassles easier and faster, but eliminating the hassles and maximizing the relationships. Retaining patients not only improves today's bottom line but prepares these patients for the future, training them in new ways to interact online, so that when the new reimbursement models emerge, together we will be efficient, connected, and engaged. To identify the key values and principles that explain what the patient experience and engagement is all about, I propose a new model using the 5 C's: Clarity, Convenience, Customization, Compassion, and Carrots. Let's illustrate each of these in more depth.

Patients are clearly demanding better clarity from their providers and payers. This can mean many different things from a clinical, operational, and financial perspective. The key is focusing on how to use clarity to drive ongoing engagement. Patients are requesting clarity of communications. This can be in the form of clear and consolidated bills, clear discharge instructions, and clarity with medical education. Think about how many times discharge instructions are only provided by a clinician during the encounter with no documentation and follow up. Think about how confusing it is to receive bills for out of pocket expenses sometimes months after the fact, and sometimes, after they have already gone into collections.

One of the most important experiences for patients is convenience. Patients are demanding more ways to interact and communicate digitally with their healthcare experience, whether that is through providing access to medical records, digital appointment scheduling or prescription refills. Patients should be able to contact their providers to address any issue by way of phone, email, text messages, applications, and the web. Think about a family with a serious chronic condition such as Cancer. Cancer patients deal with numerous providers and likely have primary and secondary forms of insurance coverage. Any inconvenience in a scheduling, payment or approval process, for example, has the potential to take away time and cause unnecessary stress to patients and families, and can take away precious time spent with loved ones who may not have much

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time left to live. In a capitalist society driven by so many conveniences, health care still remains mired in lack of access and confusing prices. Convenience includes multiple ways to contact and schedule with providers and insurance companies, simplification and clear explanation of bills and coverage levels, and having an overall unified experience both within facilities and outside of the care setting.

Customization is a broad term that means treating patients based on their individual situation. One way to analyze this is to look at behavioral, environmental and genetic factors. Some examples of this include understanding the psycho-social factors that determine whether a patient is more likely to respond to reminders through text messaging or through phone-based health coaching, whether a patient is more likely to contract a particular illness due to where they live or their environment, or whether a patient is likely to respond to a particular treatment based on his or her genetics. These factors can be used to determine the right treatment or solution for each individual patient.

Health systems must also employ compassion when dealing with patients, which will help create connections that then motivate patients to be more engaged in their health. Today, 41% of US citizens believe the healthcare system is more concerned about money than people. Showing compassion is not only about providing pleasant experiences during clinical encounters, but also impacts how we design applications and health interventions outside the healthcare facilities. For example, an application for a pediatric cancer patient must be thought out entirely different than an application to remind an adult to pay a delinquent bill.

Finally, patients need carrots that motivate them effectively. While most patients know what they need to do, the tendency to do the opposite is often very tempting. Positive reinforcement is a concept that health systems must employ to encourage healthy behaviors. This was the insight gathered by Adam Bosworth, co-founder of Keas, an employee health and wellness program that combines social media and online games to create happier, healthier workforces. Keas participants get points, badges and achievements for completing tasks and supporting their coworkers in achieving their goals. Keas believes that to successfully change behavior, people need to be effectively engaged around common, meaningful goals. It uses gaming mechanics, social interaction and small groups to motivate people to achieve their health goals.

7 What is patient empowerment, and will it work?

Motivation will lead to patient empowerment. What is patient empowerment? The idea rests on the assumption that those who participate in their own healthcare decision making are more likely to feel secure and are more likely to recover from illness. Shared decision making is especially important when it comes to deciding between a number of options for treatment, all which are clinically appropriate. In these cases, it is

important consider patient values and preferences. Today, patients often make decisions without understanding all of their various options. I myself have had multiple conditions which became chronic over time. I am sure that if I had been presented all of the options I have learned about over the years upfront, I may have been able to reverse the impact of these conditions.

Research suggests that patient participation leads to better experiences related to the quality of care received. Patients who participate in their own care show greater belief that they will recover, which in turn leads to better health outcomes. Patients with diabetes, for example, show a greater capacity to manage their condition and recover if they process the guidelines from their care team effectively. Patients who receive clear discharge instructions report higher patient satisfaction and adherence to clinical guidelines, which reduces readmissions. Previous research has demonstrated that providing patients with personal coronary risk information may assist patients in improving cholesterol levels. Additionally, another study found that a cardiovascular risk calculator led to increased patient participation and satisfaction with the treatment decision process and outcome, and reduced decisional regret. Patients need decision aids so they can make informed choices. These should not replace but supplement the counsel of healthcare providers.

8. How do we design health applications?

Offering easy, secure access to health information when and where it is needed most is the key principle of the patient-centered approach and patient empowerment. Mobile engagement is becoming one of the best options for delivering care personalization, convenience and motivation by providing targeted, relevant information through smartphones. App usage has grown significantly over the past few years, and now more than half of health consumers desire to use their smartphones more to interact with healthcare providers. Mobile interventions have much farther reach than individual providers can have. They can reach many more people beyond those seen in the clinic or hospital. And a health system that adopts these kinds of tools can improve their bandwidth and their ability to address these problems beyond the capacity of their workforce. A recent Accenture study highlighted the patients' high demand for mobile:

- Today, 33 percent of U.S. consumers are using mobile health apps, compared with just 16 percent in 2014.
- 66 percent of the largest 100 US hospitals have mobile apps for consumers. Less than 40 percent of that subset have built proprietary apps.
- At the same time, only 2 percent of patients use apps offered by their hospital. Evidently, few currently available healthcare provider apps meet consumers' expectations and needs.

- Roughly 7 percent of patients have switched healthcare providers due to a poor experience with digital customer service channels, such as mobile apps.

It's no longer enough to build one application for the entire healthcare system. While the "big bang" approach may have worked with EMR systems, with consumer apps the right mantra is "start small and act fast." Various groups of patients require specific, targeted apps. Moreover, patients may want different apps for each encounter with a healthcare system, at each turn in their patient journey. It's about understanding all of your patients' mobile interactions - and delivering the right information and tools for a smooth, rewarding patient experience.

Key Characteristics of a Compelling Patient App:

- Personalized – The UI and functionality are tailored to a specific audience: seniors; children; busy executives; moms; athletes; etc.

- Less is More –Applications should not be too busy - stick with 2-3 key features and 2-3 secondary features.

- Dynamic – New content can be added regularly by your in-house team, without having to resubmit/re-download the app.

- Has a "Mobile Hook" – Performs a helpful and frequently needed function that makes the app indispensable

- Easy to Navigate – UI elements are optimized to make the user experience easy for the target audience. There are no unnecessary steps, bulky splash screens, upfront registration, or annoying ads.

Disruptor healthcare apps are increasingly meeting consumer's unmet needs and closing that chasm. The most downloaded and highly rated health applications today at Calorie Counter, iTriage, and WebMD followed by others such as GoodRx, ZocDoc, Healow, and Dosecast.

Personal health record (PHR) applications have evolved over the years. The early attempts by large well-known companies such as Google and Microsoft, for the most part, were unsuccessful. The newer generation of applications holds more promise by combining a few key features together in one application and creating engaging user experiences.

Health Companion uses a social network model as a way to encourage users to take better control of their healthcare. Although the site does allow users to share personal health information, all records are kept secured and not shared without the patient's express permission. Health Companion also has tools for users who wish to track their medical expenses, insurance claims and record the statuses of each claim. Insurance information can be automatically downloaded from the insurance provider or manually entered into the Health Companion database. Patients can

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track their medical statistics through Health Companion, such as body measurement, cholesterol readings, blood pressure levels, calorie values and blood glucose results. The application also provides appointment reminders and alerts for medications and immunizations.

Patients Know Best is a significant PHR because of the vast importance placed on putting patients in charge of their own healthcare. The company has recently added new features in order to better enhance user experience. The application provides the ability to have online consultations for non-emergent issues, secure control over medical records and the ability to share view access with healthcare professionals, unlimited storage, appointment scheduling and reminders, a patient diary, and organization of records based on body parts with medical education for each area.

Tonic for Health is another unique company that uses patient engagement tools that combine games and graphics to provide a unique experience for patients. For example, kids who are asked to submit self-reported data on their medical condition, upon completing the survey use a fun maze to submit the results.

9. What do healthcare payers need to do?

Whether they realize it or not, health insurers have their work cut out for them. The mandate placed on consumers to purchase health insurance caused a national debate that has not ended. Consumers are starting to ask themselves whether having health insurance is actually worth it. The numbers are staggering: according to Healthcare Finance, co-payments are growing at nearly 10% annually, and premiums are increasing by over 7% annually. Even for those who do have insurance, medical care is still not necessarily affordable. According to the Washington Post and New York Times, approximately one in four who has insurance still cannot afford medical care. High deductibles of $1,500 or more seem to be the leading cause for the missed care. Medical tests, treatments and follow-up care were the most common types of care adults skipped.

The ACA is already forcing payers to shape up by placing restrictions on the medical loss ratio (MLR), which now states that insurers must spend 80% of the cost of their premium on value adding services while minimizing administrative costs. There are several ways insurers can add value to consumers to reduce the MLR.

Although there are many health insurance products for consumers, they must be customized based on health and financial situations. For example, insurers can offer base plans with a la carte add-ons, or offer perks or special benefits (free bottled water, gym memberships) to low utilizers to encourage them to continue coverage. Creative options may help insurers address the spectrum of needs: providing optimal benefits for those with large medical expenses while preserving the portion of their customer base with a

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low medical loss ratio (MLR).

Insurers also need the right tools in place to help consumers make the right decisions. Consumers must be able to both determine the kind of coverage they need and find the right balance of affordability between premiums and deductibles. Already today, tools are being developed that can integrate health plan benefit coverage level information with provider charge masters to provide expected charges to patients and consumer. Estimators and calculators can leverage predictive algorithms that warns consumers, based on income or other factors, about their risk for being underinsured if they select certain kinds of plans. In the future maybe they will predict healthcare costs and provide financial assistance by predicting and planning for expected healthcare costs.

Even after consumers have selected plans and enrolled, many still need guidance on how to get the most out of their benefits. It's important for insurers to improve onboarding materials and other member communications. If consumers have the information they need and want at the appropriate times to motivate them to take action, consumer satisfaction will increase which will lead to greater member retention.

While providers don't manage a patient's insurance, they do have an impact on the member experience, for example, in helping patients make decisions on follow-up care, such as diagnostic imaging and lab work. If insurers offered resources to providers and offices – like access to "look-up" tools that enable them to provide detailed cost and benefits information on various referral options – providers could more easily play a role in creating a positive member experience.

10. What do providers need to do?

If the challenges for payers seemed daunting the challenge for providers is even greater. Consumers interact with their providers much more often than they do with their payers, and these interactions take place both within and outside the provider facilities. Not only that but providers (unlike payers) are actually responsible for what matters most to patients: the quality and safety of healthcare. To the extent that quality and safety are improved through patient-centered initiatives, providers have direct economic, legal and moral incentives. However, this involves engaging patients towards safe and effective health activities. The promise of engagement with patients will only happen when providers first improve the experience that patients have with the system, whether that be through communications, customization, and/or providing the same conveniences of the digital age. You can see this in the slow adoption of portals. Portals were launched for patients over the last 10 years, and most have low adoption. Why? Because the healthcare industry assumed they could engage us just by providing information in a secure location. Consumers have shown through observation and research that

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adoption can be fickle and elusive.

First, providers need to understand their individual customers and populations. Collection and standardization of systems with patient and population level data is fundamental to any customer-centric reform. While the hype today is around "big data", most healthcare organizations are still struggling with having all basic patient information in one place, including clinical, demographic, financial records, logs of all calls or emails made by the patient, etc. Only when these areas are fixed should health systems attempt to develop more complex systems with genetic and environmental data for analysis. These advanced analytics systems over time will know more about us than even we know, and will be used to optimize our health and wellness. Devices will use analytics to provide automated drug dosing and alerts to clinicians and care teams about expected or encountered clinical events. Having this information in one place will improve the experience for the individual interacting with the patients as well as give confidence to patients that their provider understands them and their history. Analytics is at the core of the transformation to a customer-centric healthcare system.

Providers must also do a variety of things to improve customer experiences. They must standardize care and communications to patients, so that they don't have to worry about the quality of care being provided. When standardized care is used, quality increases, variation in care plans decreases, and costs decrease. Standardization of any process of care through the use of protocols and checklists can be expected to achieve a reduction in harmful events. And as the process of delivering standard care becomes more sophisticated, the care team can look for data coming back from the patient. Patient response data or patient-generated data can tell the care team if education and instructions have been opened and read. And more importantly, patients become contributors to their care, including treatment options, medical records, and short- and long-term care plans. This allows the care team to tailor care to the unique needs of individual patients and create personalized care plans that lead to quality outcomes, improved communication, and better and more user-friendly work processes.

Care coordination allows the organization of patient activities and the sharing of information to all of the care team involved with a patient's care. The care manager can send patient education that answers questions the patient may be reluctant to ask, gives greater understanding of symptoms, and explains options for treatment. The entire care team has visibility into what was sent and opened by the patient. Shifting to a care team model that includes more non-medical staff interacting with patients means being able to reach patients in between visits with education and care. It also means being able to identify and reach specific populations (e.g., high-spending, low-utilization, high-risk, and chronic care) with education, treatment planning, benefit

management support, healthy behavior reminders, and utilization reporting. To shift coordination tasks away from medical providers, teams needs to be composed of medical and non-medical staff. Entire multi-disciplinary teams can then share expertise, knowledge, and skill to solve the complex problems of coordinating patient-centered care. Effective care teams can assist with follow ups, identifying and overcoming barriers to engagement, motivation, education, communication, targeting specific populations, providing benefit management support, and helping navigate providers. Care coordination teams create a path within an organization's workflow that moves some coordination work away from physicians and still delivers coordinated care at the right touchpoints to engage your patients. As a result of the team's efforts, information is exchanged, care gaps are closed, and good health outcomes are delivered to patients.

What is the role of technology?

There are numerous technologies that are just now coming into healthcare that will make the industry more customer-focused. These include customer relationship management systems, business process management systems, advanced analytics, artificial intelligence and robotics. While all of these are important, there is one key to unlocking the power of data to both transform the patient experience and empower patients: application programming interfaces (APIs).

APIs allow developers to access information so they can build new applications or businesses. When healthcare providers and payers adopt APIs, patients can then have their own secure access to all of their health records and information in their own application, which will empower them and allow them to make more informed decisions. Patients will no longer have to access multiple patient portals to view their health information and can instead use one single application. Information from patient devices in the home can be sent back and forth between EMRs and other provider applications, and patients can decide what data goes to which provider.

Providers can leverage this dynamic data exchange to develop more advanced analytics and to improve clinical decision making. With APIs, providers can receive data such as patterns of adherence to clinical protocols, dosages and other information to inform departments in hospitals that are working with specific patients. Providers can also see a full longitudinal view of all patient healthcare encounters, such as primary care visits that may not be within an institution's network. Researchers will benefit from having access to large sets of clinical or claims data to conduct studies that could advance healthcare. Open APIs will also allow providers to evolve beyond EMR interfaces and create their own customized user experiences that are simpler and more intuitive than what is available today, while still leveraging the underlying platform.

In the future, providers and

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patients will share in decision making in near real-time as devices will pass information back and forth into EMRs, which will be built with clinical alert rules to inform physicians of potential conditions that can be managed by both the patient and clinician. Stanford Children's is already experimenting with this concept by leveraging APIs built for its EMR along with Apple Health Kit. Oschner Health System currently has a pilot program to prevent heart failure and hypertension that uses an API to collect body weight and blood pressure data from over 500 individuals' connected devices, which led to significant reductions in hospitalizations and improved blood pressure control.

What is the call to action?

First, providers and payers must collaborate effectively to unify the experience for patients. The patient is currently confused in the triangulation between those who are approving care and those who are providing care, which puts their health and wellness at risk. The number of integrated payer-provider organizations is growing, and there is much to emulate from models such as Kaiser Permanente. However, for the most part payers have their own programs and applications to engage members which are different from those that providers have.

To become customer-focused, providers must share data from EMRs and other relevant applications to inform payers of the health status of their members. Payers must also share data on coverages levels, care approvals, and expected reimbursements, bonuses and penalties. Only when these collaboration succeed broadly will we find the best care protocols at a reasonable cost for specific patients or groups of patients that can be assumed by the system.

Second, EMR and other companies that store patient-level data must provide open APIs to facilitate data sharing and collaboration. Patients are currently hostage to closed applications that store important data that forms the basis of their unique customer experience. Appropriate incentive structures and regulations must be in place to make this happen.

Finally, patients must take charge by demanding access to the information and resources that will inspire them towards healthy behaviors and wellness. This includes access to all of their health record information, as well as other convenient applications such as multi-channel communication with care teams and payers, digital appointment scheduling, automated prescription refills, and health education and tracking tools. Patient and consumer advocates must raise the voice of the customer to the forefront of both national and local healthcare policy and inform process and application design with deep research both at the individual and population level.

The transition from patient transactions towards a customer focus that fosters industry-wide collaboration enduring relationships is indeed all encompassing and complex, as are all great challenges. However, we are currently at a critical

convergence point of forces in healthcare that is driven by rapid advancements in data sciences and technology, massive economic challenges to the system and a combination of individual and societal forces. The time to make this vision a reality is now, and the opportunity has never been greater. When we look back twenty to thirty years from today we will see that we have created a highly advanced health and wellness system that treats patients like valued customers and is truly an example for the rest of the World.

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Chapter 17: How should we Communicate to the Public about Health Technology?

Author 1: Shelagh Maloney
Canada Health Infoway, Toronto, Canada

Abstract

To guide its public communication efforts, Canada Health Infoway (Infoway) developed a patient/citizen engagement framework. The framework identifies four components of engagement: listen to the needs and perspectives of Canadians, amplify the voice of patients and patient advocates, invest in initiatives that directly address Canadians' priorities, and influence others to support the effective use of consumer health. Infoway's Annual Tracking Survey, the ImagineNation Challenge Series, the Better Health Together public education campaign and Digital Health Week were used as examples of various components of the framework. This paper also describes some of the challenges that are associated with communicating with the public about health technology.

1. Introduction

Canada Health Infoway (Infoway) was established in 2001 as an independent, not-for-profit organization funded by the federal government to drive the digital health agenda in Canada. Infoway helps to improve the health of Canadians by working with partners to accelerate the development, adoption and effective use of digital health innovations across the country. Through its investments, Infoway has three primary objectives: to improve access to care, to improve the quality and safety of the care delivered and to drive more efficient delivery of services for patients and clinicians.

As of December 2015, Infoway has received $2.1B in funding from the federal government. This funding, along with matching investments from provinces and territories has essentially been used to usher in two waves of digital health transformation across Canada. The first wave focused on building the foundational infrastructure for digital health. The second wave focused on putting digital tools in the hands of health care providers. And now, with a new commitment of $50 million over two years from the federal government, Infoway will focus on a third wave. This wave will put digital health tools in the hands of patients and empower them to be more active members of their care teams.

To ensure that investments in digital consumer health solutions and other activities related to improving the patient experience are producing tangible benefits for Canadians, Infoway developed a patient/citizen engagement framework that guides and informs activities. This framework includes public outreach and engagement.

2. Setting the stage for consumer health investment in Canada

When Infoway was established in 2001, the Canadian health care system was largely run on paper. There was very little digitization and health care costs were escalating and expected to continue to increase due in part to

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greater demands on the system by an aging population and higher medication costs. It was against this backdrop that Canada's First Ministers created Infoway to provide national leadership and to develop a pan-Canadian approach to modernizing the health care system.

In addition to establishing an electronic health record (EHR) Blueprint as a common architecture and establishing pan-Canadian standards to ensure interoperability between systems, Infoway and its jurisdictional partners began their digital health journey by focusing on building six core systems to collect information electronically: client and provider demographics, diagnostic images in hospitals, profiles of dispensed drugs, laboratory test results and clinical reports or immunizations. This information constitutes the essence of an EHR – the secure and lifetime record of a person's health and health care history – that's available to authorized health care providers and to the individual.

Today, most of the work on the infrastructure is complete. For example, the pan-Canadian average EHR availability is 91 per cent as of March 31, 2015[1]. In terms of benefits, investments by Infoway and the jurisdictions in electronic medical records (EMRs), diagnostic imaging, drug information systems and telehealth have produced an estimated $13 billion in access, quality and productivity benefits for Canadians and the health care system since 2007[2]. And, in September of 2014, Canada's Ministers of Health described EHRs as "one of the most transformational innovations in health care in a generation"[3].

The second wave of digital health innovation in Canada focused on improving clinicians' access to digital health solutions. This effort was accelerated by a $340 million dollar investment in EMR systems by Infoway starting in 2011. An EMR is an office-based system that enables a health care professional, such as a family doctor, to record the information gathered during a patient's visit. This might include things such as weight, blood pressure and symptoms, which would have previously been hand-written and stored in a file folder in a doctor's office.

Investments in EMRs were complemented by a clinical engagement strategy that focused on establishing relationships with and providing resources to national professional associations (e.g., the Canadian Medical Association, the Canadians Nurses Association and the Canadian Pharmacists Association) so they can advocate for the adoption of digital health technology; working with the associations of schools of medicine, nursing and pharmacy to add digital health and technology to the curricula to equip young professionals with the tools they need to work in an e-enabled environment; and establishing clinical peer networks to provide clinician-to-clinician mentoring for those adopting the technology.

Canadian EMR adoption rates are a testament to the success of these investments and initiatives. According to the 2015 Commonwealth Fund Survey, 73 per cent of family physicians

and nurse practitioners in Canada were using an EMR4, triple the number from 2007. Similarly, the 2014 National Physician Survey found that 76 per cent of family physicians reported increases in quality of care since implementing an EMR5, up from 63 per cent in 2013. Infoway expects the use of EMR systems in Canada to continue to grow.

With the infrastructure largely in place, and significant uptake in EMR use by clinicians, the stage was set for the next wave; providing Canadians with online access to their information and with digital tools to enhance their roles as informed and engaged members of their health care team.

3. Canada Health Infoway's patient/citizen engagement framework

Engaging with the public, however, is not as straightforward as it may sound. Its complexity is immediately inherent as one tries to define "the public" and/or view Canadians as a single, homogenous group with a common set of attributes that summarize their collective attitudes, perceptions and needs. In 2013 Infoway developed a patient/citizen engagement framework to guide and inform outreach efforts and investments, as demonstrated in Figure 1. The framework is intended to be sensitive to the multitude and complexity of patients'/citizens' needs. It should be noted that the use of the term patient/citizen in this case is intended to convey all Canadians regardless of their health status and include all those who engage with the health system.

The patient/citizen engagement framework has four components that describe the ways in which Infoway interacts with Canadians. They are: listen, amplify, invest and influence. There are one or more activities associated with each of these components, which will be described in detail below and with examples as appropriate.

Patient/Citizen Engagement Approach

Figure 1. Canada Health Infoway Patient/ Citizen Engagement Framework.

3.1. Patient engagement: listen

First and foremost, listening to the needs and perspectives of Canadians is imperative to ensuring that outreach activities derived from these efforts are relevant and helpful to those for whom they are intended. Infoway engages with Canadians directly through its *ImagineNation* Challenge series. The Challenges seek to inspire, provoke, and promote innovation in health and health care to improve the quality of care and the patient experience for Canadians

by leveraging widely distributed knowledge, skills, and resources to accelerate value from emerging digital health solutions. Desired outcomes are identified up front (e.g. growth in the use of e-visits or improvement in quality of care through clinical information exchange), and individuals or teams register to participate via a website. They then track their outcomes, share their experiences, and receive support through a community of innovators. Teams that are most successful in delivering on the desired outcomes receive recognition, funding, and other awards.

The first Challenge, launched in 2011, reached out to Canadians and asked them to submit their best ideas for improving health and health care through innovative digital health solutions. Thousands of Canadians were inspired to send in their ideas and/or vote on their favourite idea. The ideas submitted were useful in understanding what Canadians desired from their health system and how they perceived the role of technology in allowing positive change to happen. Since 2011, there have been ten ImagineNation Challenges involving 435 team or individual submissions, 211 volunteer judges, over a dozen supporting organizations, and $2.3 million in awards. The ImagineNation Challenge series is now a core component of Infoway's innovation program.

Infoway engages Canadians directly through surveys and focus groups. Since 2010, Infoway has been conducting public opinion research to measure Canadians' attitudes, awareness and support for digital health, EHRs and consumer health tools. The surveys are conducted using an online panel of approximately 1,500 Canadians aged 18 years and older. Survey results are segmented by the following subgroups: general population, opinion leaders, seniors (55 years+), female caregivers (40 years+), those living with chronic conditions and high system users. Figure 2 provides more detail about the definition of these audience segments. From 2010 to 2013, the survey included questions about attitudes and perceptions about EHRs only, as this was Infoway's early focus. In 2013 the survey was expanded to include questions about electronic health and then digital health. These terms are often used interchangeably, but Infoway's preferred term is digital health. This refers to the use of information technology/electronic communication tools, services and processes to deliver health care services or to facilitate better health.

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Canada Health Infoway Annual Tracking Survey Key Audiences

Key Audiences	Definition
General Population	Representative sample of Canadian adults 18+ based on age, gender and region.
Opinion Leaders	Occupation = Executive/Managerial or Professional and income of $80K+; above average activism (e.g., writing on blogs/letters to media, volunteerism, talk about political and social issues) and above average early adopter.
Seniors	Representative sample of Canadians aged 55+ based on gender and region.
Female Caregivers	Women aged 40+ who have an adult family member, relative or close friend 50 years of age or older they are personally helping deal with their health care issues.
Chronic Condition	Those suffering from a chronic disease, illness or condition.
High System Users	Those who have used the health care system 20 times or more in the past six months.

Figure 2: Definition of Key Audiences: Canada Health Infoway Annual Tracking Survey

The 2016 Annual Tracking Survey6 (March 2016) showed that the majority of Canadians (75%) have heard of digital health and believe (74%) that digital health is having a positive impact on the Canadian health care system. A strong majority of Canadians agree or strongly agree that digital health helps health care providers by ensuring access to a comprehensive picture of patients' health histories (86%), helping coordinate care between multiple care providers (85%), helping provide more effective care (76%), and increasing the accuracy of health records (78%). In addition, almost all Canadians (95%) support a requirement for physicians to keep an electronic record of their patients' health information. It is important and informative to track these awareness levels over time and to understand how Canadians' thinking has evolved. For example, understanding what they perceive as the benefits and what they see as concerns (54% worry that personal health information might be used for other purposes in the future and 80% are confident that safeguards are in place to protect medical records from being seen by people who aren't permitted to see them), helps inform the messages we deliver to them.

It is also informative to track these responses over time to judge whether awareness levels have changed and whether messages have been effective. For example, 75 per cent of Canadians had heard of digital health according to the 2016 survey. That number has increased from 27 per cent in 20157 and 21 per cent in 20148. This metric is an important indicator of whether Infoway's efforts

to communicate and inform the public about digital health have been successful.

When asked which digital services they would most likely use, the results are consistent across the country and over time. Since 2010, Canadians have consistently reported that the patient online services most useful to them are the following:

- **e-Booking**, allowing patients to books appointments and receive reminders online and at their convenience
- **e-Visits** with doctors or other clinicians, including secure messaging and video visits
- **e-Renewals** so patients can request prescription renewals online
- **e-Views**, which enable online access to health records (e.g., laboratory test results, children's immunizations and other components with high value)

.

This information has shaped Infoway's current Consumer Health Investment Strategy

3.2 Patient engagement: amplify

The second component of the patient engagement strategy is to amplify the voice of patients and patient advocates. Providing a forum for discussion, education and sharing is an important component of communicating with the public.

After listening to Canadians and engaging them through surveys and focus groups, Infoway launched a public education campaign to amplify the messages that we heard and to give Canadians a forum in which to engage. While Infoway as an organization focuses on the needs of all Canadians, because of the limited budget allocated to this campaign, it was important to look at audience segmentation to ensure success. We needed to examine population subsets and their behaviour to understand their motivation and calls to action. Most particularly, we needed to identify the audiences that would be most receptive to messages around digital health. With this in mind, we identified the "health actionist" as the bull's-eye target for the campaign. Health actionists are catalysts who have the power to motivate others to take action related to health issues. By ensuring that campaign messaging was tailored toward health actionists, we increased the likelihood of driving desired actions such as social sharing and peer-to-peer discussions about digital health.

Health actionists tend to be "health educated" and actively take care of their health. They are more likely to motivate others to take a health action, likely to live in an urban area, are on the internet frequently, and are more likely to be a caregiver to someone with a chronic disease (26%). This category includes men, but skews to women, likely married with children, and averages 40 years of age.

Infoway launched Better Health Together, a public education

campaign, in September 2013. The campaign was designed to create awareness of, and support for digital health among Canadians. Our research had revealed that, while Canadians were aware of the benefits of digital health to care providers, they were not generally aware of the benefits of digital health that would accrue to them personally. For this reason the main focus of the campaign was to share stories of "real" Canadians who were positively impacted by digital health.

Year one of the campaign featured Sarah and her seven year-old diabetic son, Marcus. In a TV and online ad, Sarah described how she used digital health tools to help manage Marcus's health and interact with his care team. The campaign also featured a number of other Canadian storytellers who shared their positive experiences.

A different advertising approach was used in years two and three of the campaign. Instead of an ad featuring one storyteller, we used ads that mimicked situations but did not feature people. This allowed viewers to put themselves in those same situations. Because of the cost efficiencies realized by not using people, the budget allowed for the creation of seven ads featuring real life situations that Canadians have experienced or can experience through digital health. These included:

- Missing a doctor's call to hear lab results;
- Calling a medical clinic to arrange an appointment and getting voice mail;
- Not being able to communicate health information in the event of an emergency;
- Sitting in a waiting room surrounded by sick people when all you need is a prescription renewal.

These ads were posted on the betterhealthtogether.ca website, created especially for the campaign. The website enabled in-depth education for Canadians about digital health. Again, knowing that health actionists spend significant time online, it was important to ensure that there was an online resource that provided information about digital health in Canada. The website featured videos of the storytellers sharing their experiences, as well as background information about digital health implementation across Canada. The campaign website encouraged Canadians to post their stories, comment on what they saw and/or ask questions.

In addition to soliciting engagement through the campaign website, the campaign messages were amplified via a number of social media and other channels. Special attention was paid to ensure that amplification efforts were aimed at channels that were frequented by health actionists to ensure maximum reach. For example, in year three of the campaign, Infoway hosted a tweet chat on a blog host platform aimed at young mothers. This chat

attracted more than 140 participants and generated more than 25 million impressions in one hour. This example highlights the importance of knowing who your audience is and taking your message to them (versus expecting/waiting for them to come to you).

Another important component of the campaign and one that was especially effective in amplifying the message was strategic partnerships and relationships. Infoway had support federally, through Health Canada, as well as campaign endorsement from all provincial and territorial governments. These partnerships increased the credibility of the campaign and added weight to the message.

In addition to these partners, Better Health Together was supported by more than 25 national health care associations. For example, we knew it was important to have professional associations like the Canadian Medical Association, the Canadian Nurses Association and the Canadian Pharmacists Association support the campaign because some Canadians told us that they cared about what their clinicians thought about digital health and would ask them before they made up their own minds about it. Similarly, the professional associations shared the campaign information with their memberships; this resulted in clinicians being more informed and better able to respond to their patients' questions. Patient advocacy groups (e.g., Patients Canada, Patients for Patient Safety), disease-specific groups (e.g., Heart and Stroke Foundation, Canadian Diabetes Association, Canadian Cancer Society) and industry associations (e.g., Information Technology Association of Canada, COACH: Canada's Health Informatics Association) all supported the campaign and were instrumental in accelerating our amplification efforts.

3.3 Patient engagement: invest

The third component of the patient engagement framework is invest. As stated in the introduction, Infoway achieves its mandate by investing in projects and initiatives that advance the digital health agenda in Canada. In 2010, Infoway established a Consumer Health Strategy to guide investment in this domain. Figure 3 illustrates the program model.

Investments related to Getting Patients Online refer to the services that were identified through the listen initiatives (i.e., e-booking, e-visits, e-renewal (prescriptions) and e-viewing of one's own health information). Similarly, investments in Keeping Patients at Home refer to telehomecare initiatives. Telehomecare is defined as the electronic transmission of patient data (e.g., symptoms, vital signs) from a patient's home to a health care provider for monitoring and support over a specified time period. The evidence is clear that the benefits associated with monitoring a patient's condition remotely (e.g., fewer emergency room visits and hospital stays) far outweigh the costs associated with establishing and maintaining the service. The Consumer Health Strategy also enables investments

in new and emerging innovations that hold some promise as cost-effective means to improve the patient experience (Innovation & Learning). Finally, Building a Strong Foundation for Consumer Health enables investments that will accelerate our learning, lead to greater understanding of the consumer digital health landscape in Canada, increase engagement activities and stimulate thought leadership.

Consumer Health Program Model

Figure 3. Canada Health Infoway Consumer Health Program Model

3.4 Patient engagement: influence

The fourth and final component of the patient engagement framework is influence. Influencing others to support effective use of consumer health is paramount to long term success. Infoway looks to influence the consumer health agenda through a variety of means, including: research and evaluation, knowledge translation, empowering patients, informing policy decisions, and supporting change management.

For example, every project in which Infoway invests must include a rigorous benefits evaluation plan that will enable an objective assessment of how well project goals and performance targets were met. Information from each benefits evaluation report, in turn, contributes to a growing body of knowledge and influences the direction of future investments. An excellent example of influence in this context is work that was conducted in the telehomecare domain (known in some parts of Canada and internationally as remote patient monitoring or RPM) in 2014. Infoway commissioned an extensive review of the literature, reviewed ongoing or completed projects from across the country and received advice and opinions from a multi-disciplinary panel of experts. The result of this work, titled Connecting Patients with Providers: A Pan-Canadian Study on Remote Patient Monitoring, has been used to advance telehomecare thinking in Canada by identifying areas where there is sufficient evidence to suggest that telehomecare is an effective and cost-efficient alternative to conventional treatment (e.g., high risk pregnancy, dementia).

Similarly, in March 2014, Infoway published a white paper called Exploring the Value, Benefits and Common Concerns of e-Booking to inform and influence take-up of this technology across the country.

Infoway also makes a concerted effort to influence and inform policy decisions by communicating directly with policy makers and/or to the public to encourage them to raise issues with their local Members of Parliament. For example, in 2014 and 2015, Infoway led a campaign to celebrate Digital Health Week during the second week of November. Originally launched as a media hook to promote the Better Health Together campaign, Digital Health Week has grown into an important event for the digital health community in Canada. Many of the national associations and governments

plan announcements and/or activities (e.g., webinars, tweet chats, patient forums) to coincide with Digital Health Week. Public relations activities and earned media events also figure prominently during this week and they are often targeted to government and health care leaders who can influence policy discussions and decisions. We are planning another Digital Health Week in November 2016.

5. Challenges

Communicating with the public about health technology is complicated for a number of reasons. As previously stated, the "public" is not a homogenous group. Canadians are a very heterogeneous group with different experiences, attitudes, perceptions and biases that influence what and how they interpret communication about health technology. Infoway's public opinion research demonstrates that people's experiences with the health care system, familiarity with technology, age and socio-economic status influence their perceptions about health technology.

A second factor that impacts how we communicate with the public about health technology, or more specifically, how these communications will be received, is the extent to which digital health tools are available to them. For example, there is significant variability across Canada with respect to the digital health services that are available. Citizens in British Columbia, for example, can access their lab results online. In 2015, this service became available on a limited basis in Ontario, and is largely not available in any other jurisdiction. This fact had an impact on the response to the message communicated through Infoway's Better Health Together public education campaign. Feedback to the betterhealthtogether.ca website suggested that Canadians who did not have access to these services and had not heard of them being available, were less likely to believe the message or expect that these services were available today. Canadians who had experienced these services for themselves or who had a friend or family member who had benefited from one of the services, were more supportive of the message and more likely to discuss it with others.

Finally, when communicating with the public about health technology, one must be aware of key influencers who may impact how the public will react to certain messages. For example, focus groups conducted to inform the Better Health Together campaign suggested that some Canadians were heavily influenced by their care providers, so it was important to develop a campaign that was supported by physicians and nurses.

Similarly, provincial and territorial governments, who are responsible for implementing consumer health services amid a number of competing priorities, were very aware of the need to manage the public's expectations. Would the viewing of ads create undue pressure on governments and/or health providers to accelerate the adoption of new technology? Or would the ads create more awareness of the progress that has been achieved to date?

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6. Conclusions

As it has in many countries, the digital health agenda in Canada has evolved over the years. Early initiatives were focused on digitizing, connecting and sharing information between clinicians and building the infrastructure to support these efforts. The focus more recently has been to provide Canadians with access to their health information and online services that will allow them to be more informed, empowered and proactive members of their health care teams. In Canada, this third wave of digital health innovation includes a significant public communication effort. Communicating with the public about health technology, however, is challenging.

The purpose of this paper was to describe each of the four components of Infoway's patient/citizen engagement framework using examples of various initiatives like the ImagineNation Challenge Series, the Better Health Together public education campaign and Digital Health Week and to describe the challenges inherent in communicating with the public about health technology.

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Chapter 18: Evaluating New Health Information Technologies: Expanding the Frontiers of Health Care Delivery and Health Promotion

Gary L. Kreps, Ph.D.
Chief, Health Communication and Informatics Research Branch, National Cancer Institute Behavioral Research Program, Division of Cancer Control and Population Sciences

Abstract

The modern health care system is being irrevocably changed by the development and introduction of new health information technologies (such as health information systems, decision-support tools, specialized web-sites, and innovative communication devices). While many of these new technologies hold the promise of revolutionizing the modern health system and facilitating improvements in health care delivery, health education, and health promotion, it is imperative to carefully examine and assess the effectiveness of these technological tools to determine which products are most useful to apply in specific contexts, as well as to learn how to best utilize these products and processes. Without good evaluative information about new technologies, we are unlikely to reap the greatest benefits from these powerful new tools. This chapter examines the demand for evaluating health information technologies and suggests several strategies for conducting rigorous and relevant evaluation research.

1. Evaluation Research and Health Technology

New health information technologies (such as specialized websites, innovative new communication devices, and powerful health data analysis tools) are being developed and introduced at a rapid rate into the modern health system to facilitate improved health care delivery, health education, and health promotion [1; 2]. While these new technologies are likely to revolutionize the modern health system, it is imperative to carefully examine and assess the effectiveness of these technological tools to determine which products are most useful to apply in different contexts, as well as to learn how to best utilize these products and processes. Without good evaluative information about new technologies, we are unlikely to reap the greatest benefits from these powerful new tools [3; 4].

Evaluation research is an essential process in developing and implementing health information technologies [2; 5]. Failure to engage in careful and concerted evaluation research is pure hubris (a fatal miscalculation) that is likely to doom the success of new health information technologies. It is unlikely that new technical products will work well for users without the use of relevant evaluation data. Effective development and institutionalization of new technological products involves a series of product adaptations. Good evaluation data provides needed direction for product refinement.

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Every new health technology should have both **formative** and **summative** evaluation strategies built right in to the development process from the very beginning [6]. (Formative and summative evaluation will be discussed in more depth later in this chapter). Evaluation data provides technology developers with a broad range of critically important information about:

- level of demand for new health information technologies,
- environmental constraints and specifications for the implementation of new products,
- specific design flaws and limitations of new products,
- assessments of the relative efficiency and effectiveness of new products,
- the appropriate fit of these products for specific audiences and contexts, and
- strategies for adapting new health information technologies to fit the idiosyncratic demands of different users and unique social situations.

2. Research and Reinvention; What Do We Already Know?

Technological innovation is a process of invention and reinvention, however it appears that reinvention is the process that is most often utilized in health technology development and implementation [7]. It is usually unnecessary to develop radically new products or processes to effectively address current health care/promotion needs. In fact, the more radical the technical innovation is, the more difficult it will often be to integrate within the health care system. The technical interventions that typically work best within the health care system are developed incrementally through a process of reinvention, reinventing current processes and products to better meet health care/promotion needs.

Prior to the development of new health information technologies, comprehensive reviews of relevant literature should be conducted to identify key findings from literature in the scientific and professional fields most closely related to the technological product. It is foolish to reinvent the wheel, when good information about product demand and practices is already available. Key established research and practice findings should guide product development and implementation.

3. Formative and Summative Evaluation Research

Formative evaluation is an essential process in the development and refinement of new health information technologies. Formative research is used to test the adequacy of technological interventions, providing relevant data for improving the technologies. By examining key components of new technologies, the ways the technologies are used, and identifying constraints to system performance, formative research data

can provide clear directions for the development of improvements to these technologies.

Summative evaluation research is used to measure overall new technology impact and outcomes. Summative research is used to document the positive and negative influences and impacts of new health technologies. These data provide important measures of the utility of health information technologies for health care and promotion. Summative data should examine the costs and benefits of the technology and help health care systems determine the effectiveness and long-term utility of employing specific technological products and processes.

Formative and summative evaluation research should not be viewed as separate and unrelated research processes. Rather, formative and summative evaluation can be viewed as different ends of an evaluation research continuum. Formative research looks at the small pieces of the technology, providing a microscopic analysis of the individual components of the product or process. Conversely, summative evaluation looks at the big picture, providing a macroscopic global evaluation of the way these different components work together to accomplish relevant health care/promotion goals. Formative and summative research should work together in the evaluation of new health information technologies. Ideally, formative data informs summative research, providing pieces of the data needed to evaluate overall system impact and outcomes. Results from formative evaluation should be mined and combined in compiling summative evaluations.

4. Audience Analysis Research: Targeting the New Health Technology

Successful technological innovations depend on data gathered through audience analysis research to design programs to fit audience needs. Needs analyses are initial applications of audience analysis evaluation research that gather data from potential product users to establish levels of audience demand and opportunities for new health information technology products and processes [6]. Are there significant performance gaps (differences between the intended and actual outcomes) in current health system products and processes that necessitate technological innovation and intervention? It is essential to begin the process of health technology innovation and product development by examining the perceptions of potential users (audience members) about current technologies in the health care system, identifying limitations to these products, and developing strategies for extension and innovation to increase the effectiveness of products that are not delivering satisfactory service. Careful evaluation of current products and processes in health care/promotion is essential for guiding technological reinvention.

All technological interventions should be based upon clear evidence of what works. There is a

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wealth of important data often lying dormant in every health care/promotion setting that indicates what has and what has not worked in the past to achieve health care/promotion goals. Needs analysis data should reveal whether there is sufficient demand for new technological products and processes for achieving health care/promotion goals to initiate development of new health technologies. Furthermore, audience analysis research will help identify many important user expectations and predispositions that will undoubtedly influence product acceptance and utilization [8].

It is also important to get to know the orientations, attitudes, beliefs, and expectations of audiences for new health information technologies so user interfaces can be designed to meet consumer communication orientations [8; 9]. The more revealing data health information technology developers have gathered about the intended audiences for their products, the better they can target development of products to fit user characteristics and skills [10]. Usability testing will help technology developers to assess the extent to which they have targeted technologies to match the technical skills and needs of users [11]. (The importance of usability testing as a particularly rich evaluation research strategy for determining the extent to which health information technology programs match individual user skills and abilities will be discussed in more depth later in this chapter.)

5. Evidence Based Technological Intervention Efforts

The best technological interventions are based upon strong evidence. Evaluation data should provide evidence about what has and has not worked in the past within the health care/promotion system. It should help demonstrate the need for change and intervention within the system. It should help identify the kinds of technologies that best fit the needs of users and the demands of the social context for interventions. It should demonstrate the utility of proposed interventions, identify the most promising implementation strategies, and test the effectiveness of new health information technologies in action.

There are rich **natural data sources** that should be identified during audience analysis research efforts that can help provide evidence for directing technological intervention and provide data about the relative success of new technological interventions. For example, the evaluation researcher can identify "natural" (normally collected) records of key events (such as product performance, employee attendance, quality control, error rates, usage levels, and sales records) that can provide the researcher with interesting trend data to track system performance before and after the implementation of new health information technologies [6; 12]. Natural data collected before new technology implementation can help provide a clear **baseline measure** from which to track system changes

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that, at least in part, can be tied to the influences of the new health information technologies. (Care must be taken to recognize multiple influences on system performance due to uncontrolled events and extraneous variance, and not to overstate (or understate) the influences of new technologies. Control measures in similar contexts that have not implemented the new technologies can provide important points of comparison for clarifying the impact of new technologies.)

It is a good idea for health information technology evaluation researchers to implement **user response mechanisms** that are built right into the new technological products [13]. These response mechanisms can be both passive (provide invisible data collected automatically by tracking and recording characteristics of technology use) and active (requesting feedback, comments, and suggestions from users). Passive usage data is relatively easy to collect, but can often be misleading if analyzed in isolation of other data. For example, high time of use data may seem to indicate a successful new technology, but it might just as easily indicate that the technology is time-consuming and cumbersome to use. Active response data can suffer from validity issues concerning self-report data (discussed in more depth later in this chapter). Passive user response and active user response data should be analyzed together to clarify user reactions and ideas about the new technologies.

Prior to implementation of new technologies, as well as after technologies have been implemented, it is important to conduct **usability** tests of new health technologies. Usability tests are hands-on evaluations of users' perceptions about and abilities to operate new health information technologies [11]. Usability tests assess technology users' evaluations of their experience with products, including the ease, comfort, efficiency, speed, and effectiveness of use, as well as track these users' actual abilities to navigate the technological products and achieve health care/promotion goals [6]. Can users accomplish the goals the new technology was designed to help them accomplish? How readily can a new user learn how to use this system? Are there ways to improve the usability of this system? Usabilty data will help answer these questions and suggest strategies for refining health information technologies.

6. Methodological Issues and Constraints in Conducting Evaluation Research

A major limitation in the way that evaluation research is often conducted is the **over-use of single point of data collection** evaluation studies, based on the false assumption that one cross-sectional data set will suffice in evaluating new health information technologies. One point in time cross-sectional data will not provide the depth of information needed for most evaluations. It is important to see how new technologies are accepted and utilized over time. There are peaks

and valleys in technology use. Users have to learn about new technology products, get used to them, learn how to use them, experiment with them, and figure out how to adapt the technologies to different applications and situational demands. This learning process takes time. Gathering cross-sectional data (one point in time) is likely to miss the key moments in evolutionary trends of technology implementation and usage, missing both potential strengths and weaknesses of the technology.

A common problem experienced in evaluation efforts is **over-reliance on the use of self-report data.** Self-report data is information requested from respondents through the use of survey research tools (typically with questionnaires and interviews). In many cases self-report data has become the default measurement approach used in evaluation studies. While surveys often provide interesting information, there are serious questions about the veracity of survey responses leading to threats to the validity of survey data, especially in organizational contexts where socio-political pressures can influence responses. It is all too common for respondents to praise new technologies because they fear organizational reprisals from management for providing negative information (the mum effect threat to validity) [7]. Respondents also often try to provide the "right" answers to surveys to please researchers and management (the Hawthorne effect threat to validity) [6]. Sometimes survey respondents just give the same, most expedient answers to survey questions to get through with the survey quickly (the response-set threat to validity) [6]. Due to these threats to validity, caution must be taken in interpreting survey data in evaluation studies.

Evaluation researchers often focus on **tangential variables** (variables that are not directly relevant to research goals), especially with the use of standardized survey instruments. These standardized scales can be attractive to use due to their established reliability, availability, and ease of use (the law of the hammer) [6]. The variables measured in many of these standardized scales (such as health beliefs, personality attributes, and attitudes) are not always relevant to the technological products and processes being evaluated. These tangential variables inevitably provide weak and equivocal evaluation data. Technological evaluation research depends on the measurement of important variables that provide data of direct relevance to the goals set for the products and processes under examination.

Another problem that often limits the effectiveness of evaluation research efforts conducted for new health information technologies is over-reliance on **shallow data**, such as the number of web hits. Such data are very equivocal and difficult to interpret due to limited information. Conclusions made based on such data are often unwarranted. For example, does increases in the number of hits (log-ons) to a new web-based health information dissemination program indicate the

program has been successful at achieving health promotion goals? Not necessarily. Additional information is needed. Who is accessing the website? What is their experience with navigating and using the website? What kinds of information are users getting from the site? How are these individuals using information from the site? What impact has the information they have accessed had on their health behaviors and health conditions? Effective evaluation research of health information technologies must answer these key questions.

7. Data Reduction and Information Overload

The way that evaluation research results are presented is fundamental to making the findings from the research useful. Consumers of evaluation research need to understand the strengths, weaknesses, and overall influences of new health information technologies. All too often, evaluation data are presented in ways that do not communicate well to different audiences, increasing information overload in health care systems, rather than increasing understanding. Statistical presentations of evaluation research results are often complex and confusing for many audiences. To get the most out of evaluation research, researchers have to translate findings in clear and compelling ways. Strategic use of tables, charts, and examples can help technology managers and users interpret and apply evaluation research findings [6]. Researchers must clearly identify the implications,

applications, and limitations of evaluation research.

8. Methodological Recommendations for Conducting Evaluation Research

The following suggestions are designed to help researchers increase the effectiveness of their efforts to evaluate new health information technologies:

- **Longitudinal Evaluation Research Designs.** It is important to develop longitudinal evaluation research designs that gather data at multiple points in time to capture the evolution of technological implementation and use. In fact, it is a good idea to build in strategies for continuing measures of both passive and active evaluation data over the life of the health information technology, beginning from before implementation to establish clear baseline data.

- **Multi-methodological Research Designs.** Multimethodological research designs combine different methods to offset the weaknesses of each method with the strengths of other methods [6]. It is a particularly good idea to augment the use of self-report survey research with other measures to help establish the validity of survey results. Multiple measures can provide important complementary perspectives for analyzing health information technologies.
- **Combining Quantitative and Qualitative Data.** While

quantitative data can be powerfully analyzed statistically, quantitative data often fails to provide great depth of explanation. Alternatively, qualitative data (gathered from unstructured interviews, focus groups, observations, etc.) can usually provide great depth of information and can be profitably combined with more traditional quantitative research methods in evaluation efforts [6]. Triangulation of quantitative and qualitative measures can afford the evaluation researcher both precision and depth of analysis.

- **Unobtrusive Evaluation Measures.** Wherever possible, evaluation researchers should design non-reactive data gathering strategies into evaluation efforts, such as measures that do not depend upon respondents self reports (unobtrusive measures) to increase the validity of evaluation research [12]. By observing naturally occurring data, such as examination of archival records and the natural build-up (accretion) or wearing away (erosion) of observable elements in social contexts, researchers can often reach strong conclusions about social behavior that are not influenced by social and political constraints. Unobtrusive data can also be used to check the validity of self-report data, increasing confidence in conclusions reached from survey research [6].

- **Communication and Health Outcomes Variables.** By measuring relevant health outcome variables, evaluation researchers can assess the impact of new health information technologies on important health consequences, such as users' knowledge, attitudes, behaviors, and health states [14]. Measurement of important health outcomes is especially important in summative evaluation to identify the contributions of the technological programs and processes.

- **Translating Data into Practice.** A significant advanced step in the evaluation research process is interpreting data and applying them to action strategies for increasing the effectiveness of health information technologies. It is not enough to just describe evaluation data; data must be leveraged into real activities for achieving important health care/promotion goals [9]. Too often rich evaluation research data are merely reported and not applied to the development of interventions for refining and improving health information technologies. Translating data into practice is an essential culminating step in evaluation research.

Using Evaluation Data to Demonstrate Progress. Evaluation research should provide clear

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information about the contributions of new technologies to the accomplishment of important health care/promotion goals and outcomes [15]. By tracking progress, evaluation researchers can identify the achievements and shortfalls of new technologies, helping to direct the development of future health technologies for enhancing health care and health promotion [16].

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John Moore, Henry Lieberman / Flexibility and Constraints in Patient Interviews in World Health Strategy" eBook, (Ed.) Renata G. Bushko, FHTI, 2016. www.Futureofhealth.org From Strategy for the Future of Health (Ed.) Renata G. Bushko, IOS Press 2009

Chapter 19: Flexibility and Constraints in Patient Interviews

John Moore M.D.
Henry Lieberman Ph.D.
MIT Media Laboratory, Cambridge, MA, USA

Abstract

Increasing understanding of how to categorize patient symptoms for efficient diagnosis has led to structured patient interviews and diagnostic flowcharts that can provide diagnostic accuracy and save valuable physician time. But the rigidity of predefined questions and controlled vocabulary for answers can leave patients feeling over-constrained, like the doctor (or computer system) is not really listening to them. In addition, not hearing the patient's own words can lead to the physician overlooking subtle details that are diagnostically relevant. How can we reconcile the need for patients to express themselves with the doctor's need to understand the patient's experience in medically appropriate terms?

We present **I'm Listening**, a system for automatically conducting patient pre-visit interviews. It does not replace a human doctor, but can be used before an office visit to elicit complaint details. This information can be used to triage care and prepare patients for visits with educational materials and appropriate tests, making better use of both doctor and patient time. It uses an on-screen avatar and natural language processing to (partially) understand the patient's response. Key is a Commonsense reasoning system that lets patients express themselves in unconstrained natural language, even using metaphor, and that maps the language to medically relevant categories. For example, if a patient describes his or her pain like, "someone sticking in a knife and then turning it", the system could categorize it as sharp, intense, and localized.

1. Introduction

Jane is a 63 year old woman who is having trouble with her vision. She describes her chief complaint to the doctor's receptionist over the phone as, "I see floating things in my vision that aren't really there". Before seeing the doctor, she is given a new computerized medical questionnaire to fill out. It takes a standardized new-patient medical history, complete with disease and hospitalization history. Since her complaint is visual, she is given a vision-specific questionnaire. Among the questions, it asks, "Do you see flashes of light in your vision?" She answers, "No".

When Dr. James sees Jane, he looks over the summary of her answers. In a case like this, he suspects posterior vitreous detachment (the vitreous jelly in the back of the eye condenses over time and separates from the retina causing opacities commonly known as "floaters"). Since she answered "No" to the direct question about flashes of light, his suspicion of a complication such as a retinal tear or detachment is low. He asks a series of questions and examines her. In his exam, he sees clear evidence of posterior vitreous detachment. His exam is cursory since he sees this all of the time without complications. Just at the end of his

exam, however, he sees a small retinal tear. He is relieved that he did not miss this important finding, but he is confused. He decides to revisit the topic with Jane. "Are you SURE that you're not seeing flashes of light in your vision?". "Yes, I'm sure." she says, "Um... well... I am seeing something, they're not flashes, but they're more like squiggly little lines, kind of like those you see at Fourth of July fireworks, and they come and go."

Dr. James realizes that her answer should have been a "Yes". But she wasn't lying or mistaken, it's just a matter of how the questions and answers are interpreted. Patients sometimes don't understand the vocabulary of medical questionnaires, and when they are forced to choose an answer, the most appropriate choice is not always clear. Questionnaires put words into people's mouths. Human experience is a complicated thing; we don't have enough words in our language to capture all the subtleties of how people experience their bodies.

Our goal is to improve the use of online medical questionnaires, diagnostic flowcharts, and automated medical history and diagnostic systems. We want to provide more flexibility in the way computers interpret what patients say and how the computer responds to them. We aim to reconcile the desire of people to express themselves in their own terms with the need to categorize responses and follow predefined diagnostic procedures (and know when to depart from them).

Our key tools are a mixed-initiative natural language understanding system that can interpret patient responses and a Commonsense reasoning system that has a broad understanding of topics of everyday life. The latter is essential because it provides the ability for the patient to express themselves in metaphorical language ("like Fourth of July fireworks") that can be mapped, either by a system or by a doctor, to medically relevant vocabulary and categories.

For example, a patient can type, "I have been having stabbing pain in my right foot for five days that gets worse when I walk." The system will identify the medical problem as "pain", location as "right foot", duration as "five days", and aggravating factor as "when I walk". In addition, it is able to reason that "stabbing" pain should likely be categorized as "sharp" since a knife can be used for stabbing and knives are sharp. The system then takes a conversational approach to the confirmation of each of the attributes that were determined. The advantage of this technique is that it not only obtains crucial information for the physician in a patient-friendly manner, but it also becomes a learning tool for the patient. It is essentially a dress rehearsal for the patient before visiting the office. Patients can learn what kinds of questions to expect every time that they have a complaint so that they can express themselves more clearly and have their problems addressed more appropriately.

2. Background

2.1 Physicians as Interviewers

Traditionally, physicians consider themselves to be excellent patient interviewers. There is significant

research, however, suggesting that this is not true today. They are generally not good listeners. During a standard encounter, studies have shown that physicians interrupt patients in less than 24 seconds.[1,2] In addition, they are not good at explaining medical findings in that they often use terminology that is not well understood by patients.[3] Finally, they are not good at being thorough and performing exhaustive questioning. A study of primary care physicians shows that they asked only 59% of essential history items.[4] In addition, it has also been shown that up to 54% of patient problems are not elicited by physicians.[5] It should be clarified that much of the fault here lies on the constraints that have been placed on physicians and not on their skills. They have limited time for visits and are expected to pick up problems that are not associated with the main reason for a visit. This suggests that we need to design good assistive technologies for physicians, and there is good evidence that data collection is an area where physicians can use help.

2.2 Computer-Based Medical Questionnaires

A great deal of research has been done, starting in the 1960s, to prove the benefit of computer-administered medical interviews and questionnaires.[6,7] Bachman[8] provides an excellent review of the literature. As opposed to physicians, computer systems are very good at patiently listening, using patient-appropriate language, and being thorough. In fact, it has been shown in numerous studies that patients report sensitive health information more reliably to computers. These studies have included alcohol use[9], drug use[10], sexual activity[11], suicide attempts[12], and domestic violence[13] among others. Patients have also reported that they appreciate interacting with computer systems because they do not feel rushed and do not feel like they are being judged.

Although it is true that computer-based questioning systems are well received by patients and that they outperform physicians in eliciting thorough histories, their adoption is currently very poor. Statistics are not available, but with only 13% of doctors in this country using electronic medical records and only 4% of them using more advanced systems[14], it is clear that well less than 1% of them are using computer-based questionnaires. In addition, even though patient responses to individual encounters have been positive, little research has been done on optimizing user experience by using more complex interaction techniques so that long-term interactions can be sustained.

2.3 Major Flaws in Current Medical Questioning Systems

- Systems are not Completely Automated Current systems, such as the one outlined in the introduction, require a human to briefly interview the patient in order to choose the appropriate questionnaire for the patient's chief complaint. There are a number of significant problems with this paradigm. First of all, it involves the communication of sensitive health information to someone other than the physician. Despite new laws for health privacy such as the Health Information Portability and Accountability Act (HIPAA)[15], there is still significant risk for

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breach of confidentiality. Secondly, it typically requires that the patient come into the office to speak to a staff member and complete the survey. This defeats the purpose of automated medical questioning in that the potential for efficient triaging and staging of diagnostic laboratory tests before the visit is removed. In addition, the opportunity for the patient to complete lengthy interviews from the comfort of home is lost.

- **Focus on Efficiency Leads to Unfriendly Experience**

Current systems are designed for maximum efficiency with text-based interfaces with rigidly structured question sequences. Patients may find them novel and interesting on the first encounter, but long-term studies have not been conducted to determine patient satisfaction. Discussions with providers using such systems, however, suggest that patients find these systems tedious and impersonal on multiple encounters.

Tim Bickmore is an alumnus of the Media Lab who is now the lead of the Relational Agents Group at Northeastern University. In his doctoral thesis, he designed a relational anthropomorphic agent that used empathetic remarks and affective facial and body gestures that were appropriate to the state of the relationship in the context of exercise behavior modification. He found that subjects chose to continue interacting with relational agent over a non-relational anthropomorphic agent. In addition, they rated the bond component of the therapeutic alliance inventory higher for their relationship with the relational agent, suggesting that they had a better working relationship with this empathetic agent.[16]

There are many people in the field of human computer interaction who argue for interfaces that are maximally efficient over those that are chatty and friendly. It is certainly true that in many scenarios, users appreciate an interface that is quick and minimal, but it is hypothesized that this type of interface will not be sustainable in the area of automated medical questioning. Since medical questioning is inherently a conversational situation, there is likely significant benefit that will be obtained from enabling the interface with human-like conversational techniques.

- **Rigid Categorization and Controlled Vocabulary Limit Patient Expression**
  Current systems rely solely on forced-choice responses and do not capture the richness of patient input. This can be dangerous because important details can be lost as portrayed in the patient scenario. In addition, it can be frustrating for patients because they feel that they are not being listened to appropriately. The system always forces a choice that typically does not match exactly what the patient want to express.

- **Value of the Interaction is not**

Proven to the Patient
Patients spend a great deal of time answering questions offered by current systems, but the benefits from spending this time are not clearly demonstrated to them. If patients do not feel that the time that they spend interacting with a technology is fruitful for them, it is likely that they will resent it. In addition, they will likely resent the physician for making them speak to a computer and limiting face-to-face time.

3. I'm Listening

I'm Listening is a system for automatically conducting patient pre-visit interviews. It aims to take a dramatically different approach than current computer-based medical questionnaires in order improve patient experience and the usefulness of the data obtained. The goal is for the system to parallel the conversational approach of a physician as closely as possible. Physicians are trained to develop rapport in their interviews with patients while at the same time collecting categorized information that is crucial in diagnosis and treatment planning. They are able to make the patient feel attended to even though they must drive the majority of the interview in order to get the required information.

3.1 On-Screen Avatar

I'm Listening currently communicates with the patient through an on-screen avatar using computer-generated speech through a text-to-speech engine. The avatars, Laura and Karen, were designed by Tim Bickmore of the Relational Agents Group at Northeastern University. They are capable of changing her proximity and facial expression in order to match the emotional content of their speech.

3.2 Mixed-Initiative Natural Language Understanding System

Physicians are typically trained to take an approach with patients starting with open-ended questions and then drilling-down with more constrained questions. **I'm Listening** takes this same mixed-initiative approach to eliciting patient chief complaints. The chief complaint is the term used to describe the patient's main reason for a visit to the physician. The agent starts with the open-ended question. "What is the main reason for this visit? By that I mean, what is the one problem that is bothering you the most?" The patient is able to enter a complaint that is one sentence or shorter. The system then uses a context-specific natural language understanding algorithm to process the complaint. The algorithm uses tagging, chunking, and parsing rules specific for chief complaints and is capable of identifying the core medical complaint as well as onset, duration, frequency, location, radiation, intensity, character, and aggravating and alleviating factors. For example, a patient can type, "I have been having pain in my right foot for five days that gets worse when I walk." The system will identify the medical problem as "pain", location as "right foot", duration as

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"five days", and aggravating factor as "when I walk". The system is robust in that the patient could have also typed, "My right foot has been hurting for five days when I walk" or "For five days, there has been pain in my right foot when I walk" or even non-grammatical sentences such as "right foot pain five days when I walk."

Of course the natural language processing algorithms will make mistakes. To address this problem, the system takes a conversational approach to confirming each of the conclusions that it makes. It starts with the most crucial conclusion, which is the core medical problem coupled with the location if appropriate, and progresses to other groups of conclusions. The agent will ask, "It sounds like your problem is right foot pain, is that correct?" If any component of the conclusion is wrong, the system will elicit from the patient which component so that only that one is addressed. It might initially appear to some that such an approach is inefficient and could be tedious. In fact, however, this type of conversation is very similar to the way that a physician conducts an interview. Confirmations not only assure that details were heard correctly, but they also serve the purpose of making the patient feel as if the physician (or computer) is actually listening. If a conclusion is wrong, the system apologizes for the error and elicits the detail in a more constrained frame. It is hypothesized that this apology will help to minimize the user's perception of error rate since there is some evidence that affective support and apology are valuable in minimizing user frustration.[17]

There are a number of advantages of using this natural language approach to eliciting patient complaints. First of all, it allows for the collection of not only the patient's free text complaint, but also the categorized attributes of the complaint, which are useful for the physician. In addition, it performs this whole process in an automated fashion, so that it can be carried out in the comfort of the patient's home without requiring sensitive patient information to be communicated to any third party. It also gives the patient a feeling of being listed to, so that, when the system progresses to more forced-choice questions, these are more acceptable to the patient. Finally, it becomes a learning tool for the patient. The system always asks the patient: "When did the problem start?", "How long has it lasted?", "Is there anything that makes it worse?", "Is there anything that makes it better?", etc. Eventually the patient will start to add these details to the complaint so that the system will not have to ask. The patient starts to understand the attributes of complaints that are important in communication with the physician. Instead of saying, "Aunt Sally thinks that I have pneumonia," they will start saying, "I have been having difficulty breathing for five days that is associated with a productive cough and mild fever."

3.3 Commonsense Reasoning System

New techniques have been developed to allow open-ended responses from patients to be

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mapped to system-established choices. The goal is to let patients express themselves and to capture the richness of patient input but, at the same time, to allow the decision tree to proceed appropriately. The approach being used borrows techniques from a new trend in artificial intelligence called Commonsense computing.

The Open Mind Common Sense (OMCS) project is a distributed solution for the collection of common sense knowledge.[18] It enables the general public to enter common sense information through a web interface with 18 different semi-structured frames such as "_____ is a kind of _____" or "_____ is used for _____". In this way, knowledge is entered using natural language, but in a manner that is more reliably machine-interpretable. ConceptNet is then a semantic network representation of the knowledge in OMCS that can be used to explore concepts using advanced techniques including spreading activation.[19], [20] It also allows the translation of the machine-interpretable information back into natural language. Finally, AnalogySpace uses principal component analysis to allow users to infer new common-sense knowledge and to compare concepts.[21]

Our Commonsense reasoning system for mapping open-ended patient input to system-established choices uses both ConceptNet and AnalogySpace. The preliminary implementation allows patients to express complaints involving pain. Pain was chosen because it is the reason for over 70 million medical visits per year and because the language used to describe pain complains is some of the most complex. Rather than making the patient choose from a list the word that best characterizes his or her pain, the system gives the patient the opportunity to free-text a description of the pain. The system then stems each of the words in the input and progresses through a series of four main algorithms to attempt to categorize the input.

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Figure 1: Patient's pain description matches a pre-defined category.

- Otherwise it is determined if the stemmed input is already a node in ConceptNet, indicating that there is information concerning it in the OMCS database. If so, then it is determined if any of the predefined pain categories is a property of that node with the "HasProperty" relationship. The patient is prompted for confirmation. For example, if the input is "a knife", ConceptNet knows that "a knife" is "sharp." The system presents the association in natural language as shown below.

Figure 2: Patient's pain description has a direct relationship with one of the pre-defined categories. Confirmation is required to determine if the relationship is valid.

- Otherwise AnalogySpace is used to evaluate the possibility that the stemmed input has a "HasProperty" relationship with each of the predefined pain categories. The scores from each evaluation are compared to determine the relationship that is most likely. The patient is prompted for confirmation. For example, if the patient inputs that his or her pain is like a "chainsaw", there might not be a direct relationship between chainsaw and any of the categories of pain. ConceptNet does know that a "chainsaw" is used to cut and that a knife is used to cut and that a knife if sharp. AnalogySpace therefore rates the possibility that a chainsaw is sharp with a relatively high score. Again, the results a conveyed to the user through natural language with the suggestion that the system thinks that the relationship is possible, but that its confidence is lower.

Figure 3: Patient's pain description does not have a direct relationship with one of the pre-defined categories, but there is an indirect relationship. The confirmation language reflects the uncertainty of the inference.

- If the second and third algorithms fail, then the patient is prompted to choose directly from one or two of the predefined pain categories. If the patient thinks that the chosen categories describe the initial input well, then those categories are added as "HasProperty" relations to the input in the OMCS database.

Although this Commonsense reasoning system has been initially developed to deal with pain complaints, it can now be generalized to deal with any free-text patient input that needs to be mapped to pre-defined categories. The advantage of this approach is that, as more patients interact with the system, the system becomes more intelligent. Once one patient confirms a relationship that did not previously exist, the system will be able to relay the possibility of that relationship to the next patient with a similar input. In addition, the more patients who match a given input with a given category, the higher the confidence the system will have in that relationship and this can be expressed in the language that it uses. Quickly the system will not need to use general information to make associations, but will be able to use context-specific associations that are created from the many users interacting with it.

Just as with the natural language understanding system, not only does the physician receive the categorized version of the patient input, but also the patient's own words describing each aspect of a problem. In this way, the system is flexible yet provides a constrained output.

4. Related Work

As discussed in the background section, there has been a significant amount of work done in the area of computer-based medical questioning. This work has foc structured, forced-choice, non-conversational decision trees as opposed to our work that aims to allow conversational structure with more open-ended patient prompts while still capturing structured data that satisfies the goals of a decision tree. Outside of the field of medicine, there are many examples of natural language based conversational systems. These systems typically use statistical inference to drive program flow in cases where input is open ended. The drawbacks of statistical techniques are that the reasoning behind an inference cannot be determined and that there is no opportunity for reasoning outside of previously encountered examples. Our approach of mapping open ended responses to categorical outputs using Commonsense inference is novel in this respect because the semantic relationships between concepts can be used to construct meaningful conversational moves and new responses can potentially be mapped to appropriate outputs through the use of other semantic relationships that are known in the Open Mind Commonsense Database.

5. Conclusion

Doctors are beginning to benefit from the assistance of computers, but they are going to need even more help in the future to keep up with a tremendous influx of data and increasing need from patients. This does not mean, however, that we need to force patients to interact with unfriendly and inflexible robots in order to get the structured data that is needed. **I'm Listening** is a system for automatically conducting patient pre-visit interviews that presents a number of important advances including a mixed-initiative natural language understanding system and a commonsense reasoning system. These advances are key components that will allow for conversational systems that can mimic important aspects of doctor-patient communication so as to make the interaction friendly and flexible for patients while at the same time collecting structured and categorized that is usable by the computer and useful to the physician.

6. Future Work

Immediate work on this project involves generalizing the Commonsense reasoning system so that it can deal with a broad range of medical complaints. In addition, testing the system on a large number of patient complaints will be crucial in determining its initial performance and its learning abilities.

ance and its learning abilities.

The work highlighted here is part of a larger effort by the New Media Medicine group at the MIT Media Laboratory to enable radical new collaborations between doctors, patients, and communities. The goal is to develop technologies that allow patients to take a more active role in their care such that they become equal partners with their medical providers. One project that is being developed in parallel is a multimodal (speech and touch) workstation for doctor-patient shared decision making. A goal is to integrate the agent from **I'm Listening** into this interface so that there can be three way conversations between the doctor, patient, and technology. This will likely have profound effects on the psychological relationships that patients will have with the agent and their evaluations of the value of such a system. Another project being developed by Ian Eslick of the New Media Medicine group is a collective intelligence system for disease communities. The agent-based conversation techniques will also be adapted to allow for more patient-friendly data input in this system. It will be a recurring theme of the group's work to design technologies that not only improve the health of patients but also engage them and make them feel better about their healthcare experience.

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Christopher Previte, The Value of Impermanence in Design, Chapter 20 in "World Health Strategy" eBook, (Ed.) Renata G. Bushko, FHTI, 2016. www.Futureofhealth.org

Chapter 20: The Value of Impermanence in Design

Christopher Previte
New England Institute of Art, Brookline, MA, US
Mount Ida College, Newton, MA, US

Abstract

Many spaces on the web (social media, photo sharing, genealogy sites, etc.) ask us to document so much of our lives. There is an implied permanence to these collections and they are used as currency in making and maintaining social relationships. This need to document and save everything is only half the story however. Here we will discuss the value of impermanence and ways we can incorporate it into our design practice.

1. Introduction

Artists, designers and programmers focused on interactive design are alternately referred to as User Interface (UI) and User Experience (UX) Designers. These terms are relatively new and can include those who work in graphic and web design, programming, visual design, and mobile design and development.

UI design addresses how users interact with machines, computers, and software. It addresses all points of input and output, both physical and virtual. These can include keyboards, buttons, menus, screens, and windows. The goal of UI design is to make this interaction easy, efficient, and enjoyable.

UX design addresses the quality of those interactions governed by the UI. UX concerns are more intangible and speak to concepts such as atmosphere, personality, familiarity, and comfort. Good UX design remembers that "users" are, in fact, humans.

Despite this, the marriage of UI and UX design, and the products and spaces they help to create, often overlook many aspects of the human experience. Here we specifically want to speak about the balance between documentation and impermanence. What is permanent versus what is ephemeral. Much interactive design for the web focusses heavily on the former with little to no attention paid to the latter.

2. Documentation

noun

1. the process of classifying and annotating texts, photographs, etc.[1]

2. the photos taken during a night of sin that "document" all of the less that glamorous moments. These may include random drunk dancing, any shirt malfunctions, dress mishaps; ending with bare ass being visible to the public eye.[2]

2.1 By the Numbers

Facebook

- As of 2013, there were over 250 billion photos on Facebook[3]

- That's an average of 217 photos per user

Facebook users upload a total of 350 million new photos each day

Flickr

- As of 2013, there were about 3.57 billion photos on Flickr[4]
- Users upload an average of 586 million per year, or 1.6 million per day

Ancestry, MyFamily, Genealogy.com

- Users and employees added about 1.2 billion documents to their database last year[5]
- 2.7 million users generate an average of 75 million searches per day

Twitter

- Every second, on average, around 6,000 tweets are tweeted (over 350,000 per minute, 500 million per day and around 200 billion tweets per year)[6]

2.2 Driven by Smartphone Adoption

- 64% of all US mobile phones are smart phones[7]
- 80% of new mobile phone purchases are smart phones

2.3 Opportunities for Content Creation and Design; Opportunities for User Anxiety

- In 2014, Zhiling Tu, Yufei Yuan and Norm Archer (of McMaster University in Hamilton, Ontario), writing in the "International Journal of Mobile Communications" explained that: Smart phones and other portable digital devices have led to more and more people "carrying with them" valuable data assets wherever they go.[8]
- A 2012 study showed that 73% of respondents would feel "panicked" and 14% "desperate" if some catastrophic event caused them to lose access to their mobile devices and online life.[9]

2.4 This Need to Document and Reliance on Connectivity Creates an Imbalance in the Human Experience

- Online culture and mobile connectivity will continue to grow, but it must also evolve.
- Alternative means of interaction that speak to the entire human experience can influence user experience.

3. Impermanence
noun

1)The state of not being permanent.[10]

2)The term expresses the Buddhist notion that all of conditioned existence, without exception, is in a constant state of flux.[11]

3.1 The Buddhist Notion[12]

Early Buddhism dealt with the problem of impermanence in a very rationale manner. This concept is known as anicca in Buddhism, according to which, impermanence is an undeniable and inescapable fact of human existence. The early Buddhists did not believe in the existence of a permanent and fixed reality. According to them what was apparent and verifiable about our

existence was the continuous change it undergoes.

Take for example the life of an individual. It is a fallacy to believe that a person would remain the same person during his entire life time. He changes every moment. He actually lives and dies but for a moment, or lives and dies moment by moment, as each moment leads to the next. A person is what he is in the context of the time in which he exists. It is an illusion to believe that the person you have seen just now is the same as the person you are just now seeing or the person whom you are seeing now will be the same as the person you will see after a few moments.

Even from a scientific point of view this is true. We know cell divisions take place in each living being continuously. Old cells in our bodies die and yield place continuously to the new ones that are forming. Like the waves in a sea, every moment, many thoughts arise and die in each individual . Psychologically and physically he is never the same all the time. Technically speaking, no individual is ever composed of the same amount of energy. Mental stuff and cellular material all the time. He is subject to change and the change is a continuous movement.

Impermanence and change are thus the undeniable truths of our existence. What is real is the existing moment, the present that is a product of the past, or a result of the previous causes and actions.

3.2 The Value of Impermanence13

- Impermanence brings us hope.

- Impermanence embodies the spirit of freedom and shatters the concept of predestination.

- Impermanence denies the control of gods.

3.3 Impermanence in Action Oral

Tradition

The "oral tradition" refers to "the lore of cultures. It is transmitted by word of mouth and consists, as does written literature, of both prose and verse narratives, poems and songs, myths, dramas, rituals, proverbs, riddles, and the like. Nearly all known peoples, now or in the past, have produced it."[14]

Person Perception[15]

- Refers to the different mental processes that we use to form impressions of other people.

- Can be a very subjective process that can be impacted by a number of variables.

- We often form impressions of others very quickly with only minimal information.

- We frequently base our impressions on the roles and social norms we expect from others.

The Rest of the Story[16]
Understanding the value of personal perception as it relates to the events in our lives.
The Importance of Imagination

- Imagination is the ability to form new images and sensations in the mind that are not perceived through senses such as sight, hearing, or other senses.
- Imagination helps make knowledge applicable in solving problems and is fundamental to integrating experience and the learning process.
- A basic training for imagination is listening to storytelling.[17]
- The Swiss developmental psychologist and philosopher, Jean Piaget[18] posited that perceptions depend on the world view of a person.
- The world view is the result of arranging perceptions into existing imagery by imagination.
- Piaget cites the example of a child saying that the moon is following her when she walks around the village at night.
- Imagination is needed to make sense of perceptions.[19]

4. Balance
noun
1. A condition in which different elements are equal or in the correct proportions.[20]
2. The ability to remain on ones feet.[21]

4.1 Leaving a Place for the Viewer/ User

- It has been said that no work of art is complete until someone experiences it.[22]
- Classic art often left room for the viewer.[23]
- What the mind can imagine, is often better than what you can show.[24]
- Respect your audience's intelligence.[25]

4.2 An Example of Balance
SnapChat [26]

- Building Snapchat has taught us a lot about what makes conversation special.
- An application for sharing disappearing pictures.
- The notion of deletion by default.
- Keep what you want, and we'll get rid of everything else!
- Snapchat was missing an important part of conversation: presence.
- There's nothing like knowing you have the full attention of your friend while you're chatting.
- When you leave the chat screen, messages viewed by both you and your friend will be cleared

Impressions

- Through conversation and observation we create impressions of one another.
- Impressions however, are impermanent and with the addition of more data over time, evolve.
- Some impressions disappear entirely.
- A tool based on the impermanence of impressions could be useful in many situations utilizing a variety of ever-changing data.

5. Conclusions

Human centered design should strive to create a sense of comfort and build trust amongst users. When documentation exists with no thought of impermanence, users are denied a certain amount of control and the naturalness of human interaction. Human interaction, away from our digital life, allows us to live in the moment, be conversational, and understand that many things are temporary. What's more, our undocumented memories of these moments are allowed to evolve and carry different meanings throughout our life. In a very specific way, germane only to us, they become part of who we are through time.

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Xiu-Min Li / Chapter 22: Can Chinese Herb-based Medicines Heal the Immune System and Cure Allergies? in "World Health Strategy" eBook, (Ed.) Renata G. Bushko, FHTI, 2016. Futureofhealth.org

Chapter 22: Can Chinese Herb-based Medicines Heal the Immune System and Cure Allergies?

Xiu-Min Li, MD
Professor, Professor of Pediatrics, Jaffe Food Allergy Institute,
Icahn School of Medicine at Mount Sinai, New York City

Abstract

This chapter explores the science and practice of adapting traditional Chinese medicine (TCM) to treat the modern epidemic of allergic diseases such as eczema, asthma, and food allergies and correct imbalances in the immune system. These diseases have burgeoned with the changes associated with Western models of economic development, diet, and treating disease. They have resisted pharmaceutical cures. The TCM formulary has a long track record of treating conditions in the skin, airways, and digestion. In our research and my practice, we use derivatives of the classical formulas to treat all the organ systems involved in a disease rather than single systems and symptoms. Contemporary science gives us the ability to refine the medicines to increase potency, and make them more compatible with patient behavior. We chose this path because patients are suffering, and depriving children of their childhoods.

1. Introduction

Allergic diseases are a significant health problem in "Westernized" countries. They are a tremendous burden on quality of life for both patients and their families, and health care expenditures for the society as a whole. Food allergy in particular has no definitive treatment. For many years, the rise of allergic disease has been widely attributed to the "hygiene hypothesis" which contends that hygiene and other byproducts of modern life have deprived our immune systems of their natural enemies such as parasites and microbes, and have turned on normally harmless proteins in food. But a more varied set of explanations has emerged.

One researcher traces the beginnings of epidemic levels of sinus allergies and asthma to the creation of afternoon children's television programming, which shifted afterschool activity indoors. [i] More recently, depletion of the protective microbiome through overuse of antibiotics and Caesarian section has come under scrutiny.[ii] So have changes in gene expression—not the DNA itself but switching the genes on and off—which can be induced by environmental factors and stress. These epigenetic changes can be passed to offspring and may account for the accumulation of allergic tendencies from one generation to the next. While the specific etiology of individual cases of allergic disease is difficult to pin down, what we do know is there is an imbalance of innate immunity, which is governed by one set of T helper cells, known as Th1 and acquired immunity, Th2. The medical challenge is to reset that balance.

The term "atopic march" describes the progression of allergic disease from early infancy, in the form of eczema, through sinus allergies

and asthma, to food allergies. These are diseases of the tissue that faces the external environment where the immune system is potent—the skin, the airways, and the digestive tract.

The accustomed medical approach is to control the response through medication and curtailing exposure. Certainly these are valid and important. But medications have problems of their own. For example, corticosteroids, which are used in various formulations to control inflamed skin, sinuses, lungs and the esophagus depress innate immunity, can damage tissue, and can produce both depression and anxiety. Limiting exposure particularly to food allergens is difficult because sensitization happens early, usually to the most common foods in the customary diet, such as peanuts, milk, and eggs, which are often eaten alone or are additives to prepared foods.

Traditional Chinese medicine has been used effectively to treat diseases of the gut, airways, and skin for thousands of years. Western science allows us to study the underlying mechanisms of disease and treatment. TCM practitioners know that their medicines work, but the science allows us to understand how and why they work, and how to make them more effective.

2. Dual Approach to Research and Clinical Efficacy

After years of discussion, in 2000, the FDA recognized the importance of the movement towards alternative medicine by issuing the Guidance for Industry Botanical Drug Products, which states that active constituents in a botanical drug might not need to be identified when studying an investigational new drug if this is shown to be infeasible. Instead, the FDA will rely on other tests, including chromatographic fingerprints, chemical assays of characteristic markers, and biological assays, to ensure the quality, potency, and consistency.

In this changing landscape, we began to explore the possibility of applying the lessons of thousands of years of Chinese medicine to a modern global epidemic.

We have been pursuing this research on two tracks. One is the protocol for pharmaceutical development in full accord with our regulators. We have two certified investigational drugs, one for food allergies and one for asthma.

I also use medicines in current treatment for a range of co-morbid allergic diseases in weekend private practice, mostly with children, where we not only see very encouraging results and gain insights that can be used to refine and adjust the medicines. These patients and their parents feel poorly served by standard of care from their allopathic physicians. We also conduct “practice-based research” on a smaller scale and at less cost than full clinical trials.

It is important to recognize that these drugs work with one another. While we have registered investigational drugs for food allergies and asthma, in practice the different medicines are administered in combination to treat the co-morbid conditions. They also are delivered in different forms, some by mouth and

others via the skin, to enhance absorption.

3. Eczema

Eczema, which is often used synonymously with the term atopic dermatitis, has gained new prominence in discussions of allergic disease. It has long been considered the first sign of allergic tendencies in small children, but we are only beginning to understand how central a role it plays in the atopic march. Healthy skin is a barrier to infection and irritants. An imperfect barrier, inflamed and dry, allows these things to penetrate. This imperfect barrier has been attributed to a filaggrin mutation. The peanut-allergy epidemic has led to a new prominent line of research that attributes sensitization to peanuts not to ingestion but to infant exposure to peanut protein in the home. As discussed above, the first line of pharmaceutical defense is to reduce inflammation, but while the immediate inflammation may be reduced, persistent use of topical steroids can weaken the skin further and in infants especially weaken innate immunity to infection. Another necessary treatment is the application of emollients, but these may contain potentially allergenic ingredients that may sensitize patients. While not life threatening, as measured by various quality of life scales, eczema is even worse day-to-day than other asthma or serious food allergies.

The peanut allergy epidemic, which has attracted so much attention to allergic disease, has led to a possible role of the skin as the starting point for allergic sensitization. British researchers have found that peanut residue is stubborn and biologically active in homes where lots of peanut products are consumed. Eczematous skin is vulnerable to these residues, which can penetrate in sufficient quantities to start an immune response.

Starting with medicines to treat open wounds and burns suffered in combat dating from the bellicose Tang Dynasty (618-906), we developed a protocol of an internal remedy and two external remedies to treat the skin. We have used these to treat dozens of patients, and studied 14 of them retrospectively who began with recalcitrant eczema. They were aged six months to 52 years with various co-morbid asthma, environmental allergies, and food allergies. Half had been treated intermittently with oral corticosteroids before starting TCM, including five who had taken oral steroids in the previous three months. Three had taken immune suppressants usually used by organ transplant patients to combat rejections. All patients reported topical steroids on-and-off, including half in the three months prior to presentation. Median quality of life as measured by the SCORAD Index (0-103), was 89. [iii]

The internal remedy is *Erka Shizheng Herbal Tea*, in practice called Shi Zhen tea, an extract of nine herbs. The external ones are a bath additive containing eight individually extracted herbs, an herbal cream containing two herbs, and a paste made from herbs used in our food allergy herbal formula.

Three months after therapy began, oral steroid use fell 25%. Topical steroid use went down 21% after three

months. The reduction in both oral and topical steroid use after 3 months was 29%. Antihistamines, which all patients used, including 11 out of 14 at the onset of TCM, was reduced 32% after three months.

Eleven of 14 patients experienced at least a 50% improvement in quality of life during the first 1-3 months of therapy. At the end of the study period, 12 of 14 patients reported sustained improvement in quality of life with 10 of 14 reporting >80% improvement.

Going forward, we are creating a practice network of physicians to treat patients for recalcitrant eczema. Using these medicines requires no special training in TCM. In this way, we hope to not only relieve current suffering, but also to slow the progress of the rest of the atopic march. Q

4. Asthma

According to the World Allergy Organization 2011 White Book, some 300 million people suffer from asthma worldwide, contributing to the deaths of 250,000 people annually. In the United States, 9.3% of children and 8% of adults have asthma. Economic costs to the United States approach $60 billion each year in treatment, 10.5 million missed days of school, and 14.2 million missed days of work. About nine people die from asthma every day, well over 3,000 each year. Poorly controlled asthma can have very serious consequences for food allergy patients with no previous history of respiratory reactions. There is also the danger of "airway remodeling" causing airway smooth muscles (ASMs) to lose their elasticity, among other problems.

Inhaled corticosteroids (ICS) have been the dominant treatment for controlling asthmatic inflammation, and they, like powerful systemic steroids, have some serious side effects. Moreover, there are other conditions that have asthma-like symptoms that don't respond to steroids although they are treated with them. There is no broad-based treatment for all asthmatic phenotypes.

We faced hurdles in creating a TCM anti-asthma drug. Many TCM drugs have relied on Ma Huang, or ephedra, which is frowned on by Western regulators because it can be used to make methamphetamine. We used a 14-herb combination to create an investigational drug we called MSSM-002 which showed promise but because it had so many ingredients we studied the components and arrived at a three-herb version we call ASHMI (anti-asthma herbal medical intervention). This combination of *Ling-Zhi* (*Ganoderma lucidum*), *Ku-Shen* (*Radix Sophora flavescentis*), and *Gan-Cao* (*Radix Glycyrrhiza uralensis*), suppressed airway hyper-responsiveness and the collection of certain white blood cells in the airways, called eosinophils, which are drawn to inflammation, as effectively as the original. This research has been going on for 10 years as part of an NIH protocol.[iv]

We have now done a series of clinical studies in China in cooperation with my former fellows. We have seen that the drug is safe and as effective at suppressing asthmatic inflammation as systemic steroids but with no cytotoxicity and suppression of innate immunity. Moreover, in murine models we have seen evidence that it can

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help control neutrophilic asthma, which is dominated by another white blood cell—the neutrophil—and doesn't respond to inhaled steroids.

ASHMI inhibits the production of several inflammatory cytokines all at once. Standard pharmacological research focuses on these one at a time, in the form of monoclonal antibodies.

Finally, whereas steroids suppress innate immunity while controlling inflammation, they also are associated with mood disorders, resulting in higher rates of anxiety and depression for asthmatics in treatment than among their peer groups. This is considered especially problematic for children and teenagers. These effects can be measured in the peripheral blood. ASHMI doesn't produce these effects.

5. Food Allergies

Food allergies seem to have come from nowhere, although they have really always been with us, as literature from Greek and Chinese medicine tells us. They have grown as a public health issue over the past two decades, with most cases in commodity foods—milk, eggs, peanuts, tree nuts, wheat, and soy—which are not only common but are often incorporated in processed foods. Symptoms range from uncomfortable itching of oral allergies, which are like pollen allergies, to alarming pruritis and hives, to vomiting, to catastrophic and occasionally fatal anaphylaxis, in which two or more organ systems react.

I began studying the potential for treating food allergies with TCM when I noticed a connection between the symptoms of food and the symptoms of infection by intestinal parasites. This made sense because the proteins in peanut resemble proteins in helminths. One feature of this approach is that it addresses food allergies as a digestive problem as well as an immune problem.

I chose a nine-herb formula Wu Mei Wan (WMW). It was classically prescribed "for colic, vomiting, chronic diarrhea or dysentery, and collapse (also translated as syncope) caused by parasitic worms." We added two more ingredients particularly effective at immobilizing worms. This formula, which we called Food Allergy Herbal Formula-1 effectively cured anaphylactic peanut allergy in a murine model. Before we could adapt it to human use, we had to remove two alkaloids and came up with Food Allergy Herbal Formula-2, which also cured peanut allergy in mice.[v]

We have now been through two human trials—Phase 1 for safety, which we passed with no serious adverse events or toxicity. The Phase 2 had an equivocal result, although there were encouraging signs in the peripheral blood. The study was too brief—six months compared to the equivalent of two years for the mouse studies. And the dosing was too arduous. Subjects aged 12-48 years were expected to take 10 pills at each of three meals a day—30 in all. At least 44% of them were non-compliant.[vi]

This gives urgency to our efforts to apply Western chemistry to the herbal medicines. Using butanol, we have reduced the therapeutic dose by 80%, which the NIH has approved for another trial of 26-months duration. We

have also experimented with another solvent that appears to be even more efficient at separating the active ingredients.

As with our eczema and asthma medicines, we use supplement versions of the food allergy herbal formulas in practice, with very good results, including documented, published cases of patients with frequent severe food anaphylaxis experiencing no additional exacerbations.

We also use our medications adjunctively with the desensitizing techniques oral immunotherapy (OIT) and sublingual immunotherapy (SLIT), which involve ingestion of increasing amounts of the allergen, often provoking adverse effects, particularly gastric distress. We are also working with researchers to explore various combinations because allergies are heterogeneous diseases for which no single therapy will ever be sufficient.

6. Other Research

My colleague Dr. Scott Sicherer has said that where Western science tends to focus on the effects of one molecule on another molecule, TCM allows us to study multiple molecules on multiple other molecules. That is the basis for use of our food allergy herbal formula with Crohn's disease, for which the current standard of care involves regular infusion of an expensive monoclonal antibody. We observed that in addition to inhibiting allergic antibodies, our food allergy formula inhibited production of tumor necrosis factor alpha (TNF-α). High levels of TNF-α are also associated with Crohn's disease. Two studies have shown that FAHF-2 two is very promising for modulating the inflammatory cytokines associated with Crohn's.[vii]

A pediatric nephrologist at Mount Sinai has been exploring the use of a Chinese herb she found in our data base to try to mitigate rejection of transplanted kidneys in her patients, who currently must rely on powerful immune suppressants, and her work has been published in a major journal[viii]

We have a unique resource—the combination of a busy practice and a world-class lab team. We are using this combination in practice-based research operating under IRB rules to learn as we go. We have a bio-marker study to determine whether our patients are achieving tolerance to their allergens using individualized treatments. The initial phase was funded by parents of patients, who are also paying for treatment.

7. Altering the heritability of allergies

Food allergy parents particularly wonder what they did wrong, why their children were born allergic. In addition to trying to halt the atopic march, we are working to create an oral vaccine that would protect children from inheriting allergic tendencies, starting with peanut. It will employ as an adjuvant non-toxic cholera toxin B (CTB), which has been used safely by pregnant women and infants for 30 years in an oral cholera vaccine, delivered by a probiotic bacillus subtilis (BS) spore with the allergen and adjuvant bound to the surface. It also induces antigen-specific clinical tolerance in autoimmune disorders when co-administered with antigen by induction of IL-10 and Tregs.

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This study doesn't strictly fall under the umbrella of TCM. However, our exploration of the immune system in studying the actions of herbal medicines gives us hope that this approach will work.

We also are trying to understand what it is about food processing and preparation that elicits a violent immune response through the study of advance glycation end products.

Much of this research is being done through collaboration with other scientists around the world.

Discussion

Australian allergist Dr. Susan Prescott has expressed optimism that the allergy epidemic, which has overtaken us in a matter of decades, it might be reversed over a similar period. "In theory, the very fact that modern diseases have increased means they must be modifiable. The same factors that are promoting the disease could also be actively harnessed to reduce the risk of disease."

However, while excellent work is being conducted, much of it is being done on the same timetables and piecemeal fashion that have left us with no more ability to cure allergies than we had a century ago, and at high cost. While it would be very difficult to unwind all the environmental, dietary, medical, and behavioral changes that have contributed to the epidemic, greater understanding of the physiology is giving us clues to how to roll back the effects. Traditional Chinese medicine, which has so many centuries of treating complex, multi-organ, infectious and inflammatory disease, gives a platform to build on.

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Chapter 23: Future of Brain's Health: Prevention of Neural Inflammation with Traditional Chinese Herbal Medicine

Renna Bushko
Research Intern, Department of Pediatrics, Icahn School of Medicine at Mount Sinai & Neuroscience Program, Smith College, Northampton MA, USA Renna@7SL.com
Changda Liu, Ph.D.
Research Scientist, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY, USA
Beth Powell, Ph.D.
Senior Lecturer Neuroscience Program, Smith College, Northampton, MA, USA
Xiu-Min Li, M.D.
Professor of Pediatrics, Department of Pediatrics & Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Abstract

Inflammation in the central nervous system is commonly responsible for many serious neurological diseases and inflammatory responses in microglial cells specifically can result in harmful neurotoxic effects. Although activation of microglial cells is neuroprotective to a certain degree, excessive activation of microglia can result in neurodegeneration and can create disorders such as Parkinson's, Alzheimer's, or amyotrophic lateral sclerosis (ALS). Pharmacological strategies are being explored to inhibit microglial activation and any harmful associated inflammation predominantly through natural remedies derived from Traditional Chinese Herbal Medicine. In this review, the characteristics of microglial cells and their importance in immune function as well as natural products derived from Traditional Chinese medicinal herbs that inhibit microglial activation will be discussed. Development of new drugs from well known herbal remedies show promise in alternative drug discoveries and measures to prevent excessive neural inflammation and degeneration.

Keywords: Microglia, Microglial activation, Traditional Chinese Medicine, neurodegeneration, neuro-inflammation, herbal remedies, Parkinson's, Alzheimer's

1. Introduction

Inflammation in the central nervous system (CNS) is known to cause neurodegenerative disorders and diseases. Inflammation in the body arises when white blood cells are generated in the presence of a foreign pathogen to combat infection and maintain homeostatic integrity. Additionally, inflammation can arise from autoimmune disorders such as arthritis or more serious neurological diseases such as Alzheimer's and Parkinson's as well as many more [1].

The function of inflammation is to enclose injury and to ultimately restore tissue but it can be harmful since many chemical inflammatory mediators can also produce hypersensitivity reactions leading to progressive organ damage. Based on research so far it is evident that microglia, the immune cells of the CNS, are involved in neurodegeneration caused by

excessive inflammation [2]. The central nervous system, which consists of the brain and the spinal cord, is especially susceptible to inflammation and oxidative stress[1], ensuing irreversible neuronal and glial damage [1]. Microglial activation and chronic inflammation creates greater risk of elevated levels of neurotoxic molecules and pro-inflammatory cytokines that can further contribute to neurodegeneration [2].

Although damage to the CNS cannot be fully reversed, it can be decelerated with the use of neuroprotective compounds derived from anti-inflammatory herbal agents. These herbal anti-inflammatory agents developed from Traditional Chinese Medicine (TCM) remedies, play role in reducing inflammation and neurological impairment from oxidative stress and neurotoxin secretions. TCM has used compounds from herbs such as *Glycyrrhiza uralensis* and *Ganoderma lucidum* to cease neurotoxin secretions and to combat inflammation by downregulation of neuroinflammatory responses [2]. By using such compounds, comorbid disorders such as depression and anxiety associated with CNS cell inflammation could also be moderated [3]. Here we review recent literature on Traditional Chinese herbal inhibitors of microglia-mediated neurotoxicity.

2. Microglial Cells and Microglial Immunopathology

A variety of specialized cells compose the nervous system including neurons, ependymal cells, and microglial cells2. Of the three types of microglial cells, astrocytes are the most numerous glia in the brain and coexist with oligodendroglial cells in the CNS whereas Schwann cells reside solely in the peripheral nervous system [4]. Unlike neurons which are mostly responsible for transmitting chemical and electrical impulses for information processing, microglial cells act predominantly as phagocytes to remove excess debris from the brain left by dead or dying neurons [4] Additionally, microglia are essential for maintaining the stability of neurons, add a protective barrier for neurons against foreign objects or physical distress, and myelinate[3] neuronal axons to speed up electrical impulse transmissions. Microglia are always active and continuously survey their local microenvironment [5].

Over the last decade, microglial cells have been studied more thoroughly because most neurological disorders have been attributed to microglial activation and dysregulation [6]. Interestingly, microglia may not only be involved in neurological disorder development, but they also potentially contribute to inflammatory and adaptive immune responses in non-specific CNS regions [6]. Microglial cells undoubtedly have innate immune functions and play a large role in nervous system immunopathology. The

[1] *An inability for the body to produce antioxidants at an equal or faster rate in which free radicals are being created. Free radicals are uncharged molecules that accelerate aging.*

[2] *Types of microglial cells include astrocytes, oligodendroglial cells and Schwann cells. (Bear et. al 46)*

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CNS has ultimately evolved[4] to protect itself from immune-mediated inflammation that can damage its delicate and vital functions [6].

There are a variety of immune responses and protective measures in the brain in order to defend it, such as the blood brain barrier that prevents blood-borne substances from entering cerebral extracellular fluid [4]. Additionally, Microglial cells serve considerable homeostatic and reparative functions as well because of their ability to respond quickly to physiological and stressful stimuli while also secreting cytokines and neurotrophic factors[5]. Microglia quickly alter their phenotype in response to a nervous system homeostatic disturbance and become activated when their cell surface antigens change morphology or expression [5]. Lastly, microglia can become phagocytic when neurons are damaged or dead and need to be removed from the CNS as not to cause toxicity [6].

Although microglia already appear to have a plethora of functions, they are also responsible for host-defense. When the CNS becomes infected, inflammatory stimuli and interaction with blood- derived cells activates microglial cells to induce inflammation, cytotoxicity and initiate T-cell action through antigen exhibition, ultimately supporting the theory of microglial importance in CNS immune surveillance [6].

Microglia do not, however, function alone to protect the CNS, but rather, communicate extensively with neurons to achieve both their quiescent and reactive states [6]. Unlike in other bodily immune responses, microglia are tightly monitored by chemical responses [6] and react in different degrees of inflammatory reactions based on these neurochemical ratios [6].

Microglia and Cytokines

As aforementioned, microglial cells secrete cytokines and neurotrophic factors when exposed to physiological or stressful stimuli. Cytokines are proteins secreted by non- inflammatory leukocytes and non-leukocyte cells that are responsible for acting as intercellular mediators. These non-antibodies differ from other hormones because they are produced by varying tissue cell types rather than from lymph nodes or other specific glands making them autocrine and paracrine proteins rather than endocrine proteins (nih.gov).

Microglia are able to recognize cytokine production intracerebrally during CNS inflammation [6]. On the surface of microglia, certain receptors are able to distinguish between pro and anti-inflammatory cytokines and the balance between these two types result in microglia inducing the appropriate immune function [6].

One particular Cytokine tested

[3] *Myelin is a membranous wrapping, or sheath, around axon provided by oligodendroglia in the central nervous system and Shwann cells within the peripheral nervous system (Bear et al. 806)*

[4] *CNS evolution is both anatomical and physiological (Aloisi 165)*

[5] *e.g. Neurotrophic tumor necrosis factor (TNF-α)*

[6] *CNS signaling molecules include ATP, neuropeptides, and neurotransmitters (Aloisi 2001*

for is tumor necrosis factor (TNF-α). TNF-α is a pro-inflammatory cytokine that when released, activates macrophages (astrocytes) to promote glial phagocytosis in the CNS. Additionally, with TNF-α release into the CNS, the production of additional pro- and anti- inflammatory cytokines has been observed [6]

TNF-α and Inflammation

TNF-α is produced when TH1 cells, microglia and macrophages become activated. With its release, TNF-α attaches itself to two similar receptors TNFRI and TNF-RII [6]. Additionally, TNF-α activates a variety of transcription factors such as (nuclear factor kappa B) NF-κB to induce transcription of immune genes [6]. NF-κB transcribes TNF-α while also allowing TNF-α to activate it [3]. NF-κB is usually harvested in the cytoplasm of inactivated cells but must be transmitted to the nucleus to have any effect [3]. This activation and cascade suggests that TNF-α and NF-κB act together during immune inflammatory responses as seen predominantly when observing numerous microglia and CNS macrophages [6].

TNF-α production in the CNS is ultimately harmful because it has depressive effects. Asthma sufferers, for instance, exhibit high incidence of anxiety and depression due to increased levels of TNF-α in the peripheral and central nervous systems [3]. TNF-α promotes neuroinflammatory cascades and is toxic to oligodendroglia, causing them to demyelinate and eventually die [3]. The suppression of TNF-α prevents excess inflammation and the occurrence of associated anxiety and depression [3]. Ultimately, Cytokines are essential regulators of innate and adaptive immune responses and in both infection and autoimmune disorders of the CNS, macrophages, microglia and astrocytes have produced these cytokines to generate CNS-specific inflammation [6]. Taking a closer look within this particular inflammatory cascade, we can easily learn what herbal treatments we can utilize to stop it.

3. Traditional Chinese Medicine and Inflammation

Traditional Chinese Medicine is a practice that originated in Ancient China and evolved over thousands of years, transforming it into what we consider herbal medicine today. In recent years, the re-emergence of these remedies have been researched extensively and authenticated by their long-term use over centuries as compared to newer supplements [2]. Because of their already trustworthy ethnopharmacologial properties, these traditional herbs have been revisited in research and have been confirmed to contain neuroprotective and neurotrophic capacities useful in preventing neurodegeneratory and neuroinflammatory diseases [2]. Furthermore, during the last two decades, it was observed that various botanicals have exhibited anti-inflammatory and antioxidant functions to potentially protect the brain from inflammatory impairment [2]. These herbal extracts can generate neuroprotective effects with varying mechanisms but those specifically targeted to block microglial activation may be most effective at improving

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neurodegeneration and neuroinflammation caused by microglial activation. In the sections to follow, emphasis will be placed on traditional herbal products with discussion on their active constituents specifically in reducing inflammation and inhibiting microglial activation.

3.1 Chinese Licorice - *Glycyrrhiza uralensis* and *Glycyrrhiza glabra*

Chinese Licorice, referred to as *Gancao* in China, is a flowering plant native to Mediterranean, central and southern Russia and Asia Minor, used often in herbal Chinese medicine for its remarkable uses [7]. Utilized alongside 50 other fundamental herbs used in TCM, *Glycyrrhiza uralensis* has been traditionally used in the respiratory system and the gastrointestinal tract to reduce inflammation [8]. The family of licorice has been used medically since 500 BC and has been nicknamed "The grandfather of herbs" for its extensive medicinal history [7]. Several studies also suggest that Glycyrrhiza can be useful in treating Alzheimer's disease, a very prevalent neurodegenerative disorder [8]. Within Glycyrrhiza, the triterpene saponin GA and the aglycone GRA, have demonstrated neuroprotective and anti-inflammatory characteristics capable of reducing such inflammation commonly found culprit in patients with Alzheimer's [8]. The licorice root itself has an abundance of triterpenoid saponins (4-20%) known best as glycyrrhizin as well as potassium and calcium ions forming glycyrrhizic acid [7]. Furthermore, glycyrhhiza uralenisis contains a series of potent flavonoids capable of interacting with biomolecules via hydroxyl groups, modifying proteins to generate neuroprotective effects [8]. Some of these potent flavonoids include liquiritin, liquiritigenin, rhamnoliquiritin, neoliquiritin as well as several more [7]. For instance, the flavonoid ILG (isoliquiritigenin) demonstrated anti-inflammatory and neuroprotective effects. An isomer of ILG, LG (liquiritigenin) showed anti-depressive properties in murine models and inhibited neurotoxicity created by Aβ (amyloid-beta) peptides [8].

Glycyrrhiza glabra

Also a species of licorice, the flavonoids extracted from Glycyrrhiza glabra have also demonstrated attenuation of cerebral injuries in stroke animal models [9]. Just like many other neurodegenerative disorders, stroke can cause inflammation and neurotoxicity since blood is inherently toxic to the brain tissue. Very similar to Gycyrrhiza uralensis, the flavonoid glabridin in Glycyrrhiza glabra can enhance the survival of neurons and prevent their apoptosis [9]. Glabridin specifically, is an isoflavan and the major active flavonoid in Glycyrrhiza glabra. Isoflavans are placed in a subclass of the flavonoid compounds and have a unique structure in which an A, C and B ring are connected respectively through a Carbon 3 [9]. The hydroxyl group on the B-ring has the most anti-oxidative properties and is the most useful factor in bio-actively combating bodily inflammation [9]. In a murine model, Glycyrrhiza glabra flavonoids and isoflavans demonstrated reduction in brain malyonyldialdehyde (MDA) while elevating two internal antioxidants in

the brain; superoxide dismutase(SOD) and reduced gluthathione (GSH). Also, glabridin isoflavan significantly inhibited cytotoxicity and apoptosis in cortical neurons insinuating the neuroprotective effects of *Glycyrrhiza glabra* and its resourcefulness in traditional and contemporary medicine [9].

Glabridin

3.2 Reishi Mushroom (*Ganoderma lucidum*)

Throughout history, mushrooms have been used greatly within culinary practice, but also have been utilized specifically for the treatment of diseases [10]. In addition to plants, fungi have been studied for their anti-inflammatory and neuroprotective compounds. The Reishi Mushroom, commonly known for its anti-cancer properties is particularly well known in Traditional Chinese Medicine. Further *in vitro* evidence suggests, that this mushroom's potent anti-inflammatory characteristics also can protect against prevalent neurodegenerative disorders such as Alzheimer's and Parkinson's [10].

Although lifespan is increasing dramatically, with increased lifespan comes greater possibility of developing neurodegenerative diseases. It is estimated that nearly eighty million individuals will suffer from dementia by 2040 where Alzheimer's accounts for about sixty percent of the cases [10].

Like with Glycyrhhiza uralensis, Ganoderma lucidum has the ability to moderate Aβ hypersensitivity [10]. Furthermore, mushrooms such as *G. lucidum* have been shown to promote axon growth during brain development in the striatal region. This is possible because Ganoderma lucidum like many fungi contains palmitic, oleic, and linoleic fatty acids that have the ability to generate and promote axonal growth [10]. Unlike newer medications, studies on cell lines suggest taking high doses of fungal and herbal supplements has no adverse effects [10]. By taking extracts of *Ganoderma lucidum*, neurodegenerative diseases could be prevented earlier rather than attempting to cure them in later stages of development [10]. In *Ganoderma lucidum* alone, over 140 different triterpenes have been discovered, all of which can inhibit the production of free radical and act as anti-oxidative agents[7] [10].

With dietary supplement usage G. lucidum has demonstrated its ability to delay Alzheimer's onset - a very

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big step in the field of preventive medicine [10]. In addition to delaying Alzheimer's, *Ganoderma lucidum* has been studied in murine Parkinson's models as well. Previous studies on rats fed with *G. lucidum* oil have shown that they had fewer characteristic symptoms. Those rats who were fed *G. lucidum* also downregulated the neurotoxin 1- methyl-4 phenyl-1,2,3,6-tetrahydropyridine(MPTP), a neurotoxin highly responsible for the originating Parkinson's [10]. A lack of dopamine in both the substantia nigra and striatum is what results in Parkinson's symptoms so by reducing neurotoxin MPTA levels with G. *lucidum,* dopamine levels could be partially restored [10]. With Ganoderma treatments, these dopamine levels in mice increased in these two brain areas and involuntary movement was considerably reduced [10].

Testing Neuroprotective effects of Ganoderma Lucidum

Using a variety of lab techniques to test the neuroprotective effects of *Ganoderma lucidum* gives us confidence in its effectiveness. To test the effects of *G. lucidum*, dopaminergic neuronal cell line MES23.5 and LPS-activated microglia were used after being treated with 1-methyl-4-phenylpyridinium (MPP+)[10]. MPP+ being a metabolite of neurotoxin MPTP would have the same effects as using MPTP directly. After treatment, *G. lucidum* extracts inhibited microglia from producing inflammatory and cytotoxic cytokines such as TNF-α and Aβ [10]. This inhibition of microglial cells producing cytokines makes G. lucidum a potentially useful agent in reducing inflammation and thus neurodegerative disorders like Parkinson's as well [10].

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3.3 Anti- inflammatory effects of *Sophora flavescens* and *Sophora japonica*

Sophora flavescens is a flowering plant of the Leguminoseae (bean) family and is widely distributed in Asia and Oceania. From the fifty-two species in this family, fifteen of them have been used extensively within TCM. Although *S. flavescens* has anti-inflammatory effects on other portions of the body, purer compounds allow for anti-inflammatory function in the central nervous system as well [11]. From *S. flavescens*, pure compounds including matrine, kurarione, and oxymatrine and Sophoraflavanone G. have been extracted [11].

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Oxymatrine is one pure compound that has been studied in depth. This compound derived from *Sophora japonica,* a subspecies of *Sophora flavescens* possesses anti-inflammatory characteristics [12]. Oxymatrine(OMT), is a monosomic alkaloid derived from Sophora japonica and has a unique tetracyclic quinolizine structure [12]. Possessing anti-inflammatory, immune regulatory, antivirus, anticancer, anti-apoptosis and anti-fibrous activity, oxymatrine can be used to treat a plethora of illnesses including neurological ones [12].

In one particular study conducted by Nanjing Medical University researchers investigated the effects of oxymatrine on nuclear factor kappa B (NF-κB) and mitogen- activated protein kinase (MAPK) in Lipopolysaccharide activated BV2 microglial cells [12]. In the investigation, Nitric Oxine (NO), prostaglandin E2 (PGE2), tumor necrosis factor (TNF-α), interleukin-1beta (IL-1β) and interleukin- 6 (IL-6) were derived from the supernatants of BV-2 cell cultures. In the study, oxymatrine inhibited the production of NO,PGE2, TNF-α, IL-1β, and IL-6 while also diminished levels of inducible nitric oxide synthase (iNOS) and cycloozygenase-2 (COX-2), cytosolic inhibitor of kappa B-alpha (I-κBα)and phosphate I-κBα in the MAPK molecule kinases [12]. Furthermore, the nuclear levels of phosphate fifty-six (p65), the extracellular signal- regulated kinase (ERK), phosphate thirty-eight (p38) and c-Jun N- terminal kinase (JNK) pathways were blocked by oxymatrine [12]. After treatments with varying doses of *S. japonica* to this cell lines and released aforementioned cytokines, it was evident that oxymatrine attenuated inflammatory responses in microglia. Thus it is capable of reducing inflammation in various brain disorders [12].

3.4 Berberine

Berberine, an alkaloid extracted from plants like Berberis aquifolium, *Berberis aristata*, *Hydrastis Canadensis*, *Coptis chinensis*, *Xanthorhiza simplicissima* as well as several others has also been extensively researched for its anti-inflammatory properties. First known for its use in TCM, berberine has been used to treat a host of diseases including bacterial, fungal and viral infections. Because of berberine's ability to reduce inflammation in the central nervous system, it also acts inherently as an anti-depressant and can also act as a neuroprotector against neural disorders. In mice that have experienced traumatic brain injury (leading to neurodegeneartion), berberine has shown promise in reducing the severity of associated negative symptoms [2]. Mice who received a controlled cortical impact injury and had been treated with berberine 10 minutes after injury showed that berberine significantly diminished functional deficits and brain damage even up to 28 days post-injury [2]. Additionally, berberine reduced neuronal death, apoptosis, BBB permeability, and brain edema a day after injury [2]. While reducing any of these undesired symptoms of TBI, a significant reduction of leukocyte infiltration, microglial activation and inflammatory mediator expression was observed [2]. Berberine treatment did not have any effect on the ERK

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pathway, however it did reduced NF-κB signaling [2]. Additionally, after administering berberine *in vivo* to mice, it was observed that berberine reduced TBI brain damage by limiting glial inflammatory mediator production as well [2]. Furthermore, berberine was able to reduce the infiltration of neutrophils and slow IL-1β NO production in glia and BV-2 cells [2]. Because of this research, the notion that berberine can inhibit glia-mediated inflammatory responses following brain injury is very likely and can be a primary herbal treatment for inflammation resulting from central nervous injury [2].

3.5 Ginseng

Ginseng is a plant from the Araliacea family and it is found in a lot of locations in the world. Ginseng, or *Panax ginseng,* has an interesting name that means "all healing" [2]. In modern society, Ginseng has become a very popular commodity not only in Chinese medicine, but in Western culture as well because of its easy preparation such as in tea [2]. Although there are two known types of ginseng, white and red, TCM believes the red ginseng is more potent and effective in treatments, however now it is believed both white and red are equally as effective [2]. P. ginseng is truly an "all healing" plant because it has the ability to inhibit DNA damage, induce cancer cell apoptosis, and even inhibit cell proliferation [2]. Furthermore, the chemotherapeutic effects of ginseng are also very strong and the consumption of ginseng significantly decreased several types of cancers in the pharynx, stomach, liver, pancreas and colon in a variety of studies [2]. Ginseng extract, like that of berberine and S. flavescens all have the ability to suppress the NF-κB and MAP kinase neuroinflammatory cascades [2]. Furthermore, ginsenosides Rh2, Rh3 and compound K extracted from P. ginseng inhibited LPS-induced nitric oxide synthase (iNOS) and cytokine activation, demonstrating their potential benefit in combating neurodegenerative disorders [2]. P. ginseng not only inhibits LPS in (iNOS) ,but also inhibited the tumor necrosis factor (TNF-α) and pro-inflammatory cytokines produced by inflamed macrophages and specifically in BV-2 microglial cells [2].

Ginsenosides and inflammation prevention

The Rg3 ginsenoside was a promising compound in treating inflammatory responses. The single compound Rg3 inhibited phorbol ester-induced cyclooxygenase-2 (COX-2) as well as NF-κB generation [2]. Rg3 attenuated neuroinflammation in primary, murine dopaminergic neurons and glia [2]. Additionally, the polysaccharide ginsan extracted from P.ginseng, inhibited p38 MAP kinase pathways and NF-κB during *in vitro* studies while also inhibiting pro-inflammatory cytokines *in vivo* [2]. A fermented extract of ginseng named BST204 inhibited iNOS expression and NO production in LPS RAW macrophages as well. Because these ginsenosides demonstrated their ability to reduce NO formation, PGE2 synthesis and interfere with iNOS and COX-2 expression, it is possible that they can be useful in treating many neurodegenerative disorders such as Parkinson's and Alzheimer's [2].

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3.6 Cammelia Sinensis

Green tea is a very popular drink around the world now, however not many people know from which plant it is produced. Green tea, produced by the leaves of *Camellia sinensis*, is one of the oldest beverages in the world while also having a variety of benefits helping with for example cardiovascular disorders, obesity, cancer and it also slows the aging process [2].

From observing the effect of green tea in humans and in laboratory research, it was determined that polyphenol epigallocatechin-3 galate (EGCG) is the most therapeutic component [2]. EGCG can inhibit the production of many inflammatory cytokines such as TNF-α, IL-6, and IL-1β [2]. Because green tea compounds can also cross the blood-brain barrier, it makes it a great compound in antioxidant activity, inflammation reduction, and mediation of cell apoptosis [2]. Although there are many anti-oxidant compounds such as vitamins E and D, EGCG is more potent and more effective in reducing free radical levels [2]. Furthermore, EGCG inhibited NF-κB activities and was a neuroprotective agent in autoimmune disorders such as encephalomyelitis [2]. Like berberine, green tea also can protect against neuronal injury induced by N-methyl-D aspartate (TRAIL), inhibited LPS-induced microglial activation and protected against neuronal injury of dopaminergic neurons [2]. Lastly, EGCG inhibited LPS activated microglia secretions of both NO and of TNF-α by down-regulating iNOS and TNF-α gene expression while significantly protecting against microglial activation-induced injury both in mice and humans [2]. Based on this evidence, green tea and EGCG extract specifically, could be very effective in treating and preventing neuroinflammation and neurodegeneration [2].

10. Conclusions

Although Western medicine is used prevalently in modern medicine, a new era of using traditional medicine to find cures has been on the rise. By using the time-testedtechniques of Traditional Chinese Medicine to cure and prevent illnesses, scientists have discovered a great deal about herbal

remedies and their potential in curing and preventing illnesses equally if not more effectively than modern techniques. A few herbs, mushrooms and plants have been studied in depth and their therapeutic effects along with their safety, affordability, and availability have made them very desirable. Recently, these studied remedies have demonstrated that regular consumption can prevent or diminish the development of neurological diseases caused by excessive microglial activation and inflammation. Excessive microglial activation can induce neuroinflammation capable of causing neurodegenerative diseases such as Parkinson's and Alzheimer's and using herbal remedies could prevent and slow down epidemics of these disorders. By observing herbal remedies and studying them further, new neuroprotective agents could be discovered and the complex pathology of neurodegenerative disorders could be uncovered. techniques of Traditional Chinese Medicine to cure and prevent illnesses, scientists have discovered a great deal about herbal remedies and their potential in curing and preventing illnesses equally if not more effectively than modern techniques. A few herbs, mushrooms and plants have been studied in depth and their therapeutic effects along with their safety, affordability, and availability have made them very desirable. Recently, these studied remedies have demonstrated that regular consumption can prevent or diminish the development of neurological diseases caused by excessive microglial activation and inflammation. Excessive microglial activation can induce neuroinflammation capable of causing neurodegenerative diseases such as Parkinson's and Alzheimer's and using herbal remedies could prevent and slow down epidemics of these disorders. By observing herbal remedies and studying them further, new neuroprotective agents could be discovered and the complex pathology of neurodegenerative disorders could be uncovered.

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Chapter 24: RAGE Control: Regulate and Gain Emotional Control

Jason Kahn M.S., Peter Ducharme MSW, LCSW, Brian Travers B.A., and Joseph Gonzalez-Heydrich M.D.
Children's Hospital & Harvard Medical School, Boston, USA

Abstract

Advances in neurobiology and computer science make possible interventions designed to strengthen basic processes behind emotional control. We present one such computer-based intervention, RAGE Control (Regulate And Gain Emotional Control). This extends the usual paradigm of biofeedback by requiring relaxation in the midst of engaging executive processes in a quick reaction task. RAGE Control teaches children to simultaneously focus, react, inhibit impulses, and keep their heart rate down in the context of a traditional space battle game. The program is grounded in the theory of Cognitive Behavioral Therapy and is currently in clinical use by psychotherapists at Children's Hospital in Boston. It aims to reduce the need for psychotropic medication to help children gain emotional control. Clinical trials to test the promise of this technology are warranted

1. The case examples of John and Emily

RAGE Control (Regulate and Gain Emotional Control) is an approach to treating a wide variety of challenges faced by people every day. One of the major disorders that we are looking at initially is explosive disorders, a psychiatric condition where emotional control deteriorates rapidly. The easiest way to describe how explosive disorders affect people is through the exploration of the case studies of John and Emily. To this end, we outline two case studies, and intertwine the need for RAGE Control within the difficulties faced by Emily, John, and many like them.

John, a 13 year old enrolled at an inner city middle school, seems at first blush to be much like his peers. During a silent reading exercise, he was talking with his peers. His teacher gave him a gentle reminder in an exchange that would typically be completely unremarkable. But for John, these where the first steps toward a psychiatric explosive episode, where John, and others like him, are unable to hold their emotions in check. These situations rapidly deteriorate, creating an emotionally tense and potentially physically dangerous scenario. We want to examine whether there are certain steps that can be taken to help children like John regain control before the situation gets out of hand, while avoiding the path of medication. Further, we seek a therapy that will engage these children in a manner that he is comfortable with, making him more receptive and engaged with his therapy.

Explosive episodes unfold rapidly. When the teacher reminded John that he was supposed to be silently reading, John, he denied that he was talking. As a result, the teacher stood between John's desk and the other student's in an effort to decrease John's distractions. Moments later another student approached the

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teacher with a question and John began drawing on the desk. This exasperated the teacher and caused her to tell John to get rid of his pen because he didn't need it. In reaction, John then threw the pen across the classroom towards the trash. The teacher gave John a disappointed and exhausted look, but did not comment on his actions. John replayed by saying: "You told me to get rid of it. I don't know why you're so mad."

John then proceeded to get up from his desk and walk around the classroom. Another student, frustrated with his actions, said to him "Just sit down and read already." John began swearing at her and then told her to "mind her own business." John's teacher told him to leave, but redirecting his anger towards the teacher, John refused. The teacher had to call the office and request help from the administration to get John out of the classroom. As the teacher waited, John continued to swear at her and the other students. He also began ripping pages out of his notebook and throwing them on the floor.

John's explosive episode rippled outward. The teacher's control of the classroom was tried as John's outburst aroused the interest of the other students. John's verbal accosting of his teacher and peers put a level of stress in the environment that was neither conducive to his peers' education nor fair to his teacher. While his destruction was ultimately harmless, in the heat of the moment, there is no way for his fellow students to know that the student throwing pens and ripping apart his notebooks, all while exploring the base elements of the English language is not an immediate impediment to their safety.

Emily, a 10 year old girl who attends an affluent elementary school in the suburbs, began crying in science class and refused to continue working on the class assignment. The class had been working in small groups of four students and their initial task was to develop a timeline for a class project. Emily, who is a bright girl that excels academically, quickly came up with a possible outline for the project. However, one of the girls in her group didn't like her proposal and suggested an alternative plan. Emily, now standing and speaking rapidly, insisted that her timeline was the best way to do the project. The other girls in her group continued to disagree and asked her to consider their plan, but Emily would not. She continued to plead her case and grew more and more upset as her other group members continued to disagree with her.

After going back and forth for approximately ten minutes, one of the group members said: "We have wasted all this time arguing, just give it up." Emily replied by calling her other group members stupid and told them they were bound to fail the project. She then proceeded to walk away from the group, sit at her desk, and began to cry. When her teacher asked Emily what was wrong she would not respond and avoided looking at her. Concerned about this incident and Emily's past difficulty working with peers, the teacher called Emily's mother after school to talk about her behavior.

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Compare John's explosion to Emily's sullen withdrawal. At first glance these stories may not seem similar. However, upon closer examination, both cases reveal children ill-equipped to manage the everyday stresses of their lives. Although the presentation of their external behavior in the face of adversity differed slightly, the internal states of these two children were remarkably similar. For instance, as was evident by their nervous and impulsive dispositions, both John and Emily were faced by situations that called for them to focus their efforts and inhibit impulses, trying to engage the brain systems required to accomplish this was impeded by the negative physiological arousal they each felt. For each of them the battle between negative arousal and attempts to control it failed and led to their loss of behavioral as well as emotional control.

tional control.

For nervous and impulsive children such as John and Emily, levels of anxiety that accompany focusing attention to accomplish challenging tasks can trigger negative emotional and physiological responses which inhibit attention causing failure at the task. The reciprocal feedback where negative emotion inhibits brain attentional systems which then causes more negative emotions quickly spirals out of the child's control and is converted into uncontrollable nervousness or aggression towards others.

2. Challenges facing children with externalizing disorders

Behavioral difficulties among children and adolescents similar to John and Emily are a major mental health concern and a common issue faced by clinicians at hospitals and outpatient clinics. In early childhood, small amounts of aggression can be seen as a normative part of child development [1]. However, as children age, advancement in their development involves mastering certain tasks, one of which is the capacity to better self-regulate when encountering stress. Children who are unable to master this task face numerous challenges in adolescence and later adulthood. The Diagnostic and Statistical Manual, 4th addition (DSM IV) [2] describes several disorders that can lead to disruptive and aggressive behavior, including Anxiety disorders, Attention Deficit Hyperactive Disorder (ADHD), Disruptive Behavior Disorder (DBD), Oppositional Defiant Disorder (ODD), Bipolar Disorder, and Conduct Disorder (CD). Disruptive, impulsive, and aggressive children are at high risk for rejection by their peers, poor school adjustment and academic underachievement. They show marked deficits in self-esteem and problem solving abilities. These children are more likely to drop out of school, develop delinquency, and fail in adult work and social relationships [3, 4, 5, 6, 7]. Psychotropic medication is often prescribed so as to reduce emotional dyscontrol to a level that these children can engage in psychotherapy. In recent years the rate at which psychotropic medication is prescribed to children has increased dramatically and become a major source of societal concern 8. Development of alternative therapies that can reduce the need

to use psychotropic medication in children deserves a high priority.

3. Cognitive behavioral therapy

There are a number of different approaches to treating disorders characterized with impulsive aggression and emotional dyscontrol. However one of the most empirically validated treatments in the literature is for Cognitive Behavioral Therapy (CBT) [9, 10, 11]. In CBT, the therapist interacts with patients in a problem solving manner, providing the child with skills that he or she can use to help overcome maladaptive behaviors. The therapeutic skills taught by CBT therapists to children and adolescents presenting with impulsive aggression and emotional dyscontrol can vary to some degree. However, one of the primary goals for these patients is to obtain a better ability to self-regulate their behavior and emotions. In CBT, this skill is often obtained through the use of relaxation techniques. Relaxation techniques include Deep Breathing and Progressive Muscle Relaxation (PMR) [12, 13]. CBT often makes use of biofeedback or providing patients with information on indices of their state of arousal such as heart rate, electrodermal conductance, or skin temperature. Biofeedback is particularly useful in relaxation training [14]. Showing patients their level of physiological arousal helps them learn to control their emotional state.

The limitations of CBT and CBT-based techniques can be traced back to acronym. Cognitive behavioral therapy presumes a certain amount of cognitive operations on behalf of the patient. Starting with the work of Piaget [15], developmental psychologists have learned that the type of cognitive processes required by techniques like CBT, sometimes called concrete operations, are typically only available to children only reaching adolescence. They also require that the children be willing to engage in learning the relaxation techniques and seeing the value of applying them when they are most emotionally aroused. The techniques themselves often require that the child disengage from the task with which they are wrestling to then apply the relaxation technique and when calmer return to the task. The most behaviorally impaired children are the ones that are hardest to motive to learn these techniques and who have the most trouble seeing the value of inhibiting their anger long enough to apply them.

The theory behind RAGE Control is that a child's desire to do well in a video game can be harnessed to give him or her an opportunity to see the value of maintaining emotional control and practice maintaining it in the midst of a challenging and frustrating task. To succeed at the game of RAGE Control the child must apply the relaxation techniques while stimulating their brain attentional and rapid response systems. This is a more ecologically valid application of relaxation than practicing relaxation in the calm of a therapist's office. It is hoped that RAGE Control will provide a bridge from the use of relaxation in the office to its use in difficult situation in real life.

4. Challenges facing therapist

Relaxation and biofeedback training is effective in reducing anxiety and other externalizing behaviors among children. However, the challenge therapists often face in treating patients with these types of behaviors, like John and Emily, is their level of interest to actively participate therapy. Some patients dislike this training. Some patients are too hyperactive to sit calmly in a therapist's office and focus on a PMR script being read by a therapist. For other patients, they may feel uncomfortable doing relaxation because it doesn't feel natural to them and they feel uncomfortable trying to do it. Patients may struggle because they can't see how relaxation is effective or how it is going to be useful for them. Some are oppositional and do not see the value in engaging with their therapist at all [16].

5. RAGE Control

In response to the above challenges it is important to develop innovative and effective strategies to teach these relaxation skills to patients who otherwise are not motivated to learn them, and to give all patients the opportunity to apply what they learned in a situation that more closely approaches the clinical situations where they need to gain emotional control.

Therefore we have developed a new method to teach emotional control which is to teach patients relaxation and how to apply it during a challenging task. An instantiation of this method is a video game we are calling RAGE Control (Regulate and Gain Emotional Control). It is our first implementation of biofeedback and relaxation during a challenging task. We start with a traditional video game, inspired by the classic Space Invaders. The plot of Space Invaders, to use a generous word, runs about as deep as any of the pioneering arcade games. A hero's world is under attack by an alien armada. The hero gets into his spaceship, and forms the last line of defense between everything he holds dear and alien annihilation. The gameplay is equally simple, but compelling. The aliens traverse the screen vertically, starting at the top, making way to the player who sits at the bottom of the screen. The hero moves horizontally across the screen, firing bullets. Points are awarded for shooting aliens, and the game ends when an alien succeeds in crashing into the hero, or the aliens cross in sufficient numbers to destroy the home world.

From our point of view, Space Invaders offers an attractive starting point, blending solid game play with exceedingly simple controls. In fact, in the traditional implementation of Space Invaders, there are three controls: drive left, drive right, and fire. The task is equally simple to understand. Get under an approaching alien, and fire. Avoid the descending aliens, and don't let them by. The interface and task are elegant in their simplicity. This is not to say that they are boring. Clones of Space Invaders are still available on web-based gaming sites and still enjoy interest in an age of highly sophisticated three-dimensional games with elaborate tasks and goals.

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RAGE Control, while building on the template of Space Invaders, makes several key departures not only from Space Invaders, but the traditional approach to gaming. The most prominent of these changes is the input device. The user still makes use of a traditional input, in out case a keyboard. But unlike any game found in an arcade or on a living room console, the user also tethers him/herself to the computer using a heart rate monitor. The user's own physiology becomes part of the gaming experience, and the physical link immediately reinforces the idea that the game's narrative now depends on control of heart rate, a physiological variable. RAGE Control currently uses a pulse oximeter for heart rate input, which clips onto the users finger. The other inputs of the game are unchanged. A keyboard controls left and right movement and firing.

The activity of firing a bullet is moderated by heart rate. At the onset of the game, a threshold heart rate is calculated as sitting heart rate plus seven beats per minute. So long as the user is under their heart rate threshold, they can fire their weapon as expected. Should the heart rate go above the threshold, they begin to fire 'blanks:' visually smaller, slower bullets that will not damage the attacking aliens.

Other tasks are modified from the space invader game. We require that the child intermittently inhibit a potent impulse to fire. For this we introduce a number of friendly craft that enter the game board at random moments. Along with aliens entering from the top of the screen, 'friends' of the hero do as well, and the player now needs to avoid shooting their friends. These must not be shot. In the game narrative, we describe this as the player's friends fleeing from the alien onslaught. From a design perspective, this completes a tidy task matrix presented to the user.

Table 1: Task matrix for RAGE Control Hit

	Hit	*Passed*
Alien	Correct Hit (+100)	Incorrect rejection (β-error; -100)
Friend	Incorrect hit (Î±-error; -500)	Correct rejection (+100)

After several iterations, we decided that, as an introduction to RAGE Control, users only play for a high score. Thus, aliens striking or passing the player have no effect on game play, other than detracting from the score, while shooting aliens and allowing friends to pass increase the score. Shooting friends carries the

highest penalty. This design decision was made to ensure that users would have a chance to become familiar with the game and train themselves to regulate their heart rate.

What does the design of an active biofeedback game like RAGE Control accomplish? Patients increase their ability to regulate emotion and behavior under stressful conditions. Players of RAGE Control experience a number of challenges to their autonomic nervous systems (ANS). The sympathetic and parasympathetic nervous systems of the ANS acts as the fight or flight mechanism within the body. The sympathetic nervous system responds to excitement and fear whereas the parasympathetic works to control relaxation restoring a person's body to a normal physiological state.

RAGE Control begins by having players attend to one active task, shooting aliens. As the game progresses, players face increased ANS challenges corresponding with increased levels of the game. The next challenge player's encounter is their friends flying on the screen. This is an inhibitory task asking players to avoid hitting certain spaceships. As the levels increase the numbers of aliens and friends multiply and begin flying at a greater velocity. Adding more challenges to players ANS's we believe the game provides players with motor, emotional and performance challenges, which replicates the stressful challenges they will encounter in day to day situations. Mastering the ability to utilize relaxation with the game will generalize to other stressful encounters players face in their lives. The reason why children and adolescents are more likely to acquire relaxation skills using RAGE Control is because it grounds them in a computer game which is oftenalready an interest of this population. Therefore, therapists will be able to reach patients who may not respond to the therapists walking them through traditional relaxation training. The figure below is a design brief for Psychiatry Invaders. It is meant to capture the game from the user's perspective, describing the games goals, inputs and outputs.

Table 2: RAGE Control Game Description

Goals	Active tasks Inhibitory tasks	Destroy incoming enemies Don't destroy friends
Inputs	Traditional	Left arrow - drive left Right arrow - drive right Space bar - fire bullets
	Physiological	Oximeter - heart rate
Outputs	Under threshold	Shot fired - large, effective bullet *Hit* / *Passed* *Alien* +100 / -100 *Friend* -500 / +100
	Over threshold	Shot fired: slow, ineffective bullet Shot fired - large, effective bullet *Hit* / *Passed* *Alien* 0 / -100 *Friend* 0 / +100

6. RAGE Control Utility

The promise of RAGE Control are that we will increase the ability of children to regulate their emotions even while under stress and this will reduce the need to administer psychotropic medication. These medications come with two-fold cost to the patient and the health care system. First, the system is responsible for the direct costs associated with the medication. However, many psychotropic medications come with severe side effects, which are a burden on

the patient, their family, and the system. The use of powerful psychotropic medication to treat common childhood disorders leading to explosive episodes is a matter of deep societal concern. Our hope is that RAGE Control can augment a treatment plan in a way that can teach the patient valuable coping skills while mitigating and maybe even eliminating the use of psychotropic medication for many of these children. However, this is just the beginning of the benefits we hypothesize for RAGE Control.

Clinically, we expect that RAGE will have particular utility with adolescent boys. In addition to providing an *in vitro* environment for the child to learn how to self-regulate emotion, we believe RAGE Control will also help to strengthen the therapist-child therapeutic alliance. Research has suggested that early therapeutic alliance is associated with later treatment outcomes, but for children and adolescents the therapeutic alliance becomes more complicated with the therapist needing to form and maintain an alliance not only with the patient, but with the patient's parents/caregivers as well. Many families report that the reason they terminate therapy was quite straightforward: the child did not like it. RAGE Control is a fun activity for patients to use while in therapy, that challenges them to take the skills they acquire with their therapist and put them to use in an environment in which they are familiar. We believe this will make coming to therapy more appealing for patients who previously may have been reluctant to come engage in therapy. We think this will help to build a stronger therapeutic alliance between the patient and the therapist. By forming a stronger alliance, patients will remain in treatment longer, be able to tackle more emotionally charged issues, and have better outcomes.

The challenges addressed in an intervention that includes RAGE Control are faced by enormous numbers of people. Because of this it is easy to image RAGE Control expanding to help a variety of people beyond our initial target population of adolescents in clinical settings. Stress can be a good thing. An autonomic response can heighten the senses and increase performance. But this same autonomic response can elevate and impair judgment and degrade performance. When one finds oneself in this situation, it would be valuable to have rehearsed skills that help them overcome these challenges.

RAGE Control does not need to be used in one-on-one settings. We envision building a multi-user cooperative game version of RAGE Control. This version could be used in group and family therapy settings. One example is a social skills group, a group-based therapy where a small group of patients acquire and practice social skills in a controlled setting. Using this cooperative multi-user RAGE Control would require group members to support each other in maintaining concentration and calm so that every player can contribute to the group succeeding at the game. This means that other people in the room would need to refrain from distracting others and also from upsetting others even as they share information in order to succeed. These skills are often a goal

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of social skills groups because children require these skills when in school and adults in their work and family lives. Another aspect of the game involving social skills happens at the conclusion of the group's turn playing the game. This is an opportunity for each player to give other players positive feedback on his or her performance. RAGE Control offers a number of features group members are able to comment on including how well each player was able to keep there heart rate low, how well they were able to shoot the aliens, how well they were able to avoid shooting their friends, and how well they worked together. This helps teach group members how to search for positive attributes of each player that helps to increase members' social skills. Taking these skills into the home and school settings will help members develop better peer relations which is an important protective factor against other mental health problems in the future.

In this light, it is easy to picture RAGE Control, ported to a hand-held device, providing skills on an everyday level. Possible applications range from the student who has difficulties self-regulating during a test, or an executive trying to navigate particularly demanding circumstances. However, there are other uses that are particularly valuable in the domain of public health. For example, populations of at-risk expecting fathers could use the self-control training of RAGE Control and then use RAGE Control to teach self control to their children. It is even possible that RAGE Control could help with the impulse control in addiction recovery.

RAGE Control offers a tremendous amount of versatility, both in its current instantiation and in potential future instantiations. The current prototype application is being used at Children's Hospital, Boston in the outpatient psychiatry clinic, the inpatient psychiatry unit and the Emergency Psychiatric Department. RAGE Control can be used as a one time intervention but is more likely to be effective as part of ongoing psychotherapy. RAGE Control has the best chance at making an impact when the psychotherapist provides the tools (relaxation techniques) the child requires to succeed at RAGE Control and then helps the child see the link between using relaxation techniques to gain emotional control to succeed at the computer game and using them to succeed in difficult situations or conflicts in their lives. Future instantiations of the idea behind RAGE Control will likely include more realistic virtual reality games which could increasingly mimic the actual situations where the child often looses emotional control.

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Teresita Hernandez / Shaping a Healthy Future in World Health Strategy" eBook, www.Futureofhealth.org (Ed.) Renata G. Bushko, FHTI, 2016. Original Chapter From: Intelligent and Extelligent Health Environment (Ed.) Renata G. Bushko, IOS Press 2005

Chapter 25: Shaping a Healthy Future: Megabyte, Not Mega bite!

Teresita B. Hernández, Ph.D.
President, Health Technomics, Inc,
Annandale, VA, USA

Abstract

The globalization of obesity is not a myth. Scientific and technologic advances have increased food production and availability while decreasing demand for physical activity. These developments, in turn, have contributed to peoples' cognitive and behavioral relationship with food selection and consumption. The more you see, the more you want. Although disparities in food distribution and personal economics still exist, the problem of over consumption is becoming widespread among low income groups in developed countries and among the high income in developing countries. The development of innovative technologies such as described in this chapter may help ebb the tide of obesity and improve the global future of health.

1. The Obesity Problem—A Global Concern

The 21st century ushered in a public health concern that had had a low profile until the popular media gained insight into the increasing prevalence of overweight and obesity among the US population. The adage "big is beautiful" has lost its attraction; instead the term "obesity epidemic"1 has been added to the public health vocabulary.

The 2003 report of World Health Organization (WHO) on Diet, Nutrition and the Prevention of Chronic Diseases[2] provides the global statistics that show changes over the past four decades in food supply and consumption, lifestyle, and the prevalence of chronic diseases that could be associated with obesity. Worldwide food availability expressed as kilocalories per capita per day increased from 2358 in the mid 1960's to 2803 in the late 1990's. Among developing countries, the increase was from 2054 to 2681 over the same period; the increase was specially pronounced in East Asia where the food energy supply increased by almost 1000 kilocalories per capita per day. There is no question that with food availability and rising income, obesity has now become a major concern in both developing and highly developed countries.

2. Part of the Problem—Technology

Technology has increased food production and has made packaging and transportation faster and easier. Indeed, there is an economic research report that concludes that 40% of the weight gain of the U.S. population in the past two decades may be explained by lower food prices due to agricultural innovations, and 60 % may be due to a decline in physical activity because of technological innovations in the home and in the workplace.[3] An immediate consequence of technological innovations in agriculture and the food industry is the "super-sizing" of foods and beverages served in restaurants, fast food stores and food courts. Sizes of containers of ready-to-eat snacks and sweetened drinks have also been enlarged.[4,5]

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If consumers were conscious of how technology has affected their lifestyle, if they knew what to do about it, and if they recognized that weight gain has a large behavioral component, then the obesity epidemic might have been prevented. Research on the increase in portion sizes of food and beverage consumed by the U.S. population over the past two decades supports the economic research findings. This is especially true for energy-dense but nutrient-deficient foods and beverages such as salty snacks, beer, and sweetened carbonated drinks.[6,7] Between 1989 and 1996, data from two independent national surveys (NHANES and CSFII) show mean portion intake of cola-type soft drink (excluding sugar-free, or low-calorie) increased from 11.6 to 14.78 fluid ounces for all users; at the 95th percentile, the change is from 18 fluid ounces in 1989-91 to 35 fluid ounces in 1994-1996.[8]

3. Providing a Solution With Technology

With creative, science-based instructional and behavioral modification tools, and the willingness of health professionals to maximize the use of such tools, technology can empower individuals in fighting obesity. As the title of this Chapter implies, the focus is on using computer technology for portion size definition and control. Within the limits of this chapter, there is no intent to address the problem of obesity in its entirety. The aim is to emphasize the need for recognizing the difference between food exposure (serving) and personal behavior or choice (portion), and further illustrate the difference between a health-based serving size and a market-based serving size. These concepts—serving versus portion, and health-based versus market-based—are not always explicit, even in many of our health and nutrition messages and have therefore become a source of confusion for the public.

There was a time when parents admonished their children at mealtime "Take only what you can eat" followed by "Eat everything on your plate." In this scenario, serving equaled portion. However, especially in this country, the abundance of the food supply and the busy lifestyle that has led to the growth of the "grab and go" food industry have made traditional meal preparation and serving almost obsolete. USDA reports that the frequency of dining out rose from sixteen percent of all meals and snacks in 1977-78 to twenty seven percent in 1995.[9] In 1970, the food-away-from-home sector captured about a quarter of total food spending and in 1995, about forty percent of the food budget was spent on food away from home.[10] These developments have also changed the meaning of "small", "medium" and "large" in relation to serving sizes.

A small informal survey that we conducted recently indicated that most (about ninety percent) dietitians and nutrition students use the terms serving and portion synonymously. This is highly influenced by a serving size defined in reference to the Diabetic Exchange, the Food Guide Pyramid, and sometimes the Nutrition Facts Label. On the other hand, consumers are continually exposed to serving sizes in the marketplace. These sizes get bigger and bigger in response to

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consumers' concept of "value", meaning "more for your money". The food industry uses this concept when introducing a new product or promoting sales. The opening of a new "burrito" restaurant in a college town in Maryland advertised its main attraction as huge (four-inch diameter) rolls! A famous cookie maker sends mail advertisement for its nine-inch cookie!

4. What This Chapter Is All About

This Chapter offers a new framework for defining serving size from two perspectives—one health-based, and the other, market-based. Health-based refers to serving sizes as defined according to the Diabetic Exchange, the Food Guide Pyramid, and the Nutrition Facts Label guidelines. Market-based refers to single serving sizes encountered at grocery and convenience stores, at fast food counters, and in diners and full-service restaurants. It is important to note that serving size for a given food item varies even among the health-based references. For example, a serving size for orange juice is 4 fluid ounces in the American Diabetes Association's (ADA) Exchange List for Meal Planning, 6 fluid ounces in the US Department of Agriculture's (USDA) Food Guide Pyramid, and 8 fluid ounces in the Food and Drug Administration's (FDA) Nutrition Facts Label guidelines. However, it is even more important to note the large difference between the health-based and the market-based serving sizes. For example, the food guide pyramid size for steak is 2 to 3 ounces cooked (100g raw), whereas a restaurant serving size could be 3 to 4 times as large (See Figure 1). The pyramid size for muffin is 1 ounce while muffins served at airports or sold in bakeries weigh about 5 ounces. And among foods for which pyramid servings are not clearly defined, for example, soft drinks, "super-sizing" of containers is the growing trend. As part of our project to develop an interactive desktop reference for serving sizes, we made many trips to fast food places, kiosks, food courts, and other convenience stores. This is a sampling of what we found among containers for soft drinks: the old 8 ounce "Dixie" cup is now called "kiddies"; a 16 ounce cup is "regular" or "medium"; 22-24 is "large", "Big Gulp" is 32, "Magnum" is 44, and "Double Gulp" is 64 fluid ounces. And if the container is filled to the brim, these volumes can increase by another 2-4 fluid ounces. Unfortunately, there is no requirement to label the capacity of containers. If shown, it usually appears encoded at the bottom of the cup. So if you want to know how much you had, you either have to finish the contents or spill it!

Keeping track of how much one eats and drinks is a difficult task. Even among professionals who are trained in food science and nutrition, few, if any, can accurately slice a 3 oz piece of meat or pour 8 fluid oz of juice without measurement tools. In the real world of food consumption, we must first acknowledge that the cognitive skills used in estimating sizes and amounts are not simple skills. They are brain functions—perceptual, mathematical, memory storage and retrieval—that differ from individual to individual. The degree to which these skills contribute to the accuracy of

quantitative estimates is an area of research that we have only begun to address systematically. No professional group to date has defined an acceptable error rate in food measurement. Previous studies suggest that using visual portioning anchors tended to result in overestimation more frequently than underestimation for all types of food—solid, amorphous, or liquid—when estimation is done in real time or short-term recall.[11,12,13] In an attempt to establish a basis for a rational expectation of accuracy in portion estimation, our recently completed research suggests that cognitive adaptation to food exposure is a dominant influence in how consumers perceive portion sizes.[14,15]

Beyond these cognitive issues of measurement, scientists are beginning to document the effect of food exposure on personal consumption starting in early childhood.[16, 17] To ebb the tide of obesity, it is important to explore the extent to which technology can assist as early in the formative years as possible. Our approach is to get both health professionals and the public to think visually, recognize the difference between health-based and market-based serving sizes, and make a distinction between serving (what you SEE, in other words, exposure) and portion (what you PARTAKE, in other words, personal behavior or choice). We have developed visual tools to promote this common reference for communication. The Health Technomics Computer-based Portion Anchors (HTCPA) is one of these tools.

5. The Health Technomics Computer-based Portion Anchors (HTCPA)[18]

The Health Technomics Computer-based Portion Anchors (HTCPA) is a suite of programs that displays photographs of about 300 typical foods and 100 food and beverage containers commonly used in the U.S. Employing digital photography and a programming language that has both computational and pictorial database management capabilities, a pictorial database of at least two sizes for each food or container was created. Food was weighed and measured immediately before photographing. Foods with inedible parts, such as peel or bone, were again weighed and measured after photographing to obtain the edible portion weight. Capacity of containers was measured to the top and to about two centimeters from the top

To communicate a health-based serving, a photograph of the USDA pyramid serving size for selected foods in each of the five food groups is available for display in the program. A universally recognized secondary anchor, a nine-inch paper plate serves to reinforce size perception without having to use a ruler. Weights, dimensions, and volume, where applicable, are available for each photograph in both English and Metric systems.

Photographs were taken under standardized studio settings. To maintain constant camera position for a specific view, several measurements were made for: a) the camera angle, b) position of the contextual anchor, and c) the tripod position. The product is: *testable, portable, upgradeable, and adaptable for multiple uses.*

Edited by: **Renata G. Bushko** - bushko@fhti.org
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HTCPA can be used for education and counseling, as measurement aids for dietary assessment, and for conducting cognitive research. Portion Basics, is the primary program for use in educational settings, or as a stand-alone visual aid during dietary assessment. For purposes of education or nutritional counseling, the teacher/student/client can browse the list of foods or containers and choose an item to view in two or more sizes. For foods, weights and measures can be displayed on demand. For container, dimensions and volume capacity can be displayed on demand. For some foods, there is also a picture of pyramid size serving for comparison with market servings as illustrated for steak below.

Figure 1. Portion Basics: Your Choice

The second program, *Portion Counts,* is the clinical version for use in weight management, diet management in diabetes, or meal planning for heart healthy meals. *Portion Counts* allows the user to view the calories, carbohydrates, protein, fat, cholesterol and fiber content of each food displayed. It serves not only as a counseling tool, but can also provide reinforcement when installed on the client's computer. Figure 2 shows a computer screen from this program.

Figure 2. Portion Counts: When Calories Matter

The third and most comprehensive program, *Portion Plus*, has all the functions of Portion Basics and Portion Counts, plus additional functions for data collection, storage, and retrieval. Thus, beyond educational and clinical uses, the program can serve as a tool for cognitive research in portion size estimation. For cognitive research, the user compares the size or amount of an actual serving of food placed beside the computer with what is displayed on the screen. For research on the effect of memory on portion size estimation, or for use as a measurement aid in dietary assessment, the user compares the size or amount of food eaten at an earlier time with what is displayed on the screen. Amount in every case can be expressed as a fraction or multiple of the amount shown on the screen. A portion estimation screen in Portion Plus is shown in Figure 3.

Figure 3. Portion Plus: Size Estimation

6. Conclusion

While the problem of obesity and the phenomenon of "super-sizing" have become political as well as legal pursuits, and have created media frenzy, it is important for scientists to continue basic and applied research on this topic. There is still a long way to go in improving the quantitative aspects of portion size estimation and dietary assessment methods. But with a multidisciplinary approach and the use of appropriate technology to address the cognitive and behavioral issues in quantifying food intake, I am confident that we are on the right track in shaping a healthy future, megabyte by megabyte, not mega bite!

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A. Stibe / Persuasive Cities: Health Behavior Change at Scale in "World Health Strategy", Renata G. Bushko (Ed.) eBook FHTI 2016. FutureofHealth.org

Chapter 26: Persuasive Cities: Health Behavior Change at Scale

Agnis Stibe
MIT Media Lab, Cambridge, MA, USA

Abstract

Can you imagine a city that feels, understands, and cares about your wellbeing? Future cities will reshape human behavior in countless ways. New strategies and models of urban spaces are required for creating future cities to properly respond to human activity, environmental conditions, and market dynamics. Persuasive urban systems will play an important role in making cities more livable and resource-efficient by addressing current environmental problems and enabling healthier routines. Drawing on socio-psychological theories and integrating them with new concepts for urban design, the persuasive cities research focuses on improving wellbeing across societies. This research presents an ecosystem of future cities, describes three generic groups of people depending on their susceptibility to persuasive technology, explains the process of defining behavior change, and provides tools for social engineering of persuasive cities. Further research should continue exploring how urban design in combination with socially influencing systems could encourage healthy and sustainable behaviors at scale.

1. Perspective

As population in cities continue grow exponentially the architecture and design of future urban places will become more dominant in impacting human behavior [1]. According to social cognitive theory [2], any well-designed environment can become a strong influencer of what people think and do. There is an endlessly dynamic interaction between a person, a particular behavior, and an environment in which that behavior is performed. The persuasive cities research leverages this knowledge to engineer persuasive environments for altering human behavior on societal levels.

The proposed research reflects on novel ways of how persuasive technology [3] and socially influencing systems [4-5] enable mechanisms to perpetually support motivation of individuals comparing to conventional methods, such as those that are based on carrots and sticks. Instead, persuasive urban systems harness social influence from crowd behavior to craft influential messaging aimed at shifting behavior and attitude of an individual, who naturally is an integral part of the same crowd. Such continuous interplay can ultimately result in an ongoing process that reshapes communities and societies without any other incentives.

2. Emergence of Persuasive Cities

Ongoing research streams focus on *sensible cities* (researching sensing technologies to read human behavior in urban spaces) and *smart cities* (analyzing big data to classify groups of people based on their distinct behavioral patterns), however there is a lack of knowledge about perspective ways to achieve persistent behavioral changes at scale. Therefore, the

proposed research extends an ecosystem of future cities (Table 1) by introducing the notion of *persuasive cities* that aims to advance and refine influential strategies designed for intentionally reshaping how people think and act in urban environments.

Table 1. Ecosystem of future cities.

Role	Character		Technology
Change	Care	**PERSUASIVE**	Socially Influencing Systems
Classify	Understand	**SMART**	Big Data Analytics
Read	Feel	**SENSIBLE**	Sensor Networks

Each *layer* of future cities has its *role, character*, and supportive *technology*. Sensible cities employ sensor networks to read crowd behaviors. In other words, these cities feel human movements. These crowd behaviors further serve as an input for big data analytics that smart cities apply to classify groups of people according to similar behavioral patterns (profiles). When that is accomplished, the groups having better routines can be exemplified to other underperforming groups through intentionally designed socially influencing systems, which are at the core of persuasive cities.

3. Susceptibility to Persuasive Technology

People generally can fall into one of the three generic categories depending on their susceptibility to persuasive technology (Fig. 1). *Self-contained* people (the red circle) most likely are not open for changing anything in them. They are fully satisfied with who they are and what they do on daily basis, thus many behavioral interventions might fail in attempts to influence this group of individuals. *Self-driven people* (the green circle) typically have comparatively high levels of motivation and can achieve everything that they have envisioned. Thus, these people most likely are not looking for additional sources of encouragement, and therefore persuasive technologies might become unnecessary for this group.

However, there is another group of people that oftentimes would like to change their routines, but rarely succeed in doing so. That reminds of New Year's resolutions that in many cases end around February. Therefore, this group is entitled as January 1st (the yellow circle) and seem to be the most welcoming towards technology supported behavioral interventions designed to help achieving target behaviors. Although, Fig. 1 presents all three groups as equal circles, in reality the size of each group might significantly vary depending on the context and particular behavior.

Figure 1. Susceptibility to persuasive technology.

4. Defining Behavior Change

To achieve an envisioned target behavior, the process and components of behavior change have to be well understood and clearly defined. In the process of defining behavior change, there are three main components, namely the target group, its present behavior, and its envisioned future behavior (Table 2).

Table 2. The three main components for defining behavior change.

Target Group	Current Behavior	Future Behavior
A group of people currently having an unsatisfactory behavior. It is important to narrow down the target group as precise as possible.	**Description** A certain behavior of the target group that currently is not in line with an envisioned future behavior in a given context.	An ultimate future behavior of the target group that is envisioned to be more beneficial for everyone.
There are MIT faculty members.	**Example** Who currently commute alone in their private cars.	They could commute by bicycles instead whenever possible.

5. Tools for Social Engineering

Earlier research on persuasive technology [3] describes several ways how social dynamics can influence human behavior, which have been further refined and structured as a framework for Socially Influencing Systems (SIS) [4], depicted in Fig. 2. The SIS framework is a useful tool for scholars and practitioners aiming at improving future cities by introducing persuasive urban interventions targeted to support wellbeing.

The framework describes seven socially influencing principles that can support persuasive urban interventions. The principles are interlinked and have potential to exert stronger effects depending on the context of a particular behavioral challenge. Normative influence and social comparison seem to be more effective to achieve involvement of the target group as the two principles focus on attitudinal changes. Cooperation and social facilitation seem to be more effective to make individuals participate and do the envisioned future behavior even without a formed attitude towards it. Competition and recognition seem to be more effective in engaging the target group to do the future behavior as the principles focus on both attitude and behavior simultaneously. For example, the effects several socially influencing principles have already been studied in the context of urban mobility, e.g. bicycling [6].

Figure 2. Socially Influencing Systems (SIS) framework.

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Chapter 27: Future of Diagnostics for Personalized Medicine

Benjamin L. Miller, Ph. D.
Department of Dermatology, University of Rochester, Rochester, New York

Abstract

Unprecedented advances in our understanding of the molecular world around us and within us have the potential to drive a revolution in health care. A key aspect of bringing this revolution to fruition is streamlining and simplifying our ability to detect and quantify molecules of biomedical relevance. New "sample in – answer out" diagnostic systems, some with the potential to detect even single viruses or single copies of molecules, are under development in many academic and industrial laboratories worldwide. This chapter discusses our efforts at the University of Rochester towards the development of three complementary molecular detection systems, with applications from allergy diagnosis to monitoring infectious disease.

Introduction

Medical practice has historically centered on deductive reasoning drawn from observations; a physical exam is a structured method of acquiring these observations. Because these macroscopic measures are often relatively low resolution (although obviously important), medical practice has generally relied on a "one size fits most" treatment strategy. The extraordinarily high cost and long lead times of pharmaceutical development reinforces this model, since corporations need large patient populations to recoup the cost of getting a drug to market (and to cover development costs for the vast majority of drug candidates that never make it all the way through the development process).

We are at the dawn of a sea change in medical diagnosis and therapy, driven by exceptional advances in our understanding of the molecular makeup of ourselves and of the world around us (Figure 1). The "-omics" fields (genomics - the study of all the genes in an organism; proteomics, metabolomics, glycomics - the study of proteins, metabolites, and carbohydrates, respectively) are providing an avalanche of information about the molecules that are present and interact with each other as a part of "normal", healthy biology. Likewise, these sciences are beginning to reveal molecular signatures of human biology gone haywire, and of the infectious agents that attack us. In principle, we can use this information to make precise determinations about the state of our health, and likewise prescribe therapeutic regimens based on unique molecular profiles – a field now known as "personalized medicine". With regard to infectious disease, these techniques will allow for the more rapid recognition that an infectious bacterium is resistant to certain antibiotics (or at an even more basic level, will permit identification of a bacterial infection in hours or minutes, as opposed to current methods that require several days).

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Figure 1: Internal and external influences on our health. Having the ability to "see" these molecules in a simple fashion would allow us to more precisely and rapidly respond to health challenges.

Over the long term, we can envision a future in which the molecular signatures of health and disease are as simple to observe and analyze as our current "macroscopic" health cues. However, the gulf between these two modes of observation is broad: at the macroscopic level, we make judgments about the health of those around us on a continuous basis just by *looking*. If I watch someone doing pull-ups, for example, I can immediately come to some reasonable conclusions about their overall health. In contrast, I know nothing about their *molecular* health: do they have a gene for a particular kind of cancer? Do they carry antibiotic-resistant *Staphylococcus aureus* (e.g. MRSA) on their skin? Getting at this sort of information currently requires (for the most part) expensive instrumentation operated by highly trained personnel – and requires even more highly trained personnel to interpret the results such instrumentation produces.

Just as critical as the problems mentioned above, the complexity of today's molecular analysis equipment means that such capabilities are almost exclusively located in core laboratory facilities. Pushing our pull up-observing analogy a bit, this is analogous to needing to photograph someone doing pull ups, sending the film in for development, and waiting for the picture to come back before being able to make an observation. Time delays in diagnosis have negative consequences in terms of patient health, and dramatically increase patient costs. The situation with infectious disease (in particular, nosocomial bacterial infections) is a particularly stark example of this, and one to which we will return later in the chapter. However, rapid detection of internal disease biomarkers also has the potential to dramatically improve patient care. Having the potential to carry out rapid molecular profiling will be a key factor in the development of "personalized medicine": therapeutic strategies and drugs precisely tailored to an individual's needs. Of course, similarly dramatic changes in the way we discover, develop, get regulatory approval for, and prescribe drugs will be the second essential component of the personalized medicine revolution.

The road to continuous molecular monitoring and a personalized medical future: what are the barriers?

In a previous chapter in this series, I discussed a future in which implanted or ambient sensors were used to monitor - and act on - a person's health.[1] From a technical perspective, many aspects of this scenario (one

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version of the technological changes described in this chapter) are beginning to come in view, and progress in many areas is occurring at a remarkable pace. It's useful, however, to begin to look at the question of what barriers remain (at least in this author's view) before the personalized medical future is a reality. Many of these barriers are societal and regulatory, rather than technical.

Scientific hurdles

One of the primary obstacles in the path of continuous health monitoring and personalized medicine is the identification of biomarkers (in the broadest sense of the word) for particular disease states, and pairing these biomarkers with actions that produce a health benefit. A "biomarker", in its broadest sense, is a biological observable linked to some known (or hypothesized) health state. Representative examples of biomarkers at various stages of development are shown in Table 1. In some cases, biomarkers can be macroscopic: for example, obesity is a biomarker for heart disease and diabetes. Our primary interest here, however, is in *molecular* biomarkers: genetic, protein, and small-molecule signatures of disease. Each of the tens of thousands of different molecules present in the human body is a potential biomarker. Determining which of these alone or in combination correlate usefully with particular disease states will require basic biological experimentation on a massive scale.

Table 1: Selected biomarkers, the disease with which they're associated, and their development status.

Biomarker	Type	Condition	Health state	Status	Reference
Cholesterol	Small molecule	Elevated	Atherosclerosis	Validated	2
p53 gene	DNA	Mutated	Cancer	Validated	3
Brca1	DNA	Mutated	Breat cancer	Validated	4
Prostate-specific antigen (PSA)	Protein	Elevated	Prostate cancer	Validated, but controversial	5
Survivin	Protein	Elevated	Prostate cancer	Candidate	6

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Once biomarkers are identified and validated, the actual therapeutic response needs to be determined as well. That is to say, a biomarker is only as useful as its clinical relevance, or our ability to modify therapy based on the biomarker state. The *Her2/neu* story is a particularly successful example of this idea.[7] Breast cancer patients with tumors overexpressing the Her2 protein, a marker for highly aggressive cancer, can now be treated with an antibody specifically targeting Her2. This therapeutic antibody has dramatically improved the survival of patients with late-stage breast cancer. The Her2 story will need to be repeated hundreds – or thousands – of times as new biomarkers are discovered and validated.

The possibility of thousands of biomarkers, with thousands of biomarker-specific therapeutic agents, brings forward several questions. One of these is that as the number and complexity of different inputs increases, how is this to be sorted out? One therapeutic strategy that's already attracting notice is the application of "combination therapies". We're mostly familiar with this from the negative perspective (anyone who's taken even common over-the-counter cold and flu remedies is familiar with the idea of drug interactions), but combination therapies have become essential in many areas of human health. Treatment of HIV, for example, routinely employs a number of different therapeutic agents simultaneously, a so-called "cocktail" of drugs. As our understanding of biomarkers increases, it is likely that the number of therapeutic agents needed to be deployed based on what those biomarkers tell us will be extensive.

The combination therapy strategy has even attracted notice as a business model. Drug discovery companies such as CombinatorX are examining the utility of using mixtures of drugs to take advantage of drug interactions for several indications.

Diagnostic hurdles

Of course, before one can prescribe a new, biomarker-based "personalized" therapy, one must be able to detect (and in many cases quantitate) that biomarker accurately, sensitively, and quickly. Monitoring biomarkers on a continuing basis following therapy will be an important health-maintenance strategy in many instances as well. Development of such technology, essentially the extension of our senses to the molecular level, has been a particular focus of my laboratory and the laboratories of my collaborators at the University of Rochester, and therefore will be discussed in much greater detail below.

Regulatory hurdles

Our current method for approving drugs, medical devices, and other forms of treatment is incompatible with a personalized medical future. While this is an area that is clearly not within this author's primary expertise, it is quite clear that carrying out full FDA-style clinical trials (Phase I, Phase II, Phase III, etc.) is very difficult when the available patient population is small, as will be the case as increasingly high-resolution molecular disease signatures become

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available. Likewise, the financial burdens of such studies are untenable even today for all but the most common conditions. A foreshadowing of this problem is visible today in the "orphan drug" field. In the United States, the Orphan Drug Act provides specific protections for companies developing therapeutic agents for diseases affecting fewer than 200,000 people.8 As personalized medicine becomes a reality, molecular signatures may allow every new therapy to fall within what are now "orphan" guidelines, since individualized disease states will be defined with higher and higher resolution.

Societal issues

A personalized health future implies that an ever-increasing amount of data will be gathered, possibly continuously, about our health. As in many areas of health research, questions arise regarding how this data will be safeguarded, but also how it will be made available to people (researchers? regulators? doctors?) who can use it to do the most good.

This is a concern that in part may resolve itself through societal changes that have already begun to happen with respect to personal privacy and data security. Many of us are astounded (and somewhat frightened) by the amount of personal data many people make available on social networking web sites. Will Bob's table of cancer risk factors join pictures of Bob's weekend keg stand on MySpace or Facebook? It is possible that people may in the future have a comfort level with making this information public that those of us coming to adulthood in a much more privacy-seeking time do not have.

Addressing the technological and content front: advances in biosensors and diagnostics at the University of Rochester

A crucial aspect of expanding the range and applicability of diagnostic systems centers on the need to produce technologies able to sense the presence of molecules with diagnostic utility. Currently, such sensing methods primarily fall into two categories: simple lateral-flow tests (the home pregnancy test being one example), which generally don't provide much in the way of quantitative information, and highly complex systems capable of multiplex analysis. Both modalities obviously give useful information, and have been critically important in bringing us to the state of health we enjoy today. However, as we move forward, we need to do better. This section will focus in particular on systems able to do multiplex analysis.

A photograph of typical equipment used in modern diagnostic laboratories is shown in Figure 2. In these systems, a "chip" of some sort bearing a capture molecule specific to the target of interest is treated with a clinical sample (or alternatively, the clinical sample is added to a solution containing the capture molecule). The capture molecule is typically a DNA sequence (for genetic analysis) or an antibody (for protein analysis). After a period of time to allow molecules in the clinical sample to interact with the molecules on the surface of the detection chip,

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the chip is rinsed to remove materials that do not bind. A primary problem with current diagnostic tools is that this does not yet provide useful information in most cases. Rather, the chip must then be treated with a labeled reagent, typically a secondary antibody carrying a fluorescent group or yet another molecule that's used to capture an enzyme for a colorimetric reaction (DNA is typically labeled as part of an amplification process that occurs prior to its introduction to the chip). It is only after this multi-step process that one can actually observe whether the capture molecules on the chip bound (captured) anything from the clinical sample.

Figure 2: "Standard" automated medical diagnostic equipment. While triumphs of modern technology, these systems require expensive reagents to operate and extensive operator training.

One way to improve this process is to develop sensors that respond directly to the binding event. We have been pursuing this goal on several fronts, and have successfully developed platform technologies allowing the direct, label-free detection of both proteins and DNA. I should note at the outset that many other research groups world-wide have been pursuing analogous goals, and several have developed highly innovative strategies for molecular detection that may prove to be useful in the clinical setting (and eventually at home). Space does not permit going in to all of these in detail, and therefore we will focus on our own work, and that of our collaborators at the University of Rochester, as representative examples.

Targeting nosocomial infections with the DNA NanoLantern™

Bacterial infections acquired in hospitals following surgery (nosocomial infections) have become a problem of nearly epidemic proportions. Of particular concern is the rising fraction of these infections that are resistant to common antibiotics. Patients who acquire a drug-resistant infection as a result of their hospitalization present a significant cost burden to the health care system, and obviously have to suffer through the burden of a longer hospital stay and more complex therapeutic regimen (let alone the increased possibility of death). The problem is in many ways self-reinforcing: patients who exhibit any evidence of a bacterial infection are often prescribed broad-spectrum antibiotics. Overuse of these antibiotics in turn leads to an increase in resistant bacteria, and therefore patients are prescribed stronger, front-line antibiotics, which leads to more resistant bacteria...and so on, in a never-ending cycle. The case of *Staphylococcus* aureus (or "staph") is illustrative of the problem. As shown in Figure 3, penicillin-resistant *Staphylococcus* emerged shortly after the introduction of penicillin, and the evolutionary pressure provided by antibiotic use has led to a continuing

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escalation in the antibiotics-vs.-bacteria war.9 Vancomycin, once the drug of last resort, is now prescribed much more readily, and as of 2002 cases of vancomycin-resistant *Staphylococcus* had begun to appear. Unfortunately, a patient with vancomycin-resistant *Staphylococcus* is rapidly running out of therapeutic options.

Figure 3: Timeline for the evolution of antibiotic resistance in Staphylococcus aureus (data based on Reference 9 and after CDC agency graphics).

Guidelines established by the CDC clearly state that surveillance and the development of rapid diagnostics are critical components of improving our record against drug-resistant bacteria.[10] If an infection is diagnosed more rapidly, and with higher precision (i.e. rather than getting an initial indication of Gram-(-) vs. Gram-(+) bacteria, and waiting days to weeks to find out species and resistance profile via traditional microbiological methods, but instead getting all of this information in a matter of hours), doctors can immediately apply the correct therapy as needed. How then can one accomplish this goal?

Bacteria are defined by their genes, and in many cases genetic information encoding common mechanisms of resistance are also well known. One of the techniques we have developed over the past several years serves as a platform for rapidly detecting these genetic signatures.[11] Termed the "DNA NanoLantern™", this technology relies on two key phenomena: first, a method we have developed to identify DNA probes shaped like hairpins for target organisms of interest, and second, the ability of metal films to quench (turn off) fluorescence. The system works as follows (Figure 4): a DNA hairpin probe immobilized on a metal film (usually gold, but other metals work as well) is "off". No light emits from the sensor until target DNA binds to the probe, opening up the hairpin, moving the fluorescent group away from the metal surface, and allowing fluorescence to occur. This conceptually simple method turns out to work extraordinarily well, providing highly selective and sensitive detection of target DNA.

Figure 4: The DNA NanoLantern™. A hairpin DNA probe molecule bearing a fluorescent group at one end is immobilized on a metal film. When brought into contact with a target DNA sequence, formation of the DNA double-helix causes the fluorescent group to move away from the metal film, allowing light to be emitted following excitation with a light source. Right: representative data showing NanoLantern™ signal before and after application of target DNA.

The NanoLantern™ system is only as good as the probe DNA sequences it uses, however, and so a few years ago we developed a method for identifying useful DNA probes from genomic sequences.[12] In brief, raw genomic sequence information is fed into a computer program that predicts how the sequence will fold. This is a complicated problem, as each individual DNA base has many potential pairing partners from which to choose. Fortunately, David Mathews and his research group, colleagues of ours at the University of Rochester, have developed software tools simplifying this part of the process.[13] Next, we identify regions of the predicted lowest-energy fold that "look like" our DNA hairpin probes. This can be done by inspection (as in Figure 5, where candidate hairpins were readily identifiable in the folded genetic sequence), or automatically with software. Candidate hairpin probes are then computationally "excised" from the full sequence, re-folded, and their predicted energies checked against a set of criteria for effective probe characteristics. In the case of methicillin-resistant Staphylococcus aureus, folding the mecR gene (responsible for the resistance phenotype) yielded a probe molecule subsequently demonstrated to work effectively with a synthetic DNA target.

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MRSA detection.
Detection of synthetic DNA served as an effective "proof-of-principle", but what about detecting actual bacteria? To demonstrate this, PCR was used to amplify the target DNA sequence from cultured MRSA. The product of the PCR reaction was applied to a NanoLantern™ chip bearing the MRSA probe, while in parallel the same process was carried out on *Staphylococcus aureus* lacking the methicillin resistance gene. As expected, a positive response was obtained for MRSA, while drug-sensitive Staphylococcus gave no signal.[14]

Moving forward, we can anticipate incorporating arrays of NanoLantern™ probes into chips able to detect and diagnose a broad range of pathogens. Figure 6 shows a preliminary experiment demonstrating array capability, with identical spots of the MRSA-targeted probe arrayed using a BioForce Nano-eNabler. Each spot of this array is roughly 10 microns in diameter, making the entire array roughly 100 microns on a side (0.1 mm, or somewhat less than the size of the period at the end of this sentence). Efforts in our laboratory are currently centered on the production of chips able to diagnose a broad range of bacterial infections, with a particular focus on urinary tract infections (UTI). However, one can envision extension of the NanoLantern™ system beyond infectious disease, to rapid human genetic analysis as well.

Figure 6: A DNA NanoLantern™ microarray. Images are before (left) and after (right) addition of target DNA. The dimensions of this array are approximately 90 microns by 90 microns, or 0.000012 square inches.

Monitoring the human immune system with Arrayed Imaging Reflectometry

The NanoLantern™ system is proving to be exceptionally useful for detecting DNA targets, but what about proteins? Proteins are somewhat more complicated to detect than DNA, for several reasons. First, there is unfortunately no analog of the polymerase chain reaction (PCR), so amplification of the amount of a particular protein present in a sample is not possible. As proteins may be present in serum over a very large range of concentrations (up to 12 orders of magnitude), this means that detection techniques must have high dynamic range as well as high sensitivity. Second, proteins are much

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more fragile than DNA: "rough handling" can irreversibly degrade them. Third, although one can read off

One method under development in our laboratories, termed Arrayed Imaging Reflectometry, or "AIR", takes advantage of the optical and chemical properties of silicon, the commodity material of the microelectronics industry. As shown in the instrument schematic in Figure 7, AIR relies on our ability to create an antireflective coating on the surface of a silicon chip: by choosing the proper thickness of silicon dioxide and capture molecules, we can set up a condition whereby polarized laser light interacting with the chip at a particular angle destructively interferes with itself within the coating, preventing any light from reflecting back off the chip. When a target protein binds to the capture molecule on the surface of the chip, that destroys the antireflective condition, and light is observed reflecting off the chip. Although conceptually simple, this method turns out to work exceptionally well.[15]

Figure 7: Arrayed Imaging Reflectometry (Schematic). Left: The AIR instrument consists of a few simple optical components and a CCD camera. Laser light interacting with an antireflective coating on a chip (shown at right) undergoes partial reflection as a function of the amount of target biomolecules bound to the surface.

In early efforts, we demonstrated that AIR could be used for the detection of proteins from enteropathogenic *E. coli,* validating the platform as a method for bacterial detection.[16] More recently, we have extended these efforts to a broad range of human proteins. We will discuss two examples, as they illustrate two aspects of how such technology might be useful in the future.

The human immune system is an extraordinarily complex system. One aspect of the immune system responds quickly and generically to the presence of external agents, whether bacterial, viral, or completely inanimate, and is also responsible for the inflammatory response to injury. Proteins produced as part of this inflammatory response, termed cytokines, are in essence an amplified response to the presence of an injury, irritant, or infectious agent (among others). These proteins act as signaling molecules to activate other portions of the immune response.

Because of their importance as early indicators of inflammation and disease, we tested our AIR protein detection system by preparing a series of cytokine arrays.[17] First, antibodies to individual cytokines and other immune system markers were immobilized on AIR chips, and their ability to detect target protein in a buffered solution of excess bovine serum albumin (as a simplified analog of what would be found in the complex milieu of human serum) measured. As shown in Figure 8, this experiment was successfully

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completed for 11 targets. Importantly, detection sensitivity for several targets was comparable to that observed using an ELISA assay (the "gold standard" for protein detection, ELISA uses a multistep, labeled process analogous to that shown above in Figure 2). Furthermore, cytokine detection in doped samples of human serum was found to be straightforward (Figure 8, right). In combination, these data provided the first indication that the AIR technique could serve as a suitable method for rapidly detecting and profiling the concentrations of human proteins.

Figure 8. Array-based detection of cytokines. Left: Successful detection of 11 individual cytokines and other immune system proteins with antibody-functionalized AIR chips (where "BG" refers to background signal, and "EXP" is the signal produced by the chip in the presence of the target protein in a buffered solution of bovine serum albumin). Right: Detection of TNF-alpha and IgG in undiluted human serum.

Of course, detection of cytokines provides only one measure of the immune system's response to injury or infection. One can also screen for antibodies produced in response to a particular pathogen. This information is potentially useful as a screening measure (for example, if I find a dead crow in my front yard, is it infected with bird flu?), and also as a means of monitoring vaccine effectiveness. These "antigen arrays" may also have considerable utility in the field of allergy testing, dramatically simplifying what currently resembles a medieval torture process. Rather than placing a grid of antigen scratches on the back of a person being tested and waiting for an immune response, one would only need to obtain a small sample of serum from the patient and look for antibodies binding to an antigen array.

As a first step toward exploring the utility of the AIR technology for the production of antigen arrays, we have carried out preliminary experiments using human papillomavirus (HPV) as a model system. HPV is a widespread infection, and importantly from the perspective of human health is believed to be the primary causative agent of cervical cancer. While estimates vary with regard to the incidence of cervical cancer, many put the rate of new cases world-wide at roughly 500,000. Newly available vaccines show considerable promise for dropping this number dramatically, but how does one monitor the effectiveness of the vaccine (in terms of antibody titer) and continue to monitor the virus? To address this question, we have created AIR chips bearing "virus-like particles" (more on that in a moment) from two common forms of HPV.[18]

From the purely technical aspect of sensor design, HPV represents a particularly interesting challenge to the AIR platform. This is because unlike most of the systems we have worked with previously, it is not possible to obtain the HPV coat protein in a stable, single-copy form. Rather, this protein self-assembles into a capsule roughly

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50 nm in diameter, even in the absence of any other materials from the virus. These "virus-like particles", or VLPs, are in fact key elements of the HPV vaccine. However, at the outset of our work, it was not at all clear that one could attach such large molecular assemblies to an AIR chip and produce something that would actually function as a sensor. Fortunately, we discovered that it is indeed possible for chip-tethered VLPs to function quite well: as shown in Figure 9, chips bearing VLPs from HPV-11 are able to recognize antibodies to HPV-11 in mouse ascites fluid, and chips bearing VLPs from HPV-16 are able to recognize antibodies to HPV-16. Little cross-reactivity is observed between the two types, suggesting that sensors incorporating arrays of different VLPs will be able to produce highly specific patterns of detection with HPV antibodies

Figure 9. Left: chip image following treatment with a 1:200 buffer dilution of mouse ascites fluid containing antibodies to VLP16. The bright spots at the center indicate positive detection, while other spots serve as controls. Right: Bar graph showing selective response of anti-HPV11 containing ascites fluid to VLP11 AIR chips, and anti-HPV16 containing ascites fluid to VLP16 AIR chips.

While considerable development work remains to be done before AIR is a fully automated molecular detection system suitable for hospital, clinic, field, and even home use, the data obtained thus far indicate that it can indeed replace "traditional" methods of protein detection. By dramatically simplifying the sensing process, we anticipate that sensing methods of this type will prove broadly useful.

Towards ultrahigh-sensitivity biosensors: the two-dimensional photonic bandgap

In any scientific field, it is helpful to define absolutes: zero degrees Kelvin is the absolute minimum temperature; the speed of light is the absolute upper limit of speed (at least outside of science fiction!). For biosensing, the absolute limit of sensitivity is the ability to detect *one copy* of a target: one bacterium, one virus, one DNA strand, one protein. Several single-molecule or single-particle detection schemes have been reported by a number of research groups, suggesting that this "ultimate" goal is in reach. In our case, we have begun exploring the use of two-dimensional photonic bandgap (2DPBG) structures in collaboration with the research groups of Philippe Fauchet and Matt Yates. Conceptually, a 2DPBG confines light to a small region of space.[19] For example, the 2DPBG shown in Figure 10, constructed in silicon, is roughly one micron on a side. Confining light within such a small space allows for detection of extraordinarily small changes in the environment – such as would occur on binding a virus.

Figure 10: Two-dimensional photonic bandgap sensor. Light is confined within the area of the regular array of "holes" in the silicon; a slightly different-sized hole at the center creates a "defect" in the light confinement that shows up as a peak in the optical spectrum.

Figure 11: Optical detection of a single virus-sized latex bead in a 2DPBG. Left: Scanning electron micrograph (SEM) image of a single latex sphere infiltrated into the center defect of a 2DPBG device. Right: Optical transmission spectra of the 2DPBG before and after infiltration, showing the shift in the primary transmission peak. While acquisition of the SEM image on the left is arduous and requires very expensive instrumentation, observation of the peak shift on the right (as would be used in a diagnostic setting) is relatively straightforward and nearly instantaneous.

Conclusions

New methods of biomolecular sensing will serve as important enabling technologies in bringing truly personalized medicine from the realm of science fiction to everyday reality. As that extend our senses to the molecular world, these devices may one day make the early diagnosis of cancer as easy as "looking". As discussed at the outset of this chapter, however, dramatic advances in basic biomedical research, in the pharmaceutical discovery process, and in regulatory policy are essential to making sure that the information we gain from our new molecular senses is relevant and therapeutically actionable. If this occurs, we will indeed be at the dawn of a revolution in health care.

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Chapter 28: Designing and Evaluating Home-Based, Just-in-Time Supportive Technology

Stephen S. Intille, Ph.D.
Technology Director, House_n Consortium, Department of Architecture, Massachusetts Institute of Technology, Cambridge, MA, USA

Kent Larson
Director, House_n Consortium, Department of Architecture, Massachusetts Institute of Technology, Cambridge, MA, USA

Abstract

At MIT, a multi-disciplinary team of researchers is studying how to create pervasive computing environments for the home. We are developing technologies and design strategies that use context-aware sensing to empower people with information by presenting it at precisely the right time and place. Contrary to many visions of future home environments in the literature, we advocate an approach that uses technology to teach as opposed to using technology primarily for automated control. We have constructed a "living laboratory" that will provide a unique, flexible infrastructure for scientifically studying the power of pervasive computing for motivating learning and behavior change in the home. This facility, called the PlaceLab, is being used to study technology for creating homes that are supportive.

1. Changing Places of Living

People spend more time in their homes than in any other space. The home ideally provides a safe, comfortable environment in which to relax, communicate, learn, and be entertained. Increasingly, it is where people connect with friends and family, conduct business, manage resources, learn about the world, and maintain health and autonomy as they age. Unfortunately, technologies that are in the home are typically developed in isolation, and the general perception of homeowners is that computer devices are making life more complex and frustrating rather than easier and more relaxing. People are wary of the aesthetic, financial, and cognitive challenges of bringing new technologies into their homes. Our multi-disciplinary research team at the Massachusetts Institute of Technology is investigating how the home and its related technologies, products, and services should evolve to better meet the opportunities and challenges of the future [1]. The "n" in House n represents a variable; we believe there is no single "home of the future." Our focus is on developing *design strategies* that meet the needs of multiple constituencies. In particular, we aim to create environments that are more flexible and that better meet the physical and cognitive needs of occupants than current environments. The spaces we envision seamlessly merge digital information with the physical environment. Four of the overarching goals of the House n project are to create supportive technologies that (1) help people create and customize environments and technologies that reflect their unique needs and values, (2) help people to live long and healthy lives in their homes, (3)

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help people reduce resource consumption, and (4) help people integrate learning into their everyday activity in the home

Our research group is collectively asking the question, "How can we design spaces with technologies that are more than isolated gadgets, that are easier to use than today's technologies, and that provide real value to people in their homes over long periods of time?" Whenever possible, our team uses a participatory design approach, where we involve the stake holders in the design process. After discussions with physicians and patients interested in preventative health care, it became clear that the home of the future that would be of the most value is one that that does not use technology primarily to automatically control the environment but one that would help someone learn how to control the environment. This shift from the "controlling" home to the home that is supportive is the focus of this article.

A byproduct of this shift is that new tools are required to study technology in context of life in the home. Our team has constructed a "living laboratory" to support qualitative and quantitative studies investigating the relationships between spaces, the behaviors of people, and pervasive computing technologies. This facility, opened in summer 2004, is a single family residence with an integrated, ubiquitous sensor architecture. This architecture will be used by applications to acquire information about context, as is done in least one existing living lab (i.e. [2]). The laboratory infrastructure will also be used, however, for the quantitative measurement and qualitative study of the impact of new technologies on the behavior of people actually living in the environment.

2. Envisioning Homes of the Future

If one is to believe the majority of movies, television, and popular press articles that mention life in the homes of the future, our future homes will take care of our every need. Our homes will be so fully automated and "smart" that we will rarely have to think about everyday tasks at all. Nearly all of our time in the home will be spent engaged in leisure activities because digital and robotic agents will have taken over the mundane chores of day-to-day life.

Researchers and technologists are more cautious in their predictions, but a survey of ongoing work still shows a bias toward creating future home environments with the goal of eliminating the need to think about tasks such as controlling heating and lighting, going to the grocery store, cleaning, scheduling home appliances, and cooking. Field interviews with medical professionals, educators, and homeowners have led our group in a different direction. Simplification or elimination of everyday tasks in the home may be in direct conflict with our goals of encouraging healthy lifestyles, resource conservation, and lifelong learning. On the contrary, medical professionals suggest that developing systems that *require* human effort in ways that keep people as mentally and physically engaged as possible as they age should be the goal. Although there are some instances in which we may want to use automation to allow people to accomplish tasks they can no longer perform on their

own because of a disability or frailty, our primary vision is not one where computer technology is ubiquitously and proactively managing the details of the home.

Instead, the vision is one where computer technology is ever-present but in a more subtle way – tailored information is presented to people at precisely the time and the place when they need it so that they can learn how to take better care of themselves, learn how to conserve resources, or learn about topics that interest them. Medical experts tell us that the old adage, "use it or lose it," is applicable to both physical and mental health as we age. We want our pervasive technologies to empower people with information that helps them make decisions; we do not want to strip people of their sense of control, which has been shown to be psychologically and physically debilitating [3]. In short, we are designing pervasive computing environments that do not take over control of the environment for the home occupant as some previous systems have done (e.g. [4]) but rather help the home occupant to learn how to take control.

3. Control Versus Empowerment: An Example

To illustrate this shift in thinking, consider an example. Imagine our goal is to create an environment that uses pervasive computing technology to save energy by automatically controlling the heater-vent-air conditioning (HVAC) system. We assume that the environment has embedded sensors that can infer context such as where people are, what people are doing, and what the environmental conditions inside the home are. We also assume that the home contains computer-controlled HVAC appliances, windows, and blinds.

3.1 The automated home

One way to accomplish the goal of reducing resource consumption is to design a home environment that takes control of environmental conditions. The home uses a set of optimization algorithms to simultaneously maximize savings and comfort by automatically controlling the HVAC systems, windows, and blinds. For instance, on a day when the temperature is predicted to shift from warm to cool the home might determine the optimal cooling strategy is to shut down the AC and automatically open a set of blinds and windows to create an efficient cross breeze.

This scenario is relatively simple compared with other popular "smart home" visions. In practice, however, executing this scenario in an actual home setting is difficult. The situations in which the automatic system might succeed in optimizing temperature comfort yet fail in "doing the right thing" are many: something noisy is occurring outside, someone is smoking outside the window, someone in the home is allergic to pollen and the pollen count is high, it is raining outside, it is too quiet for a person reading when the hum of the air conditioner is off, someone did not want the blinds open because it throws glare on a computer screen, and so on. The system designer will be unable to program common-sense contingency plans for all possible contexts, and invariably

the system will perform in unexpected, frustrating, and undesirable ways.

system will actually become less predictable as it acquires more expertise, and the success of the system some or most of the time will raise occupant expectations about what the system is capable of doing. Inevitably, the system will violate the occupant's high expectations given the unexplainable "intelligence" the system sometime shows when making these control decisions. Because the system is so complex, the occupant will be left feeling frustrated – helpless to understand the behavior. Why does it keep opening the windows when, clearly, the occupant wants and needs them closed? Other common scenarios for "smart" automatic control of the home suffer from identical problems

3.2 The home that uses subtle reminders

Consider an alternative scenario. In this vision of the home of the future, the windows include a tiny light that is either embedded in the window frame (e.g. an LED) or that is projected on the window using pervasive computing display technology (e.g. an IBM Everywhere Display [6]). This home still has embedded sensors and optimization algorithms that compute a strategy for cooling the home by opening a particular set of windows. This home, however, does not proactively control the home to achieve the computed optimal settings. Instead, it uses pervasive technologies to *teach* the home occupant – in a non-obtrusive way – how to achieve the optimal settings.

For example, the light on the window will subtly illuminate. It does not interrupt the home occupant. When someone in the home notices it, that person knows the light indicates that, "it might be a good idea to open this window right now." The home thereby non-obtrusively informs the occupant of actions that the occupant might take to conserve energy or money. A similar approach can be taken when the goal is to improve health or introduce learning into everyday life.

This approach has several advantages over proactive control:

- Information can be presented that the occupant can react to without interrupting ongoing activity in potentially irritating ways; this is especially true if information can be "augmented" onto the physical environment itself using projected light.

- Leaving the occupant in control of making decisions allows the home to present options based on partial information without confusing the occupant; the occupant will naturally consider contexts that the home has not and adjust his or her actions accordingly.

- Algorithms that make suggestions can degrade gracefully; algorithms that make decisions typically do not.

- Lack of control over aspects of life has been shown to diminish health [3]; this strategy empowers the home occupant.

The occupant ultimately makes the decision whether to open the window. Therefore, the task of interpreting the suggestion in context rests with the occupant: if it is noisy outside the occupant will simply decide not to open the window, realizing that this is not a good time. This is a pervasive computing application with an exceptionally simple user interface. Would a system with such a simple interface influence behavior? Yes. Controlled studies in homes show that using such a small, simple light on an AC unit can lead to 15% reductions in AC use [7].

3.3 The teaching home and pervasive information display

The example above of the light on the AC may lead to some behavior change but it does so in a way that relies on the technology to be present. Fortunately, pervasive computing can be used to not only motivate the behavior but to *teach* at the moment when the behavior is being undertaken.

Systems that automatically make control decisions generally miss this opportunity. Occupants can become complacent if the system is functioning perfectly. Although a computer system might try to present the occupant with educational messages to explain the actions it is taking, to do this without interrupting and irritating the occupant is a challenge. The system must compute when a reasonable time to present the information might be. Even for relatively simple help applications this has proven to be difficult to do (e.g. ClipIt, the Microsoft Paperclip attempts just-in-time help but does so in ways that often requires the occupant to divert attention from the current task). On the other hand, if an occupant is unhappy with a control decision made by the home, the user is going to be in a state of annoyance and primarily interested in counteracting the home's actions – this is not the best time for the home to present explanatory information to promote learning.

A home that leaves the right amount of control to the occupant avoids the computational challenge of indirectly inferring occupant intent in order to determine the moment at which to teach. The extraordinary power of pervasive computing can come into play when an occupant decides to take an action such as opening the window. This is a "point of behavior" that can be easily identified by detecting a specific event (the opening of the window). The occupant has already made a decision to stop whatever he or she was doing to do a recommended task. The home can safely infer *directly from sensor data* that the occupant is opening the window and therefore is likely to be receptive to information that helps him or her determine how to do so. The occupant is also likely to be curious about why the home is making this recommendation. Finally, the occupant will have moved to the physical location of the object, which presents a good opportunity to teach by overlaying digital information on the physical space. In this scenario, at precisely the moment when the system determines that the occupant has decided to take action, information can be overlaid on the real world to educate the occupant about how to create the most effective cross breeze.

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Even if the occupant does not have time to stop and study information, it is possible to present feedback that results in learning. For example, as the window is opened, information might be projected onto the nearby wall that estimates the magnitude of the breeze to be created. The person may notice that, counter-intuitively, opening the window further does not always result in a stronger cross breeze. The occupant's task has not been interrupted, so even if the occupant is completely uninterested in the information, no attentional disruption has been created. Immediately after the point of action the information could be removed.

It is the potential impact on behavior of this non-intrusive, "just-in-time" learning that our group is studying. We are interested in three points in time: the point of decision, the point of behavior, and point of consequence [8]. How can we use computers to educate people about how to take control of their environment by using sensors to automatically detect these specific (and sometimes fleeting) moments in time? In this particular example, as the occupant occasionally follows the recommendation of the home he or she will gradually learn how to efficiently control the temperature in the environment in sophisticated ways. Occupants will understand that the reason the lights appear on their windows is because it is cool enough outside to setup a cross breeze. They will also gradually learn how to create a cross breeze given the geometry of their house and the prevalent wind direction: using window inlets and outlets that maximize cooling through the home; understanding how to open window inlets and outlets to maximize air flow; understanding how long it will take for cooling to occur; understanding the best times and places to establish intake air; knowing how to use fans to facilitate cross-breeze cooling. These are things that most people do not know how to do because there is no one to instruct them on how to do it when they are in need of guidance at the point of behavior. Presentation of information at the point of behavior by a pervasive computing system can fill this need. The challenge then becomes to develop algorithms that can recognize the right time and select a presentation strategy suitable for the given context. We have been conducting small user studies with mockup displays and are now implementing prototypes of some of the examples. Figure 1a shows a display that might appear on a wearable PDA or projected near the window at the moment a person is opening or closing a window: the "teachable moment." An open question that we plan to explore is how the way that information is presented and the current context influences the persuasive impact of educational messages.

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Figure 1. (a) This image shows a message that might be displayed within eyesight of a person just as that person opens a window in order to help that person learn how to conserve energy. (b) This message could be displayed on the refrigerator or on a wearable wrist computer just as someone closes the refrigerator door.

An important consequence of using pervasive computing technology for just-in-time teaching rather than control is that the information people learn in that environment will transfer to other environments where there is no computer technology. Additionally, the just-in-time teaching scenario may still use automatic control of the windows but in a way that encourages people to use their physical abilities: a young healthy person would be encouraged (using pervasive computing messaging) to exercise muscles by opening the window, whereas a frail, elderly person who cannot lift the window would be encouraged to go to the window and push a real or virtual automatic button. We are also studying how to present persuasive, pervasive messaging to motivate small behavior changes during everyday activities. For instance, Figure 1b shows a message that could be displayed on a refrigerator door (or on a wearable wrist computer) just after the door has been closed to encourage awareness of energy conservation. People who are informed that their behavior is out of line with community standards will often naturally change their activity; in this case a greater awareness of the need to keep the door shut may result.

4. Design of the PlaceLab: A Living Laboratory

The shift in focus from creating automatic ("smart") environments to environments that help the occupant learn how to take self control impacts not only the type of technology we are designing but also our outlook on how we must conduct research to evaluate our work. We could construct a mockup space that simulates a home and then show that in particular situations the home can automatically control the physical and digital environments. Several of the pervasive computing environments built in the last several years have or are doing just that (e.g. [4], [2], [9]), and we have our own test environment.

However, pervasive environments that help people learn how to take to take control themselves cannot be evaluated independently of the people using them. We need to study the *people using the technology* in realistic, non-laboratory settings for long periods of time and then measure whether our interventions are leading to learning and behavior change.

To meet this need, we have designed and built an apartment-scale residential observational facility called the *PlaceLab*, an MIT and TIAX, LLC

initiative. The PlaceLab serves as a "living laboratory" to study how people respond to new technologies. The facility is located a few blocks from MIT in a residential condominium building, and it opened in July 2004. The 1000 square foot lab consists of a living room, dining area, kitchen, small office, bedroom, full bath and half bath. This facility serves two primary functions: (1) to provide an environment in which life in the home can be scientifically studied, and (2) to provide a means for evaluating whether new types of pervasive computing interventions have a long-term and meaningful impact on behavior in the home, especially behavior related to health and well-being.

4.1 Ubiquitous sensing

The PlaceLab uses a cabinet-based integrated interior infill system [10]. Despite ubiquitous sensing technology, the Place-Lab looks like a nicely designed home to the resident without any visible technologies other than standard home electronics.

Embedded within each cabinet in the PlaceLab is a suite of sensors, as marked on Figure 2b. The sensors in the PlaceLab are used for two purposes: (1) the development of algorithms that infer what people are doing from sensor data, and (2) observation of activity in the space for research purposes. The PlaceLab is not intended to be a demonstration "home of the future." Instead it is a laboratory to study people in the home setting.

4.2 Using the PlaceLab

The PlaceLab is occupied by volunteer subjects who agree live in the home for periods of days, weeks, or months, depending upon the studies being run. While they occupy the facility, a rich dataset is collected on the behavior of the subjects. Researchers have the capability to monitor nearly every aspect of life in the home, particularly what people are doing and the interior and exterior environmental conditions in the space. Tools for the semi-automatic annotation and pruning of data aid researchers in studying the enormous amounts of data that are acquired daily by the laboratory. A suite of portable tools have also been developed that supplement the capabilities of the PlaceLab and permit studies where subjects are monitored in their own homes before and/or after they enter the PlaceLab, permitting studies that investigate pre- and post-occupancy behavior changes.

The facility is managed as a multi-disciplinary shared scientific tool in the tradition of other scientific facilities developed to study unique environments such as telescopes, microscopes, and undersea vessels. Researchers from many fields can submit proposals to a multi-disciplinary review board. These proposals are reviewed and ranked. High quality proposals are those that (1) can only be accomplished with the unique facilities of the PlaceLab, (2) will fundamentally increase scientific understanding of issues related to life in the home, and (3) consider the long-term implications of the technology, system, or architecture being studied and potential to create societal change. As in existing telescope facilities, complimentary and non-interfering studies are piggybacked to fill the facility calendar.

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Figure 2. (a) Kitchen of the PlaceLab. Each cabinet contains a sensor infrastructure. (b) Living room of the PlaceLab. (c) Locations of some of the sensors built into a typical cabinet

The PlaceLab is already being used to investigate questions such as, (1) What influences the behavior of people in their homes? (2) How can technology be effective in the home context for long time periods?, (3) Can technology and architectural design motivate life-extending behavior changes?, and (4) What new innovations for the home would most fundamentally alter the way we live our everyday lives? In summary, the PlaceLab is a multi-disciplinary, shared research facility for the study of people and their relationship with their living environments.

4.3 Studying life in the home and physical/ digital interactions

Relatively little research has been done on the relationship between the home and technology given the importance of the home in life [11]. We are using the PlaceLab's ubiquitous sensing for the quantitative and qualitative study of human behavior in the home – with and without new technologies. To do so, we are developing tools that will use the Place-Lab's sensing infrastructure to acquire and semi-automatically annotate data of interest to researchers.

The infrastructure of the PlaceLab has been designed so that video, audio, and appliance-level data can be continuously acquired from every part of the environment. For instance, the PlaceLab permits a researcher studying eating behaviors to make a request such as, "I'd like to see all the video and audio data of activity in rooms just before and after a subject opens a cabinet or appliance that relates to food storage or consumption." The researcher can collect and identify only the small subset of data relevant to that researcher's study. An algorithm developer can use the PlaceLab to acquire probabilistic data about the movement of people around

environments throughout typical days. The lab provides an excellent resource with which to study how certain technologies disrupt activity in the home [5]. The combination of sensor data and audio-video recording (e.g. [12]) creates a powerful tool set for the researcher interested in evaluating technology designed for the home with people actually living in a home.

4.4 Measuring effectiveness of applications

The last function of the PlaceLab is to allow for the *evaluation* of certain types of pervasive computing applications. We are particularly interested in studying how context impacts the presentation and motivational impact of information presented in the home environment over long intervals of time.

The PlaceLab has being designed so that pervasive com-putting applications that present digital messages at the right time and place can be created without substantial amounts of system engineering. Our goal is not to develop new sensors for every situation but to investigate what can be accomplished with a given set of ubiquitous sensors that could be realistically retrofitted into existing living environments.

Our group consulted with researchers in a diverse set of fields as we developed the Placelab. Our goal has been to design a facility and infrastructure that leads to verifiable and quantifiable advances in understanding how to use pervasive computing in homes by measuring the impact of a set of implemented examples. Studies run in this lab have a limited sample size (i.e. one house and a small set of long-term occupants), and experimental problems such as the Hawthorne effect must be carefully addressed. However, our discussions with researchers in fields as disparate as preventative medicine and product development have led us to believe the PlaceLab will enable studies that can take place in no other way.

For instance, we have built a prototype system that uses a PDA device and context recognition (in this case location within the environment and proximity to large objects) to monitor for the onset of congestive heart failure (CHF) [13]. The software uses a Bayesian framework not only to integrate evidence for CHF onset but to select meaningful questions to ask a person in a home given the context. Cameras monitor the environment and detect contextual cues (e.g. in the kitchen, at the desk). A diagnosis system pools evidence acquired over the last month and, at any moment, can determine which question that is appropriate for the given context will yield the most valuable evidence. The home occupant carries a.PDA device. Whenever the person pulls it out to use it, a simple question may be displayed that is meaningful given the occupant's current context. The person quickly clicks one multiple-choice answer with almost no interruption to the intended task. Meanwhile, the system adds this new evidence to the preventative diagnosis information. If the system detects a progression towards CHF onset, the person or a medical monitoring service can be notified.

Will systems that present motivational information and ac-quire data for preventative diagnosis such as our CHF system work when placed in the complex environment of the home? Why or why not and to what degree? How does context impact the way the information is received and attended to? This is the type of investigation we, along with our other collaborators, foresee occurring in the PlaceLab. The experimental protocols that may be used differ based on the problems being studied. Our goal has been to design a tool that allows researchers from a variety of disciplines to design and execute studies that cannot be accomplished without the home's ubiquitous sensing infrastructure. One of the computer science challenges is to enhance the sensor infrastructure so it can support more advanced event detection over time.

5. Summary

We are interested in creating design strategies for environments that use pervasive displays and context-aware sensing to empower people with information presented at precisely the right time and place. Unlike many other visions for future home environments, we advocate an approach that uses technology primarily to teach as opposed to only for automated control. Therefore, we are developing new technologies but also new tools that permit us to evaluate our technology interventions in natural settings.

We have designed and built the PlaceLab, an MIT and TIAX, LLC initiative. The PlaceLab is a flexible, sensor-rich residential research facility that enables researchers to study how people respond to new technologies and design strategies. We invite researchers who may be interested in using this shared scientific tool in their own work to contact us.

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Chapter 29: The Future of Nanofabrication and Molecular Scale Devices in Nanomedicine

Robert A. Freitas Jr.
Research Scientist, Zyvex Corp.

Abstract

Nanotechnology is engineering and manufacturing at the molecular scale, and the application of nanotechnology to medicine is called nanomedicine. Nanomedicine subsumes three mutually overlapping and progressively more powerful molecular technologies. First, nanoscale-structured materials and devices that can be fabricated today hold great promise for advanced diagnostics and biosensors, targeted drug delivery and smart drugs, and immunoisolation therapies. Second, biotechnology offers the benefits of molecular medicine via genomics, proteomics, and artificial engineered microbes. Third, in the longer term, molecular machine systems and medical nanorobots will allow instant pathogen diagnosis and extermination, chromosome replacement and individual cell surgery *in vivo*, and the efficient augmentation and improvement of natural physiological function. Current research is exploring the fabrication of designed nanostructures, nanoactuators and nanomotors, microscopic energy sources, and nanocomputers at the molecular scale, along with the means to assemble them into larger systems, economically and in great numbers.

1. Nanotechnology and Nanomedicine

"There is a growing sense in the scientific and technical community that we are about to enter a golden new era," announced Richard E. Smalley, winner of the 1996 Nobel Prize in Chemistry, in recent Congressional testimony [1]. On June 22, 1999, Smalley spoke in support of a new National Nanotechnology Initiative before the Subcommittee on Basic Research of the U.S. House Science Committee in Washington, DC. "We are about to be able to build things that work on the smallest possible length scales, atom by atom," Smalley said. "Over the past century we have learned about the workings of biological nanomachines to an incredible level of detail, and the benefits of this knowledge are beginning to be felt in medicine. In coming decades we will learn to modify and adapt this machinery to extend the quality and length of life." Smalley founded the Center for Nanoscale Science and Technology at Rice University in Texas in 1996. But he became personally interested in the medical applications of nanotechnology in 1999, after he was diagnosed with a type of non-Hodgkin's lymphoma (the same sort that killed King Hussein of Jordan). Smalley then endured an apparently successful course of chemotherapy that caused all the hair on his head to fall out.

"Twenty years ago," Smalley continued, "without even this crude chemotherapy I would already be dead. But twenty years from now, I am confident we will no longer have to use this blunt tool. By then, nanotechnology will have given us

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specially engineered drugs which are nanoscale cancer-seeking missiles, a molecular technology that specifically targets just the mutant cancer cells in the human body, and leaves everything else blissfully alone. To do this, these drug molecules will have to be big enough -- thousands of atoms -- so that we can code the information into them of where they should go and what they should kill. They will be examples of an exquisite, human-made nanotechnology of the future. I may not live to see it. But, with your help, I am confident it will happen. Cancer -- at least the type that I have -- will be a thing of the past."

The term "nanotechnology" generally refers to engineering and manufacturing at the molecular or nanometer length scale. (A nanometer is one-billionth of a meter, about the width of 6 bonded carbon atoms.) The field is experiencing an explosion of interest. Nanotechnology is so promising that the U.S. President, in his January 2000 State-of-the-Union speech, announced that he would seek $475 million for nanotechnology R&D via the National Nanotechnology Initiative, effectively doubling federal nanotech funding for FY2001. The President never referred to "nanotechnology" by name, but he gushed about its capabilities, marveling at a technology that will someday produce "molecular computers the size of a tear drop with the power of today's fastest supercomputers."

After the President's speech, Walter Finkelstein, president and CEO of NanoFab Inc. in Columbia, MD, agreed that it was conceivable that the technology could be used to develop computers chips so small that they could be injected into the bloodstream -- "Fantastic Voyage-like," he said -- to locate medical problems. In February 2000, John Hopcroft, dean of the College of Engineering at Cornell University, announced plans for a new 150,000-square-foot nanotechnology research center. The facility already has $12 million per year of earmarked funding and is expected to support 90 local jobs and approximately 110 graduate students. "The implications of this research are enormous," Hopcroft asserted, and include "the development of mechanical devices that can fight disease within the human body.

In May 2000, the National Cancer Institute signed an agreement with NASA, the U.S. space agency, to study the medical potential of nanoparticles. Nanoscience has also attracted the attention of the U.S. National Institutes of Health (NIH), which hosted one of the first nanotechnology and biomedicine conferences in June 2000. In July, the National Science Foundation (NSF) announced a Nanoscale Science and Engineering Initiative to provide an estimated $74 million in funding for nanotechnology research. Northwestern University in Evanston, Illinois will spend $30 million on a new nanofabrication facility of its own, joining existing operations such as the Stanford Nanofabrication Facility (started in 1985 with $15 million of backing from 20 industrial sponsors) and the Cornell Nanofabrication Facility, expected to attract 450 researchers in 2000, half of them visiting scientists. Cornell is spending $50 million on a new building for the

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Facility, and has just won a $20 million, five-year grant from the NSF to operate a new nanobiotechnology center which will make nanoscale tools available to biologists.

Burgeoning interest in the medical applications of nanotechnology has led to the emergence of a new field called nanomedicine [2, 3]. Most broadly, nanomedicine is the process of diagnosing, treating, and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body.

It is most useful to regard the emerging field of nanomedicine as a set of three mutually overlapping and progressively more powerful technologies. First, in the relatively near term, nanomedicine can address many important medical problems by using nanoscale-structured materials that can be manufactured today. This includes the interaction of nanostructured materials with biological systems -- in June 2000, the first 12 Ph.D. candidates in "nanobiotechnology" began laboratory work at Cornell University. Second, over the next 5-10 years, biotechnology will make possible even more remarkable advances in molecular medicine and biobotics (microbiological robots), some of which are already on the drawing boards. Third, in the longer term, perhaps 10-20 years from today, the earliest molecular machine systems and nanorobots may join the medical armamentarium, finally giving physicians the most potent tools imaginable to conquer human disease, ill-health, and suffering

2. Medical Nanomaterials

The initial medical applications of nanotechnology, using nanostructured materials, are already being tested in a wide variety of potential diagnostic and therapeutic areas.

2.1 Tagged Nanoparticles

For example, fluorescent tags are commonplace in medicine and biology, found in everything from HIV tests to experiments that image the inner functions of cells. But different dye molecules must be used for each color, color-matched lasers are needed to get each dye to fluoresce, and dye colors tend to bleed together and fade quickly after one use. "Quantum dot" nanocrystals have none of these shortcomings. These dots are tiny particles measuring only a few nanometers across, about the same size as a protein molecule or a short sequence of DNA. They come in a nearly unlimited palette of sharply-defined colors, can be excited to fluorescence with white light, and can be linked to biomolecules to form long-lived sensitive probes to identify specific compounds. They can track biological events by simultaneously tagging each biological component (e.g., different proteins or DNA sequences) with nanodots of a specific color.

Quantum Dot [4], the manufacturer, believes this kind of flexibility could offer a cheap and easy way to screen a blood sample for the presence of a number of different viruses at the same time. It could also give physicians a fast diagnostic tool to detect, say, the presence of a particular set of

proteins that strongly indicates a person is having a heart attack. On the research front, the ability to simultaneously tag multiple biomolecules both on and inside cells could allow scientists to watch the complex cellular changes and events associated with disease, providing valuable clues for the development of future pharmaceuticals and therapeutics. In mid-2000, Genentech began evaluating the dots for commercial utility in a variety of cellular and molecular assays. A related technology called PEBBLES (Probes Encapsulated by Biologically Localized Embedding) [5], pioneered by Raoul Kopelman at the University of Michigan, allows dye-tagged nanoparticles to be inserted into living cells to monitor metabolism or disease conditions.

2.2 Artificial Molecular Receptors

Another early goal of nanomedicine is to study how biological molecular receptors work, and then to build artificial binding sites on a made-to-order basis to achieve specific medical results. Buddy D. Ratner at the University of Washington in Seattle has researched the engineering of polymer surfaces containing arrays of artificial receptors. In a recent series of experiments [6], Ratner and his colleagues used a new radiofrequency-plasma glow-discharge process to imprint a polysaccharide-like film with nanometer-sized pits in the shape of such biologically useful protein molecules as albumin (the most common blood protein), fibrinogen (a clotting protein), lysozyme and ribonuclease (two important enzymes), and immunoglobulin (antibodies). Each protein type sticks only to a pit with the shape of that protein. Ratner's engineered surfaces may be used for quick biochemical separations and assays, and in biosensors and chemosensors, because such surfaces will selectively adsorb from solution only the specific protein whose complementary shape has been imprinted, and only at the specific place on the surface where the shape is imprinted. The RESIST Group at the Welsh School of Pharmacy at Cardiff University [7] and others have looked at how molecularly imprinted polymers could be medically useful in clinical applications such as controlled drug release, drug monitoring devices, and biological and antibody receptor mimics.

2.3 Dendrimers

Dendrimers represent yet another nanostructured material that may soon find its way into medical therapeutics. Starburst dendrimers are tree-shaped synthetic molecules with a regular branching structure emanating outward from a core. Dendrimers form nanometer by nanometer, so the number of synthetic steps or "generations" dictates the exact size of the particles in a batch. Each molecule is typically a few nanometers wide but some have been constructed up to 30 nanometers wide, incorporating more than 100,000 atoms. The peripheral layer of the dendrimer particle can be made to form a dense field of molecular groups that serve as hooks for attaching other useful molecules, such as DNA, which hunker down amongst the outermost branches.

In 1998, James R. Baker Jr. co-founded the Center for Biologic

Nanotechnology at the University of Michigan to bring together doctors, medical researchers, chemists and engineers to pursue the use of dendrimers as a safer and more effective genetic therapy agent [8]. For Baker, these nanostructures are attractive because they can sneak DNA into cells while avoiding triggering an immune response, unlike viral vectors commonly employed today for transfection. The dendrimer molecule is decorated with specific snippets of DNA, then injected into biological tissue. Upon encountering a living cell, dendrimers of a certain size trigger a process called endocytosis in which the cell's outermost membrane deforms into a tiny bubble, or vesicle. The vesicle encloses the dendrimer which is then admitted into the cell's interior. Once inside, the DNA is released and migrates to the nucleus where it becomes part of the cell's genome. The technique has been tested on a variety of mammalian cell types [9], and Baker hopes to begin clinical human trials of dendrimer gene therapy in 2001. Donald Tomalia, another co-founder of the Center for Biologic Nanotechnology, recently reported using glycodendrimer "nanodecoys" to trap and deactivate influenza virus particles [10]. The glycodendrimers present a surface that mimics the sialic acid groups normally found in the mammalian cell membrane, causing virus particles to adhere to the outer branches of the decoys instead of the natural cells.

2.4 Smart Drugs

Medical nanomaterials also may include "smart drugs" that become medically active only in specific circumstances. A good example is provided by Yoshihisa Suzuki at Kyoto University, who has designed a novel drug molecule that releases antibiotic only in the presence of an infection [11]. Suzuki started with the common antibiotic molecule gentamicin and bound it to a hydrogel using a newly developed peptide linker. The linker can be cleaved by a proteinase enzyme manufactured by Pseudomonas aeruginosa, a Gram-negative bacillus that causes inflammation and urinary tract infection, folliculitis, and otitis externa in humans. Tests on rats show that when the hydrogel is applied to a wound site, the antibiotic is not released if no P. aeruginosa bacteria are present. But if any bacteria of this type are present, then the proteolytic enzyme that the microbes naturally produce cleaves the linker and the gentamicin is released, killing the bacteria. "If the proteinase specific to each bacterium [species] can be used for the signal," writes Suzuki, "different spectra of antibiotics could be released from the same dressing material, depending on the strain of bacterium." This specificity of action is highly desirable because the indiscriminate prophylactic use of antibiotics is associated with the emergence of strains of drug-resistant bacteria, and most antibiotics apparently have at least some toxicity for human fibroblasts.

Immunotoxins are another class of smart drugs, in this case activating only in the presence of cancer cells. An immunotoxin molecule is an engineered hybrid of functional protein modules fabricated from two different

types of proteins: a toxin and an antibody. Toxin proteins are normally produced and released by infectious bacteria. The protein binds to the surface of a host cell, penetrates it, and kills it. Toxin molecules are so potent that just a few of them can kill a cell. Antibodies are proteins produced by the immune system to recognize and bind to specific foreign materials. An immunotoxin molecule is made by fusing a part of the gene encoding a toxin with a part of the gene encoding an antibody that recognizes surface features on cancer cells. This creates a novel gene that can be used to express a new synthetic protein molecule. This new molecule will bind only to a cancer cell (via a module from the antibody protein), then penetrate it and kill it (via modules from the toxin protein). The first experiments with mice showed that these engineered proteins successfully eliminated certain tumors. Then early in 2000, National Cancer Institute researchers confirmed that an immunotoxin made from a truncated form of Pseudomonas exotoxin was cytotoxic to malignant B-cells taken from patients with hairy cell leukemia [12]. A second clinic trial at the Universitaet zu Koeln in Germany also found that a ricin-based immunotoxin had moderate efficacy against Hodgkin's lymphoma in some patients [13].

2.5 Nanopore Immunoisolation Devices

Mauro Ferrari, director of the Biomedical Engineering Center at Ohio State University and chairman of the BioMEMS Consortium on Medical Therapeutics, has created what could be considered one of the earliest therapeutically useful nanomedical devices [14]. Ferrari and his collaborators at the Biomedical Microdevices Center at the University of California at Berkeley employed bulk micromachining to fabricate tiny cell-containing chambers within single crystalline silicon wafers. The chambers interface with the surrounding biological environment through polycrystalline silicon filter membranes which are micromachined to present a high density of uniform nanopores as small as 20 nanometers in diameter. These pores are large enough to allow small molecules such as oxygen, glucose, and insulin to pass, but are small enough to impede the passage of much larger immune system molecules such as immunoglobulins and graft-borne virus particles. Safely ensconced behind this artificial barrier, immunoisolated encapsulated rat pancreatic cells may receive nutrients and remain healthy for weeks, happily secreting insulin back out through the pores, while the immune system remains blissfully unaware of the foreign cells which it would normally attack and reject.

Ferrari believes that microcapsules containing replacement islets of Langerhans cells -- most likely easily-harvested piglet islet cells -- could be implanted beneath the skin of some diabetes patients. This could temporarily restore the body's delicate glucose control feedback loop without the need for powerful immunosuppressants that can leave the patient at serious risk for infection. Supplying encapsulated new cells to the body could also be a valuable way to treat other enzyme or hormone deficiency

diseases, including encapsulated neurons which could be implanted in the brain and then be electrically stimulated to release neurotransmitters, possibly as part of a future treatment for Alzheimer's or Parkinson's diseases.

2.6 Nanopore Sensors and DNA Sequencing

The flow of materials through nanopores can also be externally regulated. The first artificial voltage-gated molecular nanosieve was fabricated by Charles R. Martin and colleagues [15] at Colorado State University in 1995. Martin's membrane contains an array of cylindrical gold nanotubules with inside diameters as small as 1.6 nanometers. When the tubules are positively charged, positive ions are excluded and only negative ions are transported through the membrane. When the membrane receives a negative voltage, only positive ions can pass. Future similar nanodevices may combine voltage gating with pore size, shape, and charge constraints to achieve precise control of ion transport with significant molecular specificity. In 1997, an exquisitely sensitive ion channel switch biosensor was built by an Australian research group [16]. The scientists estimated that their sensor could detect a minute change in chemical concentration equivalent to a single sugar cube tossed into Sidney harbor, or roughly one part in a billion billion.

Daniel Branton at Harvard University has conducted an ongoing series of experiments using an electric field to drive a variety of RNA and DNA polymers through the central nanopore of an alpha-hemolysin protein channel mounted in a lipid bilayer similar to the outer membrane of a living cell [17]. As early as 1996, the researchers had determined that the individual nucleotides comprising the polynucleotide strands must be passing single-file through the 2.6 nanometer-wide nanopore, and that changes in ionic current could be used to measure polymer length. By 1998, Branton had shown that the nanopore could be used to rapidly discriminate between pyrimidine and purine segments (the two types of nucleotide bases) along a single RNA molecule. In 2000, the scientists demonstrated the ability to distinguish between DNA chains of similar length and composition that differ only in base pair sequence. A similar research effort at the University of California at Santa Cruz has produced nanopore devices with read rates potentially up to 1000 bases per second [18]. Because nanopores can rapidly discriminate and characterize DNA polymers at low copy number, future refinements of this experimental approach may eventually provide a low-cost high-throughput method for very rapid genome sequencing.

3. Biotechnology Devices

Biotechnology originally contemplated the application of biological systems and organisms to technical and industrial processes, but in recent times the field has expanded to include genetic engineering and the emerging fields of genomics, proteomics, transcriptomics, gene chips, artificial chromosomes, and even biobotics. Biotechnology now

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takes as its ultimate goal no less than the engineering of all biological systems, even completely designed organic living systems, using biological instrumentalities or "wet" nanotechnology. There are many good summaries of biotechnology elsewhere, so here we focus on efforts to engineer natural nanomachines to create new cellular devices.

During the 1990s, bioengineered viruses of various types and certain other vectors routinely were being used in experimental genetic therapies as "devices" to target and penetrate certain cell populations, with the objective of inserting therapeutic DNA sequences into the nuclei of human target cells *in vivo*. Retrovirally-altered lymphocytes (T cells) began to be injected into humans for therapeutic purposes. Another example was the use, by Neurotech (Paris), of genetically modified cerebral endothelial cell vectors to attack glioblastoma. This was the first therapeutic use of genetically engineered endothelial cells in humans; Phase I/II clinical studies were underway in 2000.

Engineered bacteria were also being pursued by Vion Pharmaceuticals in collaboration with Yale University. In their "Tumor Amplified Protein Expression Therapy" program [19], antibiotic-sensitive Salmonella typhimurium (food poisoning) bacteria were attenuated by removing the genes that produce purines vital to bacterial growth. The tamed strain could not survive very long in healthy tissue, but quickly multiplied 1000-fold inside tumors which are rich in purines. The engineered bacteria were available in multiple serotypes to avoid potential immune response in the host, and Phase I human clinical trials were underway in 2000 using clinical dosages. The next step would be to add genes to the bacterium to produce anticancer proteins that can shrink tumors, or to modify the bacteria to deliver various enzymes, genes, or prodrugs for tumor cell growth regulation.

In 1998, Glen Evans, then at the University of Texas Southwestern Medical Center, described the possible construction of synthetic genomes and artificial organisms. His proposed strategy involved determining or designing the DNA sequence for the genome, synthesizing and assembling the genome, then introducing the synthetic DNA into an enucleated pluripotent host cell to create an artificial organism. Genome engineers could modify an existing microbe by adding a biochemical pathway borrowed from other organisms, though this remains a difficult task because tailoring an existing system to match unique requirements demands detailed knowledge about the pathway. But ultimately, says Adam P. Arkin at Lawrence Berkeley National Laboratory, "we want to learn to program cells the same way we program computers." Some genome engineers have started by building the biological equivalent of the most basic switch in a computer -- a digital flip-flop. "Cells switch genes on and off all the time," observes MIT's Thomas F. Knight, Jr., who has pioneered some of this research. A cellular toggle switch, made of DNA and some well-characterized regulatory proteins, might be devised to turn

on a specific gene when exposed to a particular chemical. These could be used in gene therapies -- implanted genes might be controlled with single doses of specially selected drugs, one to switch the gene on, another to switch it off.

Arcady Mushegian of Akkadix Corp. [20] has looked at the genes present in the genomes of fully sequenced microbes to see which ones are always conserved in nature. He concludes that as few as 300 genes are all that may be required for life, constituting the minimum possible genome for a functional microbe. An organism containing this minimal gene set would be able to perform the dozen or so functions required for life -- manufacturing cellular biomolecules, generating energy, repairing damage, transporting salts and other molecules, responding to environmental chemical cues, and replicating. The minimal microbe -- a basic cellular chassis -- could be specified by a genome only 150,000 nucleotides bases in length. Glen Evans, now at Egea BioSciences, can already produce made-to-order DNA strands that are 10,000 nucleotide bases in length [21] and is striving to increase this length by at least a factor of ten. The engineered full-genome DNA, once synthesized, would then be placed inside an empty cell membrane -- most likely a living cell from which the nuclear material had been removed. These artificial biobots could be designed to produce useful vitamins, hormones, enzymes or cytokines in which the patient's body was deficient, or to selectively absorb and metabolize into harmless endproducts harmful substances such as poisons, toxins, or indigestible intracellular detritis, or even to perform useful mechanical tasks.

Besides their direct medical applications, biobots might be employed in molecular construction. Gerald J. Sussman at MIT notes that when computer parts are reduced to the size of single molecules, engineered microbes could be directed to lay down complex electronic circuits. "Bacteria are like little workhorses for nanotechnology; they're wonderful at manipulating things in the chemical and ultramicroscopic worlds," he says. "You could train them to become electricians and plumbers, hire them with sugar and harness them to build structures for you."

4. Medical Nanorobotics

The third major branch of nanomedicine -- molecular nanotechnology (MNT) or nanorobotics [2, 22] -- takes as its purview the engineering of all complex mechanical medical systems constructed from the molecular level. Just as biotechnology extends the range and efficacy of treatment options available from nanomaterials, the advent of molecular nanotechnology will again expand enormously the effectiveness, comfort and speed of future medical treatments while at the same time significantly reducing their risk, cost, and invasiveness. MNT will allow doctors to perform direct *in vivo* surgery on individual human cells.

4.1 Early Thinking

The first and most famous scientist to voice these possibilities was the late

Nobel physicist Richard P. Feynman, who worked on the Manhattan Project at Los Alamos during World War II and later taught at CalTech for most of his professorial career. In his remarkably prescient 1959 talk "There's Plenty of Room at the Bottom," Feynman proposed employing machine tools to make smaller machine tools, these to be used in turn to make still smaller machine tools, and so on all the way down to the atomic level [23]. Feynman prophetically concluded that this is "a development which I think cannot be avoided." Such nanomachine tools, nanorobots and nanodevices could ultimately be used to develop a wide range of atomically precise microscopic instrumentation and manufacturing tools -- that is, nanotechnology.

Feynman was clearly aware of the potential medical applications of the new technology he was proposing. After discussing his ideas with a colleague, Feynman offered [23] the first known proposal for a nanomedical procedure to cure heart disease: "A friend of mine (Albert R. Hibbs) suggests a very interesting possibility for relatively small machines. He says that, although it is a very wild idea, it would be interesting in surgery if you could swallow the surgeon. You put the mechanical surgeon inside the blood vessel and it goes into the heart and looks around. (Of course the information has to be fed out.) It finds out which valve is the faulty one and takes a little knife and slices it out. Other small machines might be permanently incorporated in the body to assist some inadequately functioning organ." Later in his historic lecture in 1959, Feynman urged us to consider the possibility, in connection with biological cells, "that we can manufacture an object that maneuvers at that level!"

Extending nanomedicine to molecular machine systems will probably require, among many other things, the ability to build precise structures, actuators and motors that operate at the molecular level, thus enabling manipulation and locomotion. For example, in 1992 K. Eric Drexler of the Institute for Molecular Manufacturing theorized that an efficient nanomechanical bearing could be made by bending two graphite sheets into cylinders of different diameters, then inserting the smaller one into the larger one [22]. By 2000, John Cumings and Alex Zettl at U.C. Berkeley had demonstrated experimentally that nested carbon nanotubes do indeed make exceptionally low-friction nanobearings [24].

4.2 DNA-Based Nanodevices

But early mechanical nanorobots might be made, at least in part, of DNA. The idea of using DNA to build nanoscale objects has been pioneered by Nadrian Seeman at New York University [25]. Two decades ago, Seeman recognized that a strand of DNA has many advantages as a construction material. First, it is a relatively stiff polymer. Its intermolecular interaction with other strands can be readily predicted and programmed due to the base-pair complementarity of nucleotides, the fundamental building blocks of genetic material. DNA also tends to self-assemble. Arbitrary sequences are

readily manufactured using conventional biotechnological techniques, and DNA is readily manipulated and modified by a large number of enzymes. During the 1980s, Seeman worked to develop strands of DNA that would zip themselves up into more and more complex shapes -- first tiny squares, then three-dimensional stick-figure cubes comprised of 480 nucleotides each, then a truncated octahedron containing 2550 nucleotides. By the mid-1990s, Seeman could fabricate nanoscale DNA stick figures of almost any regular geometric shape, by the billions per batch.

In 1999, Seeman reported yet another breakthrough -- the construction of a mechanical DNA-based device that might serve as the basis for a nanoscale robotic actuator [26]. The mechanism has two rigid double-stranded DNA arms a few nanometers long that can be made to rotate between fixed positions by introducing a positively charged cobalt compound into the solution surrounding the molecules, causing the bridge region to be converted from the normal B-DNA structure to the unusual Z-DNA structure. The free ends of the arms shift position by 2-6 nanometers during this fully reversible structural conversion, like a hinge opening and closing. "It's a very simple nanomachine," admits Seeman, "but in the scheme of molecular devices it's huge because it generates more than four times the amount of movement produced by typical molecular devices." A large version of the device might function as an elbow, while smaller devices could serve as finger joints.

Bernard Yurke at Bell Laboratories and Andrew Turberfield at the University of Oxford synthesized another DNA actuator using three single strands of artificial DNA which, when placed together, find their complementary partners and self-assemble to form a V-shaped structure [27]. The open mouth of this nanotweezer can be made to close by adding a special "fuel" strand which binds to the single-stranded DNA dangling from the ends of the arms of the tweezers and zips them closed. A special "removal" strand, when added, binds to the fuel strand and pulls it away, opening the nanotweezers again. The cycle may then be repeated.

4.3 Nanotweezers

In 1999, Philip Kim and Charles Lieber at Harvard University created the first general-purpose nanotweezer [28]. Its working end is a pair of electrically controlled carbon nanotubes made from a bundle of multiwalled carbon nanotubes. To operate the tweezers, a voltage is applied across the electrodes, causing one nanotube arm to develop a positive electrostatic charge and the other to develop a negative charge. The attractive force can be increased or decreased by varying the applied voltage -- 8.5 volts completely closes the arms, while lower voltages give different degrees of grip. Using the tool, Kim and Lieber have successfully grasped 500-nanometer clusters of polystyrene spheres, about the same size scale as cellular substructures. They were also able to remove a semiconductor wire 20 nanometers wide from a mass of entangled wires. At present,

each of the tweezer's arms is about 50 nanometers wide and 4 microns long. But by growing single-walled nanotubes directly onto the electrodes, the researchers hope to produce nanotweezers small enough to grab individual macromolecules.

4.4 Nanomotors

Other researchers are developing nanomotors for future nanorobots. Most notably, Carlo Montemagno at Cornell University has modified a natural biomotor to incorporate nonbiological parts, creating the first artificial hybrid nanomotor [29]. Montemagno started with natural ATPase, a ubiquitous enzyme found in virtually every living organism and which helps to convert food into usable energy in living cells. The moving part of an ATPase molecule is a central protein shaft (or rotor, in electric-motor terms) that rotates in response to electrochemical reactions with each of the molecule's three proton channels (comparable to the electromagnets in the stator coil of an electric motor). ATP (adenosine triphosphate) is the fuel that powers the molecular motor's motion.

Using the tools of genetic engineering, Montemagno added metal-binding amino acid residues to the ATPase. This allowed each motor molecule to bind tightly to nanoscale nickel pedestals prepared by electron beam lithography. Properly oriented motor molecules 12 nanometers in diameter were then attached to the pedestals with a precision approaching 15 nanometers, and a silicon nitride bar a hundred nanometers long was bound to the rotor subunit of each motor molecule, all by self-assembly. In a microscopic video presentation, dozens of bars could be seen spinning like a field of tiny propellers. The group's first integrated molecular motor ran for 40 minutes at 3-4 revolutions per second. Subsequent motors have been operated for hours continuously by feeding them plenty of ATP. Montemagno has been measuring things like horsepower and motor efficiency, simple tests that would be familiar to any mechanical engineer inspecting a car engine. Montemagno is also trying to build a solar-powered, biomolecular motor-driven autonomous nanodevice, wherein light energy is converted into ATP which then serves as a fuel source for the motor. "We think we'll be able to make autonomous devices that are powered by light on a scale of 1 micron or less, smaller than bacteria," he says.

Montemagno is developing a chemical means of switching his hybrid motors on and off reliably. By engineering a secondary binding site tailored to a cell's signalling cascade, he plans to use the sensory system of the living cell to control nanodevices implanted within the cell. Montemagno envisions tiny chemical factories operating inside living cells. He speculates that these nanofactories could be targeted to specific cells, such as those of tumors, where they would synthesize and deliver chemotherapy agents. Within three years he expects to have a motor assembled within a living cell, with the cell's physiology providing the energy to run it. "My 10-year goal is to make a device that harvests single molecules within a living cell, maybe

a cellular pharmacy that produces a drug, stores it within the cell, and then based upon some signal, releases it," Montemagno said in 2000. "For a technology that wasn't expected to produce a useful device before the year 2050, I think we've made a pretty good start. But we have a long way to go before it's safe to turn these little machines loose in the human body."

Nanomotor research is progressing in other laboratories as well. For instance, a 78-atom chemically-powered rotating motor was synthesized in 1999 as a proof of principle by chemist T. Ross Kelly at Boston College [30]. Ben Feringa at the University of Groningen in the Netherlands has built an artificial 58-atom motor molecule that spins when illuminated by solar energy [31]. Another potential nanorobot power source is a modified microbial fuel cell -- laboratory demonstrations of such cells contain captive bacteria or immobilized enzymes [32] which, when fed organic material, convert chemical energy into electricity that could be used to power tiny motors.

4.5 Nanocomputers

Truly effective medical nanorobots may require onboard computers to allow a physician to properly monitor and control their work. Molecular electronics or "moletronics" is a hot research topic in nanotechnology right now. For example, in 2000, a collaborative effort between UCLA and Hewlett Packard produced the first laboratory demonstration of completely reversible room-temperature molecular switches that could be employed in nanoscale memories, using mechanically interlinked ring molecules called catenanes [33]. Two independent companies -- Molecular Electronics Corp. in Texas and California Molecular Electronics Corp. in California -- have sprung up with the explicit goal of building the first commercial molecular electronic devices including memories and other computational components of computers, possibly in the next few years, using techniques of self-assembly.

4.6 Positional Assembly

As machine structures become more complex, getting all the parts to spontaneously self-assemble in the right sequence will be increasingly difficult. To build such complex structures, it makes more sense to design a mechanism that can assemble a molecular structure by what is called positional assembly -- that is, picking and placing molecular parts exactly where you want them. A device capable of positional assembly would work much like the robot arms that manufacture cars on automobile assembly lines in Detroit, or which insert electronic components onto computer circuit boards with blinding speed in Silicon Valley. Using the positional assembly approach, the robot manipulator picks up a part, moves it to the workpiece, installs it, then repeats the procedure over and over with many different parts until the final product is fully assembled.

One of the leading proponents of positional assembly at the molecular scale is Zyvex Corp., a privately-held nanotechnology research and development corporation

headquartered in Richardson, Texas [34]. Zyvex is the first engineering company with the explicit goal of creating a molecular assembler that uses positional assembly to manufacture atomically precise structures. As a first step toward this goal, in 1998 Zyvex demonstrated the ability to use three independently-controlled inch-long robotic arms to manipulate tiny carbon nanotubes in three dimensions, under the watchful eye of a scanning electron microscope that can monitor objects and motions as small as 6 nanometers at near-video scan rates. Zyvex still has a very long way to go before it can assemble nanoscale parts into useful machines, but its work is a small step in the right direction and the research continues today. Zyvex engineers are also conceiving and testing various manufacturing architectures that may someday enable massively parallel, or exponential, construction of large batches of identical molecular machines simultaneously. This might allow vast numbers of nanodevices -- ultimately including medical nanorobots -- to be produced relatively inexpensively and to molecular specifications.

4.7 Nanomedical Diagnosis and Treatment

The idea of placing autonomous self-powered nanorobots inside of us might seem a bit odd, but actually the human body already teems with such nanodevices. For instance, more than 40 trillion single-celled microbes swim through our colon, outnumbering our tissue cells almost ten to one. Many bacteria move by whipping around a tiny tail, or flagellum, that is driven by a 30-nanometer biological ionic nanomotor powered by pH differences between the inside and the outside of the bacterial cell. Our bodies also maintain a population of more than a trillion motile biological nanodevices called fibroblasts and white cells such as neutrophils and lymphocytes, each measuring perhaps 10 microns in size. These beneficial natural nanorobots are constantly crawling around inside of us, repairing damaged tissues, attacking invading microbes, and gathering up foreign particles and transporting them to various organs for disposal from the body.

The greatest power of nanomedicine will emerge in a decade or two when we learn to design and construct complete artificial nanorobots using nanometer-scale parts and subsystems including sensors, motors, manipulators, power plants, and molecular computers. If we make the reasonable assumption that we will someday be able to build these complex medical nanorobots, and build them cheaply enough and in sufficiently large numbers to be useful therapeutically, then what are the medical implications? We have space here to describe only a few of the many possibilities [2, 35-38].

One thing that would change dramatically is clinical diagnostics and treatment. Consider a patient who goes to his doctor with a mild fever, nasal congestion, discomfort, and cough. In the nanomedical era, taking and analyzing microbial samples will be as quick and convenient as the electronic measurement of body temperature using a tympanic

thermometer in a late 20th-century clinical office or hospital. The physician faces the patient and pulls from her pocket a lightweight handheld device resembling a pocket calculator. She unsnaps a self-sterilizing cordless pencil-sized probe from the side of the device and inserts the business end of the probe into the patient's opened mouth in the manner of a tongue depressor. The ramifying probe tip contains billions of nanoscale molecular assay receptors mounted on hundreds of self-guiding retractile stalks. Each assay receptor is sensitive to the chemical signature of one of thousands of specific bacterial coats or viral capsids.

The patient says "Ahh," [35] and a few seconds later a three-dimensional color-coded map of the throat area appears on a display panel held in the doctor's hand. A bright spot on the screen marks the exact location where the first samples are being taken. Underneath the color map scrolls a continuously updated microflora count, listing in the leftmost column the names of the ten most numerous microbial and viral species that have been detected, key biochemical marker codes in the middle column, and measured population counts in the right column. The number counts flip up and down a bit as the physician directs probe stalks to various locations in the pharynx to obtain a representative sampling, with special attention to sores or exudate. After a few more seconds, the data for two of the bacterial species suddenly highlight in red, indicating the distinctive molecular signatures of specific toxins or pathological variants. One of these two species is a known, and unwelcome, bacterial pathogen. The diagnosis is completed and the infectious microbe is promptly exterminated using a patient-inhaled aerosol of mobile nanorobots which the physician has programmed to seek out and destroy that one microbial strain. After a few minutes the nanorobots have finished their work and are retrieved by the doctor. A resurvey with the diagnostic probe reveals no evidence of the pathogen.

4.8 Improved Human Abilities
Another major change that nanomedicine will bring is the ability to dramatically extend natural human capabilities. As a simple example, a few years ago I designed an artificial mechanical red cell called a "respirocyte" [36]. Still entirely theoretical, the respirocyte measures 1 micron in diameter and just floats along in the bloodstream. It is a spherical nanorobot made of 18 billion atoms precisely arranged in a diamondoid structure to make a tiny pressure tank that can be pumped full of up to 9 billion oxygen (O_2) and carbon dioxide (CO_2) molecules. Later on, these gases can be released from the tank in a controlled manner using tiny molecular pumps. Gases are stored onboard at pressures up to about 1000 atmospheres.

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Respirocytes mimic the action of the natural hemoglobin-filled red blood cells. Gas concentration sensors on the outside of each device let the nanorobot know when it is time to load O_2 and unload CO_2 (at the lungs), or vice versa (at the tissues). Each respirocyte can store and transport 236 times as much gas per unit volume as a natural red cell. So the injection of a 5 cc therapeutic dose of 50% respirocyte saline suspension, a total of 5 trillion individual nanorobots, into the human bloodstream can exactly replace the gas carrying capacity of the patient's entire 5.4 liters of blood. But up to 1 liter of respirocyte suspension could safely be added to the bloodstream, which could keep a patient's tissues safely oxygenated for up to 4 hours in the event a heart attack caused the heart to stop beating. Or it would enable a healthy person to sit quietly at the bottom of a swimming pool for four hours, holding his breath, or to sprint at top speed for at least 15 minutes without breathing.

Similarly, an artificial mechanical platelet or "clottocyte" [37] could make possible complete hemostasis in just 1 second, even for moderately large wounds, a response time 100-1000 times faster than the natural system. The basic clottocyte is conceived as a serum oxygen/glucose-powered spherical nanorobot, 2 microns in diameter, that contains a compactly-folded fiber mesh. Upon command from its control computer, the device unfurls its mesh packet in the vicinity of an injured blood vessel -- following, say, a cut through the skin. Soluble thin films coating certain parts of the mesh dissolve upon contact with plasma water, revealing sticky sections (e.g., complementary to blood group antigens unique to red cell surfaces) in desired patterns. Blood cells are immediately trapped in the overlapping artificial nettings released by multiple neighboring activated clottocytes, and bleeding halts at once. While up to 300 natural platelets might be broken and still be insufficient to initiate a self-perpetuating clotting cascade, even a single clottocyte, upon reliably detecting a blood vessel break, can rapidly communicate this fact to its neighboring devices [2], immediately triggering a progressive carefully-controlled mesh-release cascade. Clottocytes may perform a clotting function that is equivalent in its essentials to that performed by biological platelets, but at only 0.01% of the bloodstream concentration of those cells or about 20 nanorobots per cubic millimeter of serum. Hence clottocytes appear to be about 10,000 times more effective as clotting agents than an equal volume of natural platelets.

4.9 Chromosome Replacement Therapy

Medical nanorobots will also be able to intervene at the cellular level, performing *in vivo* cytosurgery. The most likely site of pathological function in the cell is the nucleus -- more specifically, the chromosomes. In one simple cytosurgical procedure, a nanorobot controlled by a physician would extract existing chromosomes from a diseased cell and insert new ones in their place. This is called chromosome replacement therapy. The replacement chromosomes will be manufactured to order, outside of the patient's body in a laboratory benchtop production device that includes a molecular assembly line, using the patient's individual genome as the blueprint. The replacement chromosomes are appropriately demethylated, thus expressing only the appropriate exons that are active in the cell type to which the nanorobot has been targeted. If the patient chooses, inherited defective genes could be replaced with nondefective base-pair sequences, permanently curing a genetic disease. Given the speed with which nanorobots can be administered and their potential rapidity of action, it is possible that an entire whole-body procedure could be completed in one hour or less. Robert Austin at Princeton University has also begun early thinking along these lines, hoping someday to design a nanoprobe capable of identifying biological markers that are specific for targeted diseases. "Then you just pop open the cells, remove the bad DNA from that cell, and repair it on a single-cell level," he says. "That's a long way down the road, but it will happen."

In the first half of the 21st century, nanomedicine should eliminate virtually all common diseases of the 20th century, and virtually all medical pain [38] and suffering as well. Only conditions that involve a permanent loss of personality and memory information in the brain -- such as an advanced case of Alzheimer's disease or a massive head trauma -- may remain incurable in the nanomedical era. Because aging is believed to be the result of a number of interrelated molecular processes and malfunctions in cells, and because cellular malfunctions will be largely reversible, middle-aged and older people who gain access to an advanced nanomedicine can expect to have most of their youthful health and beauty restored. And they may find few remaining limits to human longevity in this wonderfully vigorous state. It is a bright future that lies ahead for medicine, but we shall all have to work very long and very hard to bring it to fruition.

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Chapter 30: Can we build Chromallocyte by 2039?

Renata G. Bushko, M.S.
Founder, Future of Health Technology Institute, Hopkinton, MA, US

1. Introduction

Just like Edwin Schrodinger, in his paper *"What is Life"* predicted aperiodic crystals off DNA and Richard Feynman in his lecture, *"There's Plenty of Room at the Bottom"* conceived nanorobots, Robert Freitas presents chromosome replacement *in vivo* as a painless cure for genetically based disease. *"The most essential part of living cell – the chromosome fibre – may suitably be called aperiodic crystal. In physics we have delt only with periodic crystals. [...] Compared with aperiodic crystal they are plain and dull. [...] Aperiodic crystal, in my opinion, is the MATERIAL CARRIER OF LIFE." "What is Life", Erwin Schrodinger p 4-5 (Prediction of DNA)[2]* Sixty five years have gone by from the conceptual description of genes in 1944 and their discovery by Crick and Watson in 1953 to the fully developed engineering plan by Robert Freitas to build chromallocyte. We need 30-35 more years to be able to "land chromallocytes on the liver" and replace all of its cells *in vivo*. It is our responsibility to make this happen just like we made landing the man on the moon happen back in 1969. *"With annual checkups and cleanouts, and some occasional major cellular repairs [using Chromallocyte], your biological age could be restored once a year to a more or less constant physiological age that you select." Welcome to The Future of Medicine, Robert Freitas [3]*

Figure 1. Chromallocyte (early sketch – artists' view) from Robert A. Freitas Jr. , Journal of Evolution and Technology - Vol. 16 Issue 1 June 2007 p12, Image © 2006 Stimulacra LLC (www.stimulacra.net) and Robert A. Freitas Jr(www.rfreitas.com), used with permission.

2. Nanotherapeutics: Most Promising Health Technology

Nanotherapeutic technology was selected as the most important health technology in 2002 FHTI survey (Table 1). One of the most important health technology events of this decade was the first technical description of a cell repair nanorobot ever published: 94 page paper by Robert A. Freitas Jr. "The Ideal Gene Delivery Vector: Chromallocytes, Cell Repair Nanorobots for Chromosome Replacement Therapy," published in the *Journal of. Evolutionary Technology* in June 2007 [3]. I would like to emphasize its importance and make it well known because of its potential to save 52 million people every year and the possibility of 1000-fold improvement over our current human biological abilities [4].

Table 1. Seven most promising health

technology areas selected by experts. Survey method from R. Bushko, Defining Future of Health Technology,. Future of Health Technology, ed. R. Bushko, IOS, 2002.

1	(A) Tissue Bioengineering/ Regeneration & (B) Nanotherapeutic Technologies
2	Knowledge Management Technologies (including decision support and data mining)
3	Electronic Health Record in a Standard Format with Unique Patient Identifier
4	(A) Powerful yet easy to use Self-diagnostic Technologies & (B) Vaccine Biology
5	Affordable information system access with decision support for healthcare professional
6	Internet-driven Technologies
7	Voice Recognition, (B) Psychological Aids & (C) Artificial Intelligence & (D) Controlled Medical Vocabularies

3. Chromallocyte 101 – Basic Design

3.1 What is the shape and size of

chromallocyte to minimize volume?
Chromallocytes are not able to free float in the bloodstream so their diameter can be bigger than 4 microns (size limit for free floating robots). They are restricted to vascular surfaces so they are smaller in volume than erythrocytes (95 microns^3 red cells) or granulocytes (1000 microns^3 white cells). They are less than 1% of typical tissue cell volume and up to 25% of nucleus volume to be able to penetrate cells. Chromallocyte's dimensions are: 4.18 microns x 3.28 microns x 5.05 microns in length; displacement volume (mostly diamondoid) = 69.250 micron^3; dry mass = 80 pg; mass with wet cargo = 103 pg.

3.2 What is general structure of the chromallocyte?

Chromallocyte has 10 components:

- Proboscis Manipulator
- Mobility System
- Funnel Assembly
- Chromatin Storage
- Power Supply
- Navigation/Communication
- Computers
- Sensors
- Consumables
- Structural Support

Figure 2. Chromallocyte (artist's conception) with Funnel Partly Extended. from Robert A. Freitas Jr. , Journal of Evolution and Technology - Vol. 16 Issue 1 June 2007 p16, Image © 2006 Stimulacra LLC (www.stimulacra.net) and Robert A. Freitas Jr(www.rfreitas.com), used with permission

3.3 How is chromallocyte powered?

Chromallocyte uses non-chemical power in the form of 10 acoustic power receivers. Each power receiver has a 0.4 micron piston throw and can receive 200 pW. A patient is well-

coupled to a medically-safe 1000 W/m2 0.5 MHz ultrasound transverse-plane-wave transmitter.

Medical robots can also be powered by glucose fuel cells. Tad Hogg and Robert Freitas have just completed a theory and simulation study of the *in vivo* power limits on medical nanorobots that use glucose fuel cells. This study combines engineering design and the biology of red blood cells to identify capabilities of aggregates of robots on the inside surface of capillaries. The results show that in such aggregates, individual nanorobots compete with each other for power, reducing the power available for each robot to several tens of picowatts. That's enough to operate a 3 MHz nanocomputer continuously inside each robot or to perform other important nanomedical tasks such as sensing or drug delivery or in chromallocyte's case - chromatine replacement. Despite their high power densities, modest sized groups of nanorobots will not significantly heat the surrounding tissue.[5]

3.4 Are there any computers on board?

Chromallocytes operate semi-autonomously during most of the mission but can receive various parameters from the physician via acoustic signaling. It has 10 acoustic message receivers, 10 CPU and memory units, 50 megabits of memory and 0.01micron3 of total computer volume.

3.5 How does chromallocyte replace chromatin?

It is done with the working unit called Proboscis which: (1) collects old chromatin from the nucleus, (2) has chromosome binding part, (3) transfers new chromatin to the cell's nucleus. Probiosis draws 62 pW of continuous power in normal usage.

3.6 How does chromallocyte get places?

Chromallocyte must walk on vascular and cell surfaces with up to 150 nm thickness (intestinal cells). Cell plasma membranes are covered with a fuzzy coat of glycoprotein strands - glycocalyx, otherwise known as the "sweet husk of the cell" (a network of polysaccharides that project from cellular surfaces). Chromallocyte in its current design, by Robert Freitas, has 1027 telescopic grapple manipulators. These manipulators may be shortened or lengthened during each stroke. Variable-area end-effectors may be used to enhance the propulsive effect. The grapples allow Chromallocyte to penetrate vascular, cell membrane, and nuclear membrane walls. They are stowed in the hull when not used.

Figure 3. Fully extended grapple - 250 nm (left) and grapple work envelope (right) © Robert A. Freitas Jr. , Journal of Evolution and Technology - Vol. 16 Issue 1 June 200; used with permission.

Chromallocyte can also swim in tissues (histonation) and acelluler tissue spaces (brachiation) where fibrous components are typically spaced up

to 10-100 microns apart. As Robert Freitas describes it: *"A brachiating nanorobot can [also] pull itself along individual fibrils, changing direction at fibril junctions, indirectly working its way toward its cellular target crudely analogous to the path of a sailboat tacking into the wind." [3]*

3.7 What if Chromallocyte gets lost?

Proboscis can be deployed to search for new handholds (e.g. fibrils) within a ~4 micron hemispherical work envelope. The grapples may be operated as cilia, producing slow swimming motility in the fluid. Grapples can be extended or retracted in 0.25 millisec, easily allowing execution of a 2 KHz beating motion similar to that of natural cilia .

4. Landing on the Liver: What are liver therapy stages?

In vivo liver chromosome replacement therapy will take about 7 hours and it has five stages: (1) Organ Survey, (2) Chromallocyte Preparation, (3) Patient Preparation, (4) Chromosome Replacement and (5) Patient Post-operative Process.

4.1 How many chromallocytes are needed for total liver replacement?

Chromosomes of all 250 billion hepatic tissue cells must be replaced. Liver cells often have multiple nuclei (typically 1-3) so probably multiple visits to many cells would be needed. We need to infuse 1 terabot (trillion device) chromallocyte dose. This dose would have 69 cm3 of chromallocytes in 1-liter (7% saline suspension).

4.2 How is patient prepared for the chromallocyte treatment?

Patient is placed on an ultrasonic vibrating table with comfortable encapsulated gel interface. The goal of this is to maximize acoustic power transmission into the body – energy for *in vivo* chromallocyte activities. The patient is then sedated and respirocytes injection follows while drugs are used to reduce the pulse rate. A self-guiding flexible noncannula in installed directly into the blood vessel closest to the liver. This completes the process and robots are inserted into the body (Figure 4).

Figure 4. Chromallocytes (artist's conception) floating in the vascular surface - from Robert A. Freitas Jr. , Journal of Evolution and Technology - Vol. 16 Issue 1 June 2007 - pg 12, Image © 2006 Stimulacra LLC (www.stimulacra.net) and Robert A. Freitas Jr(www.rfreitas.com), used with permission.

4.3 How would we know when to use chromallocytes?

The key of chromallocyte-based treatment is to avoid painful symptoms. This requires acting before symptoms occur. How can we do that? Robert

Linares in his chapter "*Diamond Bio Electronics*" describes molecular diagnostic devices that will allow ongoing molecular monitoring (his vision of new bio-electronic medical era) [6]:
"[...] Bio-electronic devices, will reside inside the body as opposed to next to the bedside or in the lab, and there is a high degree of real-time information coming from these devices. More importantly, the feedback loop from the time of the information gathering phase to the therapy/ drug delivery phase can be dramatically shortened in this model."

Nanosensing and nanomonitoring based on bio electronics will help us to determine the need to use Chromallocytes before it is too late.

Diagnostic devices that can monitor several targets at once - a form of molecular redundancy - can potentially increase the precision with which therapies such as the chromallocyte are administered. In *"Diagnostics for a Personalized Medical Future: Extending our Senses to the Molecular Scale"*, Benjamin Miller describes three optical sensor systems that can monitor as many as a thousand different physiological markers at a time.[7]

5. When will chromallocyte be ready for use?

If you had all the money and brain power on Earth, would you be able to build fully a functional chromallocyte in 10 years? According to Robert Freitas 10 years is not possible for any amount of money because there's just too much to do. Chromallocytes are extremely sophisticated and complex nanorobots (way beyond simpler respirocytes). Many of the challenges are mentioned in his chapter "Welcome to the Future of Medicine" in this volume. In the manufacturing area, the key technical challenges include: demonstrating Diamond Mechano-Synthesis, building nanomachines, building a nanofactory, building simple nanorobots, and then building complex nanorobots.

The first simple diamondoid medical nanorobots could be built by the end of the 2020s, followed by the chromallocytes by the end of the 2030s with a surfeit of funding, to build the structure. This is under ideal conditions assuming there would not be any significant funding or personnel constraints. It would take about 30 years if we optimistically assume that all goes well. Man would never land on the moon if we did not have a dream with a deadline of 1969.

"Although we're not that close to the operational chromallocyte, we should be able to create such things eventually, and they will certainly give us radically new alternative approaches to combating aging and other medical problems, and the chances are high that some of those alternatives will outperform the more traditional ones." Aubrey de Grey, 3/2008

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Table 2. Chromallocyte Development: Major past steps and strategic plan for the next 60 years according to interview with Robert Freitas in 2009.

2003	50th anniversary of DNA discovery	First mechanosynthesis – key manufacturing technology to build chromallocyte [8]
2007		The first technical description of a cell repair nanorobot ever published: Robert A. Freitas Jr., "The Ideal Gene Delivery Vector: Chromallocytes, Cell Repair Nanorobots for Chromosome Replacement Therapy," Journal of. Evol. Technology, June 2007. [3]
2008		Direct experiments to build and validate several of mechanosynthesis tooltips. Seminal paper: *Robert A. Freitas Jr., Ralph C. Merkle, "A Minimal Toolset for Positional Diamond Mechanosynthesis," J. Comput. Theor. Nanosci. 5 (May 2008) [9]*
2009	40th Anniversary of Man landing on the Moon	Nanofactory Collaboration active: coordinate a combine experimental and theoretical R&D program to design and construct the first working diamondoid nanofactory [10]
2019	50th Anniversary of Man landing on the Moon	Demonstrating diamond mechanosynthesis in practice
2022		Building Nanofactory
2027		Building Prototypes of simple nanorobots (eg. Respirocyte)
2029	60th Anniversary of Man landing on the Moon	Manufacturing of diamondoid medical nanorobots for life extension
2039	70th Anniversary of Man landing on the Moon	Building chromallocyte (extremely sophisticated and complex nanorobot) and landing on a human liver – **First** *in vivo* **liver chromosome replacement.**
2069	100th Anniversary of Man landing on the	Broad use of chromallocytes: Our biological age restored once a year to a more or less constant physiological age that
	Moon	we select.

Figure 5. Man Landing on the Moon in 1969 (Artist's conception) Image © 2009, Renna Bushko.

6. Chromallocyte on the Map of Strategic Technology Areas

41 different strategic technology areas that will have a profound impact on the entire economy including healthcare sector are listed in Table 3 below [11]. Chromallocytes coupled with telemedical devices and bioelectronics of other kind have potential to redefine medical care.

Table 3. Emerging technology areas that will soon have a profound impact on the entire economy including healthcare sector. Order does not reflect importance.

I	**Human-Machine Interaction - Requesting Things from Machines**
1	Hybrid Brain-Machine Interfaces (HBMI) – Thought to Computer Communication
2	Natural Language Processing
3	Automatic Voice Recognition
4	Mobile, wireless, wearable, and textile computing
5	Computer Implants (connected to tagged smart environment)
6	Neural-mechanical Hybrids
7	Haptics
II	**Machine Intelligence**
	Processing Requests
8	Data and Reality Mining
9	Common Sense Reasoning

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10	Reasoning by Analogy
11	Genetic Algorithms
12	Flexible Transistors (e.g. on plastic)
	Responding to Requests
13	Organic Light Emitting Displays (data glasses, e-paper, smart windows)
14	Speech Generation
15	Affective Computing (emotional communication)
16	Visualization of Data
17	Automatic Summarization /Abstracting
	Triggering Action
18	Decision Triggers
19	Biomechatronic Interfaces (to cells and biomechanical devices)
20	Electronic Skin
III	**Preservation of Individuality and Security**
21	Digital Rights Management
22	Biometrics (Face, Voice, DNA, finger print, behavioral pattern recognition)
23	Biometronics Ethics and Law
IV	**Human-Machine Global Network**
24	Adaptive Information Networks with Spontaneous Interoperability
25	Microphotonics (all optical Internet with super high bandwidth)
26	High-temperature Superconductivity (inexpensive power quality devices SMES1)
27	Infinite High-density Data Storage
28	Restructuring Code (Software Engineering)
V	**Intelligent Machines**
29	Mobile Robots
30	Nanorobots (Microfluidics, Nanomedicine [12] **CHROMALLOCYTE**
31	Humanoids (Cyborgs)
32	Machine Vision
33	Machine Learning
34	Human-machine Mergers
VI	**Sources of Energy**
35	Batteries, Generators (including Body-heat Batteries)
36	Chemical Molecular Energy (e.g. ATP, Glucose Fuel Cells)
37	Geothermal Energy
38	Tidal Energy (Earth's tides)
39	Wind /Turbine Energy
40	Solar Energy
41	Superconductive Generators

7. How can we prepare for health care with Chromallocytes available?

According to Gianfranco Zaccai's holistic design principle "we should start preparing for the nanorobot era now[...]. We can expect technological marvels and saved lives, but much of this opportunity will be wasted unless design plays an essential role. From the holistic design of nanofactories to the holistic design of a radically different patient/doctor/family experience, people will still need to work and cooperate with each other to analyze, diagnose, communicate, and heal. And since there will be much overlap between current medical techniques and nanomedicine, we will need to design both the overlap and the transition so that the solutions do not cause new problems. What treatment could be more "transparent" than nanotechnologies operating on their own, undetectable by the patient? Yet they will still interact with individual human beings—both patients and caregivers—who will have individual logistical, social, emotional, and physiological needs and different motivations and levels of understanding. It will be the task of design to optimize this future experience for all the people who are involved." [16]

8. Conclusions

Recently, The most important technological event was the technical description of chromallocyte - nanorobot that would be capable of replacing chromosomes on a cell by cell basis *in vivo*, throughout the body by Robert Freitas [3]. Significance of chromallocyte comes from its ability to painlessly reverse the effects of genetic disease and other accumulated damage to our genes thus preventing aging. It could reduce suffering, save lives and enhance human potential. By analogy to the successful effort to put man on the moon, we should aim at chromallocyte landing on the liver by 2039 – to commemorate the 70th anniversary of 1969 man landing on the Moon. Same strategic planning principles could be applied. We need dreams with deadlines and funding to make progress, dreaming is just not enough. We need a strategy to get there just like Mercury, Appollo and Gemini research program had strategy to put man on the moon in 1969.

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Chapter 31: Nanotechnology and its Impact on Medicine

Rob Burgess, Ph.D.
Chairman and President
Medical Nanotechnologies, Inc.

Abstract

Current clinical diagnostics and therapeutics platforms are often limited by borderline sensitivity or efficacy levels. These limitations result from low or minimal specificity for the intended target cell or organ, span a multitude of physiological disorders and result in nominal success rates for diagnosis or treatment in many cases. Diagnosis and treatment of diseases such as cancer or viral infections require next generation medical methods. Nanotechnology has the potential to significantly address diagnostics and therapeutics sensitivity and resulting unwanted side effects by providing extremely precise reagents and tools that allow for unparalleled detection and treatment at the clinical level. This is accomplished through extremely controlled nanofabrication methodologies which result in the generation of molecularly defined nanoscale materials and devices that harbor known physical properties unique to each material in question and useful for particular medical applications. The further precise targeting of these materials to specific sites within the body allows for an added layer of accuracy and potency. Research in this area is quickly advancing to the point of providing a comprehensive portfolio of nanotechnology-based diagnostic and therapeutic platforms that will be unparalleled in sensitivity, specificity and elimination of unwanted side effects.

1. Nanotechnology and Its Impact on Medicine

Nanotechnology refers the use and application of particles and/or devices which are less than 500 nanometers (nm) in size (1). Nanomedicine is defined as the medical application of nanotechnology (2), which spans a broad-based plethora of methodologies for tackling some of medicines most difficult problems. Already, a great deal of progress has been made in this area with respect to the application of nanomaterials and, more specifically, nanoparticles for diagnostic and therapeutic applications, which are defined by the Royal Society and Royal Academy of Engineering as being a size of <100nm. Many researchers now share a forward vision in the field regarding nanotechnology's eventual significant impact on the field of medicine. Dr. Peter Searson, Director for the Johns Hopkins Institute for Bionanotechnology, stated:

> Very simply, we will develop new scientific tools and create new technologies for the diagnosis and treatment of diseases and medical conditions. We will develop new tools that will allow us to develop a better understanding of how cells function and misfunction, at the molecular level. Research will also focus on the development of new diagnostic and therapeutic strategies, for example, for the early detection and treatment of cancer (3).

It is clear that the advantages of nanoparticles and nanomaterials over other platforms, such as their large surface-to-mass ratio and ability to bind and carry other molecules and absorption properties, provide a unique opportunity to diagnose and treat a variety of human disorders with higher efficacy and fewer side effects than that exhibited by existing platforms. This chapter focuses on the current advances and future prospects for nanoparticles and nanomaterials as they relate to detection, prevention and treatment of disease. In these areas it has been estimated that as far back as 2006, around 130 nanotechnology-based therapeutics or delivery systems were under development worldwide (4). To this end, in 2005 the United State National Institutes of Health (NIH) established a national network of eight Nanomedicine Development Centers "which serve as the intellectual and technological centerpiece of the NIH Nanomedicine Roadmap Initiative (5)." These centers have a central focus to probe the physical properties of nanoscale materials and biological structures in order to glean a thorough understanding of their utility and potential toxic properties. Such an understanding will create a solid foundation for the use and application of these materials in diagnostics and therapeutics-related endeavors. While this initiative has a projected completion date of 2010, a second phase has already been approved to turn this acquired knowledge into fundamental platforms for understanding and treating disease.

Others in industry are considerably ahead of the curve in driving practical applications of nanotechnology in medicine. It has been estimated that as of 2004, over 200 companies worldwide have introduced a total of 38 approved products classified as nanomedicines that have resulted in approximately $6.8B USD in sales. These products were the result of approximately $3.8B USD in research and development expenditures (6). Thus, while the NIH has funded a major attempt at the study and classification of nanomaterial and nanoparticle properties, private industry has turned this fledging science into a revenue-generating opportunity. This trend will no doubt continue as nanomedicine not only becomes a reality but nanoparticles become accepted for their unique and beneficial physical properties as they relate to therapeutic applications.

2. Nanoparticles and Medical Applications

Given their small size, even relative to individual cells and viruses, nanoparticles represent an ideal platform for the delivery of therapeutic platforms at the molecular level. Nanoparticles of a variety of different origins may be utilized for effective drug delivery or may act directly as the therapeutic agent through combined applications with external fields such as near infrared light or radiofrequency waves (Table 1). The particles may be delivered nonspecifically through natural accumulation in a particular physiological site or through site-specific targeting via a variety of agents such as antibodies, aptamers, peptides or other small molecules.

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Table 1. Examples of high-profile nanoparticles currently under study as potential carrier, therapeutic and/or imaging agents.

Composition of Nanoparticle	Potential Clinical Uses	Clinical Trials Underway
Carbon Nanotubes	Direct Therapeutic, Drug Delivery, Imaging	No
Lipid-PFCs	Imaging	No
Liposomes	Drug Delivery	Yes
Gold Nanoshells	Direct Therapeutic	No
Micelles	Drug Delivery	Yes
Paramagnetic Nanoparticles	Direct Therapeutic, Drug Delivery, Imaging	Yes
Quantum Dots	Imaging	No

2.1 Nanoparticle-Based Drug Delivery

The efficacy of a drug and its successful, specific and contained delivery within the human body is limited by the composition of the drug itself, any adjuvants used and the drug's half-life after delivery. A platform that enhances such parameters as site-specific delivery and biocompatibility while reducing toxic effects has the potential to become influential in a number of therapeutic areas. All in all, the ultimate goal of most if not all nanomedicine initiatives is to significantly increase the therapeutic index, which is a comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes toxic effects (7). Nanotechnology provides multiple methodologies to address each of these critical issues.

Perhaps the largest focus in the area of nanoparticle-based drug delivery has been on biodegradable polymers that release a drug over time. A number of these have been pursued since late 2002 and include chitosan, gelatin, hydrogels, magnetic iron oxide, PLGA and solid lipid formulations among others (8). For example, researchers at the Albert Einstein Centre in Nottingham, UK demonstrated effective nasal delivery of insulin utilizing a chitosan nanoparticle-based carrier platform (9). Cascone and colleagues in the Department of Chemical Engineering at the University of Pisa, Pisa, Italy developed and optimized a system based on nanoparticles of gelatin for the delivery of methotrexate. In order to assess the general properties of gelatin nanoparticles, particle size, drug encapsulation efficiency and release rates were extensively characterized *in vitro* (10). Gupta et al. at the University of Glasgow in Scotland have formulated a hydrogel composed of pullulan nanoparticles for delivery of nucleotide-based therapeutics thus opening the door to the reality of nanoparticle-mediated gene therapy. These studies could open the door to realistic nanoparticle-based gene therapy platforms. The same group has studied the application of superparamagnetic iron oxide nanoparticles (SPIONs) for drug delivery, combining the hydrogel and iron oxide approach by coating SPIONs with pullulan to reduce cytotoxicity and enhance cellular

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uptake (11). Poly (D,L-lactic-co-glycolic) acid (PLGA) is a biodegradable nanoparticle polymer widely studied as a drug delivery vehicle. Most recently, researchers at Wayne State University in Detroit optimized this polymer to function as a carrier for siRNA therapeutic molecules, demonstrating yet another avenue for nucleotide-based therapeutics delivery using nanotechnology (12). Solid lipid compositions at the nanoscale have also been formulated for topical delivery applications. Wissing et al. at the University of Berlin, for example, have developed a novel sunscreen delivery system based on the incorporation of tocopherol acetate into solid lipid nanoparticles, illustrating this platform as a superior delivery system than more conventional agents (13).

Other non-biodegradable nanoparticles have also been studied for their properties in the delivery of both drugs and nucleotide-based therapeutics. Magnetic nanoparticles, for example, were proposed for drug delivery as early as the 1970s (14, 15). The properties of these particles include a magnetic core that could encompass a metal or polymer coating to which drugs could be attached. The function of these coatings allows for the attachment of drugs that may act in various therapeutic scenarios. Perhaps the most popular of these magnetic nanoparticles is iron-oxide, fairly nontoxic after removal of metals used to catalyze its synthesis. To prevent corrosion and promote biocompatibility, iron oxide nanoparticles may be coated with naturally occurring polymers such as carbohydrates and protein or synthetic organic polymers including, but not limited to, PEG and polyvinyl alcohol (PVA) (16, 17). Each has its advantages and disadvantages with naturally occurring coatings lacking binding specificity and synthetic coatings posing toxicity issues. Implementing organic linkers, magnetic nanoparticles have successfully delivered both gene- and drug-based therapeutics platforms. As early as 2000, Cathryn Mah and colleagues at the University of Florida constructed magnetic nanoparticles coated with an adeno-associated virus (AAV) containing DNA sequences coding for green fluorescent protein (GFP). They demonstrated that the combination of the virus and nanoparticle yielded significantly improved GFP expression *in vitro* and in mice (18). More recently, Wilson et al. at the University of California at San Francisco performed a successful clinical trial by targeting the anticancer drug doxorubicin linked to magnetic carriers to hepatocellular carcinomas using magnets to draw the particle/drug complexes to cancerous tissue (19).

All of the above examples of nanoparticle-based drug and therapeutic delivery depend upon a number of physical factors. Even subtle differences in particle size, for example, may significantly affect the delivery system's ability to present a therapeutic moiety inside cells or even inside various organelles within the cell such as lysosomal compartments. Even particles with a similar size may have varying biocompatibility and therapeutic delivery efficiencies due to variations in shape and chemical composition. Other physical

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properties, such as sensitivity to applied external fields, may actually aid in the release of therapeutic agents once the site of intervention is reached. Gold nanoparticles and carbon nanotubes, for example, are sensitive to near infrared light (near IR) and radiofrequency (RF) waves, emitting intense heat upon exposure to these fields (20). Rapid heating of these nanoparticles could act as a methodology for dissociation and activation of attached inactive drugs. Other thermosensitive nanoparticle polymers such as polyethylene glycol (PEG) and poly-L-lactide (PLLA) have shown increased cytotoxicity in a cancer model following delivery of doxorubicin and an increase in local temperature from 37 deg. C to 42 deg. C (21).

The use and application of nanoparticles as treatment delivery vehicles follows a long-held desire to more specifically and accurately provide access to therapeutic molecules by cells within the body. Delivery to or within subcellular compartments may be accomplished via nonspecific diffusion or endocytic mechanisms, or through the use of targeting moieties that drive the nanoparticle/therapeutic entity to precise locations on the surface or within cells. Depending upon the physical nature and composition of the nanoparticle/drug complex, it may end up intracellularly within endosomes or lysosomes and be degraded over time, thus releasing the therapeutic agent gradually as may be desired depending upon the mechanism of action. The surface composition and size of the nanoparticle plays an important role in the mechanism and efficiency of entry. Nanoparticles of less than 20nm, for example, have been demonstrated to diffuse efficiently across the cell membrane (22). Larger nanoparticles have been optimized for intracellular entry via endocytic mechanisms through coating with polymers such as PEG and PLGA (23, 24).

Delivery of nanoparticle/drug complexes to the surface of specific cell types has been successfully accomplished by a number of researchers both nonspecifically and specifically targeted to unique cell surface receptors. The attachment of ligands which bind general classes of carbohydrates to the surface of nanoparticles has been demonstrated to increase nonspecific cell surface binding (25). Carbon nanotubes have successfully targeted tumor cells *in vitro* via the attachment of antibodies which specifically recognize unique receptors expressed by these cells (26). *In vivo*, targeting of nanoparticles to individual cell types has been accomplished by a number of groups. Bourges et al. at the National Institute of Health and Medical Research in Paris, France have targeted retinal pigment epithelial (RPE) cells with nanoparticle/ocular drug complexes through diffusions and transretinal movement (27). Tada and colleagues at Tohoku University in Japan have shown highly efficient targeting of quantum dot nanoparticles to tumor cells in mice using monoclonal antibodies which bind the HER2 receptor uniquely expressed on these cells (28). The specific targeting of nanoparticles and nanoparticle/drug complexes to particular cell types

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within the body and even concise organelle targeting within these cells will no doubt have a significant influence on the optimization of their therapeutic efficacies and reduction of unwanted side effects.

2.2 Nanoparticles for Targeted Cancer Drug Delivery

Perhaps one of the most exciting areas of therapeutic potential involving the use and application of nanoparticles is the treatment of cancer. Particles of various material origins have been studied extensively as carriers for cytotoxic drug delivery to cancer cells in the body. These include true nanoparticles such as dendrimers and quantum dots as well as nanoparticulate compositions of nanoparticles like solid lipids, micelles, microcapsules and lipoproteins (for review see 8). The desired advantages of using nanoparticle-based drug delivery platforms over more conventional adjuvants or carriers are to minimize drug degradation and inactivation, to increase drug availability and to reduce side effects by targeting the drug preferentially to the site of treatment.

As mentioned above, both biodegradable polymers and non-biodegradable metal nanoparticles have been successfully implemented to deliver drugs for cytotoxic purposes in the treatment of cancer. Perhaps the most thoroughly characterized to date have been liposomes, polymeric nanoparticles and micelles, due to their drug encapsulation efficiencies and biodegradation properties. All of these delivery platforms can encompass unique and specific surface modifications that increase biocompatibility and allow for the efficient attachment of targeting agents.

Liposomes, small vesicles composed of phospholipids, are perhaps the most extensively studied in this arena due to enhanced biocompatibility and efficiency at delivering water-soluble drugs. In addition, liposomes elicit no toxic or antigenic reactions. This artificial phospholipid vesicular system (50nm - 1000nm in size) can be effectively loaded with numerous water-soluble drugs within the internal aqueous core. Targeting of liposomes, as with other nanoparticles, can be accomplished with antibodies, peptides or ligands that bind specific receptors uniquely expressed on the surface of cancer cells. Recent research has suggested, however, that liposome immunocomplexes have a short half-life in the circulatory system and thus much attention has been focused on the use of polyethylene glycol (PEG)-coated liposomes, which tend to be significantly more stable upon administration (29). A number of liposome/drug platforms have now been approved for clinical investigation or are undergoing clinical evaluation for the treatment of different types of cancers including Kaposi's sarcoma, recurrent breast cancer, non-Hodgkin's lymphoma, ovarian cancer, solid tumors, metastatic melanoma and some forms of leukemia (8).

For water-insoluble drugs, micelles have shown promise as effective carriers. Micelles are nanoparticulate compositions of surfactants of between 5nm and 100nm, significantly smaller than liposomes. This small size not

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only aids in stabilizing water-insoluble drugs but enhances spontaneous penetration into interstitial body compartments that have leaky vasculature, a hallmark of tumors. It has been demonstrated that water-insoluble cytotoxic anticancer drugs incorporated into micelles preferentially accumulated into tumors as opposed to non-target tissues (30). This is termed "passive targeting" and can be a very effective delivery methodology to tumorigenic tissues (31).

Targeting cancer cells in the body with anticancer drugs has been a central focus of cancer research for the past several decades. Generally strong cytotoxins, anticancer drugs kill cells they come into contact with, whether those particular cells are tumorigenic or not. The basis of chemotherapy is to kill rapidly dividing cells in the body. Unfortunately this applies to many normal cell types, such as those of epithelial origin like skin and the lining of the stomach, and thus the premise of chemotherapeutic treatment is to kill the cancer cells before you kill the patient. Targeting cytotoxic drugs specifically to cancer cells will no doubt increase efficacy and decrease unwanted side effects such as death. Ligands that bind to cancer cells have been attached to a number of nanoparticle/drug delivery compositions and have been shown to target tumorigenic cells *in vitro* and *in vivo*. Table 2 lists some of the more prominent examples of targeting agents that have been studied for homing in on unique types of cancer cells in the body to exert a drug's cytotoxic effects.

Table 2. Examples of targeting moieties and their applications in cancer therapeutics (Courtesy Medical Nanotechnologies, Inc., Richardson, Texas).

Targeting Agent	Targeting Agent	Cancer Application	Known Example(s)
Monoclonal Antibody	Cell Surface or Internalized	Breast, Colorectal, Head and Neck, Lymphoma	Herceptin, Erbitux, Avastin, Rituximab Tarceva, Iressa
Small Molecule	Cell Surface, Intracellular	Lung	Tarceva, Iressa
Aptamer	Renal, Lung	Renal, Lung	AS1411 (in dev.)
Peptide	Cell Surface, Intracellular	Breast, Thyroid	RGD (in dev.)

Tumor cells overexpressing the HER2 receptor, for example, have been effectively targeted with liposomes conjugated with anti-HER2 antibodies. Park et al. at the University of California - San Francisco demonstrated that these immunoliposomes showed superior cytotoxic effects both *in vitro* and in rats compared to non-targeted liposomes and the enhanced therapeutic activity was attributed, at least in part, to receptor-mediated endocytic delivery of the anticancer agent inside the cells. Other successful targeting formulations of immunoliposomes include GD2-targeted fenretinide to neuroblastoma and melanoma cells and anti-VEGFR2 liposome targeting of human cancer cells *in vitro* (32, 33). PEGylated poly(lactic acid) immunoparticles have also been successfully targeted with anti-

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transferrin receptor antibodies to cell lines expressing the transferring receptor (34). Folate receptor nanocarrier targeting has also received much attention as many tumor cells preferentially overexpress this receptor during oncogenesis. Liposomes containing either daunorubicin or doxorubicin have been targeted both *in vitro* and in mouse xenograft models to a number of tumor cells and been shown to exhibit increased cytotoxicity in comparison to administration of the non-targeted complexes (35, 36). Amphiphilic micelles containing paclitaxel, a lipophilic anticancer compound, were targeted with high efficiency to folate receptor-expressing Hela cells *in vitro* and demonstrated subsequent cytotoxic effects (37). The intense focus of targeting cancer cells with cytotoxic drugs will only increase as nanotechnology-based delivery platforms continue to show encouraging results.

2.3 Thermal Ablation and Cancer

The study and application of nanoparticles for the treatment of cancer is not limited to drug delivery. In certain instances, depending upon composition and physical properties, the nanoparticles themselves may act as the therapeutic agents.
Much attention has been paid to certain nanoparticles' ability to absorb energy upon exposure to external fields such as magnetism, light or radiofrequency waves. The absorption of this energy is ultimately emitted in the form of heat (hyperthermia), with the efficiency of absorption and emission depending upon the nanoparticle composition and the field of energy to which it was exposed. Below are descriptions of some of the latest and most high profile research in this area categorized by the identity of the nanoparticles utilized in the studies.

Magnetic Nanoparticles

As early as 1957, researchers studied the use of magnetic fields in combination with an absorption platform as a method for enhanced delivery of hyperthermic conditions to specific parts of the body. In these studies, researchers developed a strategy to apply heat to cancer-positive lymph nodes through the localization of fine magnetic particles within the lymph nodes followed by "selective heat induction" via the application of a magnetic field. This resulted in the eradication of lymph node-specific cancer cells (38). Nanoparticles such as iron oxide, Fe3O4, and magnetite absorb magnetic fields at very high efficiency. This absorption ultimately results in energy emission in the form of heat. The interplay between magnetic nanoparticles and magnetism has now been exploited by a number of researchers for its applications in the hyperthermic ablation of cancer cells. *In vivo* studies of iron oxide nanoparticles administered into SCID mice implanted with human breast adenocarcinoma cells followed by exposure to an alternating current (AC) magnetic field were successful in inducing coagulation and necrosis specific to tumor cells (39). Johannsen and colleagues at the Charite-Universitatsmedizin in Berlin, Germany have shown that thermo-ablative

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temperatures can be achieved with high efficiency in a Phase I clinical trial of ten patients where iron oxide nanoparticles in solution were introduced into the prostates of patients followed by successive exposure to an alternating current magnetic field (40). In industry, the concept of magnetic nanoparticle applications in cancer treatment has reached the industrial level. The company Triton Biosystems, now known as Aduro Biotech, in Berkeley, CA has developed the NTTM and TNTTM proprietary cancer therapeutics platforms which are based upon the use of iron oxide nanoparticles and externally applied magnetic fields to induce hyperthermic ablation of cancer cells. The relatively low toxicity of iron oxide may allow for high doses of the nanoparticles to accumulate within the tumor site. Clinical trials are expected to begin in 2009 (41).

In addition to the sole use of magnetically induced heat to ablate cancer cells, combination therapeutics in which both nanoparticle-based hyperthermia and chemotherapy are applied in concert has yielded some exciting results (for review see 42). Magnetite nanoparticles combined with chemotherapeutic agents in liposomes have been used with striking success to treat malignant melanoma. Specifically, Ito and colleagues at Nagoya University in Japan developed magnetite cationic nanoparticles complexed with the chemotherapeutic agent 4-S-CAP (4-S-CAP/MCL), which acts to induce the killing of both melanocytes and melanoma cells. The *in vitro* study demonstrated that the combination of efficient hyperthermic induction by alternating current magnetic field of the nanoparticles with 4-S-CAP resulted in a significant increase in cytotoxic effects of B16 melanoma cells compared to irradiation or use of the chemotherapy alone. The researchers took the study a step further *in vivo* and demonstrated an additive effect of 4-S-CAP/MCL and magnetic field-inducing hyperthermically and chemically induced cytotoxicity following Intratumoral injections of the complex in mice (43). The same researchers recently developed a combination therapeutic platform of liposomes complexed with anti-HER2 receptor antibodies and containing magnetite nanoparticles. Anti-HER2 antibodies not only specifically target HER2 expressing cells but also inhibit the proliferative capacity of these cells. This combination of hyperthermic induction via alternating current magnetic exposure of the magnetite nanoparticles with anti-HER2 antibody effects resulted in a striking efficiency proliferative reduction and cytotoxicity in the breast cancer model cell line SKBr3 (44). Similar effects were also shown *in vivo* (45).

Nanoshells

Considered the best nanotechnology discovery for 2003 by *Nanotech Now* (46), gold nanoshells were first considered as a cancer therapeutics platform by the researchers Naomi Halas and Jennifer West at Rice University in Houston, Texas. They showed that silica nanoparticles surrounded by thin gold nanoshells could be tuned to optimally absorb

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light in the near-infrared range and convert this energy to therapeutic levels of emitted heat. SKBr3 breast cancer cells were effectively ablated *in vitro* upon exposure to near IR light when cultured in the presence of gold nanoshells. The researchers also demonstrated *in vivo* therapeutic efficacy using SCID immunocompromised mice injected with canine TVT cancer cells. Intratumoral injection followed by exposure to near IR light yielded significant tumor tissue damage as evidence by coagulation, cell shrinkage and the loss of nuclear staining (47). Halas, West and colleagues also demonstrated successful targeting of gold nanoshells to SKBr3 cells using anti-HER2 antibodies and hyperthermic ablation of these cells *in vitro* (48). Several groups, including West and colleagues, have since expanded on these studies and shown efficacy in ablating a variety of different types of cancer cells both *in vitro* and *in vivo*. These include medulloblastoma, glioma, and prostate cancer cells (49, 50). One drawback of this technology lies in the inability of near IR light to effectively penetrate beyond several centimeters below the skin's surface. Thus deep tissue therapeutics may be hindered by ineffective nanoshell excitation and heating.

As is the case for the magnetic nanoparticle cancer therapeutics platform, gold nanoshells and their application to the treatment of cancer have been taken on by industry and are now the central focus of the Rice University spinout Nanospectra Biosciences. J. Donald Payne, the company's President and CEO, made the point that nanoparticles may affect a broad spectrum of cancer phenotypes, stating:

> We believe AuroLase Therapy will have broad applications in cancer. We will initially focus on head and neck cancer to fill the significant unmet medical need in this serious cancer, and then expand to other cancers after FDA approval. We hope to start our first human trial later in 2006 (51).

Therefore it appears that the application of gold nanoshells combined with near IR-induced hyperthermia for the treatment of cancer has the solid backing of both academia and industry and may indeed become a standard therapeutic procedure for some types of cancers.

Polymer-Solubilized Carbon Nanotubes

Due to its inherent small size and extreme sensitivity to external fields, the polymer-solubilized carbon nanotube (CNT) provides one of the most promising nanoparticle platforms for the hyperthermic treatment of cancer. Carbon nanotubes are allotropes of carbon atoms arranged in a chicken wire-like configuration rolled back upon itself. CNTs typically have a length to diameter ratio greater than 1,000,000 and have been pursued for use in a variety of materials applications due to extremely high strength to mass ratios. In addition, based in their physical properties, CNTs rapidly heat up in the presence of radio frequency (RF) waves or near infrared light. These properties make

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CNT-based hyperthermic ablation of cancer cells a possibility and much research has been conducted in this area to date. One of the first studies carried out to assess the use of CNTs and near IR light demonstrated the delivery of oligonucleotides inside cells by CNTs. Exposure to light of a specific infrared wavelength resulted in endosomal release of oligonucleotides into the cytoplasm and nuclear translocation, but it also revealed efficient induction of cell death due to hyperthermic conditions (52).

Carbon nanotubes can exist as both multi-walled CNTs (MWCNT) or single-walled CNTs (SWCNT), with the greatest limitation for utility as their tendency to tightly clump, primarily as a result of van der Waals interactions between the carbon atoms (53). This bundling effects results in considerable insolubility in a variety of solvents, including water, and has been the focus of major industrial efforts to develop polymers that allow for the solubilization of both MWCNTs and SWCNTs in a variety of solvents. Zyvex Performance Materials (ZPM), based in Columbus, Ohio, is at the forefront of this effort, developing a proprietary polymer, termed
"Kentera" (Greek for "bridge"), that allows for a significant reduction in van der Waals interactions between the CNTs. Kentera acts by binding to individual CNTs through non-covalent electron stacking and thus masks and minimizes van der Waals attractions (Figure 1). In addition, Kentera's side chains can be customizable to allow for unique interactions with virtually any type of solvent, thus allowing for relatively universal and efficient CNT soluble dispersion. The side chains can also be modified efficiently to attach receptor-specific targeting agents like antibodies and small molecules. Figure

Figure 1. Carbon nanotube functionalized with KenteraTM (Courtesy Zyvex Performance Materials, Columbus, Ohio for which Kentera is a trademark). hich Kentera is a trademark).

A great deal of effort by Zyvex Performance Materials' researchers has been focused on the efficient solubilization of MWCNTs and SWCNTs in water. Formulation of a unique and proprietary version of Kentera containing aliphatic side chains has resulted in extremely efficient water dispersion of both SWCNTs and MWCNTs (Figure 2). The dispersion is stable, and even appears to aid in the CNT's ability to absorb RF waves and emit heat (54). Other polymer compositions are also effective at dispersing CNTs in an aqueous environment. Rocky Draper and colleagues at the University of Texas at Dallas have identified peptide-based polymers that solubilize CNTs in an aqueous environment with a similar efficiency to that of Kentera (55). In addition, Nish and colleagues at Oxford University, Oxford, U.K., have performed an extensive analysis of aromatic polymers and their efficiencies at dispersing carbon nanotubes and demonstrated that different polymers possess the ability to discriminate between nanotube species with respect to chiral angle or even tube diameter (56).

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Figure 2. Kentera-mediated multi-walled carbon nanotube dispersion in water. A. SEM image of raw, bundled MWCNTs. B. SEM image of 2% wt/vol MWCNTs after dispersion in water with Kentera. C. MWCNTs in water in the absence (left) and presence (right) of Kentera (Courtesy Zyvex Performance Materials, Columbus, Ohio).

The ability to effectively disperse carbon nanotubes in an aqueous environment allows for their possible applications in human therapeutics, as they now may be effectively introduced into the body at high concentrations and under normal physiological conditions. The inherent sensitivity of CNTs to either near infrared light or radiofrequency waves allows for the possibility of hyperthermic ablation of unwanted cells in the body following introduction of dispersed CNTs and exposure to an external field. Researchers at the University of Texas M.D. Anderson Cancer Center, in collaboration with Zyvex Corporation which supplied Kentera-solubilized SWCNTs, showed highly efficient ablation of human cancer cells *in vitro* and *in vivo*. Specifically, human hepatocellular and adenocarcinoma cells were grown in tissue culture and treated with Kentera-SWCNT dispersions followed by exposure to a radiofrequency wave of 13.56 MHz using a variable power RF signal generator invented by the late John Kanzius of Therm Med, LLC (Erie, PA). Enhanced bulk heating was observed, followed by massive cytotoxicity. The studies were expanded upon in New Zealand white rabbits inoculated with VX2 tumors. Following intratumoral injection of Kentera-SWCNT dispersions and exposure to the 13.56 MHz RF field massive tumor-specific cell death was observed as evidenced by thermal necrosis of the tumor tissue. In addition, the studies suggested no observable toxic effects resulting from exposure to the polymer or carbon nanotubes themselves (57). It should be noted that the Kanzius RF signal generator has been successfully used to demonstrate proof-of-concept, *in vitro* and *in vivo*, for hyperthermic ablation of tumor cells using other types of nanoparticles such as gold nanoshells (58).

While non-targeted localized introduction of the hyperthermic agent remains promising, it is also nonspecific and will in most cases result in the unwanted death of surrounding tissues, as evidenced by the research cited above. To address this detrimental non-specificity, researchers at the University of Texas Southwestern Medical Center in Dallas, Texas have focused on targeting carbon nanotubes to tumor cells using moieties attached directly to the CNTs, which bind specifically and tightly to receptors on the surface of cancer cells. In these studies, Ellen Vitetta and colleagues demonstrated the specific binding of polar lipid solubilized anti-CD22-CNTs to Daudi lymphoma cells which express the CD 22 receptor. Exposure of these cells to near IR light resulted in very specific and efficient killing *in vitro* (59). Taken together, these findings suggest that there are a multitude of dispersion and targeting

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methodologies that will allow for specific access to and ablation of, cancer cells within the body.

2.4 Nanoparticles and Cancer Diagnostics

Current noninvasive imaging techniques for the diagnosis of tumors such as magnetic resonance imaging (MRI), gamma scintigraphy or computed tomography (CT) require a certain level of signal intensity with respect to the lesioned area over healthy tissue to be effective at diagnosis. Even with enhanced image processing and other optimization techniques, often the successful diagnosis of a tumor with MRI or CT requires a relatively large pathological area. Recent years have seen the advent of contrast agents that interact with external fields to heighten the sensitivity of the diagnostic procedure by absorbing external field signals much more efficiently than surrounding tissues. Yet even a further concentration of contrast agents at the tumor site has been desired and thus nanoparticles have been pursued as carriers to increase contrast agent concentration. Some of the more high-profile nanoparticle-based cancer diagnostics platforms, both non-specific and targeted, are discussed below.

Liposomes and Micelles - Nonspecific

Liposomes and micelles have received much attention in this area due to favorable biocompatibility and conjugation properties. Tilcock and colleagues in the Department of Biochemistry at the University of British Columbia in Vancouver have shown that liposomes may be used to carry metal contrast agents either within the liposomal core or external in the hydrophobic membrane pending the use of a metal chelating agent (60, 61). Polyethylene glycol (PEG)-based micelles were also used to carry paramagnetic Gd and for both MRI and scintigraphy imaging (62). In addition to biocompatibility, another advantage of both liposomes and micelles is their small size, which allows for accumulation at very high concentrations within the tumor.

Quantum Dots - Nonspecific

Quantum dots are composed of an elemental core, such as cadmium or mercury, surrounded by a metal shell and they typically emit fluorescent light in the range of 400nm to 2000nm due to electron excitation (63). Quantum dots are superior to other types of fluorescent molecules due to a logarithmically increased ability to resist photo-bleaching, compared to fluorescent compounds of organic origin (64). A great deal of study on the utility of quantum dots in the analysis of basic cell biology to lymph system marking has been undertaken over the last several years (For review see 65). In addition, much attention has been directed at fine tuning quantum dots to fluoresce in the near IR spectra to overcome auto-fluorescence and lack of tissue penetration which typically occurs in the visible range. Parungo et al in the Division of Cardiac Surgery at Brigham and Women's Hospital in Boston have shown that these NIR

tuned quantum dots can act as effective diagnostics tools in several animal models, specifically within the lymph system (66). It should be noted that quantum dots have one important disadvantage in that their heavy metal core remains highly toxic. Thus, outer coatings that ensure safety will have to be developed. This is discussed in further detail in Section 2.8.

Gold Nanoshells - Nonspecific

Similar to that of quantum dots, the engineering process for gold nanoshells allows them to be optically tuned for maximum diagnostics effectiveness in the IR, UV and visible spectra. In addition, nanoshells lack the heavy metal toxicity issues underlying quantum dots. Non-targeted nanoshells have been shown by researchers at Texas A&M University and Nanospectra Biosciences to be good contrast agents for both computerized and photo-acoustic tomography *in vivo* (67). Finally, the combination of their hyperthermic and optical properties makes gold nanoshells a platform that may allow for dual simultaneous diagnostics and therapeutics endeavors. As mentioned above, it should be noted that gold nanoshells rely on near infrared light as the external field which does not penetrate further than a few centimeters below the skin's surface, thus limiting the nanoparticles' utility for deep tissue imaging or treatment.

Lipid-PFCs - Targeted

As early as the mid-nineties, a pioneering group of researchers lead by Samuel Wickline at the Barnes-Jewish Hospital in St. Louis, MO demonstrated the use of lipid-coated perfluorocarbon (PFC) nanoparticles as excellent targeted ultrasonic contrast agents with potentially broad biomedical applications. Specifically, they detected fibrin clots *in vivo* using an antifebrin monoclonal antibody conjugated PFCs (68). These studies have since been expanded upon to address cancer diagnostics using the same basic system. Kereos, Inc., also of St. Louis, is a company founded to capitalize on the application of lipid-coated PFCs for diagnostics purposes with a focus on using the same system to deliver drug payloads. The company now has a number of diagnostic and therapeutic molecules based on lipid-PFC nanotechnology in the preclinical pipeline (69).

Magnetic Nanoparticles - Nonspecific

Superparamagnetic nanoparticles have been extensively studied as alternative contrast agents to that of gadolinium, for example, due to a greater propensity for magnetic susceptibility. In addition, their small size, 50nm - 100nm, has been shown to allow for more extensive tissue distribution (70). A great deal of clinical research has been performed in this area with a focus on the use of iron oxide nanoparticles to characterize lymph node status for patients with a variety of cancers including breast, lung, prostate, endometrial and cervical cancers. Keller and colleagues at the Institute of Diagnostic

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Radiology in Zurich, Switzerland evaluated superparamagnetic iron oxide (SPIO) enhancement for preoperative axillary lymph node staging in breast cancer patients. They found in two cases that preoperative findings using SPIO led to a change in therapeutic approach due to increased sensitivity (71). A multicenter clinical trial of SPIO for the evaluation of mediastinal lymph nodes in patients with primary lung carcinoma also revealed a sensitivity of correct diagnosis at 92% (72). These studies have also been expanded upon for lymph node analyses in patients with endometrial, cervical and prostate cancer thus suggesting that SPIO may become a diagnostic standard for nonspecific clinical evaluation of potential lymph node metastases properties in cancer patients (73, 74).

Other Targeted Nano-diagnostics

The key to effective and sensitive diagnosis is the ability to home nanoparticles in to the precise locale of the cancerous cell type and to eliminate the diagnostic reagent from other healthy tissues within the body. A pioneering study conducted by Shuming Nie's group at Georgia Institute of Technology demonstrated the localization of three different targeted quantum dot types to tumor sites in mice using copolymer encapsulated quantum dots tagged with targeting ligands that bind specifically to tumor cells (75). Efforts have also been expanded beyond cancer diagnostics to utilize quantum dots for the detection of viral particles. Researchers at the University of Georgia, for example, have developed nanoparticles functionalized with monoclonal antibodies that recognize respiratory syncytial virus (RSV) and allow for its efficient detection both *in vitro* and *in vivo* (76). Nanoshells conjugated with anti-HER2 antibodies were targeted to tumor cells *in vitro* that express the HER2 receptor and detected via near IR optical computerized tomography (77). The anti-HER2 system was also used successfully with iron oxide nanoparticles to specifically bind HER2/neu positive cancer cells *in vitro* followed by detection in a magnetic field. A similar result was demonstrated using luteinizing hormone releasing hormone (LHRH) conjugated iron oxide nanoparticles. This allowed for specific binding to LHRH receptors on cancer cells *in vitro* followed by magnetic field detection (78). Finally, telomerase is an enzyme synthesized by cancer cells that allows them unlimited division capacity through specific DNA sequence synthesis. Researchers at the Center for Molecular Imaging Research at Harvard Medical school have developed iron oxide nanoparticles that change their magnetic state upon binding to the telomerase synthesized DNA sequence TTAGGG thus allowing for magnetic imaging of telomerase-active cancer cells (79).

2.5 Nanoparticles and Toxicity - The Question Remains

The potential toxic effects of nanoparticles remains a controversial subject and depends on a multitude of factors including the identity of the nanoparticle, the dosage and final concentrations used, clearance

rates and biocompatibility, just to name a few. Some interesting findings with respect to toxicity for a few key nanoparticles are described below.

Gold Nanoshells

Two independent groups have shown that gold nanoparticles present no observable cytotoxic effects upon entry into cells (80, 81). Gold nanorods, however, which carry small amounts of the stabilizer CTAB no matter how stringent the purification, have exhibited some cytotoxic effects determined to be due to the stabilizer itself as demonstrated by Niidome and colleagues in the Department of Applied Chemistry at Kyushu University in Fukuoka, Japan (82). Nanoshells of a gold/copper heterogenous makeup have also been studied for cytotoxic properties and exhibited none unless acted upon by an external laser to achieve the desired ablation of tumor cells *in vivo* (83-85).

Single-Walled and Multi-walled Carbon Nanotubes

In recent years carbon nanotubes have been perhaps the most controversial of all nanoparticles with respect to toxicity concerns. Synthesized as either single walled (SWCNT) or multi-walled (MWCNT), these nanotubes present several characteristics that cause concern. Methods employed to generate carbon nanotubes include arc discharge, chemical deposition and laser ablation, and each requires metal catalysts to perform effective synthesis (86-88). These catalysts, such as cobalt or nickel, have been demonstrated to be highly cytotoxic at certain concentrations (89). Thus, residual amounts of metal catalysts in the finished SWCNT and MWCNT concentrates could promote toxicity during therapeutic applications. In addition, the rapid uptake of carbon nanotubes by cells, and the fact that they are non-biodegradable, raises some issues regarding long-term biodistribution. *In vitro*, a number of studies have suggested carbon nanotube cytotoxicity using various cell types such as keratinocytes and bronchial epithelial cells as model systems. Effects observed included radical oxide synthesis, oxidative stress responses, reduction in mitochondrial function and changes in cell morphology (90, 91). Studies by Draper and colleagues at the University of Texas at Dallas have shown that carbon nanotubes solubilized by the polymer PEDOT/PSS are rapidly ingested by cells via endocytosis and appear to accumulate in endocytic vesicles (see figure 3 below). Whether this accumulation has a long-term detrimental effect on cell viability remains to be determined. *In vivo*, intratracheal instillation of carbon nanotubes at high doses in rodents caused chronic lung inflammation and fibrosis, although these studies are considered flawed and largely dismissed due to the extremely high concentrations of carbon nanotubes utilized (92, 93). Other studies indicate an asbestos like effect of carbon nanotubes when these are introduced into the abdominal cavity of mice, yet again the high non-physiological concentrations used in

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this study suggest further research in this area is needed to definitively determine the mesothelioma-inducing properties of MWCNTs. Contradicting these findings, Liu and colleagues at Peking University in Beijing, China have performed long-term (three month) studies on the effects of SWCNTs injected into the main organs of mice and have shown low toxicity, with only slight inflammation observed (94).

Figure 3. PEDOT/PSS-mediated intracellular uptake of single-walled carbon nanotubes by HEK293 cells. Arrows denote dynamic cytoplasmic endocytic vesicles containing carbon nanotubes (Courtesy Rocky Draper and Austin Edmiston, The University of Texas at Dallas).

Fullerenes

Fullerenes are nanoparticles composed entirely of carbon atoms that exist in various forms including planar, ellipsoid, tubular and spherical. They were discovered by Richard Smalley and colleagues at Rice University and Harold Kroto at the University of Sussex in 1985. Spherical fullerenes are known as Buckminster fullerenes, or buckyballs, and all have properties that may suggest their role as potent antimicrobial agents due to their potential for reactive oxidation induction during photoexcitation (95). Perhaps the most concerning toxicology issues surrounding fullerenes lie not in the effect on human but rather, the environment. Discharge of fullerenes into the ecosystem could possibly have detrimental environmental impacts due to the very antimicrobial effects that are thought to aid in the treatment of infections. For example, the median lethal concentration, LC50, for C(60) in Daphnia, a small, planktonic crustacean, was between 460 and 800ppb, raising concerns about general ecotoxicity (96, 97). In higher organisms such as largemouth bass, brain-localized lipid peroxidation was observed two days after treatment with nC60 at 0.5ppm, but the high concentrations of fullerenes used in this study suggest further research in this area is needed (98).

Quantum Dots

As mentioned above, quantum dots are semiconductor-based nanoparticles that have unique optical properties which allow the particles to act as extremely valuable diagnostic agents. Dots of different sizes emit different light patterns, and dot shape may also play a role in color emission properties although this has yet to be definitively determined (99). Studies

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on the potential toxicity of quantum dots suggest the nanoparticles promote the formation of reactive oxygen species, which may play a role in damaging cell membranes and the nuclear envelope as well as detrimentally affecting mitochondrial function (100). As toxicity is a major concern, many groups have made efforts to coat quantum dots with biocompatible surfaces. Wang et al, for example, coated cadmium selenium, CdSe, quantum dots with polyethylene glycol casings and observed a reduced cytotoxic effect on Caco-2 enterocyte cells compared with free uncoated nanoparticles (101). It is speculated that the toxicity observed with direct exposure of cells to naked Cd is actually the result of the formation of free radical Cd^{2+} ions. Adding to the controversy, other researchers have published data on a variety of quantum dot compositions that demonstrate no observable *in vitro* or *in vivo* toxicity (102).

Dendrimers

Highly branched molecules of primarily a carbon composition, dendrimers have shown much promise in their application and use for therapeutics purposes. Dendritic branches allow for the presentation of unique functional groups for both the efficient encapsulation of functional molecules and to aid in biocompatibility. Thus, therapeutic agents which are often hydrophobic in nature can be made biocompatible through coating with dendrimer compositions that have hydrophobic internal cores and hydrophilic external functional groups (103). Drugs which have biocompatible/hydrophilic properties may also be coated on the external surfaces of dendrimers branches, often at very high concentrations (104). Toxicology studies on dendrimers and their derivatives are currently very limited. One example involves the evaluation of polypropylenimine dendrimers conjugates on cultured endothelial cells. These conjugates resulted in significant DNA damage, yet this damage could be minimized or in some cases completed eliminated following chemical modification of the parental dendrimers surface amines to a neutral state (105). Researchers in the Center for Nanomedicine and Cellular Delivery at the University of Maryland - Baltimore noted a similar phenomenon for polyamidoamine (PAMAM) dendrimers following surface acetylation (106). Given the unique nature of each dendrimer composition, it is difficult to perform toxicology studies on this broad class of nanoparticles or to make wide-ranging conclusions.

3. Nanomaterials and Clinical Neuroscience

The effect treatment of neurodegenerative disorders such as Alzheimer's and Parkinson's diseases as well as amyotrophic lateral sclerosis (AML) is perhaps the primary focus of clinical neuroscience and represents an area of medicine where nanotechnology can truly have an immense and positive impact (for review see 107). These disorders are usually based upon the loss of cells present within the brain or spinal cord that play critical roles

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in the "wiring" of the nervous system. In addition, neurodegeneration is often a secondary effect of such conditions as stroke and head or spinal column trauma. The accurate diagnosis and treatment of neurodegenerative disorders is hampered by a number of challenges unique to this field of study. The central nervous system is defined by a very complex and heterogeneous population of cell types and support matrices. This complicates the delivery and overall efficacy of diagnostic platforms or therapeutic drugs. Some of the efforts at combating neurodegenerative diseases with nanotechnology have been focused on the use of nanomaterials, specifically carbon nanotubes, as scaffolds upon which neurite outgrowth can be encouraged (108). Matsumoto and colleagues at Toyo University in Gunma, Japan have expanded on these findings using carbon nanotube scaffolds coated with brain-derived neurotrophic factor (BDNF) to stimulate the growth of neurons. Biocompatible nanopolymers such as poly(-hydroxy acids)-poly(lactic acid) (PLA) have also been demonstrated to be effective as scaffolds promoting tissue regeneration after spinal cord injury. Specifically, mouse brain-derived progenitor cells differentiated into mature neurons in the presence of PLA (109). With respect to the brain, the blood-brain barrier (BBB) further hinders delivery of macromolecules such as diagnostic agents or drugs (for review see 110). Delivery across this barrier, however, could be accomplished by basing the delivery platform on nanotechnology. Immunoliposomes, for example, have been used to deliver exogenous genes to the brain using attached antibodies which bind specifically to BBB transporting receptors. These lipid bilayers are small enough to cross the BBB yet also designed to carry possible gene therapies or even large drug payloads (111). Solid colloidal nanoparticles made of biodegradable polymers have also been shown to deliver a number of therapeutic agents across the BBB. Typically less than 100nm in size, these particles can be coated with substances that make them both soluble and stabile in the blood. For example, Kreuter et al. at the Institut für Pharmazeutische Technologie in Frankfurt, Germany showed that polybutylcyanoacrylate (PBCA) nanoparticles coated with a surfactant successfully delivered a number of therapeutic agents across the BBB including analgesics, anti-cancer agents and anticonvulsants (112). Other examples include pegylated PLA or PLGA. These and other encouraging findings have solidified nanoparticles and nanomaterials as promising agents of tomorrow for the ultimate treatment CNS disorders.

4. Nanofibers and Tissue Engineering

Perhaps one of the most exciting areas of convergence for nanotechnology and medicine is that of tissue engineering. Cell/tissue transplantation is often the only mode of therapeutic intervention, especially for burn victims. Yet the practice of both auto- and allograft procedures has limitations that warrant the pursuit of tissue engineering/regeneration alternatives. Given the properties of many types

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of nanoparticles and nanomaterials, it isn't surprising that some mimic the biological environment and have been shown to aid in the engineering of various living tissues *in vitro*. As discussed for clinical neuroscience, scaffolding of nanomaterials is the primary basis for their use in tissue engineering applications. Electrospun nanofibers have shown the most promise in this area and can be synthesized from a wide variety of natural and synthetic biomaterials. The electrospinning process produces fibers of a three-dimensional nature that have been used effectively as scaffolds for the engineering of skin, vasculature, neural and musculoskeletal tissue and as carriers for the delivery of proteins, nucleic acids and drugs
(for review see 113). Nanofibers have been spun from a variety of natural polymeric materials that offer the advantage of being quite similar to macromolecules present in the body. This allows for an increased probability that introduction of the foreign nanofibers into a biological environment will be met favorably. Collagen, chitosan, hyaluronic acid (HA) and gelatin/PCL are some examples of natural polymers from which nanofibers have been successfully generated and utilized in the context of tissue engineering (114-117). Yoshimoto and colleagues at Massachusetts General Hospital investigated the interactions of mesenchymal stem cells (MSCs) seeded onto gelatin/PLC nano-scaffolds and revealed that these cells migrated inside the scaffold and subsequently produced extracellular matrix (ECM), a natural support component for virtually all tissues (118). These studies were expanded upon in a rat model implant of the scaffolds demonstrating mineralization and type I collagen synthesis which suggests the scaffolds may be utilized for bone tissue engineering (119). Li and colleagues in the Department of Biomedical Engineering at the University of Wisconsin-Madison demonstrated that PCL-based nanofiber scaffolds seeded with fetal bovine chondrocytes maintained their chondrocytic phenotype and expressed several cartilage specific genes including aggrecan and collagen type II (120). Significant advancements have also been made in the area of skin tissue engineering using nanofibers. Min et al in the Bioengineering and Biotechnology Center at Tufts University developed silk nanofibers which, given their high porosity and surface area to volume ratio, were found to promote keratinocyte and fibroblast adhesion and spreading when coated with type I collagen (121). Engineering of the vasculature may also be aided by the use of nanomaterials. This field has been a major focus of tissue engineering researchers as they seek new methods and materials to promote blood vessel formation. A biodegradable PLLA-CL (75:25) nanofibrous scaffold was developed as a scaffold to mimic the natural ECM and shown to form a well defined architecture for smooth muscle cell adhesion and proliferation (122). While these studies are encouraging, the future of nanomaterials as they apply to tissue engineering will depend upon critical factors such as safety,

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biocompatibility, biodegradability three-dimensional architecture and long-term delivery of factors needed to support cell adherence, growth, migration and differentiation.

5. Nanomaterials and Stem Cell Culture

The efficient culture, expansion and directed differentiation of embryonic stem cells have been at the forefront stem cell-based therapeutics development for the last twenty years. The ability to maintain stem cells in a pluripotential state and prevent the introduction of chromosomal abnormalities has been especially difficult with human embryonic stem cells. These cells require a unique set of growth factors, media formulations and attachment substrate upon which to adhere that ideally would mimic the *in vivo* environment (for review see 123). While progress has been made utilizing mouse embryonic feeders and substrates such as Matrigel, these components contain animal by-products which raises issues regarding the safety of cell therapeutics resulting from such culture. As such some progress has been made with the utilization of human fibroblast feeders yet these cells were originally derived using animal byproducts thus again raising concerns regarding derived therapeutic cells from a safety and FDA approval perspective (124). Finally, the use of undefined animal components often introduces yet another level of unwanted variability in the cell culture process. Defined substrates are thus needed to more reproducibly culture cells and maintain certain phenotypes. This would allow for more efficient and reliable cell culture and manipulation of embryonic and adult stem cells and provide a basis for industry standardization of cell culture protocols. To circumvent issues such as animal component-containing substrates and substrate variability, a number of researchers have begun exploring the use and application of nanomaterials as support matrices for human stem cell culture. Kommireddy and colleagues in the Institute for Micromanufacturing at Louisiana Tech University in Ruston, Louisiana have focused on surface topography as one of the most important factors influencing the attachment and spreading of mesenchymal stem cells. Their studies using titanium oxide (TiO2) nanoparticle thin films showed that these particles could be used successfully as adherence substrates and in general rougher surfaces promoted enhanced attachment and expansion (125). Mesenchymal stem cells have also been exploited for bone tissue engineering using magnetic cationic liposome nanoparticles as substrates for growth. Specifically, magnetized cells were drawn to an attachment surface with a 4000G magnet and demonstrated to differentiate into osteoblasts, adipocytes and chondrocytes, depending on the media conditions. Sheets of MSC's layered in this fashion were transplanted into nude mice and resulted in new bone formation (126). Emphasizing the importance of serum-free culture of stem cells, Sefcik and colleagues in the Department of Biomedical Engineering at the University of Virginia - Charlottesville designed a system for the application

of electrospun collagen nanofibers assembled in a 3D matrix as a biomimetic substrate for the efficient differentiation of human adipose-derived stem cells into osteogenic lineages (127). Others have focused on the maintenance of pluripotency of human embryonic stem cells in the absence of substrate feeder layers. Studies using liposomal ceramide nanoparticles as an attachment platform promoted the survival of healthy, pluripotent hES cells at the expense of differentiated cells due to a resistance to the apoptotic effects of ceramide specific to undifferentiated cells (128). In the future it can be speculated that a wide range of nanoparticle substrates will be utilized to both maintain pluripotency and drive selected and directed differentiation of these cells towards particular differentiated lineages. These advances will both eliminate cell culture variability and provide animal component-free alternatives for matrix attachment.

6. Nanorobotics and Medicine

Robert A. Freitas, Jr., who has written numerous books and publications on the subject of nanomedicine and is considered one of the world's experts in this area, stated, "In the first half of the 21st century, nanomedicine should eliminate virtually all common diseases of the 20th century, and virtually all medical pain and suffering as well" (129). This is a bold statement, yet it highlights the potential of a universal and permanent impact of nanotechnology on medicine. While targeted carbon nanotubes or gold nanoshells could be considered therapeutic "nanobots", others could include Freitas' conceptual artificial "respirocyte", which theoretically could function at over 230 times the efficiency of a natural red blood cell. Other medically relevant nanobots include "clottocytes", also conceived by Freitas, which at 2 microns in diameter and due to its incredibly efficient compact fiber mesh design, could offer clotting performance similar to that of biological platelets but at 0.01% of the same bloodstream concentration (130). At the molecular level, Nadrian Seeman, Professor in the Department of Chemistry at New York University and a pioneer in the area of nucleic acid self-assembly, has developed computer-based methodologies for the design and assembly of three-dimensional DNA structures that take advantage of nucleotide base pairing properties. Specifically, his lab has successfully applied these algorithms to assemble both a cube and a truncated octahedron from DNA (Figure 4). Seeman's group has also demonstrated the operation of a DNA robot arm inserted into a 2-dimensional DNA crystalline substrate (131). These nucleic acid-based primitive robotic structures are biocompatible and could theoretically be utilized as the basic building blocks for construction of nanorobots such as a respirocyte or clottocyte for use in medical applications. It is clear that the use of nucleic acids and their base-pairing properties will no doubt profoundly impact the development and application of nanobots for biological and therapeutic uses in the near future.

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As it stands, this is an exciting time for both nanotechnology and medicine. Major breakthroughs and basic scientific knowledge in these areas are accumulating at an unprecedented pace, and each field is rapidly evolving to produce new tools and technologies that will have broad applications across multiple disciplines. Eventually, it is inevitable that nanotechnology and medicine will mature and permanently merge to bring about new and superior diagnostic and therapeutic platforms to effectively address a variety of debilitating illnesses and disease, thus increasing the quality of life and perhaps even extending life for millions of individuals.

Figure 4. A 3-dimensional DNA-based cube (upper panel) and DNA-based truncated octahedron (lower panel). See text for descriptions.

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Chapter 32: Diamond Bio Electronics

Robert Linares, Ph.D., Patrick Doering, Bryant Linares
Apollo Diamond, Inc., Boston, MA, USA

Abstract

The use of diamond for advanced applications has been the dream of mankind for centuries. Until recently this dream has been realized only in the use of diamond for gemstones and abrasive applications where tons of diamonds are used on an annual basis. Diamond is the material system of choice for many applications, but its use has historically been limited due to the small size, high cost, and inconsistent (and typically poor) quality of available diamond materials until recently. The recent development of high quality, single crystal diamond crystal growth via the Chemical Vapor Deposition (CVD) process has allowed physcists and increasingly scientists in the life science area to think beyond these limitations and envision how diamond may be used in advanced applications ranging from quantum computing, to power generation and molecular imaging, and eventually even diamond nano-bots.

Because of diamond's unique properties as a bio-compatible material, better understanding of diamond's quantum effects and a convergence of mass production, semiconductor-like fabrication process, diamond now promises a unique and powerful key to the realization of the bio-electronic devices being envisioned for the new era of medical science. The combination of robust in-the-body diamond based sensors, coupled with smart bio-functionalized diamond devices may lead to diamond being the platform of choice for bio-electronics. This generation of diamond based bio-electronic devices would contribute substantially to ushering in a paradigm shift for medical science, leading to vastly improved patient diagnosis, decrease of drug development costs and risks, and improved effectiveness of drug delivery and gene therapy programs through better timed and more customized solutions.

1. The Vision of Bio-Electronics

The realistic vision for bio electronics has been with us for a number of decades. Since the advent of the computer chip in the 1960's, the thought or dream of putting electrical components in the body has moved from the purview of science fiction to a reasonable near term quest for this segment of life science in the early parts of this century. Some of the early applications of this branch of medicine have already manifest themselves throughout our society in early applications such as pace makers and identification sensors used in animals. While these devices are functional, they are in general large, somewhat cumbersome, and limited relative to the new generation of bio devices that is currently envisioned. As electronic and optical devices continue to shrink, a new generation of bio-electronic devices is taking shape that will usher in an era of bio –electronics where these devices will become ubiquitous in our society and persons.

Edited by: **Renata G. Bushko** - bushko@fhti.org
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Clemson University's C3B group, Center of Bio Electronics, Bio-Sensing and Bio Chips bio-electronics defines the space as:

> ..the interface of microelectronics, materials chemistry, molecular biology and information technology. These new technologies are leading to high performance devices and instruments that find application as test and measurement systems in the service of health and medicine. They find application in such areas as functional genomics (gene discovery), genetic screening, pharmacogenomics (high throughput drug screening and drug discovery), and molecular diagnostics.
> Established firmly on such manufacturing principles as
> miniaturization, modularization, systems integration, parallelism, and redundancy, these technologies promise to vastly reduce the cost of drug development, accelerate the rate of human genomics research, and enable new modes of analysis of analytes not easily measured and at sites previously unprecedented.
> CLEMSON UNIVERSTY, C3B Group[1]

Naturally, the systematic realization of these program goals will profoundly impact and improve the four traditional aspects of medical science.

Aspects of Conventional Health Care Process

1. Collect medical information from the patient
2. Interpret information with best possible speed
3. Develop a therapy solution for the patient
4. Deliver the therapy to the patient

Figure 1. Conventional Medicine

The goal of the 3B trend (bio-electronics, biosensor, biochips) is to dramatically change the paradigm in which the four target goals are achieved to improve accuracy, increase speed, reduce risk, and reduce cost. Bio-electronics allow all four to be done more effectively and with better efficacy than conventional processes. Over time they collectively revolutionize the healthcare space.

Medical diagnostics, information gathering, therapy development and solutions management fall generally into three eras.

Conventional Medicine	Human to Patient Interaction
Modern Medicine	Human and Machine to Patient Interaction
Bio-Electronics Era Medicine	Human/ Machine to Patient/Machine Interaction

Conventional Medicine has been with us for centuries, and generally deals with the collection of information and its interpretation through the interaction of the care giver-doctor and the patient. The physician gathers empirical information usually through observation and creates a diagnosis from knowledge held by that individual, collegeages or in a data base. Without taking anything away from the importance and benefits of human to human interaction, this process (from a technical analysis standpoint, and solution delivery standpoint) is slow and generalized. Human diagnosis and decision making leads to rapid problem solving for certain types of problems but lacks in good diagnosis of less common or more complicated health issues. The resolution of the data is low on the diagnosis side and mostly deals with the interpretation of symptomatic information which may be out of phase or time delayed from the root cause of the issue. Incomplete and time delayed feedback loop during therapy and delays for drug development ultimately lead to a major 'trial and error' component to this approach.

Modern Medicine, the second era, which is at the tail end of its growth curve, involves the increasingly sophisticated use of computers and equipment to collect and catalog information taken from the patient and systematically analyze it and create drug therapies based upon the information. This analysis and therapy solution is usually done in a manner where biological data and samples are taken, removed from the individual and analized in a remote location. Most of the tools needed to properly analyze the imaging information are large and need to be done in the lab. Similarly, therapies are derived in external environments and follow testing and approval procedures that are somewhat disconnected from the patient audience at the time of delivery. The benfits of this era have been:

a) A radical shift of complex monitoring and analysis to the bedside ,

b)Improvement in accuracy and speed-up of diagnosis and solution delivery,

c) Emergence of semi-custom but generalized drug and therapy development.

While it may be suggest that this era began in earnest with the discovery of penicilian it has reached a degree of maturity over the past few decades that has led to large drug development programs and more targeted drug therapies. An unintended consequence of this era however are the drug resistant strains of bacteria and organisms that remain after the generalized therapy. This outcome of our success in drug development requires ever faster speeds to detect these drug resistant species and better processes to develop new drugs and new approaches to defeat this evolutionary process.

Current standards for the speed and accuracy of patient diagnosis, drug research and therapy customization will be considered slow with the roll-out of the bio-electronics era.

Aspects of Bio-Electronic Era Health Care Process

1. Robust information at the molecular and nano scale
2. Information gathering and therapy inside the body
3. Integration and match of the therapy/ drug delivery to the exact intentions of the drug as dictated at the time of the drugs development
4. Customized delivery and tailoring of therapy timing, intensity and details

Solutions Must Have: bio compatibility, molecular scale sensing and actuation, and flexible tool kit of semiconductor type fabrications and capabilities

Figure 2: Bioelectronics Era Medicine

The result of these trends is a radical shift in the speed and detail of diagnosis and improved efficacy of the treatment. In general, the medical devices of this era, bio-electronic devices, will reside inside the body as opposed to next to the bedside or in the lab, and there is a high degree of real-time information coming from these devices. More importantly, the feedback loop from the time of the information gathering phase to the therapy/drug delivery phase can be dramatically shortened in this model.

Customizable and personalized drug delivery will be possible in the latter phases of this stage as bio factories take advantage of molecular scale sensing and fabrication capabilities. Effectively these chips will be able to sense, and output detailed molecular level information in real time.

Bio-chips running internal therapy solutions can match the effectiveness of the given therapy at the molecular level to models generated on living cells from the drug development stage, and subsequently change or tailor the course of therapy "on-the-fly" depending on the results. The results will be a revolution in medical information, drug development and therapy

The resulting speed of information collection and analysis will dramatically increase with this new era. Some forecasters of our medical future such as Ray Kurzweil believe that this information flow will mimic in healthcare what happened in the computer sciences during the last three decades with devices becoming increasingly miniaturized to the size of nano-scale devices. With this increasingly systematized and information based health care and discovery system, it is also expected that the pace of medical discovery and therapy increasing at an exponential rate. Radical improvements will occur at an increasingly faster rate. This has been described as the Moore's Law for health care.

> *"An analysis of the history of technology shows that technological change is exponential, contrary to the common-sense*

"intuitive linear" view. So we won't experience 100 years of progress in the 21st century -
- it will be more like 20,000 years of progress (at today's rate). The "returns," such as chip speed and cost-effectiveness, also increase exponentially...
...There are a great many examples of the exponential growth implied by the law of accelerating returns in technologies as varied as DNA sequencing, communication speeds, electronics of all kinds, and even in the rapidly shrinking size of technology." Ray Kurzweil, Law of Accelerating Returns [2]

2. Diamond based Bio Electronics

Diamond offers a unique and robust platform for biotechnology applications. Its material properties make it an ideal material for in-the-body devices. Because of its versatility, and robustness, a wide variety of sensor, and bioelectronics functions can be envisioned on a diamond bio-chip. In some cases these devices have already been demonstrated.

2.1 The Role of Diamond in Bio-Electronics

Diamond has three roles as a major material in the life science and bio-electronics area.

1. Diamond serves as a macro scaffold or device platform upon which traditional semiconductor or optical devices may be built,
2. Diamond may act as a macro scale device platform upon which nano scale segments of the material are functionalized,
3. Diamond may be grown in the macro-scale with consistent, engineered properties and then be reduced down to the nano scales so that the free standing nano-sized diamond has the engineered properties and orientation of the larger crystal but on the nano-scale.

Complex fabrication techniques normally reserved for semiconductor fabrication such as photolithography and ion-implantation techniques are being used on diamond in order to tailor its properties for specific applications. This means that development of diamond for advanced applications can take advantage of the large body of equipment and processing that have been developed for the silicon based microelectronics industry. Additionally, recent advances in single crystal diamond growth techniques (namely the CVD process) now make high purity, single crystal diamond a material which can be considered alongside other advanced semiconductor materials such as Gallium Arcinide, Gallium Nitride and Silicon Carbide but with full bio compatibility that other semiconductor materials lack.

Each of these single crystal type of diamond are all grown by the CVD process and each plays a different role in the type of Bio-electronic device and its functionality and utility.

2.2 Why is Diamond a Platform of Choice for Bio Electronics?

Single Crystal Diamond has a number of features that individually present the researcher and medical device developer a superior platform for the use of the material. Collectively, diamond offers a series of benefits that are unavailable in any other material.

2.2.1 Bio Compatible Material

Diamond is one of the most stable materials known to man. One of the stellar features of the material is that it does not break down in most chemicals. It remains entirely stable in the body. This is probably the singularly the most important key attribute for a bio-electronics platform.

2.2.2 Toxicology

Since diamond does not break down and remains stable in the body, it is not toxic to the body. Unlike other semiconductor materials that breakdown and subsequently toxify the patient, diamond remains intert and healthy for the body.

2.2.3 Effective bio functionality of diamond

Diamond can be functionalized to attach organic compounds, DNA and proteins. These structures have proven to be robust and stable in hostile environments. The stability of these structure are shown to be more stable that carbon platforms.

2.2.4 Nano-molecular and bio scale information

Recent work focusing on the Nitrogen Vacancy (N-V) Center in diamond have shown that it can be used to enable Molecular resolution imaging of various types of organic and inorganic compounds. These prototype imagers have the possibility of providing us with realtime 'You Tube' video of molecular and nano-scale movements, change, fatigue and interactions of living cells and non-organic devices such as artificial heart valves or artificial joint replacements.

2.2.5 Effective Fabrication Techniques

Device fabrications in diamond are currently similar in resolution and process to early opto-electrical. MEMS structures and etching are possible as well as light emission in certain crystal structures.

2.2.6 Micro Structures

Micro pipes, reservoirs, wave-guides and diving boards can be fabricated on the surface of and inside single crystal diamond with techniques similar to those used with other semiconductor materials. *(see 'Structures Formed in Diamond', US patent 7,122,837 Linares, et al, Oct 17 2006)[3]*

3. A Quick Background of Diamond

3.1 Varieties of Diamond

Diamond is quite possibly the highest utility material known to man. Its relative scarcity in pure varieties however has prevented it from entering the roadmap for high tech applications until recently. Some natural diamond have very good purity levels and crystal features but are generally small and expensive. High temperature / high pressure diamond (developed in the 1950's) is very prevalent with over 1 billion carats produced annually. Unfortunately, High Pressure diamond process limitations require large amounts of nitrogen as well as magnetically active impurities to be used. This creates a highly doped, nitrogen saturated diamond that is limited in both size, and crystal consistency.

3.2 Types of CVD Diamond

Chemical Vapor Deposition (CVD) diamond represents the current state-of-the-art in diamond crystal growth.

This type of process allows large crystals of diamond to be grown with controlled impurities and a high degree of crystal perfection. Diamond can now be grown with the CVD process in a variety of crystal sizes ranging from nano-scale crystals to large single crystals in excess of 25 mm with controlled impurities. In addition, engineered structures can be grown via CVD consisting of nanometer thick layers of diamond having varied dopants levels and/or ^{12}C / ^{13}C.

The following types of process and equipment represent current CVD diamond growth configurations.

Figure 4. CVD Techniques, J.Butler NRL [4]

Poly (nano)-Crystalline Diamond – This is a sheet of diamond which consists of millions of diamond crystals of different orientation bonded together by carbon. The benefits of this type of CVD diamond is that large surface areas can be coated with a coating of diamond crystals. The negatives are that each diamond crystal is oriented in a different crystallographic direction and is bonded to the next crystal with carbon.
Single Crystalline Diamond – These diamond crystals are chemically, physically and optically identical to high quality diamond crystals found in nature. Carbon atoms along the entire crystal structure are all oriented in the same direction. This diamond can be selectively doped and crystal structures are close to flawless. The single crystal diamond may be grown in thin films less than 1 micron or in crystals over 2 mm's thick.

CVD remains the best diamond growth system to grow single crystal diamond of different crystal sizes. Tailored nanometer sized diamond particles for cell sensors may be produced by this method as well as larger single sized pieces of diamond. Furthermore, these crystals can be tailored using the CVD process to engineer the diamond crystals with dopants or selective impurities for electrical, optical, and quantum properties.

Depending on the bio application, one of these two types of CVD diamond will be most appropriate. Nano-crystaline has proven to be a good MEMS platform, and a coating material for hardened bio applications, while single crystal diamond has been shown to have excellent properties for quantum spin states, electrodes, and sensors.

Edited by: **Renata G. Bushko** - bushko@fhti.org
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Figure 5. Top View CVD Single Crystal with HPHT Seed

Note Growth Steps on CVD Material. Shape and size of steps controlled by Chemistry, Substrate Temperature, and presence of impurities

Figure 6. Side View, CVD Single Crystal with HPHT Seed

4. Known Diamond Properties

Diamond excels in a number of properties making it the material of choice for a number of high requirement applications. The needs of bio-electronics applications require a material that not only exists in the body but does things that other materials cant. The tool kit of material attributes make diamond the ideal material for building bio-electronic devices.

4.1 Table of Diamond Properties

Property	Value
Hardness (kg/mm^2)	10,000
Sound Velocity (m/s)	18,00
Density (gm/cm^3)	3.52
Young's Modulus (GPa)	1.22
Coefficient of Friction	0.02
Thermal Expansion (ppm/oK)	1.1
Thermal Conductivity (W/cm- oK)	20
Debye Temperature (oK)	2,200
Optical Index @ 591 nm	2.41
Optical Transparency Range	UV to far IR
Loss Tangent @ 40 Hz	0.0006
Dielectric Constant	5.7
Bandgap Energy (eV)	5.45
Resisitivity (undoped, Ohm-cm)	10^{13}-10^{16}
Chemical Compatibility	Highly Resistant to Corrosion Bio-Compatible

Table 1. Properties of Single Crystal Diamond

5. Useful Features in Diamond (the toolkit)

5.1 Acoustic Waves

Because of its rigidity, Diamond has the distinction of being the best material for the passing of fast, high frequency sound waves. Diamond SAW devices can be operated at gigahertz frequencies and at high power levels. Low levels of signal noise and distortion are possible due to the diamond's stable atomic

structure. Changes in the optical or electrical output signal can be seen when different impurities attach to the surface of the diamond. Diamond is currently being used as a material of choice for high-end audiophile tweeters.

5.2 Light-wave absorption

Diamond in its intrinsic undoped form is fully transmissive to most forms of light and energy frequencies. The doping of diamond however allows the diamond to absorb radiation of varioys frequencies. Absorption cells utilizing total internal reflection can detect very low levels of impurities using a wide range of wavelengths, including, ultraviolet, visible, near infrared, and far infrared.

5.3 Engineered Defect Centers

A vacancy is a point in the atomic structure of the diamond where a carbon atom is missing. This often occurs when an impurity atom such as nitrogen causes a displacement in the carbon lattices shape because of a lattice mismatch caused by the introduction of the non-carbon atom. These vacancy defect centers cause optical, and electrical changes to the diamonds properties. The unique stability of the diamond's structure enables viewing of quantum effects in these vacancy centers at room temperature and for long periods of time. N-V concentrations of 10^{10} to 10^{12}/cc have been achieved in diamond. T2 spin lifetimes in excess of 100ms have been observed in this type of diamond at room temperature.

5.4 Electrical Insulation and Conductivity

In its intrinsic, pure form, diamond is one of the most electrically insulating materials known to man. Once doped with boron, diamond becomes electrically conductive, making an excellent semiconductor. Recent research has shown that heavy boron doping turn diamond into a low temperature superconducting material.

5.5 Light Emission

Light emission has been shown on the 111 crystal orientation of diamond when it is doped with phosphorous. Laser cavities have also successfully be constructed in diamond resulting in a diamond Raman laser amplifier.

5.6 Surface conductivity in diamond

The chemical termination of the diamond surface can be controlled by various chemical treatments of the surface. The two primary surface terminations of interest are hydrogen terminated and oxygen terminated because they represent the extremes of surface properties which can be attained on diamond (Nebel, AIST [5]). Two important properties which can be controlled by controlling the surface termination are the surface energy (wettability) and the electrical conductivity of the surface. The hydrogen terminated diamond surface is electrically conductive and is hydrophobic, while the oxygen terminated surface is electrically insulating and is hydrophilic. In addition, the hydrogen and oxygen terminated surfaces have very different chemical activity and this allows the diamond surface to be

chemically modified/functionalized in a controlled manner. In addition, the surface termination of diamond can be controllably patterned (regions of hydrogen and oxygen termination) using standard semiconductor patterning processes, and the surface termination are very stable under a wide range of chemical and thermal conditions. This makes the diamond surface a unique tool for use in sensing and modifying biological activity.

Diamond Surface Sheet Resistance

Figure 7. Diamond Surface (Sheet) Resistance vs. Oxidation Temperature – as the surface becomes oxygen (vs hydrogen) terminated, the surface conductivity is reduced by more than 7 orders of magnitude (H. Gamo [6])

5.7 Bio Functionalized surfaces

Diamond can be functionalized by a variety of means. The crystalline carbon surface of the diamond can be terminated with oxygen or hydrogen atoms creating a surface to which other compounds can be joined. Hydrogen surfaces create hydrophobic surfaces and oxygen creates hydrophilic surfaces. Once a diamond surface is terminated, the termination is very stable. In addition, the surface termination can be patterned using standard micro-electronic techniques. Once a surface has been terminated in the desired manner, active sites can then be attached which will in turn attract specific organic species.

6. Current Applied Research in Diamond

6.1 Harvard University – Walsworth, Yacoby, Lukin Groups

A collaboration of Harvard University is unlocking some very practical and interesting features of diamond defects called vacancy centers. These vacancy center defects can capture an optically read magnetic spinstate that has many useful functions that could revolutionized a wide variety of fields from quantum computing to drug discovery.

Nano scale magnetic sensing with an individual electronic spin in diamond

"Detection of weak magnetic fields with nanoscale spatial resolution is an outstanding problem in the biological and physical sciences. For example, at a distance of 10 nm, the spin of a single electron produces a magnetic field of about 1 micro Tesla, and the corresponding field from a single proton is a few nano Tesla. A sensor able to detect such magnetic fields with nanometer spatial resolution would enable powerful applications, ranging from the detection of magnetic resonance signals from individual electrons or nuclear spins in complex biological molecules to readout of classical or quantum bits of information encoded in an electron or nuclear spin memory. Here we experimentally demonstrate an approach to such nanoscale magnetic sensing, using

coherent manipulation of an individual electronic spin qubit associated with a nitrogen-vacancy impurity in diamond at room temperature. Using an ultra-pure diamond sample, we achieve detection of 30 nT magnetic fields at kilohertz frequencies after 1s of averaging. In addition, we demonstrate a sensitivity of 0.5 mT/Hz1/2 for a diamond nanocrystal with a diameter of 30 nm. Diamond Nitrogen vacancy spin states in diamond"
Amir Yakoby presentation, Rutgers University, Condensed Matter Seminar, March 10, 2009 [7]

"Harvard's 'diamond' camera', described ..in the journal Nature, consists of a special "flaw" in diamonds that can be manipulated into sensitively monitoring magnetic signals from individual electrons and atomic nuclei placed nearby.
The new work represents a dramatic sharpening of the basic approach used in nuclear magnetic resonance (NMR) and magnetic resonance imaging (MRI), which ascertain chemical structures and image inside human bodies by scanning the magnetic activity of billions of individual nuclei. The new diamond-based magnetic sensor could enable novel forms of imaging, marrying NMR's noninvasive nature with atomic-scale spatial resolution, potentially benefiting fields ranging from materials science, spintronics, and quantum information to structural biology, neuroscience, and biomedicine" Medical News Today, October 2008 [8]
[9] Walsworth, Yakoby, Lukin Groups; Harvard University, Department of Physics

6.2 Waseda University / Kawarada Group

Dr. Kawarada's group from Waseda University in Japan are world leading researchers and pioneers in the area of diamond applications. A number of their current research directions focus on the bio-functionality of diamond and the use of semiconductor device design to create life science solutions in diamond. The Kawarada/Waseda web-site describes a portion of their work as follows:

DNA sensor with diamond surface

"My research topic is the development of DNA sensor to detect the single-nucleotide-polymorphisms (SNPs). The DNA is fabricated by the sequence of four kinds of bases (A, T, G, C) and which codes the synthesis of protein. Generally, the two strands of complementary DNA makes the A-T or G-C pairs in these bases and form the double-helix structure (which is also called Watson-Crick structure). The SNP is the site where the two bases in each DNA strands cannot fabricate the pair such as A and G or C and T etc. The existence of SNP is controlling the controlactability for such diseases and the affectability of some medicine.

The merits of fabricating the sensor with diamond substrate are the high biocompatibility, simply modification on surface and the high stability both in air and in aqueous solution. And the semiconductor devices can be fabricated on the diamond substrate because the hydrogen terminated

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surface natively has the p-type surface conductive layer.

We fabricate the FET-type DNA sensor which operates stably in electrolyte solution to apply these attractive merits of semiconductive diamond surface. The gate surface of diamond FET is directly exposed to the electrolyte solution and the DNA is immobilized on this surface. This FET is operated as the sensor to measure the surface potential on gate surface, while FET generally operates as the "switch" controlling the drain-source current by the applied gate voltage. The surface potential on gate becomes more negative when the single strand DNA (target DNA) is hybridized with immobilized single strand DNA (probe DNA), because DNA is natively negatively charged by the ionization of phosphate groups in it. This surface potential change induces the more holes in the surface conductive layer and the conductivity of gate channel (the conductance between drain and source electrode). The detection of target DNA by the electrolyte solution gate FET is applied to detect the mismatched DNA. ..." *Kawarada Group, Waseda University Japan, Web Site [10]*

7. Summary and Conclusion

Diamond fits the prerequistite requirements for a bio-electronics platform. It is 100% bio-compatible, and has useful semiconducting and optical properties. Additionally, diamond has a device fabrication and modeling tool kit that has been utilized in mass computer-chip production.

These techniques, and the increasing availability of large area, high purity diamond, give researchers and application engineers new ideas on how to extend and radically change healthcare as we currently know it. New studies into understanding the quantum effects of diamonds atomic and nano scale features will lead to a ubiquitous use of diamond in health care and our broader society. Healthcare is on the verge of a sea-change with the ushering in of the Bio-electronics Medicine Era. We expect that diamond will play a leading role in this revolution.

As we see diamond play an increasing leading role in our life's extension, and become ubiquitous in health care in the form of sensors, bio-chips and diamond-nano-bots, our appreciation for diamond will rise to a new level, transforming our view of diamond from "A Diamond is Forever' to " A Diamond Helps Us Live Forever".

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Chapter 34: Maintaining Your Health from Within: Controls for Nanorobot Swarms in Fluids

Tad Hogg, Ph.D.
HP Labs

Abstract

Molecular electronics and nanoscale chemical sensors could enable the construction of microscopic sensors capable of detecting patterns of chemicals as they flow passively in a fluid. Information from a large number of such devices allow the estimation of properties of tiny chemical sources in a macroscopic tissue volume. Although such devices cannot yet be fabricated, estimates of plausible device capabilities in small blood vessels allow the evaluation of their performance for typical chemicals released by tissues in response to localized injury or infection. The devices can readily discriminate a single cell-sized chemical source from the background chemical concentration, providing high resolution sensing in both time and space. By contrast, such a chemical source would be difficult to distinguish from background when diluted throughout the blood volume as obtained with a blood sample. These microscopic, programmable devices could also aid treatments, such as precisely targeting drug delivery and improving speed and accuracy of microsurgery.

1. Introduction

Nanotechnology can potentially revolutionize health care. A current example is the medical uses of nanoparticles, capsules containing drugs or imaging enhancers whose surface chemistry preferentially binds to specific biological targets. More ambitious future developments of the technology should allow for the manufacture of much more complicated devices, particularly programmable machines comparable in size to bacteria and able to sense and modify their environments. Such microscopic robots ("nanorobots") could provide significant medical benefits by operating within the body [1, 2], greatly extending the capabilities of today's much larger ingested or implanted medical devices. These current medical devices include pill-sized cameras to view the digestive tract, as well as implanted glucose and bone growth monitors to aid treatment of diabetes and joint replacements, respectively. Such devices gather information continually over a period of time, in contrast with the more limited monitoring possible with a series of conventional laboratory tests.

Nanorobots would be small enough to move through the tiniest blood vessels. For example, the robots could operate as passively circulating sensors to detect patterns of chemicals. Communicating results to external detectors would allow real-time *in vivo* monitoring of many cells. The robots could also act on their environments, e.g., releasing drugs at locations with specific chemical patterns or mechanically manipulating objects for microsurgery.

Realizing these benefits requires fabricating the robots cheaply and in large numbers. Such fabrication is beyond current technology. Nevertheless, ongoing progress

in engineering nanoscale devices could eventually enable production of such robots. One approach is engineering biological systems, e.g., bacteria executing simple programs [3]. However, biological organisms have limited material properties and computational speed. Instead we focus on machines based on plausible extensions of currently demonstrated molecular-scale electronics, sensors and motors [4, 5, 6, 7, 8, 9] as early versions of components for stronger and faster microscopic robots than is possible with biological organisms. These nonbiological robots contain nanoscale sensors and electronics within a protective, biocompatible shell. Of particular interest are biomedical applications requiring only modest hardware capabilities, as those applications will likely be among the first uses of the technology as it develops. Understanding the behaviors of such "first generation" nanorobots will identify design tradeoffs among hardware capabilities, control methods and task performance.

A major challenge for nanorobots arises from the physics of their microenvironments and the hardware limitations of the robots, which differ considerably from experience with today's larger robots. For example, the physical environment will often consist of cells in fluids dominated by viscous forces. Second, thermal noise is a significant source of sensor error and Brownian motion limits the ability to follow precisely specified paths. Third, relevant objects are often recognizable via chemical signatures rather than visual markings or shape. Fourth, the tasks involve large numbers of robots, each with limited abilities. Moreover, a task will generally only require a modest fraction of the robots to respond appropriately, not for all, or even most, robots to do so. This observation contrasts with teams of larger robots with relatively few members, such as robot soccer or surveillance: incorrect behavior by even a single robot can significantly decrease team performance.

To illustrate the potential of microscopic robots for medicine, this paper describes plausible robot capabilities from early nanotechnology based on extrapolations from current laboratory demonstrations of nanoscale devices. The physical properties of task environments are then discussed in the context of a prototypical diagnostic task of finding a small chemical source in a multicellular organism via the circulatory system. Theoretical studies suggest these robots can give significantly better performance than current medical technology, not only for diagnostics but also for interventions such as drug delivery and aiding microsurgery. Thus we can expect benefits from even relatively early developments of nanotechnology, which will in turn pave the way for more significant applications as the technology matures.

2. Capabilities of Microscopic Robots

Minimal robot capabilities needed for biomedical tasks include chemical sensing, computation and power. Additional capabilities, enabling more sophisticated applications, include abilities to stick to specific cell surfaces, to communicate and to move.

2.1 Sensing

Large-scale robots often use sonar or cameras to sense their environment. These sensors locate objects from a distance, and involve sophisticated interpretation algorithms. In contrast, microscopic robots for biological applications will mainly use chemical sensors, e.g., the selective binding of molecules to receptors altering the electrical characteristics of nanoscale wires.

Microscopic robots and bacteria face similar physical constraints in detecting chemicals [10]. For example, diffusion of the chemicals and Brownian motion of the sensors make it difficult to determine the direction of a chemical source directly. Nevertheless, random motion modulated by the detected concentration can allow for the tracking of chemical gradients to their sources. Current molecular electronics [9] and nanoscale sensors [11, 12, 13] indicate that even today's sensors are effective at detecting concentrations well below those of many chemicals in the body that may prove medically interesting.

In addition to chemical sensing, robots could sense other properties of their environment, such as, measuring fluid flow rates at speeds relevant for biomedical tasks [14], allowing robots to examine microfluidic behavior in small vessels. Since boundaries significantly alter fluid behavior far into the vessel [15], several such sensors, extending a small distance from the robot surface in various directions, could detect changes in the vessel geometry. Such estimates of local geometry might, for example, help distinguish normal vessels from leaky new vessels formed within tumors.

2.2 Communication

Several forms of communication could be useful for nanorobots. The simplest form of communication is receiving electromagnetic or acoustic signals broadcast from outside the body. Such signals could activate robots only within certain areas of the body, perhaps within centimeter length scales.

Mutual communication between nearby robots and detectors outside the body require more difficult fabrication and increase robot power use compared to robots that just receive broadcast signals, but such communication abilities increase the range of tasks for the robots. For instance, acoustic communication among nearby robots (e.g., within about 100^{1}m of each other [1]) allows for coordination of their activities.

For limited communication with the attending physician, the robots could carry nanoscale structures with high response to some external signals. Such structures could respond to light of particular wavelengths when near the skin, or give enhanced imaging via MRI or ultrasound. Such visualization mechanisms, combined with a selective ability to stick to vessel walls, allows for the detection of aggregations of devices at specified locations near the surface of the body. This visualization technique could be useful even if the tissue volume of interest is too deep to image effectively at high resolution. In particular, robots could use various

areas near the skin (e.g., marked with various light or ultrasound frequencies) at centimeter scales as readout regions during operation. For example, robots that have detected certain chemicals could aggregate at the corresponding readout location, which would then be visible externally. Robots could choose how long to remain at the aggregation points based on how high a concentration of the chemical pattern they detected. Robots with local communication capabilities could compare observations while in these aggregation regions, allowing further computation to influence the communicated result, e.g., by changing how long the devices remain at the readout location or whether they aggregate in other locations at a later time. This indication of whether, and (at a coarse level) what, the devices have found could help decide how long to continue treatment. These aggregation points could also be used to signal to the devices, e.g., instructing them to switch to another preprogrammed mode of operation.

2.3 Locomotion

Biomedical applications will typically involve robots operating in fluids. A key physical property is the ratio of inertial to viscous forces for an object moving in fluid, which depends on the size and speed of the object. This ratio is called the Reynolds number. Using typical values for density and viscosity (e.g., of water or blood plasma) and noting that reasonable speeds for robots with respect to the fluid [1] are comparable to the fluid flow speed in small vessels, i.e., ≈1mm/s, motion of a 1-micron robot has Reynolds number of about 10^{-3}. Thus, viscosity dominates the robot motion, giving smooth flow with different physical behaviors than those of larger organisms and robots [16, 17, 15]. For instance, robots applying a locomotive force quickly reach terminal velocity in the fluid, i.e., applied force is proportional to velocity rather than the more familiar proportionality to acceleration of Newton's law $F = ma$. By contrast, a swimming person has Reynolds number about a billion times larger, and viscous forces are minor.

Another physical effect, Brownian motion, randomly changes location and orientation of microscopic robots, thereby limiting the time over which they can reliably compare different locations or directions. This behavior contrasts with long range path planning with maps of the environment often used for larger robots.

2.4 Power

Robots require power. To quantify power requirements of microscopic robots, moving through the fluid at 1mm=s dissipates about a picowatt [18] to overcome fluid drag and the inefficiencies of locomotion. Communication could use power of a similar order of magnitude. For comparison, a typical person at rest uses about 100 watts. For tasks of limited duration, onboard fuel created during robot fabrication could suffice. Otherwise, the robots could use energy available in their environment, such as converting externally generated vibrations to electrical energy [19] or chemical generators, e.g., a fuel cell using glucose and

oxygen in the bloodstream [1].

3. Tasks for Microscopic Robots

This section describes some task scenarios enabled by the robot capabilities described above.

A prototypical task is responding to chemical signals, e.g., released in the blood by tissue injury [20] or monitoring chemical behaviors within individual cells [21, 22]. The robots may detect signals and initiate response more rapidly than natural mechanisms (e.g., immune cells). They could also identify the signal's cause (e.g., a type of infecting bacteria) and, unlike cells, communicate that information to an attending physician [1], providing earlier and more accurate diagnosis. As an example, Fig. 1 illustrates the environment of robots operating in small blood vessels. The number of robots involved in the task determines the time required for each vessel to have likely had at least one robot pass through it. For example, a person has several billion capillaries and circulation takes about a minute to complete a transit through the body. For high resolution diagnosis involving low concentration chemicals released into a few tiny vessels, using about a billion robots would give several opportunities for passing robots to detect the chemical during operation time of about an hour. Using multiple detections is important for reducing false positives due to sensor errors and a low background concentration of the chemical in the bloodstream [23]. A billion robots is considerably more than are used today with teams of larger robots, e.g., for robot soccer. However, such large numbers should be manufacturable as nanotechnology develops, just as today's semiconductor fabs routinely produce chips with about that many transistors. As a point of comparison, a billion of the microscopic robots discussed here would have a total mass of only a few milligrams and a total volume of a few cubic millimeters. This volume of robots is about a millionth of a person's total blood volume.

3.1 Diagnosis

The robots could detect localized high concentrations that become too low to distinguish from background concentrations when diluted in the whole blood volume as obtained with a sample for laboratory analysis. Moreover, if the detection consists of the joint expression of several chemicals, each of which also occurs from separate sources, the robot could identify the spatial locality, which would not be apparent when the chemicals are mixed throughout the blood volume. Similarly if the chemical is released in bursts, sensors nearby during a burst would encounter much higher local concentrations than the time averaged concentration. Furthermore, by recording events over time (e.g., minutes to days), the sensors could collect information on changes (e.g., in response to an external stimulus such as introduction of a drug) that would be impractical to obtain from repeated blood samples. By collecting enough measurements, the robots could distinguish between a strong source and many weak sources producing the chemical at the same total rate. The strong source would

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give high count rates for a few robots (those passing near the source) while multiple weak sources would have some detection in a larger fraction of the robots. Thus robots could not only determine whether sources of a specified pattern of chemicals exist, but also provide information about their structure.

Fig. 2 illustrates the problem of distinguishing a single source from two, nearby weaker sources. The combined chemical production from the two weaker sources is the same as of the single stronger source. In this example, fluid flows through branching vessels passing near the source(s). The chemical from the source(s), taken to have a diffusion coefficient of a small protein, diffuses to the nearby vessels and into the moving fluid within them. The chemical moves downstream through the vessels as it continues to diffuse in the fluid. The concentration patterns in the two cases are similar, with only slightly more variation along the vessel with two sources compared to the single one. At low concentrations typical of chemicals released into the blood in response to initial stages of infection or minor injury [24], the robots would typically encounter only a few dozen molecules of the chemical with their sensors. Thus, observations from multiple robots passing through these vessels are needed to reliably determine number and strengths of the sources. This example illustrates a benefit of a swarm approach to diagnosis: a combination of observations from multiple robots in nearby vessels to improve diagnostic accuracy. Robots with other types of sensors could provide additional information about the sources. For example, fluid flow sensors would allow for correlation of chemical detections with properties of the flow and the vessel geometry (e.g., branching and changes in vessel size or permeability to fluids). The robots could also detect some properties of cells outside but near the small blood vessels, such as electrical activity of nearby nerve cells [25].

The information retrieved from the robots could be analyzed in a conventional computer with far more computational resources than available to any individual microscopic robot. This computer would have access to information from many robots, allowing evaluation of aggregate properties of the population of cells that individual robots would not have access to, e.g., the number of cells presenting a specific combination of chemicals. This combined information allows for the estimation of spatial structure and strength of the chemical sources, in analogy with reconstructing tissue structure from a series of X-rays at various angles as used with computer-aided tomography (CAT) scans.

3.2 Modifying Microenvironments

Chemical sensing, as used for the diagnosis task, forms the basis for more complex tasks. Specifically, robots able to locate chemically distinctive microenvironments in the body could modify those environments.

For example, the robots could carry specific drugs to deliver only to cells matching a prespecified chemical profile [1, 26]. Robots could achieve this aggregation if they can alter their

surface properties to stick to the vessel wall or through active locomotion to follow the chemical gradient to the source. This aggregation process is another opportunity to benefit from the coordinated behavior of several robots. In particular, fluid flow moves the chemical downstream of the source so robots will tend to detect the chemical only after they have already passed the source. Attempting to follow the chemical gradient to the source would then require considerable power use to move a bit upstream against the flow. A cooperative approach can be more effective; instead of the robot that detects the chemical then moving upstream to the source, it can emit an acoustic signal to other robots further upstream in the vessel. Such robots, notified of the detection, can then move to the vessel wall and approach the source with, rather than against, the fluid flow [23].

As another application, robots aggregated at chemically identified targets could perform precise microsurgery at the scale of individual cells. Since biological processes often involve activities at molecular, cell, tissue and organ levels, such microsurgery could complement conventional surgery at larger scales. For instance, a few millimeter-scale manipulators, built from micromachine (MEMS) technology, and a population of microscopic devices could act simultaneously at tissue and cellular size scales. An example involving microsurgery for nerve repair with plausible biophysical parameters indicates the potential for significant improvement in both speed and accuracy compared to the larger-scale machines acting alone [27, 28]. Such detailed manipulations extend current efforts [29] to simultaneous actions on many cells with behavior determined according to a program computed within the devices in response to local environmental conditions.

The robots could monitor environmental changes due to their actions, thereby documenting the progress of the treatment in far greater detail than is possible today. With external communication, the treating physician could monitor the robots' progress and decide whether and when they should continue to the next step of the procedure. Using a series of steps, with robots continuing with the next step only when instructed by the supervising person, maintains active human control of the robots.

4 Evaluating Robot Behaviors

Because it is not yet possible to fabricate nanorobots, studies of their behavior must rely on theory and simulations. As technology develops to fabricate early versions of the robots, simple experiments with them will help validate the simulations. This section describes some of these evaluation possibilities.

4.1 Theoretical Studies

A variety of theoretical approaches allow estimating the task performance of nanorobots with the capabilities described in this paper. The simplest approach relies on estimates of individual capabilities to indicate the plausible range of tasks the robots could perform [1]. More detailed studies consider the combination of robot capabilities and the physical

properties of the task environment. One such theoretical approach estimates typical behavior of the robots using a statistical approximation [30]. This method has been applied successfully to teams of small numbers of large robots. Microscopic robots, with limited computational capabilities, will likely use simple controls, with minimal dependencies on events in individual robot histories, for which this statistical approximation is ideally suited. The approach can also readily incorporate spatial variations such as fluid speeds and chemical concentrations [31] relevant for nanorobot tasks. Simulations of groups of robots provide a more detailed look at their behaviors. These simulations can include various levels of detail, giving a tradeoff between physical accuracy and computation required to simulate large numbers of robots over relevant time scales. Such simulations can readily include individual robot histories and correlations in behavior that are not easily treated with the statistical approximation discussed in the previous paragraph.

Theoretical studies identifying tradeoffs among control complexity and hardware capabilities can aid future fabrication. Specifically, control can compensate for limited hardware (e.g., sensor errors or power limitations), providing design freedom to simplify the hardware through additional control programs. Thus the studies can help determine minimum hardware performance capabilities needed to provide robust systems-level behavior.

One challenge for theoretical studies is the poorly characterized physical parameters of the microenvironments the robots will operate in. In a bootstrapping process, early nanorobots, with limited capabilities, could help quantify these properties, thereby leading to more accurate behavior models and improved robot designs. Thus much remains to be done in developing detailed theoretical evaluation of nanorobots. Nevertheless, current studies suggest robots, even with limited capabilities of early nanotechnology fabrication, should give improved diagnosis and treatment, both in speed and spatial resolution. For example, they could rapidly aggregate at cell-sized chemically distinctive locations or aid larger machines with microsurgery. The precision of localization and the robots' programmability gives them a degree of flexibility to alter microenvironments, e.g., by releasing drugs, well beyond that possible with either large scale surgery or nonprogrammable chemically-targeted drug delivery with nanoparticles. The full range of biomedical situations that could benefit from this flexibility, e.g., nerve repair [28], remains to be seen.

4.2 Validation Experiments

As technology advances to constructing early versions of microscopic robots, experimental evaluations will supplement theoretical studies.

One such experiment is embedding the devices in bacterial biofilms to monitor chemical signals exchanged among the bacteria. In this case, the robots could be fabricated on a surface and the film grown over

them, greatly simplifying constructing the robots. The surface could provide power and communication during operation. This experiment would test the ability of the chemical sensors and the onboard computation to detect patterns of chemical activity, as well as the durability of the robots. Another early validation experiment is operating the robots in manufactured microfluidic channels [15]. This would test the robots' ability for independent operation without direct connections to external devices for power or communication. Such studies would allow testing the robots' ability to infer properties of their microenvironments, such as vessel branching, based on fluid flow nanoscale sensors, and calibrating the chemical sensors with known concentrations introduced in the fluid. The robots could also demonstrate the ability to aggregate at chemically defined locations. After such *in vitro* experiments, early *in vivo* tests could involve robots acting as passive sensors in the circulatory system. The chemical patterns found would quantify properties of microenvironments in the body. Such nanorobots will be useful not only as diagnostic tools and sophisticated extensions to drug delivery capabilities [32], but also as an aid to develop robot designs and control methods for more active tasks. These free-floating devices could extend current capabilities based on sensors tethered to nanowires introduced through the circulatory system [25].

5. Discussion

The nanorobot capabilities and tasks described in this paper highlight key control principles for microscopic robots. By performing the task in stages, the person deploying the robots remains in the decision loop, especially for the key decision of whether to proceed with treatment (e.g., release a drug) based on diagnostic information reported by the robots. Information retrieved during treatment can also indicate how well the procedure is working and provide high-resolution documentation of what was done, thereby helping improve future treatments. More generally, this control approach illustrates an important technique for using microscopic robots: local, distributed control to achieve robust responsive behaviors on small scales in space and time, combined with feedback from a slower, larger central control (e.g., a person) to verify performance and consider global constraints using information from many devices.

Safety is important for medical applications of microscopic robots. Thus, evaluating a task protocol should consider its accuracy allowing for errors, failures of individual devices or variations in environmental parameters. For the tasks discussed in this paper, statistical aggregation of many robots' measurements provides robustness against these variations; a technique recently illustrated using DNA computing to respond to patterns of chemicals [33]. Furthermore, the devices must be compatible with their biological environment [34, 35] for enough time to complete their task. Appropriately engin surface coatings and structures should prevent

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unwanted inflammation or immune system reactions during robot operation [34, 36].

Despite the simplifications used to model nanorobot behavior in current studies, the estimates with plausible biophysical parameters show even relatively modest molecular hardware could provide useful *in vivo* sensing and manipulation capabilities [1, 28, 20]. These capabilities give far more rapid, flexible and specific performance than is possible with today's larger devices. While engineering challenges for manufacturing these robots preclude definite estimates of when they might be available, quantifying their benefits compared to existing technology can guide and motivate investment in their development. Moreover, early versions of microscopic robots will enable detailed quantitative research studies of tissue microenvironments well before the robots are ready for clinical use. The improved understanding will, in turn, identify tasks for more capable robots and appropriate tradeoffs between size and capability for hybrid systems combining coarse centralized control with the flexibility of cell-sized robots in biological microenvironments.

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Figures and Captions

Figure 1: Schematic interior view of a small blood vessel with red blood cells (≈7μm diameter) and a bacteria-sized robot (small cylinder near the wall at upper left). The cells occupy about 1/5-th of the vessel volume, a typical case for small blood vessels.

Figure 2: Example of chemical concentration in branching vessels near one or two cell-sized sources (indicated by the ovals between the branching vessels). Chemical concentration in the fluid ranges from 0 (black) to a maximum 3 nanomolar solution (white). Fluid flows from left to right, with average speed of a millimeter per second, a typical speed in small blood vessels. The width of the figure corresponds to 100 microns.

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Ray Kurzweil and Terry Grossman/ Fantastic Voyage: Live Long Enough to Live Forever - The Science Behind Radical Life Extension Questions and Answers in "World Health Strategy" eBook, (Ed.) Renata G. Bushko, FHTI, 2016. Futureofhealth.org From Strategy for the Future of Health (Ed.) Renata G. Bushko, IOS Press 2009

Chapter 35: Fantastic Voyage: Live Long Enough to Live Forever The Science Behind Radical Life Extension Questions and Answers

Ray Kurzweil
Inventor and Author
and
Terry Grossman, M.D.,
Medical Director, Frontier Medical Institute

Abstract

Putting an end to human aging is now becoming a reality, and immortality is no longer just a dream. Through what we are calling "Fantastic Voyage," we provide a guide to achieving life extension through various means, thereby slowing down aging and disease processes.

The three components of Fantastic Voyage are: **Bridge One** - Aggressively applying today's knowledge. **Bridge Two** - Putting biotechnology, such as gene technologies, to use with therapeutic cloning and rejuvenation medicine. **Bridge Three** - Putting nanotechnology to use by developing a means to rebuild our bodies and brains with nanobots.

Many of these technology solutions can be simulated today through the use of targeted supplements, designed to address the specific needs of an individual, such as insulin resistance, cholesterol and homocysteine levels, and inflammation.

To slow aging now, we propose a program of supplementing aggressively, eating foods that impede aging and disease processes, and reversing inflammation through diet. We also provide guidance to customize each program to the specific needs of the individual.

Emerging technologies in rational drug design, tissue engineering, gene therapy, and nanobots (among others) promise a future of automated life extension. The use of such technologies, and the resulting dramatic increases in productivity in all areas of human endeavor, will enable us to live in a world in which all our physical needs can be met.

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1. What's the key message?

We make the scientific case that immortality is within our grasp. We explain how to slow down aging and disease processes to such a degree that you can remain in good health until the more radical life-extending and life-enhancing technologies – now in the research and testing pipeline – become available.

2. What sort of life-extending technology are you referring to?

Fantastic Voyage is a guide for aggressively applying today's knowledge – we call it Bridge One – to enable you to live long enough to take advantage of the full development of the biotechnology revolution – Bridge Two.

3. What are some examples of this?

Biotechnology is providing the means to actually change your genes: not just designer babies but designer baby boomers. We'll also be able to rejuvenate all of your body's tissues

and organs by transforming your skin cells into youthful versions of every other cell type. Already, new drug development is precisely targeting key steps in the process of atherosclerosis (the cause of heart disease), cancerous tumor formation, and the metabolic processes underlying each major disease and aging process. The biotechnology revolution is already in its early stages and will reach its peak in the second decade of this century.

4. And this will bring radical life extension?
Well, biotech is Bridge Two, which, in turn, will allow you to reap the benefits of the nanotechnology-AI (artificial intelligence) revolution – Bridge Three – which does have the potential to allow you to live indefinitely. With nanotechnology, we can go beyond the limits of biology, and replace your current "human body version 1.0" with a dramatically upgraded version 2.0, providing radical life extension.

5. And how does that work?
The "killer app" of nanotechnology is "nanobots," which are blood-cell sized robots that can travel in the blood stream destroying pathogens, removing debris, correcting DNA errors, and reversing aging processes. The nanotechnology revolution will reach its peak in during the 2020s.

6. Haven't there been promises in the past along these lines?
Until recently, there was relatively little that could be done about our short life span, other than to rationalize this tragedy as "a good thing." But that is now changing. We have devised a new program that enables even older baby boomers like ourselves to live long enough to live forever by aggressively reprogramming our biochemistry to forestall aging and disease processes.

7. Where is this ultimately going to take us?
Within a quarter century, nonbiological intelligence will match the range and subtlety of human intelligence. It will then soar past it because of the continuing acceleration of information-BASED technologies, as well as the ability of machines to instantly share their knowledge. Intelligent nanorobots will be deeply integrated in our bodies, our brains, and our environment, providing vastly extended longevity, full-immersion virtual reality incorporating all of the senses (like the "Matrix"), "experience beaming" (like "Being John Malkovich"), and vastly enhanced human intelligence. The result will be an intimate merger between the technology-creating species and the technological evolutionary process it spawned.

8. How do I slow down aging now?

- The most unique aspect of our program is to supplement aggressively. Our bodies evolved in a different era when short life spans were in the interest of the species, thereby freeing up scarce resources for the young and those caring for them. So we need to reprogram our biochemistry to change the ancient programs in our genes. We provide a detailed guide to which supplements will

contribute to your health and slow down aging based on your particular health situation.

- Eat foods that slow down aging and disease processes. For example, sugars and simple starches increase insulin resistance, a key source of aging, so we recommend a low "glycemic index" diet. Sugar and starch also promote what's aptly called AGEs (advanced glycation end-products), which are damaging cross links that form between the body's proteins.

- Chronic inflammation underlies every step in heart disease, and promotes all major degenerative diseases, but you can reverse inflammation with anti-inflammatory foods. For example, it's important to emphasize the anti-inflammatory fats found in such foods as fish, nuts, and extra virgin olive oil.

- Each of us is different, so we provide guidance on how to customize your program based on test results, including genomic tests. We also provide guidance on exercise and stress management.

This sounds complicated.

Fantastic Voyage is not a one-trick pony. Many popular health books provide a single key idea. But our bodies are complex, and no one message captures the key to slowing down aging. There are a dozen important aging and diseases processes, and we provide programs to address each one. So we don't give you menu plans and schedules. Rather, by truly understanding how your body works, you can set your own priorities, and devise your own customized program.

9. Can we really forestall diseases like heart disease and cancer?

The leading causes of death – heart disease, cancer, stroke, respiratory disease, kidney disease, liver disease, and diabetes – do not appear out of the blue. You don't catch them walking down the street one day. They are the end result of processes that are decades in the making. We help you understand how longstanding imbalances in the metabolic processes underlying life functions can lead to disease.

Conventional medical care is geared toward dealing with long-term degenerative processes only after they erupt into advanced clinical disease. But by this time it is often too late. It's like approaching a cliff, but walking backward. You need to recognize that you're getting closer to the edge and stop. Once you fall off, it's difficult to do anything about it. That's what *Fantastic Voyage* is all about: to provide the knowledge and the specific steps to take, sooner rather than later, to extend your life, your vitality, and your well-being.

10. Why are you delivering this message now?

Technical progress progresses exponentially, and we're just now reaching the rapid part of the curve. Our paradigm shift rate – the

rate of technical progress – is doubling every decade. The capability of specific technologies such as genetic sequencing and nanotechnology is doubling even faster: every year. These emerging transformations in technology will usher in powerful new tools to expand your health and human powers. Eventually, the knowledge represented in *Fantastic Voyage* will be automated within you. Today, however, you have to apply that knowledge yourself.

11. Give me a surprising idea to slow down aging.

Supplement with phosphatidylcholine (PtC), a fatty substance that is a major component of cell membranes. As you age, the PtC in your cell membranes diminishes dramatically, and is replaced with hard fats and cholesterol. This is one important reason that an elderly person's skin is less supple, and organs less effective. Supplementing with PtC can stop and even reverse this process.

12. What's another one?

The prescription drug metformin can significantly reduce the effects of insulin resistance. One adult in three has what's called the "metabolic syndrome," also known as "Syndrome X," which results in a serious inability to process sugar and refined carbohydrate foods like pasta and bread. Most people who have this are not even aware of it. Moreover, almost all adults develop some level of insulin resistance as they age, which is a major contributor to heart disease, stroke, and other diseases. Metformin combats this aging process. In animal tests, metformin (and an earlier version of this drug called phenformin) extended life spans, and produced similar metabolic changes as caloric restriction, even though the animals were not eating less.

13. So how have you guys done in the aging department?

Ray: My father's premature death at age 58 from heart disease and my own diagnosis of type II diabetes at the age of 35 defined my early health concerns. The conventional medical treatment made my diabetes worse and did little to alleviate my concern about a genetic predisposition to heart disease. As an inventor, I studied the literature, devised my own program, overcame my diabetes, and wrote a best-selling health book about the experience. More recently, I have become aware of a more insidious challenge: middle age. Working with Terry over the past five years, we applied the same belief in the power of ideas to the problem of aging.

I take 250 supplements a day and really feel that I'm reprogramming my biochemistry, just like I would reprogram my computers.

I'm 56 chronologically, but my biological age, according to an extensive set of tests, is about 40, not much changed from 16 years ago. In many ways, I'm healthier and younger than I was 20 years ago. I have no indications of diabetes. My glucose, HgA1c (a test of glucose levels over the past 90 days), cholesterol, homocysteine (test of methylation processes), C-reactive protein (test of

inflammation levels), and other test levels are all at ideal levels. My overall feeling: so far, so good. Terry: It is said that among the things you can do to enjoy a long and healthy life, it is best to start by "picking your parents wisely." I am fortunate that both are alive and well at 80 years of age. They are physically and mentally active and enjoy a varied social and cultural life. So it would appear that I started life with "a leg up" on longevity, thanks to their genes. Things aren't always so straightforward in medicine, however. My genomic testing revealed that I harbor several harmful genetic tendencies. Although I have enjoyed excellent health so far, I am now at the stage of my life where one's genetic predispositions have a way of manifesting themselves as "full blown" diseases. But with the genetic information I now possess, I've been able to take specific measures to maintain my health, using the best of the Bridge One ideas we present in Fantastic Voyage. I am very optimistic about what the future Bridge Two and Bridge Three therapies will be able to do for both myself and the rest of humankind.

14. Isn't it natural to age?

It may be "natural," but we don't see anything positive in losing our mental agility, sensory acuity, physical limberness, sexual desire, or any other human ability. We view disease and death at any age as a calamity, as problems to be overcome. Until recently, there was relatively little that could be done about our short life span other than to rationalize this tragedy as a good thing. We now have another option.

15. Your book promises the end of aging, not just slowing it down. Is that realistic?

We are in the early stages of multiple profound revolutions spawned by the intersection of biology, information science, and nanotechnology. With the decoding of the genome and our efforts to understand its expression in proteins, many new and powerful technologies are emerging. These include rational drug design (drugs designed for very precise missions, with little or no side effects), tissue engineering (regrowing our cells, tissues, and organs), reversal of aging processes, gene therapy (essentially reprogramming our genetic code), nanobots (robots the size of blood cells built from molecules placed in our bodies and bloodstreams to enhance every aspect of our lives), and many others.

16. Isn't it a bit of hyperbole to say you can live forever?

Consider the metaphor of maintaining a house. How long does a house last? The answer obviously depends on how well you take care of it. If you do nothing, the roof will spring a leak before long, water and the elements will invade, and eventually the house will disintegrate. But if you proactively take care of the structure, repair all damage, confront all dangers, and rebuild or renovate parts from time to time using new materials and technologies, the life of the house can essentially be extended without limit.

The same holds true for our bodies and brains. The only difference: while we fully understand the methods underlying the maintenance of a house, we do not yet fully understand all of the biological principles of life. But with our rapidly increasing comprehension of the biochemical processes and pathways of biology, we are quickly gaining that knowledge. We are beginning to understand aging, not as a single inexorable progression, but as a group of related biological processes. Strategies are emerging for fully reversing each of these aging progressions, using different combinations of biotechnology techniques. In the meantime, we can slow each aging process to a crawl, using the methods outlined in this book.

Many experts, including the authors, believe that within a decade we will be adding more than a year to human life expectancy every year. At that point, with each passing year, your remaining life expectancy will move further into the future.

17. Aren't the designs of nature optimal?

Biological systems are remarkable in their cleverness. In the 15th century, Leonardo da Vinci wrote, "Human ingenuity may make various inventions, but it will never devise any inventions more beautiful, nor more simple, nor more to the purpose than nature does; because in her inventions nothing is wanting and nothing is superfluous." We share da Vinci's sense of awe at the designs of biology, but we do not agree with him on our inability to improve on nature. Da Vinci was not aware of either biotechnology or nanotechnology, and it turns out that nature, for all its apparent creativity, is dramatically suboptimal.

18. Tell me more about bridge two: biotechnology.

As we are learning about the information processes underlying biology, we are devising ways of mastering them to overcome disease and aging and extend human potential. One powerful approach is to start with biology's information backbone: the genome. With gene technologies, we're now on the verge of being able to control how genes express themselves. We now have a powerful new tool called RNA interference (RNAi), which is capable of turning specific genes off. It blocks the messenger RNA of specific genes preventing them from creating proteins. Since viral diseases, cancer, and many other diseases use gene expression at some crucial point in their life cycle, this promises to be a breakthrough technology. Ultimately, we will actually be able to add new genes by "infecting" our cells with specially designed viruses that insert new genes in our genome in just the right place.

Another important line of attack is to regrow our own cells, tissues, and even whole organs, and introduce them into our bodies without surgery. One major benefit of this "therapeutic cloning" technique is that we will be able to create these new tissues and organs from versions of our cells that have also been made younger – the emerging field of rejuvenation medicine. For example, we will be able to create new heart cells from your skin cells and introduce them into your

system through the blood stream. Over time, your heart cells get replaced with these new cells, and the result is a rejuvenated "young" heart with your own DNA.

Drug discovery was once a matter of finding substances that produced some beneficial effect without excessive side effects. This process was similar to early humans' tool discovery, which was limited to simply finding rocks and natural implements that could be used for helpful purposes. We are learning the precise biochemical pathways that underlie both disease and aging processes, and are able to design drugs to carry out precise missions at the molecular level. The scope and scale of these efforts is vast.

19. And Bridge Three?

As we peer a couple of decades into the future, nanotechnology will enable us to rebuild and extend our bodies and brains and create virtually any product from mere information and inexpensive raw materials, resulting in remarkable gains in prosperity. We will develop means to vastly expand our physical and mental capabilities by directly interfacing our biological systems with human-created technology.

As one example, the interneuronal connections in our brains compute at only 200 transactions per second, millions of times slower than even today's electronic circuits. Circa late 2020s, billions of nanobots traveling in the capillaries of the brain will interact directly with our biological neurons providing a vast expansion of human intellect. They can also provide full immersion virtual reality from inside the nervous system by shutting down the signals from our "real" senses and replacing them with the signals that are appropriate for a virtual environment.

Another example is our red blood cells. Despite the elegant way our red blood cells carry oxygen in our bloodstream and deliver it to our tissues, it is a very slow and cumbersome system. There's a design for such robotic red blood cells called "respirocytes" by Rob Freitas, a nanotechnology expert, which are thousands of times more efficient than biological red blood cells. Analyses show that with these respirocytes, you could sit at the bottom your pool for four hours without taking a breath.

There is another Freitas design that will be able to augment your immune system, basically robotic white bloods. It will have the capability to destroy any virus, cancer cell, or other invader hundreds of times faster than our biological immune system. We've actually watched our own white blood cells destroy a bacterium through a microscope. Although our white blood cells are clever, they are very slow, the process of killing a germ takes over an hour. The robotic versions will do a more thorough job in seconds. They will be able to download software from the Internet to combat specific types of pathogens. If that sounds particularly futuristic, we'd point out that we already have brain implants, such as the FDA approved neural implant for Parkinson's Disease, that can download new software from outside the patient.

The reality is that biology will never be able to match what we will be capable of engineering, now that we are gaining a deep understanding of biology's principles of operation.

20. What about government opposition to new technologies such as stem cell therapy? Is that going to hold things up?

These obstacles end up being stones in the river of progress; the broad progression of technology just flows around them. Stem cell research is a good example of this. The research has continued despite opposition from the government and elsewhere. And the controversy has only served to accelerate other ways of accomplishing the same thing, which ultimately will provide superior approaches. For example, there has been substantial recent progress on transdifferentiation: turning one type of cell, such as a skin cell, into another type. After all, what's the difference between a skin cell and a pancreatic Islet cell, or a heart cell? They all have the same genes. The difference is that different genes are expressed, and we're learning the molecular triggers that control gene expression. By adding certain chemicals such as peptides and short RNA molecules to cells, we can transform their cell type. This has already been demonstrated. If you want new heart cells, creating them from your own cells has important advantages: you'll have an inexhaustible supply of them, and these new cells will have your DNA, thereby avoiding an immune system response.

In general, opposition to technology tends to focus narrowly on very specific techniques. The flow of progress in biotechnology, nanotechnology, and other new methodologies is so broad and diverse that these types of controversies do not significantly affect the overall rate of advance.

21. If people stop dying, isn't that going to lead to overpopulation?

A common mistake that people make when considering the future is to envision a major change to today's world, such as radical life extension, as if nothing else were going to change. The three intertwined revolutions of biotechnology, nanotechnology, and "strong AI" (artificial intelligence at human levels and beyond) will result in other transformations that address this issue. For example, nanotechnology will enable us to create virtually any physical product from information and very inexpensive raw materials, leading to radical wealth creation. We'll have the means to meet the material needs of any conceivable size population of biological humans. Nanotechnology will also provide the means of cleaning up environmental damage from earlier stages of industrialization. In recent years, gains in prosperity have resulted in declines in population growth, although a dramatic drop in the death rate will reverse that to some extent. But dramatic increases in productivity will enable us to provide for all of our physical needs.

22. Won't it get boring to live many hundreds of years?

If humans lived many hundreds of years with no other change in the nature of human life, then, yes, that would lead to a deep ennui. But the same nanobots (robots the size of blood cells) in the bloodstream that keep us healthy (by destroying pathogens and reversing aging processes) will also vastly augment our intelligence and experiences. By traveling noninvasively into the capillaries of the brain, these nanobots will interact directly with our biological neurons to create full-immersion virtual reality experiences from within the nervous system, and provide intimate connection to greatly enhanced intelligence. We won't be bored.

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Chapter 36: What are Similarities and Differences between the Singularity and Methuselarity?

Aubrey D.N.J. de Grey, Ph.D.
aubrey@sens.org
Methuselah Foundation

Abstract

Aging, being a composite of innumerable types of molecular and cellular decay, will be defeated incrementally. I have for some time predicted that this succession of advances will feature a threshold, which I here christen the "Methuselarity," following which there will actually be a progressive decline in the rate of improvement in our anti-aging technology that is required to prevent a rise in our risk of death from age-related causes as we become chronologically older. Various commentators have observed the similarity of this prediction to that made by Good, Vinge, Kurzweil and others concerning technology in general (and, in particular, computer technology), which they have termed the "singularity." In this essay I compare and contrast these two concepts.

1. The singularity: a uniquely unique event in humanity's future

"Unique" is, of course, an over-used word to describe momentous events – arguably, even more over-used than "historic." How, then, can I dare to describe something as uniquely unique?

Well, I will begin by pulling back a fraction from that description. There are actually, in my view, two possible events in humanity's future that merit this description. But I do not feel very bad about this qualification, because I believe that those two events are, in all probability, mutually exclusive. The singularity is one; the demise of humanity is the other. Hence my choice of the indefinite article: the singularity is not "the" uniquely unique event in humanity's future, because it may not occur, but if it does occur, nothing comparable will either precede or follow it.

The singularity has been defined in many related but subtly distinct ways over the years, so let me begin my discussion of it by making clear what I mean by the term. I adhere to the following definition: "an asymptotically rapid increase in the sophistication of technology on whose behaviour humans depend." I do not use the word to mean, for example, "the technological creation of smarter-than-human intelligence" (which is the definition currently given by SIAI, the Singularity Institute for Artificial Intelligence[1]) – despite my agreement with the view that the technology most likely to bring about the singularity (and, indeed, the one that was originally used to define it) is precisely the one that SIAI study, namely recursively self-improving artificial intelligence (of which more below). I am sticking to the more abstract definition partly because it seems to me to encapsulate the main point of why the singularity is indeed uniquely unique, and partly because it will help me to highlight what distinguishes the singularity from the Methuselarity.

One aspect of my definition that may raise eyebrows is its use of the word "asymptotically" rather than

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"exponentially." I feel sure that von Neumann[2] would agree with me on this: the mere perpetuation of Moore's Law3 will not bring about the singularity. A gravitational singularity, which is of course the etymological source of the term, is the centre (not, I stress, the event horizon) of a black hole: the point at which the force of gravity is infinite – or, to be more precise, the point arbitrarily near to which gravity is arbitrarily strong. The distance between the singularity and any point of interest (inside or outside the event horizon) at which gravity is finite is, of course, finite. This is an asymptotic relation between distance and strength: if point X is distance Y from the singularity, it is not possible to travel from X, along the line between X and the singularity, by a distance greater than Y, and experience continuously increasing gravity. Exponential (though not inverse exponential! – see below) relations are not like this: they have no asymptote. If the force of gravity exerted by a particular body were exponential (though still increasing with decreasing distance from the body), the relation between distance from that body and gravity exerted by it would be defined in terms of distance from the point furthest away from it ("on the other side of the Universe"). Call the gravity exerted at that point X and suppose that the gravity exerted at half that distance from the body is 4X (which is the same as for gravity in real life). Then the gravity exerted by the body at a point arbitrarily close to it is not arbitrarily large – it is just 16X, since that point is exactly twice as far away from the point of minimum gravity as the 4X point is.

Having belaboured this point, I now hope to justify doing so. Will the technological singularity, defined as I define it above, happen at all? Not if we merely proceed according to Moore's law, because that does not predict infinite rates of progress at any point in the future. But wait – who's to say that progress will remain "only" exponential? Might not progress exceed this rate, following an inverse polynomial curve (like gravity) or even an inverse exponential curve? I, for one, don't see why it shouldn't. If we consider specifically the means whereby the Singularity is most widely expected to occur, namely the development of computers with the capacity for recursive improvement of their own workings,[4] I can see no argument why the rate at which such a computer would improve itself should not follow an inverse exponential curve, i.e. one in which the time taken to achieve a given degree of improvement takes time X, the time taken to repeat that degree of improvement is X/2, then X/4 and so on.

Why does this matter? It might matter quite a lot, given that (in most people's view, anyway) the purpose of creating computers that are smarter than us is to benefit us rather than to supersede us. Human intelligence, I believe, will not exhibit a super-exponential rate of growth, because our cognitive hardware is incompatible with that. Now, I grant that I have only rather wishy-washy intuitive reasons for this view – but what I think can be quite safely said is that our ability to "keep up" with the rate of progress of recursively self-improving computers

will be in inverse relation to that rate, and thus that super-exponentially self-improving computers will be more likely to escape our control than "merely" exponentially self-improving ones will. Computers have hardware constraints too, of course, so the formal asymptotic limit of truly infinite rates of improvement (and, thus, truly infinite intelligence of such machines) will not be reached – but that is scant solace for those of us who have been superseded (which could, of course, mean "eliminated") some time previously. There is, of course, the distinct possibility that even exponentially self-improving systems would similarly supersede us, but the work of SIAI and others to prevent this must be taken into account in quantifying that risk.

Let us now consider the aftermath of a "successful" singularity, i.e. one in which recursively self-improving systems exist and have duly improved themselves out of sight, but have been built in such a way that they permanently remain "friendly" to us. It is legitimate to wonder what would happen next, albeit that to do so is in defiance of Vinge.[5] While very little can confidently be said, I feel able to make one prediction: that our electronic guardians and minions will not be making their superintelligence terribly conspicuous to us. If we can define "friendly AI" as AI that permits us as a species to follow our preferred, presumably familiarly dawdling, trajectory of progress, and yet also to maintain our self-image, it will probably do the overwhelming majority of its work in the background, mysteriously keeping things the way we want them without worrying us about how it's doing it. We may dimly notice the statistically implausible occurrence of hurricanes only in entirely unpopulated regions, of sufficiently deep snow in just the right places to save the lives of reckless mountaineers, and so on – but we will not dwell on it, and quite soon we will take it for granted.

A reasonable question to ask is, well, since even a super-exponentially self-improving AI will always have finite intelligence, might it not at some point create an even more rapidly self-improving system that could supersede it? Indeed it might (I think) – but, from our point of view, so what? If we have succeeded in creating a permanently friendly AI, we can be sure that any "next-generation" AI that it created would also be friendly, and thus (by the previous paragraph's logic) largely invisible. Thus, from our perspective, there will only be one singularity.

In closing this section I return to my claim that the singularity and the demise of humanity are, in all probability, mutually exclusive. Clearly if our demise precedes the singularity then the singularity cannot occur. Can our demise occur if preceded by the singularity? Almost certainly not, I would say: the interval available for our demise between the development of recursively self-improving AI and the attainment by that AI of extremely thorough ability to protect us (even from, for example, nearby supernovae) will be short. (I exclude here the possibility that the singularity will occur via the creation of AI that is not friendly to us, only because I think humanity's life expectancy in that scenario is so very short that this is equivalent from our point of view to the singularity not

occurring at all.) The "area under the curve" of humanity's probability of elimination at any time after the singularity is thus very small. I am, of course, discounting here the possibility that even arbitrarily intelligent and powerful systems cannot protect us from truly cosmic events such as the heat death of the Universe, but I agree with Deutsch[6] that this is unlikely given the time available.

2. The Methuselarity: the biogerontological counterpart of the singularity

In a recent interview, Watson was asked what would be the next event in the history of biology that would compare in significance to his and Crick's discovery of the structure of DNA, and he replied that there would never be one.[7] I think he was correct. However, I agree with him only if I am rather careful in defining "biology" as the *discovery* of features of the living world, and excluding biotechnology, which for present purposes I define as the *exploitation* of such discoveries. In biotechnology I believe that there will certainly be a counterpart, something that will outstrip in significance every other advance either predating or following it: the Methuselarity.

For almost a decade following my graduation in 1985, I conducted research in artificial intelligence. I switched fields to biogerontology shortly after becoming aware that the defeat of aging was vastly less on biologists' agenda than I had hitherto presumed. I was not, at that time, aware of the concept of recursively self-improving AI and the singularity, though perhaps I should have been. But even if I had been, I think I would still have made the career change that I did. Why?

Humans are very, very good at adjusting their aspirations to match their expectations. When things get better, people are happy – but if they stay better and show every sign of continuing that way, people become blasé. Conversely, when things get worse people are unhappy, but if they stay worse and show every sign of continuing that way, people become philosophical. This is why, by all measures that have to my knowledge been employed, people in the developed world are on average neither much happier nor much less happy now than they were when things were objectively far worse. This is a good thing in many ways, but in at least one way it is a problem: it dampens our ardour to improve our lives more rapidly. In particular, it depletes the ranks of "unreasonable men" to whom Shaw so astutely credited all progress.[8] There are far too few unreasonable men and women in biology, and especially in biogerontology. I am proud to call myself an exception: someone who is comfortable devoting his life to the most important problems of all, even if they appear thoroughly intractable.9 In my youth, I felt I could make the most difference to the world by helping to develop intelligent computers; but when I discovered the truth about biologists' attitude to aging I knew that I could make even more difference in that field.

Why is aging so important? Aging kills people, yes, but so do quite a few other things – and moreover, life is about quality as well as quantity, and

intelligent machines might very greatly improve the quality of life of an awful lot of people, not least by virtue of providing essentially unbounded prosperity for all. Even if we take into account the fact that aspirations track expectations, such that what really matters is to maintain a good *rate of improvement* of (objective) quality of life, it is hard to deny that the development of super-intelligent machines will be of astronomical benefit to our lives. But let's be clear: quantity of life matters too. There is a well-established metric that folds together the quality and quantity benefits of a given technological or other opportunity: it is the "quality-adjusted life year" or QALY.[10]

Historically, mainstream biogerontologists have been publicly cautious regarding predictions of the biomedical consequences of their work, though this is gradually changing. But even privately, few biogerontologists have viewed aging as amenable to dramatic change: they have been aware that it is a hugely multi-faceted phenomenon, which will yield only incrementally to medical progress if it yields at all. This places them in a difficult position when arguing for the importance of their work relative to other supplicants for biomedical research resources. Yes, there is always a benefit to a QALY, and yes, progress against aging will deliver QALYs – but the force of this argument is diminished by two key factors, namely the probability of success (which biogerontologists cannot provide a conclusive case for being high) and the entrenched ageism in society, which views it as "fair" to deprioritise health care for the elderly. This quandary is well illustrated by the current "Longevity Dividend" initiative, which seeks to focus policy-makers' minds on the ever-dependable lure of lucre associated with keeping people youthful, rather than on the moral imperative.[11]

But this is in the process of changing – indeed, of being turned on its head. This is for one reason and one only: it is becoming appreciated that aging may be amenable to comprehensive postponement by regenerative medicine.[12,13] And the reason that makes all the difference is because it creates the possibility – indeed, the virtual certainty – of the Methuselarity.

Having tantalised you for so long, I cannot further delay revealing what the Methuselarity actually is. It is the point in our progress against aging at which our rational expectation of the age to which we can expect to live without age-related physiological and cognitive decline goes from the low three digits to infinite. And my use here of the word "point" is almost accurate: this transition will, in my view, take no longer than a few years. Hence the – superficial – similarity to the singularity.

I have set out elsewhere, first qualitatively[14] and then quantitatively,[15] the details of my reasons for believing that the application of regenerative medicine to aging will deliver this cusp; thus, here I will only summarise. Regenerative medicine, by definition, is the partial or complete restoration of a damaged biological structure to its pre-damaged state. Since aging is the accumulation of damage, it is in theory a legitimate target of regenerative medicine, and success in such a

venture would constitute bona fide rejuvenation, the restoration of a lower biological age. (The bulk of my work over the past decade can be summarised as the elaboration of that "theory" into an increasingly detailed and promising project plan for actual implementation16 – but I digress.) This rejuvenation would not be total: some aspects of the damage that constitutes aging would be resistant to these therapies. But not intrinsically resistant: all such damage could in principle be reversed or obviated by sufficiently sophisticated repair-and-maintenance (i.e., regenerative) interventions. Thus arises the concept of a rate of improvement of the comprehensiveness of these rejuvenation therapies that is sufficient to outrun the problem: to deplete the levels of all types of damage more rapidly than they are accumulating, even though intrinsically the damage still present will be progressively more recalcitrant. I have named this required rate of improvement "longevity escape velocity" or LEV.[14,15]

It is important to understand that LEV is not an unchanging quantity, as it might be if it were a feature of our biology. Rather, it will vary with time – and exactly how it will probably vary is a topic I address in the next section. LEV will, however, remain non-zero for as long as there remain any types of damage that we cannot remove or obviate. Thus, the formal possibility exists that we will at some point achieve LEV but that at some subsequent date our rate of progress against aging will slip back below LEV. However, I have claimed that this will almost certainly not happen: that, once surpassed, LEV will be maintained indefinitely. This claim is essentially equivalent to the claim that the Methuselarity will occur at all: the Methuselarity is, simply, the one and only point in the future at which LEV is achieved.

3. The singularity and the Methuselarity: some key differences

Having described the singularity and the Methuselarity individually, I now examine how they differ. I hope to communicate that the superficial similarities that they exhibit evaporate rather thoroughly when one delves more deeply.

Perhaps the most important contrast between the singularity and the Methuselarity is the relevance of accelerating change. In the first section of this essay I dealt at some length with the range of trajectories that I think are plausible for the rate of improvement of self-improving artificial intelligence systems – but it will have been apparent that all the trajectories I discussed were accelerating. It might intuitively be presumed that, since aging is a composite of innumerable types of damage that accumulate at different rates and that possess different degrees of difficulty to remove, our efforts to maintain youth in the face of increasing chronological age will require an accelerating rate of progress in our biomedical prowess. But this is not correct.

The central reason why progress need not accelerate is that there is a spectrum not only in the recalcitrance of the various types of damage that constitute aging but also in their rates of accumulation. As biomedical

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gerontologists, we will always focus on the highest-priority types of damage, the types that are most in danger of killing people. Thus, the most rapidly-accumulating types of damage will preferentially be those against which we most rapidly develop repair-and-maintenance interventions. There will, to be sure, be "spikes" in this distribution – types of damage that accumulate *relatively* rapidly and are also *relatively* hard to combat. But we are discussing probabilities here, and if we aggregate the probability distributions of the timeframes on which the various types of damage, with their particular rates of accumulation and degrees of difficulty to combat, are in fact brought under control, the conclusion is clear: we are almost certain to see a progressive and unbroken decline in the rate at which we need to develop new anti-aging therapies once LEV is first achieved. (I do not mean to say that this progression will be absolutely monotonic – but the "wobble" in how rapidly progress needs to occur will be small compared to the margin of error available, i.e. the margin by which the average rate of progress exceeds LEV.) This conclusion is, of course, subject to assumptions concerning the distribution of these types of damage on those two dimensions – but, in the absence of evidence to the contrary, a smooth (log-normal, or similar) distribution must be assumed.

The other fundamental difference between the singularity and the Methuselarity that I wish to highlight is its impact on "the human condition" – on humanity's experience of the world and its view of itself. I make at this point perhaps my most controversial claim in this essay: that in this regard, the Methuselarity will probably be far *more* momentous than the singularity.

How can this be? Surely I have just shown that the Methuselarity will be the consequence of only quite modest (and, thereafter, actually decreasing) rates of progress in postponing aging, whereas the singularity will result from what for practical purposes can be regarded as infinite rates of progress in the prowess of computers? Indeed I have. But when we focus on humanity's experience of the world and its view of itself, what matters is not how rapidly things are changing but how rapidly those changes affect us. In the case of the singularity, I have noted earlier in this essay that if we survive it at all (by virtue of having succeeded in making these ultra-powerful computers permanently friendly to us) then we will move from a shortly-pre-singularity situation in which computers already make our lives rather easy to a situation in which they fade into the background and stay there. I contend that, from our point of view, this is really not much of a difference, psychologically or socially: computers are already far easier to use than the first PCs were, and are getting easier all the time, and the main theme of that progression is that we are increasingly able to treat them as if they were not computers at all. It seems to me that the singularity may well, in this regard, merely be the icing on a cake that will already have been baked.

Compare this to the effect of the Methuselarity on the human condition. In this case we will progressively and

smoothly improve our remaining life expectancy as calculated from the rate of accumulation of those types of damage that we cannot yet fix. So far, so boring. But wait – is that the whole story? No, because what will matter is the bottom line, how long people think they're actually going to live.

These days, people are notoriously bad at predicting how long they're going to live. There is a strong tendency to expect to live only about as long as one's parents or grandparents did (just so long as they died of old age, of course).[17] This is clearly absurd, given the rapid rise of life expectancies throughout the developed world in the past half-century and the fact that, unlike the previous half-century, that rise has resulted from falling mortality rates at older ages rather than in infancy or childbirth. It persists, I believe, simply because the rise in life expectancy has been rapid only by historical standards: unless one's paying attention, it's not been rapid by the standards of progress in technology, so it easily goes unnoticed.

This will not last, however. As the rate of improvement in life expectancy increases, so the disparity between that headline number and the age which someone of any particular age can expect to reach also increases. But here's the crux: these two quantities do not increase in proportion. In particular, when the rate of improvement of life expectancy reaches one year per year – which, in case you didn't know, is only a few times faster than is typical in the developed world today[18] – the age that one can expect to reach undergoes a dramatic shift, because the risk of dying from age-related causes at any given age suddenly plummets to near zero. And that is (another way of defining) the Methuselarity.

To summarise my view, then: the singularity will take us from a point of considerable computing power that is mostly hidden from our concern to one of astronomical computing power that is just slightly more hidden. The Methuselarity, by contrast, will take us from a point of considerable medical prowess that only modestly benefits how long we can reasonably expect to live, to one of just slightly greater medical prowess that allows us confidence that we can live indefinitely. The contrast is rather stark, I think you will agree.

4. Epilogue: the Methuselarity and the singularity combined

Those who have followed my work since I began publishing in biogerontology may have noticed a subtle change in the way that I typically describe the Methuselarity's impact on lifespans. Early on, I used to make probabilistic assertions about future life expectancy; now I make assertions about how soon we will see an individual (or a cohort) achieve a given age.

The reasons for this shift are many; some are down to my improved sense of what does and does not scare people. But an important reason is that my original style of prediction incorporated the implicit assumption that the Methuselarity would occur in the context of a continued smooth, and relatively slow, rate of reduction in our risks of death from causes unrelated to our age. I only belatedly realised that this assumption is unjustified – indeed,

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absurd. And the singularity is what makes it particularly absurd.

Roughly speaking, we prioritise our effort to avoid particular risks of death on the basis of the relative magnitude of those risks. Things that only have a 0.01% risk per year of killing us may not be considered worth working very hard to avoid, because even multiplied up over a long life they have only a 1% chance of being our cause of death. This immediately tells us that such risks will move altogether nearer to the forefront of our concerns as and when the Methuselarity occurs (or is even widely anticipated), because the greater number of years available to get unlucky means that the risk of these things being our cause of death is elevated. It seems clear that we will work to do something about that – to improve the efficiency with which we develop vaccines, to make our cars safer, and so on. But there would appear to be only so much we can do in that regard: first of all there are things that we really truly can't do anything about, such as nearby supernovae, and secondly there are quite a few moderately risky activities that quite a lot of us enjoy.

The singularity changes all that. What the singularity will provide is the very rapid reduction to truly minute levels of the risk of death from any cause. You may have thought that my earlier mention of snow reliably saving careless mountaineers was in jest; indeed it was not. Moreover, the residual risk that our rate of improvement of medical therapies against aging will at some point fall below LEV will also essentially disappear with the singularity. (Clearly the possibility also exists that the singularity will precede, and thus bring about, the Methuselarity – but that does not materially alter these considerations.)

One of my "soundbite" predictions concerning the Methuselarity is that the first thousand-year-old is probably less than 20 years younger than the first 150-year-old. The above considerations lead to a supplementary prediction. I think it is abundantly likely that the first million-year-old is less than a year younger than the first thousand-year-old, and the first billion-year-old probably is too.

The singularity and the Methuselarity are superficially similar, but I hope to have communicated in this essay that they are in fact very different concepts. Where they are most similar, however, is in the magnitude of their impact on humanity. The singularity will be a uniquely dramatic change in the trajectory of humanity's future; the Methuselarity will be a uniquely dramatic change in its perception of its future. Together, they will transform humanity... quite a lot.

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Chapter 38: Use of a 3D-printed punch template for multiple wounds within a single tissue culture well, in order to establish a barrier function in a novel in vitro model of stratified epithelial wound healing

Author 1: Luis Alonso-Pastor
Changing Places Research Group, Media Lab, Massachusetts Institute of Technology, Cambridge, Massachusetts.
Author 2: Miguel Gonzalez-Andrades
Institution, City, Country Schepens Eye Research Institute and Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts.
Author 3: Jerome Mauris
Institution, City, Country Schepens Eye Research Institute and Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts.
Author 4: Andrea Cruzat
Institution, City, Country Schepens Eye Research Institute and Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts.
Author 5: Claes H. Dohlman
Institution, City, Country Schepens Eye Research Institute and Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts.
Author 6: Pablo Argüeso
Institution, City, Country Schepens Eye Research Institute and Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts.
Author 7: Kent Larson
Changing Places Research Group, Media Lab, Massachusetts Institute of Technology, Cambridge, Massachusetts.

Abstract

We describe a straightforward *in vitro* wound assay to evaluate the healing and restoration of barrier function in stratified human corneal epithelial cells. In this assay, the reproducibility and uniformity of these injuries was dependent on the application of comparable pressure on the punch and the generation of a concentric incision groove in the tissue culture plate around the punch wound. In this injury model, the use of a 3D-printed punch t0emplate facilitated the generation of multiple wounds within a single tissue culture well.

1. Introduction

The first 3D printing patent application was filed by a Dr Kodama in Japan, in 1980 [1]. In 1984, Charles W 'Chuck' Hull made, in effect, the world's first 3D printer under the US patent number US4575330, and with the name: "Apparatus for production of three-dimensional objects by stereolithography" [2].

The first main impact of 3D printing in healthcare came in 1999 when, using the technology developed at the Wake Forest Institute for Regenerative Medicine, a laboratory-grown organ was successfully transplanted into a patient for the first time [22]. Since then, many different steps have been done and many research, healthcare applications and commercial uses on this very promising field: Wohlers Associates as well as some industry observers forecast that the 3D printing market will generate revenues of $20 billion by 2020, and an impact of between $230 and $550 billion per year by 2025 [3]. The largest impact will be on consum-er users ($100 to $300 billion), direct manufacturing ($100 to $200 billion) and the creation of tools and molds ($30 to $50 billion)

[4]; this last market niche is where the 3D-printed punch template fits.

In the other hand, the repair of wounds through collective movement of epithelial cells is a fundamental process in multicellular organisms [5]. In stratified epithelia such as the cornea and skin, healing occurs in three steps that include a latent, migratory, and reconstruction phases. Several simple and inexpensive assays have been developed to study the biology of cell migration *in vitro* [6]. However, these assays are mostly based on monolayer systems that fail to reproduce the differentiation processes associated to multilayered systems [6, 7].

On this paper we link the design and low cost potential of a conventional 3D printer and the biomedical needs in order to develop a simple and inexpensive assays to study the biology of cell migration *in vitro* in the Re-epithelialization process. Re-epithelialization is an essential biological process critical to restore an intact barrier in organ systems such as the cornea, skin and gastrointestinal tract following a wound [5].

2. Design process

The 3D template was modeled using AutoCAD Mechanical design software (Autodesk; San Rafael, CA). Models were exported as STL-files and processed using ReplicatorG (MakerBot Industries; Brooklyn, NY). 3D printing was carried out on a

MakerBot Replicator 2 (MakerBot Industries) using polylactic acid (PLA) filament.

Figure 1. Definition of the design process of the 3D-printed 6-hole punch template. A) First drafts and ideas. B) Production Issues: The number of holes made the template a very high precision element, and the MakerBot print process stopped. C) The template is made by polylactic acid (PLA) filament. A calibration of the autoclave is needed in order to clean and reuse the template without damaging it. D) Example of a 3D-printed 6-hole punch template. E) Evolution of the template design: from a matrix of 300-holes into a matrix of 10-holes, and finally a 6-hole matrix.

The 3D-printed 6-hole punch template (Fig. 1) was learning by doing iterative design process. From the beginning of the design the goal was to create a template as efficient (in number of holes) and as eco-friendly as possible, with a conventional 3D printer.

The first iteration was designed with polylactic acid and 300-holes matrix, but after several productions (print process stopped), structural (Fragility of the template), and material issues (autoclave calibration), the final template was made with a 6-hole matrix.

3. Biomedical approach

Re-epithelialization is an essential biological process critical to restore

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an intact barrier in organ systems such as the cornea, skin and gastrointestinal tract following a wound [5].

Numerous models and methods of injury have been described to study the migratory process in corneal epithelial cells [6]. Human corneal *ex vivo* models have been developed, but their use has been hampered by the difficulty of obtaining healthy human donor tissue and poor standardization due to cornea-to-cornea variability [6, 7]. The use of *in vitro* models can simplify the characterization of specific biological processes that are difficult to study *in vivo* because of their complexity. For this purpose, tissue engineered scaffolds have been developed, but are expensive and difficult to produce and manipulate [3]. Culture models using human corneal epithelial cell lines, on the other hand, offer a series of advantages such as simplicity, high level of reproducibility and relatively low costs [6, 7].

Unfortunately, most culture models evaluating human corneal epithelial cell migration are based on monolayer cultures, which fail to reproduce the three phases of epithelial healing. The aim of this study was to develop and characterize a simple and reproducible *in vitro* model of wound healing that could potentially be used to study the different phases of healing in stratified epithelium.

4. Biomedical results

Analyses of the wound morphology revealed that use of plastic or metal tips in rotating scratch injury models produced modest results in terms of shape and circularity (Fig. 2).

*Figure 2. Morphometric analysis of epithelial wounds. Stratified cultures of human corneal epithelial cells were injured by rotation using a plastic or metal tip (rotating scratch model), or using dermal punchs (0.5, 1.0, 1.5 or 2.0 mm diameter) followed by epithelial debridement (punch model). Morphology of the injured area was analyzed by measuring main parameters of the wound shape, including circularity, area, perimeter and Feret diameter. The area and perimeter of the wounds ranged from 0.3 to 3.3 mm2 and 2.9 to 7.0 mm, respectively. The values for circularity and Feret diameter ranged from 0.48 to 0.87 and 0.8 to 2.1 mm, respectively. Use of plastic or metal tips produced modest results in terms of shape and circularity. Punch injuries followed by epithelial debridement using a disposable plastic tip (i.e., 1.0, 1.5 and 2.0 mm punch) produced consistent shapes and high circularity values. Results are displayed as mean +/- SD (N=9). Significance was determined using one-way ANOVA with Bonferroni's post-hoc test. *p<0.05; ***p<0.001. ns, non-significant.*

On the other hand, punch injuries, particularly those followed by epithelial debridement using a disposable plastic tip (i.e., 1.0, 1.5 and 2.0 mm punch), produced consistent shapes that were associated with high circularity values.

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On the other hand, punch injuries, particularly those followed by epithelial debridement using a disposable plastic tip (i.e., 1.0, 1.5 and 2.0 mm punch), produced consistent shapes that were associated with high circularity values.

The reproducibility and uniformity of these injuries was dependent on the application of comparable pressure on the punch and the generation of a concentric incision groove in the tissue culture plate around the punch wound. In this injury model, the use of a 3D-printed punch template facilitated the generation of multiple wounds within a single tissue culture well (Fig. 3).

4.1 Promotion of wound closure

In our experiments, the wound closure was significantly promoted following addition of serum to the cell culture media (Fig. 4a). Here, the wounded area was re-epithelialized by more than 40% at 24 h, by approximately 90% at 48 h, and a complete closed wound was observed at 72 h. The presence of proliferative activity following addition of serum was further demonstrated by staining for proliferating cell nuclear antigen or PCNA, a marker of growing cells entering the early S phase of the cell cycle [8,9]. Clusters of PCNA-positive cells appeared within the concentric incision groove around the punch wound, but not in actively migrating cells, a phenomenon known as migration-proliferation dichotomy (Fig. 4b).

Figure 4. Serum promotes re-epithelialization and wound closure. Circular wounds of 1 mm in diameter were made using a punch template. (a) Morphometric analysis demonstrated that the extent of re-epithelialization was enhanced in the presence of culture media containing serum. In the absence of serum, none of the wounds was able to completely re-epithelialize at 72 h, whereas in the presence of serum, the wounded area was significantly reduced at 48 h and completely closed at 72 h. Results are displayed as mean +/- SD (N=18). Significance was determined using the Mann-Whitney test. ****$p<0.0001$. (b) In control experiments, the presence of proliferative activity was demonstrated by staining for PCNA (green) in subconfluent cultures of human corneal epithelial cells. Following injury to stratified cultures, clusters of PCNA-positive cells appeared within the concentric incision groove around the punch wound (arrowheads), but not in actively migrating cells (asterisks). Nuclei were counterstained using DAPI (blue). Scale bar, 100 µm.

Direct visualization of the migratory process by time-lapse microscopy revealed an initial accumulation of cell mass within the incision groove in the tissue culture plate followed by unified sliding of the healing epithelium towards the wound (Supp. Movie 1). During this migratory phase, most cells at the leading edge remained at the wound edge and were not actively replaced by other cells. Cell-tracking experiments showed that the average rate of migration of cells at the leading edge during this phase was 0.27 µm/min (Fig. 5a).

Figure 5. Wound healing involves migration by unified sliding of cells at the leading edge and stratification front. Circular wounds of 1 mm in diameter were made using a punch template. The migration of individual human corneal epithelial cells in stratified cultures and in the presence of serum was analyzed by time-lapse imaging. (a) Cell-tracking experiments revealed that cells at the leading edge and stratification front migrated with an average trajectory speed of 0.27 and 0.17 µm/min respectively. (b) Following a wound, epithelial cells

Cells at the stratification front moved behind the leading edge at a slower average rate of 0.17 µm/min. Both the leading edge and the stratification front maintained similar trajectories and relative position (Fig. 5b).

4.2 Restoration of barrier function

Restoration of the transcellular and paracellular barrier function in *in vitro* models of wound healing is critical to understanding the biological processes associated with the reconstruction phase of healing. To determine whether wound closure was associated with restoration of transcellular barrier function in our model of stratified epithelial wound healing, we took advantage of the rose bengal penetration assay. In this assay, uptake of rose bengal by the cell culture is dependent on the character of the apical glycocalyx and the ability to synthesize cell surface mucins [10-11]. The presence of a fully functional glycocalyx barrier protects against rose bengal uptake, whereas positive staining of the epithelia indicates the presence of a compromised transcellular barrier. As shown in Figure 6, monolayer cultures of corneal epithelial cells stained positively with rose bengal. In contrast, stratified cultures were characterized by the presence of islands of stratified cells that excluded the dye. Analyses of the stratified culture immediately after wounding (t = 0 h) resulted in a defined staining of the wound margins, indicative of epithelial damage induced by the cutting edge of the

punch. Subsequent to the initial wound, cell migration was characterized by the presence of a leading edge of monolayer cells that stained positively for rose bengal, and a stratified zone behind the edge that contained areas of rose bengal exclusion. This stratified zone was observed within the wound at 24 and 48 h, and mostly covered the entire wound at 72 h.

Figure 6. Barrier function is restored as epithelial cells migrate en bloc. (a) Circular wounds of 1 mm in diameter were made using a punch template. The extent of rose bengal dye penetrance was assessed at 0, 24, 48 and 72 h following culture in serum-containing medium. Induction of stratification in control cultures resulted in the formation of islands of stratified cells that excluded the dye. A defined staining of the wound margins was observed immediately after wounding (arrowheads). Epithelial migration was characterized by uptake of dye by cells at the leading edge but not behind the stratification front (dotted line). Closure of the wound at 72 h was associated with the complete restoration of barrier function. (b) For immunofluorescence microcopy, stratified cultures in chambered slides were wounded using a 1.5 mm punch and manually scraped using a pipette tip. Occludin (green) was detected at the cellular margin after wounding (arrows), and was restored to the intercellular junctions within the stratification front during migration. Cells at the leading edge (asterisks) extended lamellipodial protrusions as shown by actin staining (red) and were characterized by lack of occludin localization at the cell-cell junction. Nuclei were counterstained using DAPI (blue). Scale bars, 50 mm (top), 20 mm (middle), 100 mm (bottom).

In addition to the transcellular barrier, the formation of tight junctions is crucial for the establishment of paracellular barrier function in polarized epithelial sheets. Analyses of stratified cultures immediately after wounding revealed abrupt interruption of the tight junction-associated protein occludin at the wound margin (Fig. 6b, upper panel). During the migratory phase, epithelial cells at the leading edge of the migrating sheet extended lamellipodial protrusions and were characterized by lack of occludin localization at the cell-cell junction (Fig. 6b, lower panel). However, occludin expression was restored to apical intercellular junctions within the stratification front behind the leading edge, indicating that tight junctions are immediately formed after the epithelium becomes multilayered, and suggesting the presence of a reconstruction phase and the normalization of the barrier function of the epithelial sheet during wound closure.

5. Generation of wounds

Two types of corneal epithelial cell injury (rotating scratch and punch) were performed in areas equidistant to the center of the culture in six-well tissue culture plates (Corning Inc.; New York, NY). For the rotating scratch injury, wounds were produced by manually rotating a standard 200 µl plastic pipette tip (1 mm diameter; Eppendorf; Hauppauge, NY) or a 0.5 mm titanium-coated diamond burr (Sona Enterprises, Hangzhou, China) at a 90-degree angle over the culture

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for approximately 5 sec. For the punch injury, wounds were produced by pressing (300-450 g/mm2) and rotating (180º) the metal cutting edge of a 0.5, 1.0, 1.5 or 2.0 mm Miltex dermal punch (Integra Miltex; York, PA) at a 90-degree angle over the culture for approximately 1 sec. The pressure unit was calculated by dividing the weight applied on the punch by the surface area covered by the punch. To maintain sharpness, each punch was only used for approximately 20 wounds. Next, cells within the wound were scraped for approximately 5 sec by rotation of the retractable internal plunger of the punch (0.5 mm punch) or by rotation of a 10 µl disposable SHARP® Precision Barrier Tip (Denville Scientific; South Plainfield, NJ). For the latter, tips were inserted within the punch with the help of a metal rod (1.5 and 2.0 mm punch) or connected to a 100 rpm cordless power precision screwdriver and inserted within the well with the help of a 3D-printed 6-hole punch template (1.0 mm punch). The 3D template was modeled using AutoCAD Mechanical design software (Autodesk; San Rafael, CA). Models were exported as STL-files and processed using ReplicatorG (MakerBot Industries; Brooklyn, NY). 3D printing was carried out on a MakerBot Replicator 2 (MakerBot Industries) using polylactic acid filament.

6. Discussion

Here, we have established a simple and inexpensive *in vitro* model of wound healing that displays features associated with the re-epithelialization of stratified epithelia that include unified sliding of cell sheets and restoration of epithelial barrier function.

In summary, we have developed a simple and inexpensive *in vitro* model of wound healing using an immortalized epithelial cell line grown as a multilayered culture. The method enabled us to obtain reproducible wounds that were associated with the coherent migration of epithelial sheets and the restoration of barrier integrity. This model may prove a useful system to better understanding the factors controlling the different phases of human wound healing in stratified epithelia, and could constitute a valuable tool for preclinical wound healing research

7. Conclusions

The use of non-expensive 3D printed tools provides an important research tool to study the mechanisms leading to barrier function in stratified epithelia and may facilitate the development of future therapeutic applications.

We have established a simple and inexpensive *in vitro* model of wound healing that displays features associated with the re-epithelialization of stratified epithelia that include unified sliding of cell sheets and restoration of epithelial barrier function.

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Chapter 39: Future of Medical Knowledge Management and Decision Support

Robert A. Greenes, M.D., Ph.D.
Professor of Radiology and of Health Science & Technology, Harvard Medical School, Professor of Health Policy & Management, Harvard School of Public Health & Director, Decision Systems Group, Brigham and Women's Hospital, Boston, MA, US

Abstract

Information and knowledge abound to such an extent that we cannot cope effectively with them. Strategies for targeting selected information and knowledge to the point of need are greatly needed in many health care settings – in clinical practice, to support problem solving and decision making needs of both the provider and the patient; in health care institution management, in education;, and in research. The increased need is exac-erbated by the growing interdisciplinary and multi-institutional nature of practice, education, and research.

Some possible models for implementing such strategies involve the setting of context for use of in-formation and knowledge by defining the problem and task in advance. This requires that information and knowledge providers support the use of a taxonomy of problem/task contexts for access to their resources, and that infrastructure provide support for integration methods that incorporate these resources into workflow and process that are compatible with and helpful to the problem solving or decision making task. Guideline modeling is one technology for representing workflow and process characteristics of such tasks that could be use-ful for this purpose.

A variety of other issues must be considered as well, to move beyond source-oriented information and knowledge resources, to the timely and efficient incorporation of targeted resources in problem-specific settings. The common requirement is for a standards-based approach to taxonomy and interface development.

1. The hazards of prognostication

Attempts to predict the future are typically off the mark. Beyond the challenges of fore-casting the stock market or the weather, dramatic instances of notoriously inaccurate prog-nostications have been those by the US patent office in the late 1800s about the future of inventions, by Thomas Watson in the 1930s about the market for large computers, and by Bill Gates in the early 1990s about the significance of the Internet. When one seeks to make predictions about health care, one finds that, beyond the usual uncertainties regarding the future, additional impediments to forecasting are the discontinuities introduced by advances in biomedical science and technology, the impact of information technology, and the reor-ganizations and realignments attending various approaches to health care delivery and finance. Changes in all three contributing areas themselves can be measured in "PSPYs", or paradigm shifts per year.

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Despite these risks in forecasting, I believe that certain trends are sufficiently clear that I am willing to venture a few predictions. The predictions I wish to make actually suggest a goal for the future that can be achieved, if we can align the prevailing political, financial, biomedical, and technical forces toward that end. Thus, in a sense this is a call to action, to shape the future rather than just let it happen. This chapter seeks to lay out the direction we are heading in knowledge management and decision support, and to delineate an information technology framework that appears desirable. I believe the framework to be discussed is of importance to the health care-related knowledge management and decision making activities of the consumer and patient, the health care provider, and health care de-livery organizations and payers. The approach is also relevant to the other dimensions of academic health care institution activities, notably the conduct of research and the processes of education and learning.

2. Information glut is not a good thing

We are not information-starved at present, but it may seem that way. Information comes in many forms, ranging from raw data to summaries of results, from narrative documents such as textbooks and journal article, to formal representations of knowledge, rules and guidelines encapsulating best practices, or automated decision support tools. The information focus may pertain to the domains of basic science, clinical practice, preventive medicine, public health, health services research, or a variety of specialized arenas.

The information sources are widely distributed, ranging from local repositories and programs on one's own desktop, to those within the local enterprise (hospital, university, practice networks), to national or international sites accessible via the Internet. Not only is this panoply of sources distributed, but it is heterogeneous in format, software platform, mode of access, and manner of representation or encoding of information. Even within lo-cal enterprise networks, multi-vendor platforms and incompatible protocols often compli-cate access.

Knowledge may be defined as that which results from the organization, analysis, or extrapolation of data to derive a higher level conceptualization of phenomena or processes. "Knowledge differs from data or information in that new knowledge may be created from existing knowledge using logical inference. If information is data plus meaning then knowledge is information plus processing" [1]. Knowledge can be either in human-readable form only, as are textbook and journal content, or capable of being executed in some fash-ion, as are the rules in knowledge bases of decision support tools.

With respect to knowledge resources, as with information more generally, we are inundated with so many alternatives that it is difficult to sift out those particular items that are most pertinent and of highest quality. Chaos reigns in the generation of health care-relevant knowledge – many producers, many variations in method, review, sponsorship, dissemination approach,

and business models. The traditional publishing industry is in dis-array [2], libraries are groping with new roles and missions [3], and Internet-based health knowledge providers are struggling to determine how to sustain and grow their activities [4]. The knowledge dissemination industries in the form of educational institutions are also facing upheavals, as virtual classrooms, distance learning, and other models of education are refined [5].

3. The problem-oriented paradigm as a coping strategy

Although potential users of information are faced with many modes of information access, providers, and types of information, they are typically driven by a single problem or task. They seek high quality information, but restricted to those items relevant for that problem or task. Where the information comes from is less important than its value for the task at hand. The information, in addition, is most useful if it can be made available immediately ("just-in-time"), in the context of the application that is being used for solving the problem or carrying out the task. Ideally, the information resources can be selected automatically based on specific data already known. Furthermore, among those resources selected, deci-sion support tools can be primed with pre-existing data, can be used to update or collect additional targeted data, can implement recommendations, and can facilitate workflow.

My thesis is that problem-based information organization is a particularly useful coping strategy, when it is necessary to select pertinent items from a vast array of possibili-ties, especially when it is necessary to assemble different kinds of information at the same time.

Yet we note a marked contrast between the production and the use of information – its production is primarily *source-oriented,* whereas the use of it is primarily *problem-oriented* (Fig. 1). The production process can be considered to be the province of a set of vertical silos, those entities and services responsible for the creation and distribution of the information. Settings in which use occurs can be viewed as a horizontal set of cross-cutting planes corresponding to problems or tasks, which ideally intersect the silos at the precise points where information pertinent to the problems reside.

Figure 1. The orthogonal relationship of information producers and users.

In this chapter, we shall discuss a variety of settings in which problem-based organization of information is useful. We then focus on methodologies for providing the necessary in-frastructure to support problem-based access and use.

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4. Centrality of information needs in the academic health sciences university

The modern academic health sciences center has a combined mission of education, research, and service, where the latter includes both clinical and non-clinical activities. The academic health sciences are now experiencing the birth of many new fields, and the integration of previously separate disciplines, the growth of "big science" initiatives, and the establishment of physical and virtual collaborations spanning multiple disciplines, institu-tions, and geographic boundaries. As a result, both the opportunity and the necessity exist to rethink traditional approaches to development of an information infrastructure to support the activities of the academic health center.

Integration is the new byword, with most activities increasingly dependent on the information infrastructure. Among the new interdisciplinary and cross-cutting activities with such dependency are, for example: molecular imaging, telesurgery, robotics, nano-technology, functional genomics, proteomics, drug development, health care or biomedical data warehousing, integrated delivery networks, consumer health, distance education, digital libraries, and networked clinical trials.

5. Health and health care information

5. 1 The problem-oriented medical record

The problem-oriented medical record was introduced by Weed in the 1960s [6,7] as a strategy for clinical record keeping, which has at its core the notion that clinical observations (Subjective and Objective), Assessments, and Plans (together referred to as the SOAP note) should be organized by the problems to which they relate. This was proposed both as a means for focusing a clinician's thinking, when writing a progress note, making it easier to review a patient's progress by problem subsequently, and as a means to tie observations to assessments, and assessments to plans, thus enhancing the accountability of the record. Weed and his colleagues developed a computer-based multiple-choice problem-oriented data entry interface for generating the SOAP note for many of the problems in internal medicine, in the 1970s, although no published citations are available describing this ambi-tious work; the limited success of this project can be attributed in part to the primitiveness, by today's standards, of the user interface technology available at the time, rather than to a fundamental flaw in the concept. While the problem-oriented mode of record keeping has not been popular without use of a computer, many aficionados still do maintain their clini-cal records that way even manually [8]. With the ability to present the same data in multiple views, either by source (e.g., progress notes vs. labs vs. xrays vs. orders), by chronology, by specialist domain, or by problem, computer systems could today support problem-oriented record keeping more effectively.

Another advantage of a problem-oriented view of a patient's problems is that it al-lows one to focus on the other associated information resources that could be useful. This might include directories of specialists that

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are appropriate for referral for that problem, bibliographic references or textbook materials, guidelines, appropriateness criteria, or other decision support resources for the physician, as well as educational materials or instructions for the patient. Thus delineation of a problem provides a framework for organizing a wide variety of information resources. We shall return to this notion later.

5.2 The Integrated Delivery Network (IDN)

The evolution of the health care environment has been a striking example of the need for integration of information from diverse sources, and focusing them on specific problems or tasks. We have seen a spate of mergers and affiliations in the mid-to-late 1990s, resulting in the formation of integrated delivery networks (IDNs) [9], motivated by the need for in-creased efficiency and decreased cost. Related goals have been the need to reduce redun-dancy yet attract referring physicians and patients with a full range of services, improve-ment in economies of scale by growth of market share and retention of patients and providers in the network, and increased clout for negotiation with payers.

Yet IDNs introduced a new level of complexity in health care, necessitating assimilation of multiple formerly independent hospitals, clinics, practices, and specialty services, each with their own cultures, modes of operation, and information systems. With respect to the latter, disparate electronic medical record systems might often be operating in the enti-ties to be assimilated, along with incompatible information systems and different patient identification schemes. Clinical data and images must be communicated across these multiple systems.

Furthermore, because of the culture of fiscal restraint and cost-effectiveness, prac-tices have been subjected to increasing scrutiny with respect to cost, quality, risk, appropri-ateness of services or referrals, and adherence to clinical practice guidelines and constraints. Thus, education and decision support must be provided across the IDN to reduce errors and increase safety, and to promote adherence to “best practices”. Purely logistical functions become more complicated in an IDN, and help is needed for such tasks as getting oriented and navigating among resources, scheduling of services, finding and initiating consultations, requesting referrals, and even learning about transportation and parking. Communication support is needed across the network for email, teleconferencing, accessing support groups, obtaining consults, etc. Patient instructions need to be provided and home care services offered and coordinated.

Partners HealthCare System, Inc., the IDN formed in 1993 with the merger of the Brigham and Women’s Hospital and Massachusetts General Hospital, plus affiliations and mergers of a number of smaller hospitals and practices in Eastern Massachusetts, provides an example. While parts of the information environment were quite sophisticated, such as the Brigham Integrated Computing System (BICS) [10] at the Brigham, there was no con-

sistent system across the entire IDN.

As efforts were being devoted to beginning the integration of the clinical infor-mation systems environment, in 1995, the Decision Systems Group focused on a different problem for Partners HealthCare, that of creating and maintaining a Web site, called Part-nerWeb, for the IDN's component health care delivery sites, including Massachusetts General Hospital and Brigham and Women's Hospital. Overall, more than 250 clinical, admin-istrative, and research departments or divisions were producing content. The PartnerWeb system [11] was designed to make available information such as descriptions of depart-ments and services, directories of specialists, seminars, educational programs, research ac-tivities, training programs, news and announcements, appointment requests, fund raising, and other functions.

Our goal was to have a consistent design for the site, to the extent possible, and to make it easy for these entities to contribute content, and to update their information, with-out requiring each to have their own Web staff, or to have a huge central Web development organization. The component-based design, one of the first of its kind for Web site man-agement when it was initially developed in 1995, provided interfaces for authors and edi-tors to tools for providing information about administration and organization, profiles of staff, descriptions of services, calendar event entries, news items, publications, training programs, and other categories of content. Authors were organized into editing groups, each with an editor responsible, as determined by the department or division, and a hierar-chical process was put into place for content development, review, edit and approval, and publication.

Separate form-based tools or components were used for each kind of content (Fig. 2). Components available to editing groups depended on the content domains and foci, and as various departments or divisions identified new requirements that we considered suffi-ciently generic, we expanded the range of form tools available. This approach provided a number of advantages, including a uniform look and feel, ease of changing the look without redesigning individual pages, the ability to select resources for presentation for specific problems or purposes, and reduction of the need for significant Webmaster services.

Figure 2. The earliest home page for PartnerWeb shows links to a variety of kinds of content resources, the content for each of which was managed by a different form tool editing component, and the Web display of which was generated dynamically from the component's database.

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5.3 Data and knowledge needs of physicians

As noted earlier, a practitioner needs to assemble information that relates to a patient's specific problem, including past medical history, clinical findings, images, diagnoses, and medications, as well as order sets, formularies, lists of relevant specialists, knowledge resources (textbook and journal articles, appropriateness criteria, guidelines, and other decision aids), and instructions and materials to provide to the patient. Health care information systems typically provide each kind of information as a separate resource, or the user must use the Web to go outside of the health care system to find knowledge resources such as articles or decision aids for problems when they need such information. The organization of material is not generally done by problem, and dynamically made available at the point of need, except in some experimental settings.

The issue of sorting quality knowledge content from chaff faces the health professional. Believing that there is a business in providing this knowledge, and developing a re-lationship with the health professional, multiple entrants have been attracted to this market, with different production approaches and business models. The result is that these resources tend to be in silos reflecting the various producers – resources for journals, textbooks, news, guidelines, clinical trial directories, risk assessment tools, etc. The "dot coms" have epitomized the frenetic exploration of approaches to knowledge generation and delivery to both patients and providers; as the hard times in this sector have shown, identification of viable business models for these entities as alternatives to traditional publishers has still been elusive.

5.4 The health care consumer / patient

Patients or consumers seek information about symptoms, diseases, treatments, or proce-dures, as well as about healthy lifestyles and disease prevention. This may be in the form of textbook and magazine articles, discussion lists, chat groups or support groups, directories of services or providers, clinical trials databases, logistic information about a health care facility (directions to it, scheduling information, virtual tours, etc.), news items, interactive risk assessments, and other decision aids. Provision of information to this market has also been a broad area of activity in the dot.com sector, with a number of national sites offering content. Other national providers of content include disease-oriented societies (such as the American Diabetes Association or the American Cancer Society), and the government (MedlinePlus from the National Library of Medicine and HealthFinder from the Depart-ment of Health and Human Services, coordinated by the Office of Disease Prevention and Health Promotion.

For patients, information relevant to the problem should ideally be organized so as to focus the inquiry and foster easy navigation and pursuit of relevant subtopics, with in-depth exploration where needed, and identification of appropriate

related topics. In addition, a feature lacking from most national information sources but being increasingly incorporated into portals associated with health care delivery organizations, is that information about a disease or problem should be coupled, when needed, with resources for follow up – including how to obtain care, from whom, how to schedule it, where to go, and how to get there.

Thus we believe the emphasis should be on "closing the loop", i.e., when a problem is identified, resources for its solution are made available, including the means for obtaining local follow up and care. This was the approach we pursued in a 1997 National Library of Medicine-funded contract to develop and evaluate HealthAware, a prototype resource for consumer health information [12,13]. Distinct from national health information sites, the aim of HealthAware was to provide access to both generic and locally developed content, through a portal to a health care delivery system, in this case that of Brigham and Women'sHospital, a participant in Partners HealthCare. The HealthAware system was built with the component-based, distributed authoring, dynamic page generation approach used in PartnerWeb, described above. It included in addition to generic content and locally developed materials, a number of tools for interactive risk assessments, finding a doctor for referral, appointment request, ask-a-doctor, chat groups, support groups, search, and problem-specific FAQs (Fig. 3). It was designed to link to resources of the IDN's Web site, such as the doctor directory of PartnerWeb, or its lists of educational seminars, its appointment re-quest function, or "virtual tours" offered by some clinical services. Extensive usability test-ing and rewriting for appropriateness of literacy level went into the design.

Note that without an approach that links content to local resources, health care in-formation is still readily obtainable, but the user must make all the links. National health information Web sites have largely provided content without local linkages; health care fa-cilities are now seeking to provide health information portals on their Web sites that do a better job of local linkage (to build patient loyalty and to facilitate follow up), and the national sites are changing their business models to offer their content for use in this context through co-branding.

Figure 3. A screenshot from the heart attack topic home page in the cardiovascular disease section of HealthAware. This shows the visual layout into hierarchies of subtopics corresponding to horizontal tabs, plus various interactive tools arrayed along the left margin. In addition, the tools are integrated into the con-tent at appropriate points. The content organization and tool-specific materials were developed through a component-based approach using a distributed authoring environment with editorial responsibility for editing

While HealthAware was only a prototype, and covered only selected medical problem domains, further evolution of the Web strategy at Partners is now incorporating many of the features of the above systems plus others, aimed at providing access to an increased range of resources. Yet the problem still remains how to best organize information in a problem/context-specific way. This involves the development of various user interface paradigms and models of usage. Experimentation is being done for example, in how best to support clinical trial information access, data entry and interface to the EMR of the host environment, and integration of clinical practice guidelines into primary care, particularly for chronic disease management.

6. Health Care Education

Problem-based learning has become a popular form of education of medical students, since the introduction of this approach at Harvard Medical School in the mid-1980s [14]. The approach is one in which realistic problem solving scenarios or simulated cases are presented, and the student must determine how to work up, assess, and treat the cases. Case materials are assembled that are relevant to a problem, and supporting references and related materials are provided, or must be found by the student. In so doing, a case becomes a springboard for discussing underlying pathophysiology, similar or contrasting conditions or related teaching points. Further, in contrast to the traditional lecture mode, the student learns how to find and assess appropriate information resources, as he or she would often need to do in actual practice, rather than simply memorizing facts, which quickly become outdated. This approach to learning of course also builds on the notion of the problem-based medical record, since the cases are focused on specific problems as instructional paradigms.

In educational contexts in general, not just those involving clinical medicine, it would be useful if study of a topic could be augmented by an information environment that could provide, among other things, such resources as: relevant lecture notes, visual materials, references, access to instructors or experts, access to fellow students, discussion boards, self-test questions, and perhaps databases and software tools for exploration. Ideally, these should be organized and accessible by topic or subtopic primarily, and only secondarily by source. Some Web products are now available that provide collaborative support for discussion groups, and for linking resources such as the above, to foster the establishment of instant communities of individuals pursuing a topic of common interest. A course repre-sents such an instant community. Distance learning environments may find it useful to em-ploy such tools to increase the interactivity and cross-fertilization of learning that is typically lost in non-classroom instruction.

In CME as well, we would like to have a curriculum that organizes resources in a problem-specific fashion. It should reflect one's specialty, the kinds of cases seen, the kinds of problems encountered,

updates about recommended approaches, self-assessment questions, and other resources. In the classical study by Covell et al in 1985 [15], it was found that many questions arose in the course of an office clinical session for which an-swers would have been useful, although not readily available, not only for the immediate care of the patient, but also to enhance the physician's knowledge. What better time to provide such information than when the question is immediate and pertinent? Thus CME should be delivered in the context of care, and when impractical, should be associated with an offline curriculum that reflects the real-time context in which the questions occurred.

7. Multidisciplinary Research

We have discussed the birth of new fields and the development of others at the intersection of existing fields. Biomedical and health care research these days frequently involves many collaborators, multiple disciplines, and often multiple institutions. These areas of research share characteristics with many other fields, and we will not discuss the domains in detail here. The common element, though, appears to be the increase in complexity of many fields, and the need for organizing both access to information and to people.

Collaborative groups must form, often in "virtual space", and must be able to find each other, participate in discussion groups, and provide and access shared data and knowledge of common interest. This is particularly important as a means to break down geographic and disciplinary boundaries. Collaborative tools such as those discussed above for supporting education can also be used to support communities of researchers.

8. Group Collaborative Work

A common theme from the above discussions is that there is a dual requirement for supporting problem solving, whether it is in clinical medicine, education, or research. First, it is necessary for relevant information resources to be available to the individual participant at the time of need. Secondly, the various human participants must often be able to be brought together around a focus of interest or problem. The problem definition in effect spawns an instant community of interest or affinity group. Early use of the Web was pri-marily aimed at enabling an individual to have access to multiple information resources. Now the focus is as much on bringing people as well as resources together. This will be important in further evolution of telemedicine for home/office doctor-patient interaction, for medical specialty consultation, for distance-based learning, for collaborative research, and for a large number of other problem solving activities that involve interactions of peo-ple as well as access to infromation.

9. Requirements for a Knowledge-Based Infrastructure

The essential challenge of enabling problem-based information access is to have an infra-structure and tools to reconcile the two disparate views of source-oriented produc-er/distributor

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and problem-based user of information resources. There are thus dual issues in achieving problem-specific selective access to relevant information resources:

1. Components: the relevant resources, tools, and services to provide specific kinds of in-formation must be available and identifiable.

2. Integration methods: the knowledge models, workflow models, and interfaces with user environments must underlie applications, to be able to incorporate information re-sources at appropriate points.

9.1 Components

There are two primary issues involved in designing and providing component services that function as information sources:

1. The services must be able to identify and characterize their information content, in terms of descriptive axes and terminologies that are known by and relevant to applications that will be accessing them.

For the Web to be organized to provide information content as component services, we need to develop standards for encoding the types of information resources that a service contains, and to describe the domain/subdomains to which the information relates. Templates for each of these would need to be defined that provide detailed attributes relating to these, such as form of resource, language, encoding scheme, terminology scheme used, etc. Attributes that enable quality to be assessed should also ideally be standardized, such as s ponsoring organization type, source of content, how validated, when updated, etc.

2. Tools must be able to locate and access information resources.

A variety of kinds of tools might be used for this purpose. The component services should have APIs that enable them to be queried with respect to their descriptive axes, and searched for particular resources. Further, the component services might be required to register themselves with respect to lookup services, such as provided in distributed object resource environments. The invocation of queries might be via agents, bots, search engines, or other mechanisms.

The coordination of the development of axes and taxonomies for indexing of information resources for specific domains and subdomains needs to be under the aegis of editorial boards, ideally convened by professional specialty organizations focused on those areas of endeavor. Besides their expertise in the areas, such editorial boards are probably in the best position to assess quality indicators.

9.2 Integration methods

Two kinds of capabilities must also exist to enable applications to integrate external infor-mation resources into problem-based contexts:

1. The application must be able to provide a knowledge model that characterize its problem solving approach in terms of the types of information resources that would be use-ful, ideally identifying specific points in the process where they are most needed.

For example, in a clinical encounter, the SOAP note in the problem-oriented

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paradigm has an implied knowledge model, in which identification of a problem determines what da-ta elements (subjective and objective) are relevant. Once data elements have been recorded, their values should determine what assessments are appropriate. Having recorded the as-sessments, these choices should determine the appropriate plans for further workup or treatment. Thus there is an underlying guideline for management, with a set of rules that go from proble m definition to data, from data to assessments, and from assessments to plans.

A Role for Guidelines: For clinical practice, we can therefore use clinical guidelines as a basis for creating the underlying knowledge framework. Associated information resources, such as the evidence for a particular decision or action, a dose calculation tool, or instruc-tions for the patient regarding side effects of a medication or preparation for a forthcoming procedure, can be tied to particular steps in a guideline.

We have been carrying out considerable work in development of a sharable representa-tion model for computer-interpretable clinical guidelines, called GLIF (GuideLine Inter-change Format) [16,17]. Clinical guidelines are of interest for a number of reasons, primari-ly to encourage best practices and reduce unjustified practice variation. They can hopefully reduce medical errors [18] and encourage high quality care, and are ideally evidence-based. While guidelines have been produced for decades, and distributed in read-only form, in textbooks, journal and magazine articles, and more recently via CDROM and the Web, they are not typically sufficiently well structured to enable them to be directly executed. Not only are phrases inexact or vague, but logic is not always fully specified, and the medical data elements and actions referred to in decision steps or in recommendations are impre-cise.

Computer-based guidelines are potentially useful in a wide variety of applications, including consultation, risk assessment, determination of appropriateness of a procedure or a referral, audit and quality review of care, automated alerts and reminders, the specifica-tion of the management protocol of a clinical trial, and in educational simulations.

We are pursuing the goal of trying to standardize the representation of computer-based guidelines, for the variety of applications described above. Because of the enormous effort involved in creating high quality, evidence-based guidelines, and the even greater effort in structuring them sufficiently to enable them to be automated, it would be useful if the representation were sharable. This is because additional adaptation and interfacing is needed to map authoritative guidelines to vendor-specific clinical platforms, to their EMRs, and to local constraints or preferences for medical practice, and to revise these adaptations, when the guideline is updated. GLIF development has been carried out by our group at Harvard, in conjunction with medical informatics groups at Stanford and Columbia, in a collaborative project known as InterMed, funded in part

by the National Library of Medicine, the Department of the Army, and the Agency for Healthcare Research and Quality. Recently, the InterMed group initiated cooperation with the HL7 standards development organization, to establish a Clinical Guidelines Special Interest Group within HL7 to further pursue the definition and adoption of a standardized approach to computer-based guidelines (Fig.4).

Figure 4. A GLIF-encoded guideline for evaluation of post-nasal drip syndrome (PNDS) as a cause for cough. Underlying the flow chart view for laying out or visualization is a formal representation, based on an object-oriented data model. [Courtesy of M. Peleg, Stanford University]

For the particular purpose described in this paper, that of providing a predictive framework for assembling information resources for a clinical encounter, guidelines appear promising as a basis for representing the knowledge, and our research group is pursuing this. This is particularly feasible for settings in which a patient's problem, and the stage of disease and treatment plan are known from the patient's EMR. Patients with chronic dis-eases, such as diabetes, hypertension, congestive heart failure, or asthma tend to have mul-tiple clinical encounters over the course of their disease. Not only does the patient have a known problem, but he or she is typically in a particular state of evolution or management of that problem (which we term "clinical management state" or CMS) [19], for example, stable hypertension on beta blocker drug therapy with no comorbidities or complications. Patients tend to stay in a CMS for a period of time, further defining the framework for the clinical encounter, in terms of the data needed, likely assessments and plans, and other in-formation resources that may be useful. Patients may transition to other CMSs, in which case the encounter is based on the new CMS.

The guideline structure for a CMS can be used to predict what data elements need to be retrieved from the EMR, what new data are required, what assessments are likely to be made (and whether they should be automatically triggered or suggested based on the data), the plans that are

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likely (again, possibly triggered, based on the various possible assess-ments), other information resources that may be useful, such as instructions or educational materials for the patient, and references, decision aids, and other materials for the provider.

For clinical care, therefore, a knowledge model can be constructed by combining (a) clinical management states identifying classes of patients, and (b) clinical guidelines for the decision making and process flow associated with the states. This framework enables information resources to be associated with classes of patients, and more finely with particular activities represented by guideline steps.

For other arenas of activity, such as education and research, other knowledge models and frameworks would of course be needed. To the extent that activities can be classified by a state model, and the decisions and process flow predicted by a guideline model, the above approach might be useful for them as well.

2. An interface paradigm must exist for determining how to integrate external information resources into applications, in a form that is helpful to the user, facilitates workflow and task performance, and does not overwhelm.

Given a knowledge model, we must determine how best to integrate the information access and decision support functions with the workflow and processes of the target application. For example, if the application is one for clinical encounter record keeping, a set of forms can be generated for data entry that are predicted by the guideline. Once data are entered, a set of forms for selecting appropriate assessments can be generated, with highlighted assessments corresponding to those predicted by the guideline based on values of the entered data. Subsequently, forms for entering plans and orders could be generated with highlight-ed plan/order elements based on the particular assessments that have been chosen. Infor-mation buttons can be associated with elements for which there are corresponding infor-mation resources in the knowledge model (Fig. 4). A critical pathways/care plan application would use a guideline to extract pertinent data from the record to match against thresholds in the care plan model. An application that used guidelines to determine appropriateness of referrals or procedure orders might be inte-grated with the order entry or scheduling functions of the information system, such that a form requesting data determined by the guideline to be necessary for assessing appropriate-ness of the referral or order might be displayed, and explanations and other supporting doc-umentation provided. Other clinical and non-clinical applications might integrate the knowledge in different ways, for which paradigms need to be determined.

Figure 4. A prototype user interface for entering assessment into a progress note for a clinical encounter in a primary care setting for a patient with moderately well controlled diabetes. An underlying guideline suggests potential assessments by highlighting selections, based on data that have been entered or retrieved from the EMR about the patient's subjective and objective evaluation. The physician may inspect the rationale for highlighted suggestions, and if he or

10. Other Issues

Many other considerations are important with respect to development of an infrastructure to support knowledge management and decision making. For example, with respect to privacy and confidentiality of data, how should interactive decision support resources access and interact with local data? If the resources are accessed through an API to an external service, how is protection of patient data assured? Or must they be operated only as services internal to a health care institution? More fundamental issues relating to standardized en-coding of medical data elements must be solved for generic services to be useful. Further, the data relating to outcomes need to be able to be pooled if we are to be able to do assess ments of the decision support tools themselves. For that matter, where should "ownership" of the medical record reside? At present, there is essentially no such thing as a complete patient medical record – portions providing institution- or practice-specific records exist in various places. The whole record would need to somehow be a synthesis of all these disparate sources. This is exactly the reverse of the ideal paradigm, in which the record would exist *in toto* under the aegis of the patient or some trusted authority, and views of it could be obtained, upon authorization, by institutions or practitioners or the patient, based on a need for specific information; they would then in turn update the primary record with new information as it was obtained.

The "holy grail" of clinical knowledge management and decision support is a set-ting in which all patient data are encoded in structured form using standard terminology, and longitudinal records of all patients are maintained. Cross-sectional research that is ap-propriately monitored to comply with human research study requirements could be done on this corpus of data. In effect, this would enable every patient to become part of a clinical trial, since it would be possible to retrieve the aggregated experience of patients with simi-lar findings, in order to determine the distribution of diagnoses, responses to therapies, and long term prognoses. Knowledge in this setting would be able to be dynamically derived from such collective experience. We are a long way from achieving this goal,

but the essential first steps are to begin to organize problem solving tasks, identify and formalize the data elements required for them, and associate the appropriate decision aids and other knowledge resources with those tasks.

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Chapter 40: AI Introduction to Healthcare

Renata G. Bushko, M.S.
Director, Future of Health Technology Institute, Hopkinton MA, USA

Abstract

We work hard on creating AI-wings for physicians to let them fly higher and faster in diagnosing patients - a task that physicians do not want to automate. What we do not work hard on is determining the ENVIRONMENT in which physicians' AI wings are supposed to function. It seems to be a job for social/business analysts that have their own separate kingdom. For the sake of all of us (potential patients!) social/business consultants and their methodologies should not be treated as a separate kingdom. The most urgent task is to achieve synergy between (1) AI/Fuzzy/Neural research, (2) Applied medical AI, (3) Social/Business research on medical institutions. We need this synergy in order to assure humanistic medical technology; technology flexible and sensitive enough to facilitate healthcare work while leaving space for human pride and creativity. In order to achieve humanistic technology, designers should consider the impact of technological breakthroughs on the organizations in which this technology will function and the nature of work of humans destined to use this technology. Situated (different for each organization), Strategic (based on an in-depth knowledge of Healthcare business), and AI-Enhanced (ended with a dynamic model) method for introducing technology to Healthcare allows identifying areas where technology can make medical work easier. Using this method before automating human work will get us closer to the ideal where there is no discontinuity between design and use of programs; where the technology matches users' needs perfectly - the world with humanistic technology and healthcare workers with AI-wings.

1. Is there a Cure for Diagnomania?

Diagnomania is an obsession with automating medical diagnosis while ignoring a real-world environment where diagnosis takes place. Medical AI research community suffers from diagnomania: it has been concentrating on the medical diagnosis for more than a decade despite of the fact that physicians do not want to automate it. Diagnomaniacs do not want to hear what an experienced neurosurgeon says: " I will never decide to operate on a patient based on a diagnosis of a machine." They ignore social setting of medical practice. Diagnomania, not physician's resistance to technology, is the reason that "the field of AI, which has attracted commercial attention recently as expert systems have been successfully implemented in industry has produced only a handful of narrowly focused commercial Because of Diagnomania healthcare workers do not have AI-wings yet and patients do not get a full advantage of achievements of modern computer science. It is time to change that! Diagnomania is not terminal. The cure involves internalizing that physicians and nurses do not deliver patient care in

isolation but they function in communities of operating procedures) as much as their cognitive powers. These structures should not be ignored in defining AI projects aimed at creating new tools for healthcare!

On the contrary, the nature of medical workplace should drive the type and extent of research/application projects in healthcare. In addition, a unique organizational environment of healthcare institutions is what makes medical knowledge elicitation different from knowledge acquisition for other non-medical expert systems. Thus, we can increase both a rate of success of AI projects and accuracy/speed of medical knowledge acquisition by building models reflecting the nature of medical workplaces.

2. What is the Nature of the Medical Workplace?

The nature of clinical work in medical communities of practice is highly nonroutine [2] and emergency-driven. It requires constantly inventing new ways to cope with unforeseen contingencies under time pressure and with limited resources. Patient care environment forces workers to "carry out their routine tasks and - often simultaneously - respond to unforeseen combinations of events [2]".

Medical work is based on dynamic, cross-functional, inter-departmental, and inter-organizational collaboration that requires constant communication and effective sharing of professional knowledge. It takes place in healthcare institutions that are constantly restructuring themselves in order to survive in a turbulent, competitive environment. Especially now healthcare executives must actively work on strategic repositioning of their organizations and their work is much like that of clinicians but their goal is a healthy organization in addition to healthy patients. CEOs and CIOs define social/business setting for medical practice, thus indirectly affect medical communities of practice.

Figure 1. Healthcare worker in isolation and in a social context

3. What kind of Tools Can Informate[1] Medical Work?

The irregular and ad-hoc nature of medical work (clinical and administrative) can be addressed by AI in three ways: (1) achieving high adaptability of programs (reasoning by analogy, approximate reasoning, machine learning, incorporation of neuro-fuzzy work validation methods), (2) getting automatic programming to work (healthcare workers create their own decision-support systems); (3) using social techniques and AI business modeling to precisely identify real need for medical decision-support systems within the reach of current technology.

(1) It is imperative that medical decision-support systems are flexible,

[1]Automating means introducing technology without paying attention to its effect on people; Informating goes beyond automating and prepares people and business process for technological change [9]

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non-brittle, and able to do "guessing" given incomplete knowledge. Research on analogical reasoning in large knowledge bases strives to create such adaptive applications but more work is still needed [3] [4] [5]. Neural and fuzzy solutions provide flexibility but we do not have good ways to validate them, thus we cannot rely on them in "main stream" patient care. (2) Automatic programming that could eliminate time/space discontinuity between design and use of programs is not mature enough to handle medical applications. (3) Social/business modeling (e.g., Situated, Strategic, and AI-Enhanced method) of the medical workplace, can and should be used NOW to define application areas where today's AI can really help by being incorporated into an enterprise-wide Integrated Healthcare Information System (IHIS).

4. Why do We Need Situated, Strategic, and AI-Enhanced Method?

4.1 Why Situated?

Representing knowledge about technology in medical workplace is difficult because technology has a dual nature: it is easily manipulated by humans, but also molds behavior and organizational practice. "This reciprocal causation of dialectical relationships implies that a general predictive model of the interaction of technology with organizations is not meaningful [6]."

The specific institutional context (situation) has to be understood and this is the essence of the situated approach. We cannot count on preexisting, general knowledge relevant to a specific workplace. The only way to represent knowledge about a workplace is to do the "field work";

experience it - immerse in it and then represent it.

Thus, in order to understand a real medical community of practice a researcher/developer must have skills of a social scientist who is sensitive to the subtleties of motivational factors, power struggles, and frustrations within organizations

4.2 Why Strategic?

We need to include knowledge about strategic positioning of a medical institution in an economic environment as a part of the workplace analysis because it affects the way communities of practice function and evolve (e.g., by the year 2000, nearly 80% [today 45%] of community hospitals will belong to hospital systems [7] which will change communication patterns within medical communities of practice). A structurational model of technology derived from Gidden's theory of structuration can provide a framework for building a guidance system for situated and strategic organizational knowledge representation. Giddens' theory describes reciprocal interaction of social actors and institutionalized social practices [Figure 2].

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Figure 2. A Framework for Strategic Knowledge Representation

4.3 Why AI-Enhanced?

Capturing real-time dynamics of a distributed business/medical process in a model allows for the discovery of bottlenecks in information flows and enhances the quality and speed of knowledge acquisition. A knowledge engineer communicates better with healthcare workers if model is used as a focal point; automatic knowledge acquisition tools can reuse "modeling knowledge". In addition, AI modeling enables technology designers to create a model of a future workflow (e.g., mediated by AI applications) before investing in implementation. This prepares users for the change, facilitates discovery of possible difficulties, and helps planning new applications' integration with Healthcare Information Systems. For example, modeling healthcare work with SYMMOD[2] allowed to encode, hard to otherwise capture, knowledge about handling delays in radiology report distribution and made emergency-driven nature of physician-radiology communication process explicit.

Because medical knowledge "happens" in reaction to events (it is not static), an AI modeling tool able to represent this kind of knowledge has to easily support the following: (1) Multiple levels of abstraction, (2) Multiple logical views of the same process - different workers talk about the same process differently, (3) Emulation of dynamic interdependencies among activities and data over time; (4) Self-documentation; (5) Dynamic tracking of incomplete information - model assumptions [8].

5. Expectations

Using Situated, Strategic, and AI-Enhanced analysis of the workplace before automating human work assures that new technology makes this work easier and thus users fully accept it. Once researchers/designers get to use this method there will be more medical decision-support systems that are actually accepted and used in many areas of practicing medicine (e.g., patient referral, data analysis, policy monitoring, lab data analysis, health-education); there will be more enterprise-wide, scaleable AI applications integrated with Healthcare Information Systems. It is imperative that research on new ways to enhance

[2]SYMMOD is a symbolic modeling environment developed at a Digital Equipment Corp. that combines techniques of business analysis and discrete modeling with knowledge-based methods

medical work starts from the workplace analysis. AI modeling makes this analysis easier - a dynamic model helps to capture knowledge about the environment in which physicians and nurses work. Environment awareness enhances the quality and speed of knowledge acquisition. Situated, Strategic, and AI-Enhanced method of technology introduction will simply give healthcare workers AI-wings that let them fly where they want not there AI-designers think they should.

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Chapter 41: Artificial-Intelligence-Based Hospital-Acquired Infection Control

Klaus-Peter Adlassnig [a,b,1], Alexander Blacky , Walter Koller
[a] *Section on Medical Expert and Knowledge-Based Systems, Medical University of Vienna, Spitalgasse 23, A-1090 Vienna, Austria*
[b] *Medexter Healthcare GmbH, Borschkegasse 7/5, A-1090 Vienna, Austria*
[c] *Division of Hospital Hygiene, Clinical Institute for Hygiene and Medical Microbiology, Währinger Gürtel 18-20, A-1090 Vienna, Austria*

Abstract

Nosocomial or hospital-acquired infections (NIs) are a frequent complication in hospitalized patients. The growing availability of computerized patient records in hospitals permits automated identification and extended monitoring for signs of NIs. A fuzzy- and knowledge-based system to identify and monitor NIs at intensive care units (ICUs) according to the European Surveillance System HELICS (NI definitions derived from the Centers of Disease Control and Prevention (CDC) criteria) was developed and put into operation at the Vienna General Hospital. This system, named Moni, for monitoring of nosocomial infections contains medical knowledge packages (MKPs) to identify and monitor various infections of the bloodstream, pneumonia, urinary tract infections, and central venous catheter-associated infections. The MKPs consist of medical logic modules (MLMs) in Arden syntax, a medical knowledge representation scheme, whose definition is part of the HL7 standards. These MLM packages together with the Arden software are well suited to be incorporated in medical information systems such as hospital information or intensive-care patient data management systems, or in web-based applications. In terms of method, Moni contains an extended data-to-symbol conversion with several layers of abstraction, until the top level defining NIs according to HELICS is reached. All included medical concepts such as "normal", "increased", "decreased", or similar ones are formally modeled by fuzzy sets, and fuzzy logic is used to process the interpretations of the clinically observed and measured patient data through an inference network. The currently implemented cockpit surveillance connects 96 ICU beds with Moni and offers the hospital's infection control department a hitherto unparalleled NI infection survey.

1. Introduction

The increasing availability of digitalized medical data of patients in a hospital permits comprehensive identification and monitoring of nosocomial infections. The now routinel used information systems in hospitals are one of the basic foundations of this procedure. The systems are capable of storing, transferring and retrieving an ever-increasing body of digitalized data concerning the patients' medical history, the outcome of physical examination, the different outcomes of laboratory tests, and the findings of various clinical investigations. These

systems are known as hospital information systems (HISs), whose many functions include the administration of data pertaining to the admission, transfer and discharge of patients in order to render these data accessible to medical information systems (MISs) at the different wards and out-patient departments that contain the medical data of patients, as laboratory information systems (LISs) with the respectively gained laboratory findings, as well as patient data management systems (PDMSs) at ICUs with clinical, laboratory, equipment-based and nursing data.

High-quality knowledge-based support for making medical decisions based on these patient data stored in the respective information systems requires that medical knowledge be represented in a formal manner and stored in a computer system. This may be in the form of interpretations of rare or complex laboratory findings, or computer-based definitions of symptoms, diseases and treatment processes, and their inter-relationships, or rules or tabulated forms of medical decision-making procedures, to name a few.

Advances in methods of formal representation and processing of medical knowledge achieved in the fields of artificial intelligence, fuzzy set theory, and fuzzy logic permit computer-based processing of medical knowledge originally available in natural language [1]. A few examples of these are the definitions of nosocomial infections issued by CDC [2–4], HELICS [5], and KISS [6].

2. The MONI programs

At the individual clinics of the Medical University of Vienna (Vienna General Hospital), a number of algorithmic and knowledge-based identification and monitoring programs for microbiological findings and nosocomial infections have been introduced and implemented on this basis. These have been accompanied by a number of flexible statistical evaluation modules. The systems include the following:

- Moni/Germ: Germ and antibiogram monitoring for pre-defined species using specifically defined resistance patterns in newly submitted microbiological reports;
- Moni/Cross: Cross-infection monitoring by collecting information as to whether germs with resistance patterns are passed on, which—within a specific time period—have been previously registered in a different patient;
- Moni/Trend: Frequency and trend monitoring by collecting information as to whether there have been increases in the frequency of pre-defined germs beyond a “basic level” indicative of an epidemic event and how strong these deviations are; and
- Moni/Surveillance: Monitoring for nosocomial infections by collecting information as to those patients in whom the definitions of nosocomial infections represented as complex fuzzy rules are completely fulfilled, fulfilled to a certain extent, or not fulfilled at all, as indicated by the collected data in the respective information systems.

3. The Moni/Surveillance program

Figure 1 shows the methods that constitute the basis of Moni/Surveillance, a comprehensive monitoring program developed for nosocomial infections at ICUs to be surveyed by the infection control team of the hospital.

All of the Moni programs are directly connected to the LIS of the microbiology department (currently this is the electronic data processing (EDP) system of the Municipality of Vienna; later on it will be the MOLIS system of Vision4Health) as well as the PDM systems of the ICUs (here: CareVue classic of Philips). On the one hand, the Moni programs actively provide information about germs and nosocomial infections in the individual patient, give reasons, and permit rapid intervention. On the other hand, the output statistics provide information about existing germs and infections at the wards, out-patient departments, or the entire medical facility.

Figure 1. Interplay of the applied formal methods in Moni/Surveillance

The following screenshots show some steps of the Moni surveillance system established for the clinical department of hospital hygiene at the Vienna General Hospital:

Figure 2. Indication of those ICUs at which patients developed a suspected or confirmed nosocomial infection according to the most recent data. The color codes indicate whether they were suspected cases, i.e., the HELICS definitions of nosocomial infections were only partly fulfilled, or whether they were confirmable cases in which the definitions were completely fulfilled.

Figure 3. In one patient at the neurosurgical ICU the definition of a catheter-associated symptomatic urinary tract infection (refer to UTI-B-k above right) is fulfilled by 100%; the underlying originally measured and observed patient data and the intermediate medical concepts derived from these data are shown as explanation, if requested.

Figure 4. Tracing the logical conclusion chain shows that the patient received a urinary catheter; this data element was documented in the PDMS and passed on to Moni/ Surveillance through intermediate steps.

Figure 5. An increased level of C-reactive protein (CRP) is present 100% as a clinical symptom because a determined value of 6 mg/dl (see Figs. 6 and 10) is definitely an elevated value.

Figure 5. An increased level of C-reactive protein (CRP) is present 100% as a clinical symptom because a determined value of 6 mg/dl (see Figs. 6 and 10) is definitely an elevated value.

4. Methods

Figure 8 shows the implementation of a part of the definition of septicemia of the HELICS document [5] into a formal rule. This—like all other definitions of nosocomial infections—exists in natural language. It is "primary septicemia with clinical signs of sepsis and two-fold common skin germs in blood." The elements of this rule are decomposed into their constituents (Fig. 9). They contain a number of sub-definitions of clinical and microbiological concepts that are finally evaluated by importing data from both, the PDM systems of the Vienna General Hospital and the LIS of the microbiology department. Some of these concepts, as can be seen in Figure 10 based on the example of "CRP increased", are defined as fuzzy quantities.

Figure 7. "Other findings of a urinary tract infection" can be fulfilled by several means; here pathogens were found in urine.

Figure 8. Definition of septicemia with its top level concepts that need to be further decomposed into their constituents.

When the medical data of a specific patient are mapped in, the individual fuzzy concepts are processed and combined through fuzzy logic.

Technically, the rules and concept definitions are represented by using the Arden representation scheme [7]. Arden is a medical knowledge representation and rule-based inference standard supported by HL7 [8]. The basic building blocks of Arden are so-called medical logic modules (MLMs). Each of these modules is usually responsible for one action to be taken on the basis of incoming medical data of a particular patient. Such an action may be an allergy alert, a recommendation for a change in the drug dose, etc. For Moni/Surveillance we created larger building blocks or so-called medical knowledge packages (MKPs). They consist of a number of interwoven MLMs, each contributing to the overall task. Within

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these MKPs, there are MLMs for simple mapping and pattern matching tasks, others for aggregating detailed information, and yet others for the final logical inference steps. At present 47 MLMs form the MKP for Moni/Surveillance. An Arden rule engine residing on an Arden server attached to a database with patient data from the connected ICUs holds and processes the MKPs, or MLMs respectively (see also [9]).

Figure 9. Decomposition of the concept of "clinical signs of septicemia" for today (t), yesterday (t-1d), and tomorrow (t+1d) (for retrospective studies).

5. Results

Currently we have implemented 24 fully computer-based definitions of nosocomial infections as they occur in adult ICU patients according to the European surveillance system HELICS [5]. There are six forms of septicemia, nine forms of pneumonia acquired at the ICU, six forms of urinary tract infection, and three forms of central venous catheter-induced infection.

At present, twelve ICUs with adult patients at the General Hospital of Vienna, comprising 96 beds in all, are connected to Moni/Surveillance. In a currently ongoing test and fine-tuning phase, the system is being evaluated and optimized.

The results obtained thus far not only demonstrate the technical feasibility of the system; the medical results already show that it is an exceptionally valuable means of identify ing clinical cases of nosocomial infection in an automated manner (currently such identification is performed by the inf ec tion control personnel).

Figure 10. The medical concept of "CRP increased" is defined by a fuzzy quantity. Under 1 mg/dl "CRP increased" = 0, i.e., it is not fulfilled. At 3.5 mg/dl "CRP increased" = 0.5, i.e., it is fulfilled to a certain extent (here by 0.5). A CRP value of 6 mg/dl and beyond means "CRP increased" = 1 and thus the medical concept is completely fulfilled.

6. Conclusion

By applying methods of artificial intelligence and fuzzy theory, the existing identification and monitoring program Moni/Surveillance has been equipped with knowledge-based intelligence that performs complex analytical steps automatically, substantiates these, and thus renders them comprehensible and reproducible.

We believe that routine application of this program will make a significant contribution to quality management at the Vienna General Hospital. In

particular, it will assist the treating physicians in reducing the rate of nosocomial infection at the ICUs and may therefore potentially serve as a significant cost-reducing measure.

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Chapter 44: Doctor of the Future with Knowledge of 1000 Best Physicians and Medical Traditions from 50 Cultures

Renata G. Bushko
bushko@fhti.org
@RenataBushko
Founder, Future of Health Technology Institute, Happier, Longer Lives.™ www.fhti.org

In 2057, your personal pharmacists/nurse/physician could very well be Dr. Zuzu, not a human at all but a distributed Intelligent Caring Creature (ICC) with the combined knowledge of 1,000 of the best physicians, pharmacists, and nurses from different medical specialties from 50 cultures. You would visit Dr. Zuzu at its office in the Cyberspace

Dr. Zuzu will be prepared to respond to many requests related to maximizing joy and pleasures of life, no longer with a focus as in current medicine on reducing pain because most diseases have been eliminated and the probability of the rest of them was minimized in the neonatal phase through chromosome replacement. Effective preventers (stress reducers) helping ICCs also contributed to low-sickness levels.

To facilitate ease of patient-physician communication, Dr. Zuzu will have multiple personalities, sex, age, voice and cognitive style depending on the situation and the patient. This includes the ability to become a humanoid version of the best friend from high school in order to maximize its convincing power and emotional closeness. This way Dr. Zuzu will be able to relate well to emotional states of its young and elderly patients.

Based on the genetic profile of each patient Dr. Zuzu will develop a long-term educational and care plan based on personalized interactive movies, illustrating major behavioral points that should be reinforced to maximize life's capacity, length, and pleasure.

Dr. Zuzu's ability to annotate and retrieve from image and video libraries will allow a just-in-time health education or compliance program. Dr. Zuzu will also be able to prescribe and then develop (in its virtual R&D lab) personalized drugs just for its patient

Dr. Zuzu will help its patients not only to maintain good health but also deal with bad health in a compassionate and emotional way. Through Dr. Zuzu you will access to the essence of millions of stories of other people going through a given condition including:

- Encoded mental states
- Most common thoughts
- Activities and words that helped them to make it through the rough experience

Dr. Zuzu's collective common sense knowledge will allow it to always say the right thing or to produce a right virtual companion you can interact with through direct retinal projection, in difficult cases.

Dr. Zuzu will charge its patients per knowledge injection and per successful interaction that will be automatically recorded based on your positive response recorded in your data stream. The payment will be expected also in the form of knowledge – your permission to use your data to further improve Dr. Zuzu's

common sense and medical knowledge. This way your personal ICC will revitalize its curing and educational ability.

What about the patients?

All Dr. Zuzu's patients will be equipped with computers in their homes and cars in the form of data glasses, windows, mirrors and e-wallpaper. In addition, they will have on-body sensors and nanocomputers inside their bodies allowing continuous screening, monitoring and data collection about their physical and emotional state (e.g. EKG, GSR). They will also have bathroom MRI machines, shower skin mole detectors, toothbrush protein analyzers, smart beds monitoring sleep pattern, and sensors equivalent to a hospital pathology lab, checking daily basic lab results.

Their on- and in-body sensors will be able to report pain or any unusual physical or emotional state directly to Dr. Zuzu. They could also do it via a voice-enabled telehealth tool at any time since Dr. Zuzu understands 105 human languages and 1,005 machine languages.

Another communication option will be hybrid brain-machine interface, allowing a patient to send a request to Dr, Zuzu just by thinking about requesting an extraordinary virtual experience.

Dr. Zuzu will always listen to all its patients (no limit on amount) and will process their vital signs and test results, relating all the findings and looking for unusual patterns. Dr. Zuzu will be able to warn patients about incoming health problem (e.g., pain) using its case-based and memory-based predictive engine. For example, it could warn you: "Please, call your surgery robots before leaving for work, to remove a splinter that will cause pain in three hours and 15 minutes – just when you have to change plains in Denver."

Dr. Zuzu's will have a rich library of health stories extracted from life-long medical data. These stories will be parsed and represented in the knowledge base for further retrieval and then turned into video scripts out of which context-specific educational health movies will be assembled for other patients in need.

What if Dr. Zuzu gets sick itself?

Dr. Zuzu will use self-treatment through knowledge injections. Another option is to call on other Intelligent Caring Creatures and get a byte of support. Most of the time Dr. Zuzu is in perfect shape – never tired and never competitive or jealous, never anxious or annoyed.

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Chapter 45: What is Digital Medicine?

David Williamson Shaffer, M.S., Ph.D.
Lecturer, Harvard Medical School, Harvard University Graduate School of Education, Massachusetts General Hospital Department of Dermatology, Boston, MA, US
Colleen M. Kigin, M.S., M.P.A., P.T.
CIMIT (Center for Innovative Minimally Invasive Therapy), Massachusetts General Hospital Institute for Health Professionals, Boston, MA, US
James J. Kaput, Ph.D.
University of Massachusetts
G. Scott Gazelle, M.D., Ph.D.
CIMIT, Harvard Medical School, Harvard School of Public Health, Massachusetts General Hospital Department of Radiology, Boston, MA, US

Abstract

Changes in health care are a fundamental part of social and intellectual evolution. The modern practice of scientific medicine depends on the existence of the written and printed word to store medical information. Because computers can transform information as well as store it, new digital tools cannot only record clinical data, they can also generate medical knowledge. In doing so, they make it possible to develop "digital medicine" that is potentially more precise, more effective, more experimental, more widely distributed, and more egalitarian than current medical practice. Critical steps in the creation of digital medicine are careful analysis of the impact of new technologies and coordinated efforts to direct technological development towards creating a new paradigm of medical care.

1. Introduction

The last two decades have seen the beginning of a digital revolution that is creating a new information economy, and with it new paradigms for business, politics, and culture. Not surprisingly, the field of medicine is undergoing dramatic change as well.

Public conversation about health care in this time of change has tended to address questions of policy and technology. Politicians, practitioners, patients, and the health care industry more generally are concerned with access to care, reimbursement policy, improvements in quality of life, and the role that technology plays in raising or lowering the cost and efficacy of medical care. [1] [2] Much of this discussion has focused on local changes, looking at the current state of health care in comparison with the practice of medicine in the past 40 or 50 years. Policy makers ask, for example, whether Health Maintenance Organizations (HMOs) provide care that is more or less expensive — and more or less effective — than the employer-based fee-for-service insurance system that developed in the United States after the Second World War [2] [3] [4].

If we step back not 30-50 years but 3000-5000 years, we can see that the nature of medicine itself is changing. Technologies of the digital revolution do not just alter the cost of health care, the range of diseases that can be treated, or overall quality of life for patients. These technologies are

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fundamentally transforming the practice of medicine.

2. Background - From Healing Art to Medical Science

Disease and healing have been a part of the human condition as far back as the science of archaeology can take us. Skeletal remains of early hominids show evidence of disorders such as hypervitaminosis A and yaws, and excavations have uncovered bodies with evidence of wounds successfully treated, dislocations successfully replaced, and broken bones successfully set. [5] [6]

The development of scientific medicine is a relatively recent phenomenon, however. It is only in the last few thousand years (a blip in the span of human evolution) that early medical texts begin to define medicine "as something over and beyond mere healing, as the possession of a specific body of learning, theoretical and practical, that might be used to treat the sick." [6] It is no coincidence that the distinction of medicine as something "beyond mere healing" emerges around the same time as the development of writing. The development of medicine as a body of learning was intimately connected with the ability of physicians to record observations about specific patients and specific diseases, to share these observations, and to theorize about how the human body functions. Hippocrates and Galen, the giants of early Western medicine, made their marks by collecting, extending, and codifying medical knowledge in extensive writings.

By today's standards, the medicine of Hippocrates, Galen, and their successors appears systematic, but not yet scientific. A fifteenth century physician's admonition to "let not the sun go down behind the hill without your having gone out, or if you can not, take before meals a little exercise" [6] is good advice for general health. But these words were offered as a method for avoiding bubonic plague, against which regular exercise is little defense. Prescriptions such as this for controlling the interactions of miasmic vapors and bodily fluids were based on the notion of humoral balance — medical care based on the importance of balancing emotional states. [7] This was a theory of disease, to be sure, but not yet scientific medicine.

The development of scientific medicine as we know it today was made possible by the invention of the printing press. In 1543, just over ninety years after Guttenberg produced the first printed bibles, Vesalius published his seminal text on human anatomy. In the centuries following Vesalius, modern medicine was developed through collaborations between investigators and theorists over time and across space. While printing was not the only factor involved in the creation of scientific medicine, these collaborations were made possible in large part by the publication and distribution of medical texts. [8] [9] Scientific medicine depends on the recording, collecting, and comparing of observations, the formation of theories, and the building of new understanding on the foundation of prior work — all of which are possible on a large scale

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only with the ability to store and distribute information widely.

3. Human Cognitive Evolution

In a recent book, *Origins of the Modern Mind* [10], psychologist Merlin Donald describes the development of human cognitive abilities in a series of stages, where new cognitive abilities are built on top of — and co-exist with — older forms. These stages of cognitive development are associated with specific cultural practices, including the practice of medicine.[1]

In Donald's analysis, human cognition departed from its primate roots some 2 million years ago when early hominids began to develop a system for mental representation based on mimesis — the ability to represent events using gesture and re-enactment. Mimesis is, for example, when we follow someone else's gaze or pointing gesture because we understand that the gesture means they want us to look at something. Recognition that a gesture can refer to an event or object (rather than being the thing of interest itself) makes it possible to communicate intent, and is only possible if the person seeing the gesture and the person making the gesture have a shared understanding — that is, if each has a model of what is taking place in the mind of the other. Mimesis made it easier for early humans to coordinate group activities — and also provided the basis for the healing arts in gestures of understanding, support, and sympathy.

Donald argues that the social advantages of mimetic communication drove the evolution of language. Humans began to use ritualized or standardized gestures, and language developed as a more efficient way to communicate these standard gestures or symbols. The development of language created the next stage of cognitive development: a "mythic" culture based on the telling of stories or narratives that carry important cultural information. Here, then, some 300,000 years ago, was the cognitive origin of the incantations, magic, myth, and rituals of healing. [13]

Donald identifies the next stage of cognitive development as a "theoretic" culture based on written symbols and paradigmatic thought. Beginning 30,000-50,000 years ago, accounting and other complex record keeping drove the development of external representations. The existence of such external representations made it possible for literate humans to think analytically by looking for relationships among recorded ideas — and thus to develop a scientific culture based on external records and external notations for thinking such as writing and mathematics. Theoretic culture requires large-scale storage of information, such as the accumulation of texts in a library. This "external memory field" acts as a medium in which analytic thinking can take place. Literate people access the cultural record (books and other written materials), use and transform that information to take appropriate actions,

[1] *Donald's thesis has been the foundation of much scholarly discussion, including a range of responses in a special issue of Behavioral and Brain Sciences [11]. However, despite significant controversy, the substance of Donald's argument remains intact [12].*

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and make new contributions to the external corpus of human knowledge.

It is hardly surprising, then, that the development of a science of medicine depended on writing and the dissemination of medical information made possible by the printing press. It is not just that the scientific method requires accurate record-keeping. The development of scientific thinking itself is intimately linked to external recording of information. Anatomy texts and patient charts are not just symbols of modern medicine — they are essential tools in the development of scientific medicine in a theoretic culture.

Donald's picture of a theoretic culture based on the external storage of information has been extended into the digital age by authors such as Shaffer and Kaput [14], who suggest that new digital tools are creating a fifth stage of cognitive evolution where computers and other new media not only store information for us, but *process* information as well. This has profound implications for the practice of medicine.

4. A new stage of development

Donald's theoretic culture depends on the externalization of memory. Cognitive theorists whose information-processing perspective matches Donald's analysis [15] explain cognition as an interaction among long-term memory, short term (or working) memory, and the process of transforming information internally. There is some doubt as to whether mental activity can be as cleanly segmented as such a model suggests; [16] however, it is clear from Donald's analysis that theoretic culture depends on external *storage* of information and internal *processing* of information.

What happens when information can be transformed externally as well? To take an example from Shaffer and Kaput, computers make it possible for a researcher to perform a statistical analysis without making a single computation by hand. Software does the necessary calculations and produces a results table or visual representation of data that the researcher can use to understand the phenomena in question. The computer is processing the information so the researcher can focus on the more interesting problem of interpreting the results of the analysis. In the same way, a clinician who orders a CT or MRI relies on a computer to gather and process a vast amount of information and render it into a useful model of internal anatomy. In both cases, the computer is not just storing information; it is taking information in one form and returning it in a fundamentally altered form without additional action by the researcher or clinician.

We are thus on the verge of a new cognitive culture, dependent on the externalization of symbolic processing as well as on externalization of symbolic representation.[2] As humans developed gestural communication, language, and writing, they created mimetic, narrative, and analytic ways of thinking that interact and compliment

[2]*We are not suggesting here that information-processing is the only important aspect of mental activity. We argue here that a new digital culture is being created as we develop new ways to execute well-specified algorithms, which are a limited by important subset of thinking.*

each other. Mimetic, mythic and theoretic cultures, in turn, developed the art of healing into the science of medicine, where the experimental method and the other tools of modern medicine augment — but do not replace — compassion in the delivery of health care. The development of computational media makes possible a digital culture, and with it, we argue, a new era of digital medicine.

5. Information and Knowledge

In order to understand how computers will create an era of digital medicine, we need to understand what it means to "process medical information." If processing medical information means only keeping more detailed medical records, or making sure that a medication delivered matches the medication ordered, then digital medicine will be a useful adjunct to clinical practice, but hardly a transformation of medicine as we know it.

It is true, of course, that computers can not imbue data with meaning. But this does not prevent them from transforming information and thus making it more available and more useful. As Wendell Berry writes: "Knowledge refers to the ability to do or say the right thing at the right time." [17] Knowledge in this sense requires the selection of (and ultimately action upon) information appropriate to a particular context: knowledge is what remains after the irrelevant and distracting pieces of information are removed and only the useful information remains.[3]

3Theorists of information make distinctions between data, information, and knowledge.[18] Information, they argue, is data combined with "meaning" — with some framework for interpretation. Knowledge is internalized information and the ability to apply that information in action. In this scheme, data is what can be stored on a computer disk. Information is the meaning of that data in "the collective mind of a society." Knowledge exists in an individual person's mind. In a theoretic culture, these distinctions are sensible: data is the external memory field which forms the medium of culture and thought. What matters is how people acquire the data (turn it into information) and how they put it to use internally (act knowledgeably). In this view, however, a computer by definition can do nothing more than store data. Data transformed remains data, and only human beings can add value to data by giving it meaning and turning it into knowledge. But in transforming data, computation augments "thinking" as well as "memory." Instead of data, information, and knowledge, we suggest in the following paragraphs that in digital culture the critical progression is from information, to knowledge, to understanding, and finally to wisdom. These two frameworks can be summarized in the following table:

Digital Clulture	Information	Knowledge selection of context-appropriate information	Understanding creation of a mental model of situation based on multiple contexts	Wisdom choice of appropriate actions based on understanding of situation

Theoretic Culture	Data	Information data + meaning	Knowledge information that is internalized and used

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By transforming information, computers generate knowledge any time they sort through, discard, and simplify information and raise its utility. The table of results from the regression is easier to use and more meaningful to a researcher than listing of the raw data. A CT scan is more useful to a clinician than a collection of individual x-ray images. Both are examples of how a computer can generate knowledge.

Of course, generating knowledge is not the final step in most activities — clinical or otherwise. There is a long way to go between completing and interpreting a statistical analysis and answering a research question, just as conducting a CT scan is only one step in the process of diagnosis and treatment.

Knowledge is context-appropriate information: a window into a particular system. We turn knowledge into understanding as we view the same situation from enough perspectives to develop a robust mental model of the underlying system. The goal of a clinician in assembling medical knowledge — whether general knowledge about physiology and pathology, or specific information about an individual patient — is to come up with an understanding of what is happening in the body and why. Finally, understanding leads to action. This produces new information, which can be turned again into knowledge, and then used to refine understanding. Wisdom is built up from this accumulatedexperience of creating understanding, taking action, and evaluating the outcome in clinical (and other) venues.

Computers can be good at generating knowledge, but computers are notoriously bad at generating understanding and wisdom [16]. So-called expert systems have a terrible track record in medical diagnosis [19]— and in many other complex domains to which they have been applied. The first chess playing program to beat a human chess master (the famous Deep Blue) was able to match human performance in a relatively simple domain (chess is far less complex than even a relatively trivial task like doing the dishes after dinner). In the foreseeable future, human beings may come to rely on machines to help generate knowledge about the world. But we will almost certainly rely ultimately on ourselves and on other people to develop understanding and act with wisdom.

6. So, What Is Digital Medicine?

Put simply: digital medicine is the transformation of health care that is coming about as computer technology is used in the creation and application of medical knowledge.

The traditional role of the clinician is as the intellectual agent of patient care. The clinician examines a patient. From the examination comes a diagnosis, and from diagnosis a plan for treatment, which is also carried out by a clinician. At each stage in the process (examination, diagnosis, planning, treatment), the clinician turns information into knowledge by deciding what data are relevant, what the data mean for the health of the patient, when and how to use instruments or administer medication.

In digital medicine, technology helps in the process of turning clinical

information into medical knowledge. CT and MRI scans are digital examinations because they collect raw data and produce segmented images of the underlying anatomy. Implantable cardiac defibrillators are digital treatments because they collect information about cardiac function and determine, based on parameters set by the clinician, whether at a given moment the heart needs artificial stimulus. Modern health care policy is digital because computer simulations and statistical tools are used to evaluate cost-effectiveness and quality of life impacts of data too complex to be analyzed using pencil and paper. [20] [21] [22] Tissue engineering, genetic sequencing, and telemedicine are digital medicine because none are possible without the power of modern computers to transform complex information into medical knowledge. [23] [24] [25]

Although digital medicine is made possible by advances in information processing, the changes brought about by digital medicine will be more than just diagnostic and analytic; digital medicine will impact therapeutic interventions as well. Minimally invasive techniques such as MR-guided therapy and radiation therapy are digital procedures because they make it possible to destroy or excise tissue using computer-augmented images of patient anatomy more precisely and with less damage to healthy tissue than is possible with traditional instruments alone [26] [27] [28]. As digital medicine improves our ability to generate and act upon medical knowledge using technology, robotically-augmented tools will be able to use sophisticated sensors to deliver drugs or carry out procedures beyond the limits of human performance, such as guiding a micro-catheter through a tortuous distal vessel, or delivering extremely precise bursts of energy to destroy cells along a tumor margin. [29] [30]

Digital medicine, in other words, is the augmentation of human abilities through the external generation and application of medical knowledge that will make health care safer and more effective by enhancing our ability to diagnose and treat disease.

7. The Ten-thousand Foot View

It is impossible at this early stage in the development of digital medicine to predict what specific diagnostic and therapeutic techniques will be developed as digital technology transforms medicine. It is possible, however, to identify some of the ways in which digital medicine will differ from the practice of scientific medicine overall.

7.1 Digital Medicine Will Be More Precise

Digital tools will make it possible to create knowledge about the human body at a level of detail previously unimaginable. Computers can collect information that is difficult to obtain or hidden in signals too noisy to interpret, and then render that information into medically-useful knowledge. [31] Mappings of the human genome have already provided a new class of treatments (gene therapies) [32]. Minimally-invasive tools make it possible to deliver drugs, energy therapies, and devices to more parts of

the body with less disruption to surrounding tissue [33] [34]. New imaging techniques make it possible to diagnose complex conditions quickly and accurately: where today we can use CT to characterize tumors and response to therapy, tomorrow we may be able to target specific neurons for pain or as the cause of seizures [35] [36]. As computational technology advances, we will be able to gather more precise diagnostic information and intervene with computer-guided and computer-assisted therapies that are less invasive and more effective at treating specific conditions.

7.2 Digital Medicine Will Be More Effective

Digital tools will make it possible to target therapies more precisely to specific diagnoses. External generation of medical knowledge is a critical component in the emerging sciences of modeling and decision analysis. [20] [21] [22] As patient data becomes more standardized and more portable,[4] and as more sophisticated tools are developed for monitoring the course of treatments, it will be possible to assess the impact of interventions — and thus to manage conditions — more effectively.

7.3 Digital Medicine Will Be More Experimental

One of the most important effects of digital tools is to make it possible to simulate anatomy, physiology, pathology, and therapeutic interventions. Computational chemistry has made it possible to generate and perform preliminary tests on candidate formulations for new drugs [37] [38], and first-generation simulation systems are currently available to help train clinicians with new devices and procedures [39] [40] [41]. As computing power advances, simulations will become more realistic and more robust. Data from real patients will make it possible to plan procedures and tailor treatment regimes to individual idiosyncrasies. High-fidelity simulations will increase the rate at which new devices and therapies can be developed, as prototypes can be rapidly created, tested, and adapted in the simulated environment, and safety and efficacy can be tested in a virtual patient before clinical trials are conducted. Digital tools will make it possible to experiment and explore in silico more rapidly and far more safely than is possible *in vitro* or *in vivo*.

7.4 Digital Medicine Will Be More Distributed

As more procedures can be done less invasively, conditions that once required inpatient hospital stays can be done in a doctors office, with the patient returning home the same day. Telemedicine is already making it easy to get expert consultations from remote locations [42] [43], and the ability of digital tools to transform information by altering its location makes it easy to create and access knowledge and expertise across wide areas. As digital technology produces new sensors and new communications tools, inexpensive monitors will able to gather data about patients during the

4 We recognize, of course, the central importance of protecting patient confidentiality as new tools are developed to help clinicians evaluate the impact of treatments.

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course of their everyday lives and transmit it the physician. [44] Telecommunications will make it possible for examinations to be carried out from a patient's home [45], and digital networks will make it possible for patients to get high-quality information and medical advice from virtually anywhere at virtually any time. [46]

7.5 Digital Medicine Will Be More Egalitarian

New tools are making it easier for patients to make informed decisions about their health care options: from pre-packaged medical decision support systems [47] to internet forums where patients can "ask the experts", chat with people who share their conditions, or look up the latest medical information on a wide range of topics. Home testing kits are available for ovulation, pregnancy, insulin level, and other assays that previously required access to a sophisticated laboratory. In each case, the delivery of context-appropriate information — that is, the generation of medical knowledge — is made more accessible by new technology. As digital technology makes it easier for patients to access medical information — both general medical information, and information about their own health — the doctor/patient relationship will have the potential to become more of an equal partnership. The clinician will continue to have specialized knowledge and skills. But patients will increasingly have the opportunity to use the doctor as expert advisor, to help them weigh alternatives and make a wise and well-informed decision, rather than relying on the clinician as sole source of medical knowledge.

Taken together, these transformations will potentially change the role of the clinician in the health care system. As medical knowledge is generated in partnership with digital tools, clinicians will be able to focus their attention on their higher calling: the role of the physician will be to manage a wide range of clinical resources for the good of the patient, with the emphasis on complex problems of ethics, on the wise application of the power new technology brings, and ultimately on making sure that the vast medical knowledge of digital tools is grounded in human compassion.

8. Looking ahead

What medicine will become in the digital age is impossible for anyone at this point to say with certainty — just as Vesalius himself would not have been able to predict the transformation of medicine made possible by the development of the printing press. In the field of health care, it is clear that computers and other computational media will have a tremendous impact on the practice of medicine. Computers make it possible not just to store medical knowledge, but to create it. In doing so, they make it possible to develop digital medicine that is potentially more precise, more effective, more experimental, more distributed, and more egalitarian than modern scientific medicine.

Of course, this process is neither inevitable or deterministic. The development of scientific medicine

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was made possible by the invention of the printing press, but it would be ridiculous to suggest that the invention of the printing press alone created modern medical practice. Digital tools have already had an impact on health care, and fortunately the effects have been, for the most part, for the better. But there is thus much to be gained by taking a proactive approach to the development of digital medicine.

In an era of rapid and fundamental change, we can stand by passively and allow events to unfold, or we can take an active role as agents of change, trying to understand the impact of new technologies and directing them to the best possible ends. Critical steps in any such effort will be a careful analysis of the impact of new technologies and coordinated efforts to direct technological development towards creating a new paradigm of medical care. We hope that the ideas presented above will begin a larger discussion about the potentially deep and lasting effects of new technology on the practice of medicine.

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Chapter 46: How Can We Build Trustworthy, Secure and Transparent Health Apps?

Urs-Vito Albrecht
Hannover Medical School, Peter L. Reichertz Institute for Medical Informatics of the Institute of Technology Braunschweig and Hannover Medical School, Hannover, Germany
Ute von Jan
Hannover Medical School, Peter L. Reichertz Institute for Medical Informatics of the Institute of Technology Braunschweig and Hannover Medical School, Hannover, Germany

Abstract

Nowadays, smartphones, tablets and other "smart" devices along with the apps running on them are ubiquitously used in all areas of life. Health and medicine are no exception. However, while undoubtedly offering many exciting possibilities in these areas, using technologies that were originally designed with other purposes in mind holds many risks, especially in the highly sensitive context of health. Avoiding risks or mitigating their effects requires efforts on the part of all parties concerned, i.e. not only users, but also manufacturers and distributors of apps. While there are increasing efforts to educate the former about potential risks, the latter are often unaware of pitfalls they may run into when developing and distributing apps that are meant to be used in a health related context. This paper will point out a number of aspects developers need to be aware of.

1. Introduction

The popularity of mobile apps is steadily increasing, be it for private as well as professional purposes. The health sector is no exception. Here, apps are being used for various reasons: to keep fit and to track one's health status or obtain support for those who have to deal with health problems, but also in professional settings, e.g. for diagnostic or therapeutic purpose. Apps that may be used as reference are also quite popular. The great variability of possible combinations of settings as well as user and application types makes it considerably difficult to define specific criteria for "what makes an app a good app". While there are always "hard criteria"(often technical) that need to be taken into account, such as compliance to basic standards with respect to privacy and security, high quality implementation of the provided functionalities, integration of evidence based content etc., there are additional "soft criteria" that must also be taken under consideration. These are highly dependent on the specific circumstances an app can be used in as well as on the individual requirements of the targeted users. Even an app that meets the aforementioned hard criteria may be problematic if it does not meet the demands of its users. Apps that are too demanding may easily lead to operating errors because those operating them do not understand what they are being asked to do. On the other hand, apps that do not provide the content and functionalities users expect, i.e. are "too simple, will soon lose their user base. Similarly,

apps that contain "more than the user bargained for", e.g. implement functions that are not absolutely necessary for providing what is promised, such as evaluating the entrusted data in a manner that does not benefit the user but rather the manufacturer or a third party (without telling the users about this) will also not have a good standing [1]. Keeping the balance between all these aspects is not always easily done.

This paper will consider some of the most important factors manufacturers of health related apps will need to respect in order to be able to provide trustworthy, secure and transparent health apps, starting with the development phase up to the distribution of the finished product via the app stores.

2. Current Status

The chances of mobile apps are as manifold as their risks [2, 3, 4]. While there are many aspects users themselves need to consider in order making the "app experience" safe, nowadays, they are often left to their own devices when it comes to finding accurate information about an app before installation. Since not all manufacturers openly provide sufficient information about their apps, their own background, and other relevant aspects. However, transparency is a decisive factor with the potential of contributing to an app's (commercial) success. Thus, transparency should also be in the best interest of those who develop or distribute apps.

Another aggravating factor is the sheer number of apps available for choosing from. In former times, software development used to be the domain of professional developers – apart from a few non-professional enthusiasts – and successfully distributing the final product also took considerable effort. In contrast, developing and distributing a mobile app is a task that can easily be done by almost anyone (based on the tools and distribution channels for the major mobile platforms), contributing towards the rapid growth of the mobile app market. While on the one hand encouraging, especially in the context of health related apps, this can potentially be problematic: Here, depending on the functionality they provide and the designation a developer gives it (e.g. use for diagnostics or therapy), an app can easily enter the domain of so called "medical devices" that require special attention throughout their lifecycle. In an app context, depending on the risk category an app belongs to (and the respective jurisdiction), this may for example require quality assured development processes (and documentation thereof) – steps that should be respected for any app development. Additionally, registration with a "notified body", extensive testing, and official certification (e.g. as demonstrated by the CE mark in the European Union) or regulatory approval (as is the case in the United States) may become necessary. Often, developers are unaware of the requirements they need to follow, especially when distributing their apps internationally, which is easily the case when using the sales infrastructure provided by the mobile app stores. User cannot rely on the stores to recognize test an app's

quality or to ascertain whether they may fall in the "medical device category" and have undergone the necessary procedures before they are published. While the rules provided by the stores for developers who register for distribution commonly specify that apps may not cause harm to their users or damage to the devices they run on – and there are often statements to the effect that such apps will either be initially rejected or removed from the stores, there is often no clear definition of what is considered "harmful", a "risk" or a "hazard" and which measures developers should take to prevent them [5, 6]. Also, while the stores often check for what they consider "explicit content", and developers are also often required to state for which age categories their apps are "safe" to use, there are usually no special provisions for health related content, where potential damages may be much more serious and may also have lasting (bodily) consequences for users.

3. Steps to be Taken by Developers

Due to the low barriers of developing apps and only negligible restrictions of the stores when it comes to the quality of apps, developers are mostly on their own when it comes to developing safe and trustworthy apps. On the other hand, they also have to bear the legal consequences should problems with their apps arise. It is their responsibility to inform themselves about the market conditions, applicable legal and regulatory requirements (e.g. with respect to medical device regulation, data protection laws, etc.) and to implement the necessary steps [7].

Also, quality assurance throughout all phases of an app's lifecycle is of utmost importance. As for software in general – independent of whether there is a health related area of application – there are a number of norms to be considered, e.g. the ISO 9001 as well as the ISO 250xx series of norms and others. Some of these norms define the minimum set of measures to be taken by developers, and– depending on the jurisdiction – following them may even be a requirement for apps that fall into the medical device category, although it does not appear as if any of these norms are commonly applied in an app context.

While norms are also applicable outside of software development and are used in various industries, e.g. for production processes, there are also those that specifically apply to software rated as a "medical device". Here, IEC 62304 as well as ISO 13485 must be mentioned. "Quality" can be seen from various angles: as described ISO 9001, quality rests on satisfying the implicit and explicit needs of the customers, and on measuring customer satisfaction. Extensive documentation of all steps taken is also part of ISO 9001's understanding of quality. On the other hand, ISO 13485 takes this understanding of quality to the next level by describing how quality management needs to be implemented in medical device contexts and specifically aims at ensuring patient safety. Within the European Union, a quality management system implemented according to ISO 13485 fulfills the requirements of the medical device directive 94/42 EWG.

2.1. Use-Case Specific Quality Criteria

While not specifically targeting software in the medical device context, developers of health related apps should nevertheless keep the quality definitions of ISO 25010 in mind, as these are of importance from the users' point of view. Essentially, five points are described as playing a role for high quality software: First of all, the software should be suitable for the specific use case (1). Secondly, its focus should not be too narrow, but rather be adaptable (2). Software should also aim at performing efficiently and effectively (3), while minimizing risks to the user's financial or social status, his health or environment as far as possible (4). It should also be of practical benefit and fulfill the needs of the user in a comfortable and satisfactory manner, and this also includes good usability and that users can trust that the software performs as they expect (5). The foundation for these rather "soft" criteria is of course that the hard criteria often mentioned in the context of software quality are fulfilled first. These will be described in the following paragraphs as well as table 1.

2.2. Product Related Quality Criteria

As mentioned before, many of the relevant product related criteria that developers should respect are described in ISO 25010. Based on this norm, but also supplemented by aspects mentioned in PAS 277:2015 4 and guidelines put forth by other organizations [8], Table 1 lists essential points to be respected.

Table 1. Quality criteria for software also applicable to health apps.

Criterion	Explanation
Functionality	The app needs to fulfill the explicit and implicit needs of its users. Implemented functions need to satisfy these needs as user expect (functional integrity), and they must have been implemented must in a sound and safe manner.
Efficiency	The app should not make undue use of the available resources. Ideally, it should perform its functions in an efficient manner, including quick reactions to user input and rapid calculation and presentation of the results wherever necessary.

Compatibility	There are two levels that can be counted under "compatibility". First of all, an app should peacefully coexist with other apps installed on the same device and not interfere with their functions (unless intended). Where it makes sense, interoperability is also an important factor, e.g. by using standardized formats for exchanging data with other apps, as well as non-mobile software and services.
Usability	Via an appealing and easy to use interface, users should be able to make efficient and safe use of the provided functions. Functions should be easily accessible, and not require too much effort with respect to learning how to use them. An important factor is also the protection against use errors. In order to provide a good experience for all potential users, accessibility need to be taken care off. And finally, an aesthetically pleasing interface is an additional boon.
Reliability	Reliability includes not only that an app performs satisfactorily under normal conditions. In case of errors (hardware or software), basic functionality should still be available if at all possible (fault tolerance). If there is a temporary interruption or failure, it should be possible to recover the previous state and/or data (recoverability).
Data Protection/Privacy	All data entered into an app needs to be protected against unauthorized access. This may also make it necessary to implement role based access models if there is a need for multiple users to gain access to the data. It should be possible to track access to data as well as any changes to the responsible party (traceability).
Data Security	Data must be kept safe not only by providing means to protect against unauthorized access, but also via adequate encryption for storage, as well as transmission. In addition, there should be means to protect against data manipulation.

Maintainability	Apps should be designed to be easily maintainable. A number of factors can contribute to this. Using a modularized approach, an app can be easily extended, or existing modules from other apps can be reused. Of course, this necessitates well-documented code and well-designed interfaces between the modules. This is especially important since even minimal changes in one module may have serious effects on other parts of an app. Also, care should be taken to guarantee that the app and its functionality can be easily analyzed and tested against predefined criteria to ensure its functioning after any changes. Modifications should not lead to any unintentional changes in functionality.
Portability	To ensure continuing function over a longer period of time, due to the rapid development in mobile technologies, apps should be constructed such that they are easily adaptable to new hard- and software. On a similar note, wherever possible standardized formats should be used for storing/exchanging data in order to allow for easy exchange of data with similar software.
User Safety	Best practice approaches should be used to ensure that potential health related risks are avoided. In cases where it is not possible to rule out potential risks, protective mechanisms need to be implemented, e.g. via alarm functions. Also, users need to be informed about any potential risks to their health.
Compliance with legal and regulatory requirements	Developers need to respect legal and regulatory requirements as they are applicable. Since apps distributed via the app stores often target international audiences, developers need to inform themselves about the respective legislation before they put their apps on the market. If necessary, the apps should be restricted to specific markets.

Transparency	Developers need to respect legal and regulatory requirements as they are applicable. Since apps distributed via the app stores often target international audiences, developers need to inform themselves about the respective legislation before they put their apps on the market. If necessary, the apps should be restricted to specific markets. • Imprint: Information about the developer, but also meta-data regarding the app, i.e. version numbers, date of release etc. • Rationale: Information about the purpose the app serves, the users it targets and whether it has been designated as a medical device or not. • Functionality: There should be a clear description of the integrated functions, possible limitations as well as usability aspects and accessibility. • Validity and reliability: Methods employed for quality assurance as well as the information sources used to implement the app's content and functionalities should be disclosed to allow users to form an opinion about the app. • Data handling: Information about measures used to ensure data protection and privacy, but also about whether the app uses external storage, or shares any data with the developer or third parties.

5. Conclusion

Even though, from a technical point of view, it is quite easy to successfully develop and distribute an app, other aspects are not as easily taken care of. There are many legal as well as ethical aspects to consider. This is not only important to protect users, but also developers. For example, apps that were not originally designed as medical devices, but later on add functionality making them medical devices, can easily cause regulatory, legal, or financial problems for the developers if adequate documentation and quality assurance were not used throughout the development process. Developers and distributors need to be made aware that in a health context, there are many additional aspects to be respected in order to be able to provide save and trustworthy apps. On their side, this may reduce the risk for liability, while also protecting the users.

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Chapter 47: Future of Computer Implant Technology and Intelligent Human-Machine Systems

Kevin Warwick, Ph.D.
Professor of Cybernetics, Department of Cybernetics, University of Reading, UK

Abstract

Linking the human nervous system and brain directly to a computer opens up innumerable possibilities, not only in the future world of medicine, but also as a potential waya of technically evolving all humans. This, however, presents something of an ethical problem. Nevertheless, the only way to actually find out what is realistically possible and what is not is to carry out practical experimentation using implant technology and to witness the results. This chapter describes the most recent self-experimentation trials carried out by the author and his team.

1. Introduction

Technically, we are now in a position to make a useful direct connection between the human nervous system and computer technology. This has come about partly due to significant advances in the means of establishing a bond between biology and technology. The chances of a body rejecting technology or of infection setting in, although still not zero, can now be regarded as almost negligible if extreme care is taken. At the same time, the increased capabilities of computers, both in terms of computing power and networking, have opened up a whole new raft of possibilities.

As a result, we have, in recent years, witnessed a number of experiments involving animals, for example rat reward and punishment and maze following tests [1,2] and monkey remote signalling [3]. But where the trials are of considerably greater interest is where humans are involved. Various studies have involved the employment of implants to try and bring about some basic movement or control for those who are paralysed, however some of the most significant are those by Philip Kennedy [4] allowing stroke victims to control basic elements of their local environment simply by thinking about moving.

Using implant technology to help those who have a mental or physical problem, such as a paralysis, allowing them to do things that they would not ordinarily be able to do, is seen by most to be a good thing. However, the same technology can also potentially augment all humans, giving them abilities over and above those of other humans.

Clearly this presents something of an ethical issue as to whether the technology should be developed at all. Indeed it is, in itself, an intriguing question as to whether it is a good thing or a bad thing to 'evolve' humans in a technical, rather than a biological, way.

Reasons for wishing to consider extending human capabilities are manifold. Indeed it is part of human nature to try and do so. Nowadays, for example, all sorts of possibilities arise when the abilities of machine (computer) intelligence are compared with the finite, limited brain size of

humans – clearly it can be seen that the two entities have distinctly different modes of operation and in a number of ways the machine exhibits distinct performance advantages.

Obvious examples are the mathematical, number crunching, abilities of a computer and the networked computer's memory base. These are both reasons why we use computers as we do now – simply because an individual human brain cannot compete. Nevertheless, such computer abilities have led to a redefining of, and a change in our understanding of intelligence [5]. What was once thought to be an intelligent act in humans, now comes directly into question when a machine clearly outperforms a human.

Technology has also been employed externally to improve on the humans' limited range of sensing the world around them. So technology can give a picture of what is going on in the infrared or ultraviolet spectra, even translating X-ray signals into visual images that human brains can understand.

Another factor is that human brains have evolved to think in at most, three dimensions, whereas computers are able to 'think' in n-dimensions. Space around us is, of course, not three dimensional, as categorised by humans, but can be perceived in as many dimensions as one wishes. Machines therefore have the ability of understanding the world in a more complex, multidimensional way when compared to humans. This is an extremely powerful advantage for machine intelligence.

Perhaps the biggest performance difference, in an intellectual sense, between humans and machines is that of communication. Each human brain operates on relatively complex electro-chemical signals, which are converted into mechanical signals, sound waves in speech or hand movements to operate a keyboard. In reality such mechanical signalling is a very slow, error prone means of communication. As a result, human languages are nothing more than finite coding systems that cannot hope to convey more than a small fraction of what we would really like to communicate with another including our thoughts, wishes, feelings and emotions. Problems occur due to the wide variety of different languages and the indirect relationships and cultures between them. In comparison, machine communication is tremendously powerful, not only because of its usually inherent parallel nature, as opposed to human serial communication.

Looking at these mental differences between humans and machines, it is clear that humans can benefit enormously by the use of external cooperation, as indeed we do now. However a direct link could offer so much more. For example, by linking human and machine brains together could it be possible for us in this Cyborg (part human, part machine) form to understand the world around us in twenty or thirty dimensions? Even four or five dimensions would be worth it. Could it be possible to tap the mathematical and memory capabilities of computers directly, thereby probably changing the operation of the human part of the Cyborg brain? What will the human brain make of extra sensory

information being fed directly in? Perhaps most importantly of all, by linking the human brain directly with a computer, might it be possible to communicate directly between human and machine, and even person to person purely by electronic signals – something that could be regarded as thought communication?

All of these questions present an exciting new frontier for research linking humans and machines closer together. As a result, in the 1990's various scientists speculated on a future in which implant technology became a norm for all [6]. In one example Peter Cochrane, who was then Head of British Telecom's Research Laboratories wrote [7]; 'Just a small piece of silicon under the skin is all it would take to enjoy the freedom of no cards, passports or keys. Put your hand out to the car door, computer terminal, the food you wish to purchase and you would be dealt with efficiently. Think about it: total freedom; no more plastic'.

However, apart from heart pacemakers and the like to overcome a problem, no one had actually experimented with implants to provide extra abilities. Until that is, 24 August 1998 when, as reported in [8], a silicon chip transponder was surgically implanted in my upper left arm. With this in place, the door to my laboratory opened when I approached, the corridor light came on automatically and a voice box in the entrance foyer welcomed me with "Hello, Professor Warwick" when I entered the building.

But the identifying signals my 1998 implant transmitted were not affected by what was going on in my body and signals transmitted to the implant from the computer did not affect my body in any way. For that, we needed something more sophisticated. Hence, as soon as the 1998 tests were concluded, we immediately set to work on a new implant experiment.

2. Neural Implant Operation

On March 14, 2002, an array of one hundred silicon electrode needles was surgically implanted into the median nerve fibres of my left arm, at the Radcliffe Infirmary, Oxford, UK. Each one of the electrodes was 1.5 mm in length, the total array measuring 4 mm x 4 mm. With the entire median nerve fascicle estimated to have a maximum diameter of 4mm, this meant that each of the electrodes penetrated well into the fascicle.

During the two-hour operation, a first incision was made centrally over the median nerve for a length of just over 4 cm, directly up to the wrist. A second incision was then made, proximally to the first, 16 cm up the inside arm towards the elbow. This second incision was 2 cm in length. Following a tunnelling procedure to connect the two incisions together, a piece of open tubing was run between the incisions, creating a clear passage. The array, with its connecting wires, was then passed down the tubing from the incision nearest the elbow to that nearest the wrist.

Once the array had been successfully passed down the tubing, the tubing was removed from the wrist end, leaving the array in position over the exposed median nerve fascicle by the wrist. Wires from the array travelled

up the inner arm, exiting at the second incision where they were attached to an electrical terminal pad. The array was pneumatically inserted into the radial side of the median nerve fascicle under microscopic control. Once the array was successfully in position, both incisions were closed.

3. Input/Output Signals

With the array acting as a direct electrical connection into the human nervous system, it was found to be eminently possible to transmit neural signals directly from the peripheral nervous system to a computer. These neural signals could be readily generated by simple finger movements. The signals were transmitted to a computer, either by a straightforward hard wire from the terminal pad via an interface unit, or though a radio transmitter attached to the pad.

It was, however, also possible to stimulate the nervous system, via the array, transmitting current signals from the computer to bring about sensations. In experiments to investigate appropriate current signals to be input, it was found that currents of less than 80 uA in magnitude had little perceivable effect at that value, though certain of the electrodes produced a recognisable effect, the associated applied voltage being 40 to 50 volts. The exact voltage applied depended on the input resistance being encountered on each particular electrode. Due to the variability of the human nervous system this resistance was though, not identically the same on a day-to-day basis.

Stimulation currents above 100uA had little extra effect on nerve stimulation, indicating that a non-linear thresholding characteristic was being exerted by the nervous system in response to the current. The current was in fact being applied as a bi-phasic signal with 100 usec inter signal break periods. It could be said, in fact, that this signal waveform, which was the most successful tried, closely emulated the first harmonic of motor signals recorded.

The array allowed motor neural signals to be detected from the small collection of axons around each electrode. Because the majority of signals of interest occurred at frequencies of below 3.5 KHz, low pass filters were employed to ensure that higher frequency effects, including those due to noise, were either removed from the procedure or, at least, significantly reduced. In this way, it was relatively easy to generate useful motor neural signals simply by making controlled finger movements. In the cybernetic experiments carried out, these motor neural signals were transmitted directly to the computer, where they could be made use of to operate a variety of networked technological implements [9].

Whilst motor neural signals could be generated and employed from the first day of experimentation onwards, in the first stimulation tests, whilst wearing a blindfold, a mean correct identification rate of 70% was achieved. What this means is that without prior warning, on average, seven times out of ten I could successfully detect when a current stimulation had occurred and when it had not. Further details on this are

given in [10]. These stimulation tests did not commence until six weeks after the implant operation, and it took approximately two weeks of continued testing to arrive at suitable current types to obtain this detection rate.

An important feature of obtaining suitable current signals, recognisable on the nervous system, was, effectively training of the brain to decipher the signals. In a sense, therefore it was a mutually convergent exercise with, over a period of weeks, more recognisable signals being inserted with, at the same time, the brain learning about the signals patterns and what they meant. This learning continued in the further weeks of the experiment.

Towards the end of the entire experiment, which concluded with the implant being extracted on 18th June 2002, over three months after the original implantation, a mean perception rate of stimulation of over 95% was being achieved. To all intents and purposes though, because of several factors apparent in the method of experimentation [10], realistically this figure should be seen, in a practical sense, to be as near to 100% as could be achieved.

Before discussing the cybernetic applications actually carried out with the implant in place, it is important to realise that the whole project was conducted in association with the National Spinal Injuries Centre at Stoke Mandeville Hospital, Aylesbury, UK. One aim of the project was therefore to assess the practicability of employing the same type of implant to help those with a spinal injury. The aim was not so much one of attempting to restore movement to otherwise motionless limbs, but rather to consider the possibilities of using motor neural signals to control technology and thus bring about a considerable lifestyle improvement.

The long term goal would therefore be, where necessary, to direct brain implants to allow an individual who is paralysed to control their local environment by neural signals – in popular terminology, to switch on lights or perhaps drive their car just by thinking about it. In this sense, our experiment was useful in assessing the present state of technology.

4. Application Studies

In order to demonstrate the sort of applications possible, thereby indicating the range of potential use for implant technology of this type, a variety of applications were performed.

The first implementation was to make use of the neural signals being transmitted to control an articulated hand. The aim of the hand, referred to as the SNAVE hand, is to mimic the operation of, in particular the control mechanisms inherent in, the human hand. Effectively, neural signals responsible for moving fingers in my own left hand were also used to operate the articulated hand.

Sensors in the fingertips of the hand allow for the grip shape to be adapted as well as the applied force being modified as necessary. Hence appropriate tension can be applied via the hand in order to avoid object slippage. In tests, whilst wearing a blindfold, sensory data from the fingertips was fed back down on to my

nervous system. As more force was applied to an object, so the amount of neural stimulation was increased. At the same time, the hand's movements were being controlled from my own nervous system. Over a two week period of regular experimentation I learnt to judge, to very fine detail, within + 5%, a force just sufficient to grip an object.

As a follow on from the articulated hand investigation, on 20th May 2002 a team at Columbia University, New York City, teamed up to bring about an internet link. With myself in the Internet real-time labs in the Computer Science Department of Columbia University, the implant was put on-line onto the Internet. The articulated hand experiment was then repeated, although this time, signals from the neural implant were transmitted via the Internet to directly control the articulated hand back in the Cybernetics Labs at Reading University in the UK. As well as this, feedback information was transmitted from the hand's fingers in the UK to stimulate my nervous system in New York. A 100% success rate in signal recognition was achieved in this one off trial and the articulated hand was controlled adequately despite the delay in signal transmission due mainly to the distance involved.

Neural signals were also employed to control the directional movements of an electric wheelchair. For this purpose a sequential state machine provided a simple solution, the machine being halted, by neural signals, to select the desired travel direction – forward, backwards, left, right. Experiments were also carried out to selectively process signals from several of the implant electrodes over time in order to realise fine control.

Due to the chair mobility, a short-range digital radio link was brought about between the implant and the wheelchair driver control mechanism. The radio transmitter/receiver unit was worn as a gauntlet arrangement on my lower left arm. After about one hour of learning time, quite reasonable control of the wheelchair was achieved. Subsequently, considerable success was achieved in driving the wheelchair around a cluttered, external environment.

One further experiment was to investigate the possibility of extra sensory input to the human nervous system. To this end, ultrasonic sensors were positioned on a baseball cap. The output from these sensors was fed down on to the radio transmitter/receiver gauntlet to provide neural stimulation via the implant. When an object was in the vicinity of the sensors, the stimulation rate was high, whereas as the distance increased, the stimulation rate decreased. With no object present, no stimulation occurred.

Tests were carried out in a normal (untidy!) laboratory environment. Whilst wearing a blindfold, I was able to readily navigate around objects in the laboratory by means of, what turned out to be, a highly accurate ultrasonic sense of distance. Obviously, drawing universal conclusions from a one off experience would be wrong, however what can be reported is that my brain adapted very quickly, within minutes, to its new sensory input.

Importantly, the stimulation pulses

being received were linked directly with the ultrasonic detection, in terms of an indication of how far away any objects were. The pulses were not witnessed as one of the normal five human senses. When an object was brought rapidly into my ultrasonic 'line of sight', a reactive, automatic recoil occurred to, what felt like, a dangerous situation.

he final experiment carried out involved my wife, Irena, who had two electrodes inserted in her median nerve through microneurography, in roughly the same location to my own implant.

By means of one of the electrodes in particular, strong motor neural signals could be obtained when she moved her fingers. The output from this electrode was linked directly to a computer and was connected such that my own nervous system was stimulated each time Irena moved her fingers. The process was also linked up in the reverse direction, with Irena's nervous system being stimulated when I moved my fingers. So when Irena moved her fingers three times, I felt three pulses on my nervous system, and vice versa.

What we had brought about was a direct electrical connection between the nervous systems of two individuals. Through this connection, motor neural signals were transmitted from person to person to successfully achieve a simple radiotelegraphy signalling system.

It is apparent that with implants fitted not in the peripheral nervous system, but rather directly in the motor neural area of the brain, the same type of signalling between two individuals could be considered to be the first, albeit rudimentary, steps in thought communication.

5. Conclusions So Far

The practical implant study carried out gives rise to a host of implications [11]. Firstly, by positioning such arrays in the motor neural area in the brain, this should bring about a variety of technological control systems operated merely by the individual thinking about moving. In essence, just about any technical device that can be controlled should be operable in this way, domestic implements providing the obvious immediate application field.

For those people who are paralysed, implant technology should therefore open up a whole new world. Whilst we should not be overenthusiastic in claiming that it will all happen today or indeed tomorrow, at least we can say that a number of things appear to be technically quite possible. Directly from the results of our experiments, it should be possible for a paralysed person to switch on lights, make the coffee and even drive their, suitably modified, car.

In the tests carried out, a wheelchair was driven around under the control of my neural signals. The same should be possible for someone who is paralysed. Also an articulated hand was controlled from my nervous system. The same should be possible for someone who has had their hand amputated. Further, I benefited from an extra (ultrasonic) sense. The same should be possible for someone who is blind – not to repair their blindness

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in any way, but to allow them an alternative sense.

One part of the study was the investigation of infection and rejection as regards the interaction between my body and the implant. The run of wires up the inside of my arm was an attempt to reduce the effects of infection. In fact, no indication of infection was witnessed during the trial period, the two operation sites on my left arm being monitored closely over that time.

As for rejection, results were far more encouraging than could have been imagined. Firstly, mentally my brain had tuned in more and more to the signals used for stimulation. Secondly, when the extraction operation took place it was found that scar tissue had grown round the implant, pulling it tightly into the median nerve fibres. When the scar tissue was removed, it was discovered that the implant had neither lifted nor tilted from the nerve fibres – it was exactly where it had been positioned over three months earlier.

On the negative side, where the wires exited from my arm they were subject to quite severe mechanical bending stresses and this resulted in gradual breakage of the wires [12]. In fact by the end of the experiment only three wires (therefore three electrode connections) were still operative. Clearly the mechanical strength of the wires will need to be improved if long-term implants are to be considered. However, if a device were to be completely implanted, then perhaps this would not be a problem. A complete implant, of this type though, would need a light/compact power supply and aerial.

6. Implications for the Future

The programme of research presents quite an ethical dilemma. Very few people would argue against the use of implant technology, as long as it has been shown to be safe, to help those with a disability of some kind. However the use of the same technological base in order to upgrade humans raises some serious questions. Who gets an implant and who doesn't? Will it be left purely to commercial enterprises to push the technology on or is it something for which some key political decisions need to be made?

Our own research is now clearly focussed on motor neural brain implants as the next step. Many research questions arise though, in terms of number and positioning of implants. Also the extent and range of signals to be bi-directionally transmitted is of major concern. Of the tests to be carried out, thought communication ranks as something of a priority. However this will mean that more than one person will need to be implanted for scientific, rather than medical, purposes – which could be difficult from an ethical standpoint

Giving humans extra abilities by technologically upgrading them (into Cyborgs!) [11] now appears to be becoming possible. Shouldn't humans be allowed to simply get on with it – as has (largely) been the case with previous technical improvements – and become superhuman? Humans are now in a position whereby we have the potential to evolve our own destiny. Perhaps issues affecting such a move are now as much social and ethical as

they are technical.

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Chapter 48: Healthwear: Medical Technology Becomes Wearable

Alex (Sandy) Pentland, Ph.D.
Professor of Media Arts and Sciences & Director, Human Dynamics Research Group MIT Media Laboratory, Cambridge, MA, US

Abstract

Widespread adoption of sensors that monitor the wearer's vital signs and other indicators promises to improve care for the aged and chronically ill while amassing a database that can enhance treatment and reduce medical costs.

1. Introduction

The concept of computing is rapidly expanding from simply using a desktop PC, where people sit and type for a small part of the day. Every day, more than one billion people carry around portable computation devices that have sensors and Internetcapable connections—but we call them cell phones rather than computers.

The most recent cell phones go far beyond telephony: They are truly wearable computers. These location-aware devices have sensors for detecting sounds, images, body motion, and ambient light level, have a secure Internet connection, and can download and upload programs as well as audio and image files. They also can serve as a situation aware intelligent assistant, whether as personal agents that use the digital equivalent of 3M's
Post-it notes to augment reality or as a means of forming tight-knit intellectual collectives in which people can supercharge their social networks.

As part of this change in the way we use computers, my research group at the MIT Media Lab (http://hd.media.mit.edu) has been developing healthwear, wearable systems with sensors that can continuously monitor the user's vital signs, motor activity, social Interactions, sleep patterns, and other health indicators. The system's software can use the data from these sensors to build a personalized profile of the user's physical performance and nervous system activation throughout the entire day—providing a truly personal medical record that can, we believe, revolutionize healthcare.

2. Healthwear Overview

Until recently, researchers have had little success in extending healthcare into the home environment, yet there clearly is a huge demand for this service. Americans currently spend $27 billion on healthcare outside the formal medical establishment because they find it difficult to access, expensive, and painful (www.rwjf.org). A clear demand for better integrating the home into the healthcare environment exists. Not only that, but a dramatic shift in the composition of the US population makes it absolutely necessary to develop such distributed systems.

2.1 Caregiver Shortage

Although the US had 25 caregivers for each disabled person in 1970, the success of our healthcare system will lower the ratio of caregivers to at-home disabled to 6 to 1 by 2030 (www.

agingstats.gov). How will those six people care for a disabled person? Certainly, a centralized system of visiting nurses is not an option for providing this care—such a system would leave too few individuals working at other jobs in the economy to support it.

Thus, a more highly distributed system is not only desirable, but absolutely necessary. These statistics provide the driving force behind the development of healthwear. This concept offers an unobtrusive method for acquiring in-depth knowledge about the body that could help manage chronic medical conditions such as cancer, diabetes, degenerative disorders of the nervous system, or chronic pain. Perhaps just as importantly, the deployment of continuous monitoring devices provides an excellent opportunity to fully inform medical providers about a patient's condition, thus helping the patient obtain the best treatment possible.

Already, health-conscious individuals are wearing small digital pedometers and exercise monitors. Indeed, some companies such as Nissan in Japan give such devices to employees to heighten health awareness and decrease medical insurance costs. In the future, people who dress for success may also wear a healthwear personal trainer that helps keep them active, knowledgeable, and involved.

2.2 Opportunities and Concerns

As new sensor, computing, and communication technology becomes available, healthcare professionals will be able to organize huge medical databases for use in tracking every test taken and medicine prescribed over an individual's lifetime. In addition to helping drive down healthcare costs, this data can provide powerful epidemiological information for use in improving our knowledge about keeping society healthy. For example, today because the huge expense of clinical trials limits the size and sensitivity of drug testing, harmful interactions are often detected only months or years after a drug is introduced to the general populace. Continuous, quantitative behavior logging has the potential to generate enough data so that researchers could discover these interactions more quickly.

Another application that is potentially even more important is the early detection of epidemics like SARS or biological weapons attacks. Today, reports of the treatment of an unusual number of patients with similar symptomatology at a medical facility often provide the first warning of a potential epidemic. Widespread continuous monitoring could detect such outbreaks much sooner by noticing when unusual numbers of people are behaving lethargically or staying home from work.

However, creating such an information architecture requires safeguards to maintain individual privacy. Indeed, we believe that this issue demands immediate, thoughtful attention and public debate, perhaps beginning with the current concern about using cell phone signals to track people. The current forces for creating huge databases and big medicine are powerful and all too successful. The potential solution is

Edited by: **Renata G. Bushko** - bushko@fhti.org
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to place control and ownership of as much personal information as possible in the hands of the individual user, sharing only information cleansed of identifying features. This power-to-the-people approach favors using wearable sensing devices rather than sensors in the surrounding environment because the information starts out in the control of the individual, and the legal tradition in the US is that individuals own the data collected from their bodies.

3. MIThril

In J.R.R. Tolkien's Middle Earth stories, mithril is a precious metal used to craft armor with properties that protect its wearer from evil. The term thus seems an apt name for the technology that provides the basis for healthwear. Highly flexible, the MIThril architecture provides a modular system tied together by wireless networking protocols and a unified multiwired-protocol power and data bus for sensors and peripherals [1].

Figure 1. MIThril system. Plugging the biosensor hub into a cell phone or wireless PDA provides a system that offers input, output, and general computation functions and can support a wide range of physiological measurements.

3.1 Hardware Components

Figure 1 shows the MIThril system. Designed for use with either a modern programmable cell phone or a wireless personal digital assistant (PDA), MIThril offers input, output, and general computation functions and can support a wide range of physiological measurements.1,2 The MIThril hardware architecture is designed to be modular and easily configurable so that it can handle a variety of sensors and tasks. The software architecture supports using the ad hoc, on-the-fly combination of sensor signals from multiple users to control signaling and outputs.

A sensor hub interfaces with the MIThril body bus, which combines the Philips I2C multiple device serial protocol and power lines. The sensor hub provides a bridge to the sensor data, enabling data acquisition, buffering, and sequencing, and it can be used as a stand-alone data-acquisition system [2]. This is particularly useful for large-group applications that do not require real-time processing, wireless communication between users, or complex user interaction and thus do not require a cell phone or wireless PDA to be part of the system

Currently supported devices include accelerometers for motion detection, IR active-tag readers for location and proximity detection, audio input and output devices, battery monitors, GPS, analog two-channel EKG/EMG, two-channel galvanic skin response sensors, and skin-

temperature sensors. MIThril uses an RS-232 interface to communicate with a wide range of commercially available sensors for monitoring pulse oximetry, respiration, blood pressure, EEG, blood sugar, and CO2 levels.

3.2 Software Architecture

The core MIThril software components include the Enchantment Whiteboard, the Enchantment Signal system, and the MIThril Real-Time Context Engine. These tools provide the foundation for developing modular, distributed, context-aware wearable and ubiquitous computing applications. The Enchantment Whiteboard implements an interprocess communications system suitable for distributed, lightweight, embedded applications. Unlike traditional interprocess communications systems such as RMI and Unix/BSD sockets—which are based on point-to-point communications—the Enchantment Whiteboard uses a client-server model in which clients post and read structured information on a whiteboard server.

This architecture lets any client exchange information with any other client without the attendant complexity in negotiating direct client-to-client communication. These exchanges can take place without the client knowing anything at all about the other clients. Clients can subscribe to portions of the Enchantment Whiteboard, automatically receiving updates when changes occur. Further, clients can lock a portion of the whiteboard so that only the locking client can post updates. It also supports symbolic links across servers, letting whiteboards transparently refer to other whiteboards across a network.

Intended to act as a streaming database, the Enchantment Whiteboard captures the current state of some system, person, or group. On modest embedded hardware, the board can support many simultaneous clients distributed across a network while making hundreds of updates a second. We have used the Enchantment Whiteboard with the Enchantment Signal system for bandwidth-intensive voice-over-IP-style audio communications between teams of up to 50 users.

4. Life Patterns

The MIThril system provides a modular framework for real-time understanding of sensor data. The results of this process can be used locally for reminders and wearer feedback, or they can be broadcast to other users to enable smart-group communications and increased awareness of other members' health and activity levels. Pattern recognition techniques are the basis for modeling and interpreting the output of the wearable sensors. The standard pattern-recognition approach breaks this process into four stages:

- Sensing. A digital sensing device measures something in the real world, resulting in a digital signal of sampled values. For example, a microphone sensor converts continuous fluctuations in air pressure—sound—into discrete sampled values with a specified resolution, encoding, and sampling rate.

- Feature extraction. A raw sensor signal is transformed into a feature signal more suitable for a particular modeling task. For example, the feature extraction stage for a speaker-identification-classification task might involve converting a sound signal into a power-spectrum feature signal.

- Modeling. A generative or discriminative statistical model—such as a Gaussian mixture model, Support Vector Machine hyperplane classifier, or hidden Markov model—classifies a feature signal in real time. For example, a Gaussian mixture model could be used to classify accelerometer spectral features as walking, running, sitting, and so on.

- Inference. The results of the modeling stage, possibly combined with other information, are fed into a Bayesian inference system for complex interpretation and decision making.

We use machine-learning techniques to record raw sensor measurements and create statistical models of users' behavior and the surrounding context. Most commonly, we use hidden Markov models —which are also the basis of speech recognition systems—for behavior modeling. We have used this approach to build systems that use sensor measurements of hand motions to perform real-time recognition of American Sign Language and even to teach simple T'ai Chi movements [3]. Typically, these systems have vocabularies of 25 to 50 gestures and a recognition accuracy greater than 95 percent. We have also applied this same basic approach to audio and video to accurately identify the setting in which conversations take place—in a restaurant, in a vehicle, and so on—and even to classify the type of conversations a user engages in during the day [4,5].

Once we model the behavior and situation, we can classify incoming sensor data to build a model of the user's normal behavior. We can then use this model to monitor health, trigger reminders, or even notify caregivers. Information about the wearer's social interactions is particularly interesting. Understanding face-to-face encounters is critical to developing interfaces that respect and support the wearer's social life. Social interactions are also very sensitive indicators of mental health. Thus, an important challenge for our behavior modeling technology is to build computational models that we can use to predict the dynamics of individuals and their interactions.

The number of parameters is a significant factor in a model's learnability and interpretability. The requirement for minimal parameterization motivated our development of coupled hidden Markov models (CHMM) to describe interactions between two people, where the interaction parameters are limited to the inner products of the individual Markov chains

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[6]. As a practical matter, a CHMM is limited to the interactions between two people. We have therefore begun using a generalization of this idea, called the "influence model," which describes the connections between many Markov chains as a network of convex combinations of the chains [7]. This allows a simple parameterization in terms of the "influence" each chain has on the others, and we can use it to analyze complex phenomena involving interactions between large numbers of chains.

To apply the influence model to human networks, we have extended the original formulation to include hidden states and to develop a mechanism for learning the model's parameters from observations [8]. Modeling human behavior this way allows a simple parameterization of group dynamics in terms of the influence each person has on the others, and we have found that it provides a sensitive measure of social interactions.

5. Healthwear Application

Several ongoing projects hint at the capabilities healthwear will offer. These applications include medical monitoring and feedback systems for those with chronic medical conditions, monitoring social networking to reinforce healthy behavior, and mental monitoring to detect the symptoms of depression or dementia.

5.1 Medical monitoring and Feedback

Healthwear promises to be especially effective for monitoring medical treatments. Currently, doctors prescribe medications based on population averages rather than individual characteristics, and they check the appropriateness of the medication levels only occasionally—and expensively. With such a data-poor system, it is not surprising that medication doses are frequently over- or underestimated and that unforeseen drug interactions occur. Stratifying the population into phenotypes using genetic typing can improve the problem, but only to a degree. Continuous monitoring of motor activity, metabolism, and so on can be extremely effective in tailoring medications to the individual.

For example, consider Parkinson's patients. For them to function at their best, their medications must be optimally adjusted to the diurnal variation of symptoms. For this to occur, the managing clinician must have an accurate picture of how the patient's combined lack of normal movement (hypokinesia) and disruptive movements (dyskinesia) fluctuates throughout a typical day's activities. To achieve this, we combined the MIThril system's wearable accelerometers with standard statistical algorithms to classify the movement states of Parkinson's patients and provide a timeline of how those movements fluctuate throughout the day.

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Two pilot studies were performed, consisting of seven patients, with the goal of assessing the ability to classify hypokinesia, dyskinesia, and bradykinesia (slow movement) based on accelerometer data, clinical observation, and videotaping. Using the patient's diary as the gold standard, the result was highly accurate identification of bradykinesia and hypokinesia. In addition, the studies classified the two most important clinical problems—predicting when the patient "feels off" or is about to experience troublesome dyskinesia—perfectly [9].

5.2 Memory Glasses

Regardless of age, we've all had our moments of forgetfulness. We accept such memory lapses as human fallibility, but we would be grateful if researchers could find a way to cue our natural memory and help us overcome these lapses. Perhaps such a device also could, for example, help improve an elderly person's memory or provide critical cues for emergency medical technicians, doctors, or firefighters in a nondistracting way. Toward this end, we are developing memory glasses that might someday help people with challenges ranging from complex memory loss to simple absent-mindedness.

Figure 2 shows a prototype of this wearable, proactive, context-aware memory aid based on the MIThril platform and wearable sensors [10]. Memory glasses function like a reliable human assistant, storing reminder requests and delivering them under appropriate circumstances. Such a system differs qualitatively from a passive reminder system such as a paper organizer, or a context-blind reminder system such as a modern PDA, which records and structures reminder requests but which cannot know the user's context.

Perhaps the major obstacle to this vision is that people resist being reminded to exercise, take their medicine, or skip that extra helping of dessert. Subliminal memory aids—visual and audio reminders that lie just below the user's threshold of perception—may offer one way around this problem. Our research shows that under the right conditions, subliminal text or audio cues can jog the memory much like overt cues even though the person receiving the cues is not aware of them. In one experiment, for example, subliminal text cues improved performance on a name-recall task by 50 percent compared to the uncued control [11]. Perhaps more important than this positive effect, our research suggests that incorrect or misleading subliminal cues do not interfere with memory recall. This contrasts starkly with the effect of overt miscues, which have a significant misleading effect.

Figure 2. Memory glasses. A wearable, proactive, context aware memory aid, the memory glasses system combines the MIThril platform with wearable sensors to provide a device that functions like a human assistant, storing reminder requests and delivering them under appropriate circumstances.

A practical system might use a Bluetooth connection between cell phones to obtain the names of nearby friends. Similarly, a combination of information about location, proximity to others, time, and surrounding sounds could assist in situation recognition. The system could then use this context information to trigger the appropriate prompt, which would flash across the user's glasses or be communicated through an earpiece. If the system presented the prompt subliminally, users would not consciously process the reminder and so would be unaware that the prompt was jogging their memory. Thus, the subliminal prompts that the memory glasses provide would not interrupt a user's daily routines.

6. Social Networking

Reinforcing an individual's social support system may be the most effective way to encourage adopting more healthy behavior patterns. Thus, one aspect of healthwear's core functionality is interpersonal communications supported by continuous biomedical sensing [12].

6.1 Embedded Social Networking

Healthwear's social networking capabilities answer broad and immediate needs. For example, aging parents now commonly live far away from their families. Healthwear can help in such a situation by promoting communication between family members when it senses a suspicious change in an elder member's behavior. In one version, healthwear occasionally but continuously leaves phone messages reminding grown children to call their parents and vice versa. However, when a marked change in behavior occurs—such as decreased food consumption, socializing, or sleeping—healthwear increases the frequency of these reminders. The system would not tell people something is specifically wrong or describe why it left a particular message, nor would it call the doctor except in extreme circumstances, because doing so could violate people's privacy and might actually interfere with proper medical support. Instead, healthwear strengthens the social support network when the need is likely to be most significant.

6.2 DiaBetNet

Children also need social support networks, and they tend to be extremely sensitive to social context. We focused on this tendency when we created DiaBetNet, a computer game for young diabetics that uses belt-worn motion sensors, a wireless Internet connection, and a standard PDA for an interface [13]. DiaBetNet capitalizes on their passion for social games to encourage children with diabetes to keep track of their food intake, activity, and blood sugar level.

A typical day in the life of a diabetic child using DiaBetNet would unfold as follows. In the morning, the child clips his wireless accelerometer and DiaBetNet case—with wireless Internet connection, PDA, glucose meter, and wireless receiver for the accelerometer—onto his belt and goes off to school. Throughout the day, the PDA records his activity from the accelerometer, data from measuring glucose and injecting insulin from the

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glucose meter, and user-entered information about food consumption.

At any time, the user can see a graph on the PDA that summarizes the day's activity, carbohydrate consumption, and glucose data. From time to time, a wireless Internet connection sends this data to a secure central server.

DiaBetNet is a group gaming environment that requires guessing blood-sugar levels based on information that wearable sensors collect: The more accurate the answers, the higher the score. For example, imagine that a user named Tom begins to play DiaBetNet with others on the wireless network. Transformed into his cherished alias, Dr. T, Tom finds that his fellow players were all within 30 milligrams per deciliter of guessing their blood sugar levels correctly, but his guess was closer than anyone else's. Tom challenges a DiaBetNet player called Wizard and looks through Wizard's data. Although Wizard was euglycemic in the morning, he ate a late lunch. Therefore, Tom decides that Wizard's glucose level would be high and guesses 150 mg per dl. Wizard guesses his glucose to be 180 mg per dl. Tom wins again and grabs five more points. He shoots a brief conciliatory message to his vanquished foe and signs off. In clinical trials, 93 percent of DiaBetNet participants successfully transmitted their data wirelessly to the server. The Game Group transmitted significantly more glucose values than the Control Group. The Game Group also had significantly less hyperglycemia—glucose 250 mg per dl—than the Control Group. Youth in the Game Group displayed a significant increase in diabetes knowledge over the four-week trial. Finally, more youth in the Game Group monitored their hemoglobin levels [14].

6.3 Mental Monitoring

Healthwear technology also can assist in the early detection of psychological disorders such as depression. Even though they are quite treatable, mental diseases rank among the top health problems worldwide in terms of cost to society. Major depression, for instance, is perhaps the leading cause of disability in established market economies [15].

Researchers have long known that speech activity can be affected in pathological states such as depression or mania. Thus, they have used audio features such as fundamental frequency, amplitude modulation, formant structure, and power distribution to distinguish between the speech of normal, depressed, and schizophrenic subjects [16]. Similarly, movement velocity, range, and frequency have been shown to correlate with depressed mood [17].

In the past, performing such measurements outside the laboratory was difficult given the required equipment's size and ambient noise. However, today even common cell phones have the computational power needed to monitor these correlates of mental state. We also can use the same methodology for more sophisticated inferences, such as the quantitative characterization of social interactions. The ability to use inexpensive, pervasive computational

platforms such as cell phones to monitor these sensitive indicators of psychological state offers the dramatic possibility of early detection of mental problems.

Perhaps the most sensitive measure of mental function is social interaction, which clearly reveals attitudes, emotions, and cognitive function [18]. To investigate this idea, we are using a MIThril-based device dubbed the sociometer to collect data about daily Interactions with family, friends, and strangers such as:

- How frequent are the interactions?
- Are the interactions energetic or lethargic?

Are the interactions appropriate without long gaps or frequent interruptions?Using these sociometers we collected almost 1,700 hours of interaction data from 23 subjects. Participants in this study also filled out a daily survey that provided a list of their interactions with others. The sociometer and conversation-detection algorithms classified 87.5 percent of the conversations as greater or equal to one minute, a far greater accuracy than achieved using the survey method.

The few conversations that the automatic sociometer method missed typically took place in high-nise,multiple-speaker situations [19]. Once collected, researchers can use the influence model, a statistical framework that is a generalization of the hidden Markov models commonly used in speech recognition, to model the interaction data. Modeling spoken behavior this way allows a simple parameterization of group dynamics in terms of the influence each person has on the others. Our initial experiments show that these influence parameters are effective indicators of status within a social network and the degree of coupling to the social network [20].

7. Summary

Judging from the adoption rates of advanced cell phones and wearable health tools such as pedometers, within this decade much of the US population will likely have access to continuous, quantitative monitoring of its behavioral health status, coupled with easily accessible biosignals. How will this change our lives and our society?

An exciting possibility is that with the widespread adoption of healthwear, researchers could, for the first time, obtain enough data to really understand health at a societal level. For example, correlating a continuous, rich source of medication data from millions of people could make drug therapies more effective and help medical professionals detect drug interactions more quickly. If correlated with medical conditions, the data could illuminate the etiology and preconditions of disease far more powerfully than is possible today and, further, serve as an early warning system for epidemic diseases like SARS.

Comparing the medical data with genomic and protonomic data from different population samples could provide a powerful method for understanding complex gene and environment interactions. However, when considering the effects of

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healthwear systems, we would be wise to recall Marshall McLuhan's dictum that "the medium is the message." The way in which a new technology changes our lifestyle may well be more important than the information it conveys. Healthwear will likely be considered more personal and intimate than traditional health tools because it will form a constant part of a user's physical presence. Psychological studies have shown that clothes do indeed make the man.

Thus, healthwear will not only be part of what the user wears but part of who that user is. Body-worn technology will likely change our self-perception and self-confidence in ways that are today unpredictable. While it could be more effective at promoting healthy behavior than traditional approaches, healthwear also could be more seriously abused. However, with more than one billion cell phones already being worn every day, there is no escape from being absorbed into this far more intimately connected new world. Our goal now should be to design this technology to make that world a very human place to live.

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Chapter 49: Health. Care. Anywhere. Today.

David Andre, Ph.D. and Astro Teller, Ph.D.
Director of Informatics and CEO, respectively, BodyMedia, Inc, Pittsburgh, PA, USA

Abstract

What if clinical quality medical equipment were available to every consumer in a form factor that was inexpensive, accurate, and easy to use? What if this equipment provided information that previously was un-measurable or very difficult to measure? What if the physiological state of individuals, at resolutions measured in thousandths of a second instead of in visits per year, could be measured easily, making it possible to ascertain caloric intake and expenditure, patterns of sleep, contextual activities such as working-out and driving, even parameters of mental state and health. What aspect of healthcare wouldn't change? We present a system that is available today that enables this vision. This award-wining multi-channel wearable physiological monitor has enabled the collection of more than 90 million minutes of data in natural settings from thousands of subjects engaged in diverse activities. Data modeling efforts are resulting in applications that present meaningful and actionable information in real-time to users and their designated collaborators (physicians, family members, counselors, coaches, etc.) We describe the SenseWear system, its design, and a summary of validation studies, current commercial applications, and ongoing research. This discussion will show how the convergence of design for wearability, advances in machine learning, and improvements in wireless technology will manifest the future of health care as personal, ubiquitous, and collaborative.

1. Introduction

In 2005, the United States spent approximately 1.8 trillion dollars on healthcare. Of this, approximately 0.6 trillion can be attributed to diseases or conditions caused by the genetic makeup of the patients. Approximately 1.2 trillion is attributed to poor lifestyle choices – people not taking care of themselves. Despite this at most 9 *billion* (0.5% of the total) dollars were spent on helping people better manage their health. Why is this? Certainly, convincing people to change their behaviors is difficult, but a large part of the problem is that you can't manage what you can't measure. You wouldn't try to fly an airplane without instruments, but most people try to navigate their lives without a dashboard for their bodies. Most traditional devices for measuring physiological signals are large, bulky, and expensive. Polysomnography machines [1] measure how well a patient sleeps, but require a (probably restless) night in a sleep clinic with many wires and electrodes glued to their bodies. Measuring energy expenditure requires an indirect calorimetry machine [2], and although some are becoming more portable, they require breathing into a tube and carting around heavy equipment for the analysis.

Surely, however, the advances in

miniaturization and electronics can provide medical devices and computers that are smaller, cheaper, more sophisticated, and more personalized [3, 4, 5]. On the computing side, this push has culminated today in the explosion of handhelds (mobile phones, iPods, gameboys, digital cameras, PDAs, etc.) as the new computing platform—cheaper and more sophisticated enabling smaller and more personal interactions. On the medical side, similar advances have been made. Watches with ambient temperature sensors and glucose monitors, heart straps for joggers, pedometers for dieters, etc. [6, 7, 8, 9]. There are clinical body monitors your doctor can prescribe and your nurse can administer such as holter monitors and ambulatory blood pressure cuffs. These devices are becoming wireless and less dependent on professionals for their application. More and more they are providing the means to transmit information back to caregivers quickly and seamlessly. So is that all that is required? No. The killer applications are just starting to emerge; applications from weight management to fitness to disease management. But the critical element in all of these areas is the interpretation and presentation of the data.

Wearable body monitoring goes from delivering potentially interesting data to delivering life altering information when it does enough of the data analysis to provide consumable, actionable nuggets of body knowledge automatically to wearers and their overseers. This is the difference between the sheet music and the violin concerto, the difference between the haystack and the needle. In that sense the future of wearable body monitoring will be a story about data and data analysis, as much as it will be a story about form factors and size reduction. The physical monitors are conduits to these distilled facts about our bodies, not the value in and of themselves, just as mobile phones are the conduits for wireless spoken communication between people. But even more than portability for mobile phones, wearability is a requirement for physiological sensors. If you can't stand wearing it, you won't wear it. And that means that the constraints of wearability in the most physical and practical sense, the constraints of where sensors can gather useful information on the human body, and the constraints of wearability, sociology and fashion all need be attended to for this vision to be realized. Fundamentally that means that the lines between design (industrial, mechanical, product, communication) and traditional engineering (e.g. electrical engineering, software engineering, biomedical sensing, and data modeling) will continue to blur as the ubiquitous, pervasive, and collaborative computing revolutions manifest a future of computing and healthcare that is wearable, personal, and sympathetic.

This chapter will discuss the design, current applications, and future of the SenseWear system. The first sections will describe the sensors, hardware, software and the design parameters and capabilities that enable the tracking of multiple channels of physiology at resolutions up to 32 Hz,

in natural settings, for extended time periods, with high degrees of comfort. The sociological challenges of introducing physiological devices and new models of human health metrics to medical research and to consumers will be discussed. This will be followed by an introduction to the data-mining prediction and classification that underlie the utility of the SenseWear system, along with a discussion of the value of context for interpreting physiological measurements. Finally, a promising and diverse array of research findings and ongoing initiatives will be summarized.

2. The SenseWear system.

As mentioned in the introduction, a device that can begin to transform health care must meet two difficult criteria. It must provide medically accurate data about a person's life but be designed well enough that it is unobtrusive and easy to wear. The system must be simple enough for the consumer but provide information useful to the healthcare professional. Although BodyMedia, Inc has several wearable body monitoring products, this chapter focuses on its SenseWear system, which includes a wearable armband that senses acceleration, heat flux, galvanic skin response, and temperature and records the data and derived measures over that data for later presentation to the user.

2.1. Designing a physiological computing device for everyday use

The design of a wearable physiological computing device is an effort in finding the synergy among competing criteria ranging from physiological accuracy to comfort, and mechanical engineering to social acceptability. The design of a product that is to be in continuous contact with the human body twenty four hours a day is to design for an extreme environment. People carry all sorts of devices around with them every day, such as PDAs, cell phones, wallets, wrist watches, etc. BodyMedia first had to ask what makes people comfortable and then design all the electronics, sensors, and packaging around those human needs. Through the creation of a multi-channel, ergonomic and durable sensor hub, individuals who would otherwise be tethered to machines are being granted greater freedom. For others, they opt to wear the device, though they would never have been suffered the annoyance and cost of a lab device, because the device provides them benefits worth the effort to wear it. In the development of SenseWear, BodyMedia prototyped a number of devices ranging from chest straps to smart rings. These prototypes and the development of the design criteria were informed by studies on wearable computing and medical devices such as those used for sleep apnea research, actigraphy measurements, the accuracy of accelerometers for energy expenditure measurements, and on materials such as elastic straps [10, 11, 12, 13, 14, 15]. The criteria for the SenseWear Armband included that it had to: accurately work for up to two weeks under continuous use (24/7); work during active athletic and work situations as well as during sleep; be easy to manufacture and robust

enough to survive everyday use in low (0 ˚C) and high (45 ˚C) temperature environments; be small enough to keep the overall monitor height and footprint unobtrusive beneath clothing; be non-invasive and non-irritating to the skin and hypoallergenic; have extremely low power consumption; and be cost effective.

To meet these objectives the area of the body where the device would be worn had to be: similar in size and shape on men and women between the 5 and 95% size range; relatively large in surface area (at least 2 in. by 3 in.) to accommodate the required components, including batteries and electronics; low in mobility (non-bending or stretching even during high activity); and have a continuous circumference for easy attachment and detachment. Fig. 1 shows how the upper arm meets many of these criteria. It is unoccupied 'real estate', gender-neutral, least obtrusive and low in the number of collisions, a relatively soft area where a device can be worn comfortably, and is generally concealed by clothing. On the upper arm it is also the case that device weight in this area does not induce fatigue and an adjustable strap accommodates a one size fits all design.

Many of the objectives were met through engineering novel design features. The symmetrical flexible wings (shown in Figure 2) stabilize the device, accommodate diverse arm sizes, and create sufficient pressure for the sensors to function. A proprietary hypoallergenic and non-latex elastic strap was developed for appropriate tension and repeatable attachment. Iterative user testing was conducted with hospital patients, football players, factory workers, rescue workers, firefighters, and the general public. The goal in making this wearable device was actually to make it as invisible to the user as possible. Very comfortable, very easy to use, something that blends into your life so you forget it is there. In a case study, a high school student wearing the monitor for two weeks said, "You kind of get used to it and don't even know you're wearing it." [16].

Figure 1.Wearability maps for heat flow, GSR, acceleration, heart rate, and temperature.

2.2. The SenseWear Pro2 wearable body monitor

The SenseWear Pro2 Armband is a sensor hub worn on the back of the upper right arm (tricep area, Fig. 2) [17]. It enables continuous collection of low-level physiological vital sign streams and derives from those accurate statements of human body states and behaviors. The device contains five different sensors. A two-axis accelerometer tracks the movement of the upper arm and provides information about body position. A proprietary heat-flux sensor measures the amount of heat being dissipated by the body by measuring the heat loss along a thermally conductive path between the skin and a vent on

the side of the armband. Skin temperature and near-armband temperature are also measured by sensitive thermistors. The armband also measures galvanic skin response (GSR – the conductivity of the wearer's skin) which varies due to sweating and emotional stimuli. The unit also contains a wireless chip and can communicate wirelessly with scales, blood pressure cuffs, and other medical systems. It can transmit collected sensor data with 916 MHz wireless body-LAN connectivity to a wireless communicator unit with <1 mW power output. The armband is made of flexible ABS, attaches with an elastic Velcro strap (custom designed to have stretch, air/water permeability, and hypoallergenic properties so as to mimic the skin to the greatest extent possible), weighs less than 3 oz., stores 14 days of continuous body data and has enough power for 14 days of continuous wear from a single AAA battery. Using a 4MHz MSP chip from Texas Instruments it transforms the raw physiological data such as movement, heat flux, skin temperature, near-body temperature, and galvanic skin response into snapshots of the user's life.

Each sensor is monitored 32 times per second, and data is tracked over a period of time (typically a minute but this can be adjusted through software). Currently, 41 different features of this multi-dimensional raw data stream are gathered as separate channels. For example, the variance of the heat flux is a channel, as is the average of the heat flux values. Some channels are fairly standard features (e.g. standard deviation) and others are complex proprietary algorithms. Then typically, these summary features for the epoch are stored and the raw data discarded to save memory. The raw data values can be retained (reducing the recording time, of course) through a simple software switch.

Enclosed in a shock and splash proof thermoplastic housing, the monitor straps to the user's right upper arm. At 0.8 in. tall by 3.4 in. long and 2.1 in. wide, the housing squeezes under all but the tightest shirtsleeves with barely a bulge. As it is wearable and unobtrusive, the Armband 'sees' people in the context of their natural daily activities rather than from the constrained viewpoint of a laboratory.

2.3. What SenseWear senses is not what it reports

Having multiple sensors is very important to the success of the armband and its ability to accurately monitor the physiological states of the wearers. Multiple sensors allow for the disambiguation of contexts that might confuse a single sensor. For example, if a wearer's motion is high, it might be due to exercising or to being in a moving vehicle. However, the signatures of temperature, sweat, and heat flux are typically quite different for exercise and being in a car. The algorithms in BodyMedia's software utilize the physiologic signals from all the sensors to first detect the wearer's context and then apply an appropriate formula to estimate energy expenditure from the sensor values. The armband can recognize many basic activities such as weight-lifting, walking, running, biking, resting, and riding in a car, bus, or train. Other activities are classified into combinations of these basic

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activities; for example, baseball could be broken down into a combination of mostly near-restful activity and running. Key to the armband's utility is that it can be worn comfortably during a person's normal life, and does not require any time in the laboratory for uncomfortable measurements.

Fig. 2. SenseWear Armband front with time stamp button, back showing sensor interface, and shown on arm.

The algorithms are all created using a proprietary algorithm development process that utilizes a data-driven machine learning approach. Data is first collected at clinical sites with laboratory equipment such as metabolic carts or metabolic chambers. Next, compressed channels are created from this raw data that can stored on the armband that are useful for determining both the wearer's activity as well as measures such as energy expenditure or sleep state. After this, context detectors are developed that classify the wearer's context. Finally, for each context, a specific algorithm is created using automated machine learning techniques to predict the measure of interest (such as energy expenditure). Section 5 describes the algorithm development process in more detail. At this point, accurate algorithms have been developed for energy expenditure, sleep, physical activity, and the set of activities mentioned above: weight-lifting, walking, running, biking, resting, and riding in a car, bus, or train.

2.4. Wireless technology

The SenseWear system includes a 916 Mhz wireless technology that allows the armband to communicate securely and wirelessly with other devices including computing devices (PCs, PDAs), display devices (watches, kiosks), and other medical devices (blood glucose meters, weight scales, blood pressure cuffs, pulse oximetry meters). BodyMedia has enabled these devices with the SenseWear Transceiver (Figure 3), allowing them to communicate with the armband. Users can take their measurements on these other devices, press the button on the armband, and the measurements are stored in the armband along with the data it records itself. All of the recorded data can then be transmitted to a PC via a wireless communicator (Figure 4) that connects to USB port on the PC. Alternatively, the data can be uploaded to a web-server via a wireless gateway (Figure 5) which contains either a standard or cellular modem, depending on the application.

Figure 3. The SenseWear BioTransceiver that allows medical devices to communicate with the armband.

Figure 4. The SenseWear Wireless Communicator (left) and Wireless Gateway (right) allow communication with a PC or a web-server.

This ability to communicate with different devices allows the user to receive feedback anywhere – whether on the go, at their home, or in their doctor's office. Furthermore, their trusted health advisors (e.g. friends, nurses, nutritionists, coaches, physicians) can look at the information on a printed report given to them by the user, online, or on their own PC. Figure 10 shows a representation of the entire system, with the armband serving as a hub for information that is reported to the web, to a PC, to a custom remote device (such as a baby monitor), to a cellular phone, or to a watch display.

Figure 5. A platform for immediate and remote body monitoring

3. Current Applications of the SenseWear system

The thing that is really going to change society with respect to health care, wellness and fitness is the ability for people to start to learn about themselves. BodyMedia's design mantra is, 'make it fun and meaningful to see how you feel.' The BodyMedia platform creates a feedback loop: people want to manage their own health but until now, trying to do it was like dieting without a scale. The feedback loop is the presentation of actionable information that is otherwise unavailable to them (e.g. sleep/awake states each night down to a per minute basis if desired). This information allows people to assess progress toward their health goals. There are numerous applications that can be supported once data is being tracked. People could track elements of their health as closely as they track their financial portfolios. Having baseline data from an aggregate population and

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from individuals themselves, it is becoming possible to flag individual anomalies and detect potential health problems.

The armband interface is highly customizable. It can be programmed to beep or vibrate when calorie-burn targets are met or as a reminder to take medicine. It is a communications 'hub' collecting and transmitting data from multiple devices worn on the body, all toward the goal of keeping the wearer alert to danger signals and mindful of health necessities. This system provides comprehensive, actionable feedback about a person's body and lifestyle that can be shared with researchers, physicians, dieticians and personal trainers via the Internet (Fig. 7). Internet applications can allow consumers to enter additional data such as calories consumed and body fat measurements to add further meaning to the body data gathered from their armbands. BodyMedia's goal is to help people become more aware of themselves in ways they have never done before and have a fun and engaging time doing that. One opportunity that has significant benefits is to employ a human relationship such as that with a physical fitness trainer. Similarly Debra Tate showed that the combination of online information and regular feedback from a coach along with the ability to self-monitor diet and calorie estimates resulted in preliminary successes [18].

The SenseWear system has been deployed in several applications to date. The first application was a research software package called the Innerview Research Software that was designed for researchers and clinicians to use. This piece of software offers the ability to customize the armband's recording rates as well as reports, summaries, and detailed information about the sensor values that were recorded. Figure 6 shows a report, with one screen showing totals, daily totals of energy expenditure, steps taken, amount of sleep, amount of lying down, and amount of physical activity. For example, you can see that David played soccer on Monday and went snowboarding on Friday from these graphs. The lower part of the figure shows the software's ability to display detailed information. You can see at the top of this part of the figure an auto-journaling of Friday and Saturday, showing when David was physically active, was motoring (in a moving vehicle), sleeping, sedentary, and lying down. The bottom of the graph shows a minute by minute plot of energy expenditure, heat flux, and skin temperature. The sensor values shown in the report are configurable in the software.

The Innerview Research Software has been used at thousands of sites for a variety of purposes. Some of these include to analyze exercise physiology data, serve as a measure for tracking medical conditions such as pain or physical activity during recovery from surgery, examine skin temperature in soldiers, build emotion-detecting algorithms from the data collected by the armband [19], analyze a person's reactions to architectural spaces [20], and as a variable in longitudinal studies of disease causation. Other applications have included the study of sleep behaviors, competitive sailing, human computer interactions, and

stress response in car and tank drivers. Groups studied range from professional athletes to the elderly to children. The products have survived intact in extreme environments such as Mt Everest, the North Pole, the South Pole, the highest lake in the world, the Pittsburgh Steelers training camp, and National Guard live firefighter training sessions inside burning planes.

Figure 6. Reports from the Innerview Research Software

A case study such as the following can help to illuminate the power of this kind of free-living body information. Using the Innerview Research Software, Perini et al [21] investigated the relationship between physical activity estimates and energy expenditure estimates with the recovery of a subject with Sydenham's Chorea. Sydenham's Chorea is a childhood disease that causes rapid and frequent involuntary movements but is benign in that spontaneous recovery will occur in a few weeks. This subject was treated with antibiotics, steroids, and antiepileptic therapy. At the outset, the subject was burning 1910 kcals/day as measured by the armband, with frequent involuntary muscle movements. In the following few days, the subject burned fewer and fewer calories per day as measured by the armband and additionally scored lower on several indicies (TAS, flogosis) of the progression of the disease. After six days, the subject was nearly back to normal, with only minimal choreic movements in the limbs. Blood tests revealed normal TAS and flogosis levels and the armband showed only 1400 kcals/day expenditure. At day 10, energy expenditure as measured by the armband increased in conjunction with some reappearance of symptoms. The SenseWear system with the Innerview Research Software is being increasingly used in clinical situations in Europe.

In addition to the Innerview Research software, the SenseWear system is utilized by several commercial web applications to address issues of wellness, weight-loss, and fitness. Apex Fitness and BodyMedia launched bodybugg (a private labeling of the BodyMedia technology) to the general public in the US at the start of 2005. On a daily basis, the bodybugg weight

management system (the left side of Figure 7) monitors and calculates a patient's caloric intake and expenditure and returns to both the patients and their care providers the difference between the two as the patient's day-by-day caloric balance. In providing this information, bodybugg is a weight management system that uses the continuous monitoring and collecting of physiological data to show the effect that lifestyle has on weight loss. Depicting calories burned, calories consumed, activity duration, and steps per day, the product strives to increase personal awareness of health and parameters of weight management. The ability for a third-party to view the data (in this case, the personal trainer or Fitness Professional) provides the user with a greater sense of integration and allows the third-party to give significantly better feedback. The bodybugg program (www.bodybugg.com) has thousands of users and is growing quickly.

Other variants of weight-management software have also been developed. One such system, designed for clinical weight management and diabetes management, has been piloted since 2003 with great results, with many subjects losing weight – even as much as 80 pounds. Another related application is The Wellness Project. This variant focuses on meeting calorie burn, step, and physical activity duration goals in the context of an online community setting. Groups can compete amongst their members or among different groups. The right side of Figure 7 shows this web application.

Figure 7. The bodybugg web application.

Figure 7a. The Wellness Project web application.

One question many have when first encountering the armband is whether people will actually wear the armband over long periods of time. Fig. 3 illustrates the amount of time users of the device actually wore it. That 83% of users wear it for more than 7 hours a day is a testament to the wearabilty

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of the device. To the extent that industry and commercial review is an indicator of reaching the goals for appropriate design, the SenseWear system has won both the Industrial Design Excellence Award and the Medical Device Excellence Award [22, 23]. In fact, it is interesting that BodyMedia is the only company in the world ever to win top honors in both of these awards for the same product platform.

4. The sociological context of the modeling of human health

4. The sociological context of the modeling of human health

Traditionally, models of human health have been models of how the human body works. That the previous sentence sounds like a tautology exposes how deep the bias goes that you cannot model human health without modeling how the human body works. This bias is understandable since until very recently there did not seem to be any alternative.

But the ability to put very small high performance computers on the human body in natural environments over long periods of time has opened a new avenue. That avenue is the modeling of human health through the modeling of the data given-off by the human body, often without any initial deep understanding of why that data is what it is. In Section 6, evidence will be presented that this method is accurate in powerful, valuable, and broad ways. But first, asks the skeptic, “Is this even good science?” “Should this even be allowed to count as a model of human health?”

Science is the making of models of the world and the testing of those models to show their predictive value. A model is nothing other than a simplification of the world, ideally reducing non-essential aspects of the world and retaining just those elements that are ‘useful’ (that are required for accurate predictions to be made). The ‘models’ or algorithms that BodyMedia constructs are mathematic simplifications of large amounts of raw data gathered with its devices, gathered in the presence of medical gold-standard lab equipment (such as metabolic carts (Fig. 8) or polysomnography machines) [2, 1]. Ideally, these algorithms have captured the underlying trends in the data so that when worn by a person not in the presence of medical gold-standard equipment, the result a BodyMedia device returns accurately predicts what the medical gold-standard lab equipment would have returned in

the same situation. So these are models of human health. They just happen to be models of what the body is doing rather than why it is doing it. These models are tested against the very same yardstick as classic models of human health: their ability to accurately predict what is happening to the body in question.

Fig. 8. Metabolic cart in a lab setting.

The next natural question, once the legitimacy of the method has been satisfied, is the real value of the method. There is a prevalent assumption, in both the medical industry and the general public, that any model built or â€˜learnedâ€™ by a machine (as all statistical mathematical models are to some degree) could not possibly be as accurate, or as useful as a model built by a person. More specifically, there is often an unarticulated assumption that when these models are wrong they will be wrong in much larger or much more problematic ways than equivalent models built by a person. The first response to these concerns is that real-time or long-term body monitoring in natural environments involves tens of thousands of times as much data as the current models of human health are built upon (periodic readings of blood pressure, cholesterol, bone density, etc.). Kuhn [24] describes the institutional adoption of new paradigms as a 25-year process; and it took the medical community the better part of a century to build a set of models of human health around this data. So waiting for a community, even one as smart and as dedicated as todayâ€™s medical community, to build this next generation of models as we move, metaphorically, from physiologic snap shots to physiologic movies, is not realistic.

The second issue is that statistical mathematical models are built by trying to minimize some error function with respect to the predictions that connect the dependent axes (the inputs, which are in BodyMedia's case the raw data measured many times per second by the SenseWear Armband) to the independent axis (the output, the predicted value, in this case BodyMedia derived values such as sleep state, calories burned in the past day, body position, etc.). Assuming that the data has been properly collected (an assumption that is necessary for verification in all model building exercises) the people and situations on which these mathematical models are built and tested represent the conditions that happen the most often or are the most important to predict correctly. Models such as the ones

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built by BodyMedia are constructed explicitly to minimize these errors when applied to unseen subjects. This cannot honestly be said for more traditional models of human health because they have, as an additional constraint, that the model is understandable to the researcher building the model. The case can be made that special cases not seen during the training and testing phase of a statistical mathematical model may be predicted incorrectly in the real world. Of course, when these same special cases are withheld from human researchers building more classic models of human health, the same risk for a model that miss-predicts in these same situations exists.

5. Data modeling, data mining and sensor fusion from multi-sensor streams

'Bioinformatics,' is the intersection of life science and computer science. The SenseWear system allows for the gathering and interpreting of multiple streams of vital sign data which is then used to derive statements about the human body, such as calories burned, sleep, and activity type. The fundamental insight for BodyMedia is this—instead of monitoring individual parameters (symptoms) that healthcare institutions are used to looking at—blood pressure, pulse oximetry, cholesterol level and so on—BodyMedia monitors lower level vital signs many times a second, and then builds mathematical models of the data collected. These models are built in the context of the 'right answers' from medical gold standard equipment such as metabolic carts for energy expenditure or polysomnography for sleep states. This process of building mathematical models goes by several names in different disciplines, but is most commonly called supervised machine learning in the computer science community.

The process of supervised machine learning is the building of a model in some chosen representation (such as an artificial neural network, a decision tree, or a probabilistic network). Input signals are collected in the presence of the labels to be predicted by the model being learned. This set of input signals and labels is often referred to as the training set. These labels are usually either classifications (e.g. 'Astro was jogging between 2 and 3 pm') or regression values (e.g. 'Astro's level of energy expended in the past minute was 5.65 kcals'). These labels are treated as ground truth though in practice there is almost always some error in them. Statistical machine learning techniques (e.g. back propagation in the case of an artificial neural network) are then used to create, train, or 'learn' a model such that the model accurately relates the inputs to the known outputs (labels). These techniques often search through possible model frameworks to find the best one. The models are compared using methods such as statistical bootstrapping and cross-validation, which measure the ability of the model to generalize to unseen data. After the best model is selected, it is evaluated on a completely unseen set of data.

There is considerable science in picking from existing model representations or making a new representation when going through

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this supervised machine learning process. In addition, it is often the case (as it is with BodyMedia) that the predictions are not made by single classification or regression models, but by hierarchical or networked groups of these models. For example, for a stream of vital sign signals collected by the SenseWear Armband, a first model might attempt to classify the kind of activity represented by these signals (e.g. jogging, biking, resting, sleeping, etc.). Then, for each of these particular activities, a specialized model has been built that is particularly good at rating some prediction problem (e.g. energy expended per minute) for that particular kind of activity (e.g. biking). BodyMedia approaches the data modeling process through a variety of statistical methods including symbolic modeling where expert knowledge exists (e.g. Decision Trees, Production Systems,etc), numeric modeling to fill in gaps in expert knowledge (e.g. Neural Networks, Bayesian Networks), state modeling for body states such as sleep states that shift in predictable ways (e.g. Hidden Markov Models, Partially Observable Markov Models), and clustering when all else fails or when labels are not available.

The bottom line, however, is that for real world problems, what generally makes the most difference is the quantity and quality of the training data available to the models being learned. To date the combined time that users, researchers, subjects, and customers have worn SenseWear Armbands amounts to over 300 million min over the past 5 years. Data from approximately 100 million minutes, from over 3000 individuals, have been collected by BodyMedia to form a corpus of physiological data. Of those 100 million minutes of physiological data (the inputs in our discussion above), around 10 million min of that data have been explicitly labeled as to their classification (e.g. 'lying in bed') or their level (e.g. stage 2 sleep according to the polysomnography machine). These 10 million min of streaming physiological data have been accrued from over 500 subjects with over 120 different labeled activity types.

Figure 9 shows the rate at which this data stream is increasing. The advantage of receiving all of this data is that even where the data is not annotated or explicitly labeled, the data can be used to improve the algorithms – both by helping in testing the algorithms but also through semi-supervised learning techniques. Exactly because this data improves the algorithms, users have some impetus to provide data, which can improve the information they themselves receive from the system. This creates a virtuous data cycle that encourages the use of the system and the contribution of data toward the general good.

Figure 9. Hours of data uploaded to BodyMedia, by day.

Fig. 10. Activity and condition map: sedentary, vehicle, aerobic, resistance vs. fever characterized by heat, motion and heart rate.

The next question many ask is reasonably, 'Are all these different parameters really necessary?' The challenge in real world (i.e. out-of-the-hospital) body monitoring is that there are a lot of states of the human body that are ambiguous when seen from the perspective of a single sensor. By choosing sensors carefully, a higher dimensional space of streaming vital signs can disambiguate these human body states, dramatically increasing what a wearable device can determine; and increase the accuracy of any indirect measurements derived from the lower-level vital signs.

Fig. 10 shows a simplistic example of how multi-sensors can disambiguate human body states that would appear ambiguous to any single sensor. In this example, the challenge is to identify the type of state the human body is currently in. The use of multiple sensors can also help to more accurately capture the correct level from a particular category. For example in Fig. 11, a model that could see only the motion of a person would credit the person with a higher level of energy expended per minute during the 'walk around the block' activities rather than during the 'climbing stair' activities. This is, it turns out, generally false. And that can be seen by the model built by BodyMedia through the use of multiple sensors. Again in Fig. 11, we see that the rate the person is producing and releasing heat is higher during the stair climbing activities and the models can take advantage of this additional information to more closely approximate what a metabolic cart (one of the medical gold standards on the subject of energy expenditure) would say under these same circumstances.

In practice, these examples do not capture the complexities the models

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must address. For example, it is possible that if during a period sensor A is increasing and sensor B is decreasing, or vice versa, then the output should be judged to be increasing, but if both or neither of the sensors is increasing, then the output should be judged to be decreasing. This sort of relationship cannot be captured by any first order statistical models as the correlations between A, B, and the output are all zero. This conceptual example highlights the demands on the models being learned to capture arbitrarily complex relationships in the data, not just linear trends. As an example of this, in Fig. 12, examples from four classes of human activity are shown. In all four cases, the two axes represent two orthogonal dimensions of motion and the points represent a trace in that two dimensional space over two seconds. What we see here are patterns that might be thought of as 'strange attractors' that help to identify and differentiate these different activities. These patterns are not just a matter of the amount of motion per minute, but the kinds or patterns of motion that occur in sequences over short (or even over long) periods of time.

Fig. 11. Sensor data from accelerometery and heat flux comparing flat walking and stair climbing.

Fig. 12. Longitudinal and transverse accelerometer data from the armband for biking, running, driving, and office conditions (in micrograms per millisecond).

What does all this amount to in the end? These learned models allows BodyMedia, with very high accuracy, to say to a new user who puts on a SenseWear Armband statements such as, "You burned 400 calories over the past hour" or "You were in bed for 8 hours last night, but you only slept for 5 hours and with frequent interruptions." The following table shows our current accuracies for a set of new vital signs we derive from the raw data.

Algorithm	Accuracy	Algorithm	Accuracy
Energy Expenditure	Error < 10%	Lying down duration	Error < 1%
Exercise Duration	Error < 3%	Sleep onset	Error < 3 minutes
Exercise type recognition	Error < 5%	Wake Time	Error < 3 minutes
Step count	Error < 2%	Sleep Duration	Error < 5%
Sedentary duration	Error < 3%	Motoring Duration	Error < 5%

Independent researchers have written many validation papers about the SenseWear system, especially with respect to comparing energy expenditure measurements from the system to estimates from gold-standard laboratory equipment. These include tests on normal individuals from 18 to 75 on a variety of exercise equipment comparing against indirect calorimetry, such as Jakicic et al [25], Fruin and Rankin [26], Wadsworth et al [27], and McClain et al [28], all showing significant correlations. Several researchers have examined disease-specific populations, such as cardiac patients [29] and patients with chronic obstructive pulmonary disease [30], finding good results as well. In a very interesting preliminary study, Mignault et al [31] compare the armband to doubly labeled water over a ten day period. The subjects were diabetics examined as part of a larger study. In these patients, the researchers noticed no significant differences between the doubly labeled water technique and the estimates from the armband. The correlations were extremely high (0.9696), with a technical error of measurement of only 104 kcal/day (less than 5%). The authors conclude: "... preliminary analyses suggest that the [...] Armband is an acceptable device to accurately measure total daily energy expenditure in type 2 diabetic patients over a 10-day period".

Human body data, when aggregated, also has tremendous value beyond the value of the individual statements to individual users. The revolution in the financial services industry over the past 30 years came as a direct result of the access to and real-time analysis of the world's minute-to-minute financial vital signs. Wearable physiological computing is just at the beginning of a similar revolution as a natural outcome of pulling additional meaning from the long-term, detailed, objective and accurate views of the physical states of large numbers of people and transforming these into meaningful, desirable, and actionable applications. We envision utilizing this data scientifically for data mining and commercially as a resource for creating and improving algorithms. It will be possible to compare a user's data with similar users, creating empirical definitions of what is the norm and what is abnormal. These data mining challenges and opportunities on large collections of group data are in their infancy, but an active area of effort for BodyMedia.

6. Research and development directions

While there are many exciting on-going applications discussed above, BodyMedia is engaging in continued refinements to the platform and the development of new body monitoring capabilities. These including the integration of new sensors and the ongoing development of data models to extract new physiological features and contextual activities. Some of the areas that BodyMedia is focusing on include: fine-grained sleep detail (e.g. Rapid Eye Movement); personal duress; fatigue, alertness, drowsiness; mental stress, anxiety; hydration, perfusion, homeostasis; surrogates for glucose level; calories consumed (when, and approximate quantity); biometric identification ('finger printing'

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based on personal biometrics); heart information taken solely on the upper arm; and core body temperature prediction. Efforts to make the device more unobtrusive are also underway.

Fig. 13. A prototype version of a future BodyMedia platform for ambient computing.

For all of these areas, BodyMedia has collected some anecdotal data and discovered, in many cases, compelling signs that significant opportunities for armband-based monitoring exist. For example, in the case of measuring heart signals from the upper arm, BodyMedia has discovered a new, patent-pending, method of obtaining electrical signals from the heart solely from electrodes placed on the upper left arm continuously, and for extended periods of time. This latest BodyMedia innovation can record ECG data from the upper arm, as well as other locations on the human body previously considered impractical by conventional standards, without wires, adhesives, or other equipment. BodyMedia has integrated the technology into prototype versions of the armband using one non-adhesive electrode and one adhesive electrode. Production of a non-adhesive system is underway. Their invention is particularly noteworthy because it challenges conventional wisdom in electro-cardiology that ECG can only be observed using electrodes spaced on "either side" of the heart. Al-Ahmad, Homer, and Wang [32] have presented preliminary results of validating these prototypes, showing that the armband measures heart rate and beat-to-beat variability comparably to a Holter monitor. Preliminary results in incorporating heart rate information into the equations for energy expenditure are supporting McClain et al's [28] finding that the incorporation of heart rate can reduce the error of the algorithms for certain activities. Fig. 13 shows a prototype of a new version of the device that incorporates heart-rate electrodes in a patch version of the armband.

To accomplish many of these research goals for additional body state prediction, further additional sensors may need to be added to versions of the body monitors made by BodyMedia. BodyMedia is experimenting with acoustic sensors; optical sensors, pressure and barometric sensors; GPS digital compass, and gyroscopic elements; ambulatory blood pressure; micro-needles for the administration of medication and sample collection; ambulatory pulse oximetry; bioimpedance [33], and near-body ambient air and environmental sensors. The potential to increase the understanding of human physiology in natural settings and humans' physiological interactions with their environment is substantial

.

7. Conclusions

As many pundits have commented, the current state of healthcare is problematic. Costs are skyrocketing and the current institutions are breaking under the load. Consumers are getting saddled with more of the financial responsibility of their own healthcare. Dissatisfied with their options and their care, many patients fail to comply with the treatments and programs that can best help them. Patients and caregivers alike have a hard time managing that which they can't see – and it is exactly those things that go unmeasured that are costing us the most – 1.2 *trillion* dollars last year alone.

In attempting to address these problems, we must take into account several factors. First, healthcare will increasingly come to be ruled by consumers due to the power of the market. Second, consumers will need personal health care tools to help them manage their health and wellness through helping them manage the root causes of their health and wellness – their choices and behaviors. Nearly all of the tools that consumers end up using will require as inputs physiological information about their bodies. This will require wearable body monitoring that is simultaneously medical-grade and consumer-desirable.

BodyMedia is today addressing this need by following a few simple principles. We strive to find the new vital signs that resonate with consumers and the behaviors they wish to manage. In addition to incorporating our increasing knowledge of the human body, we also directly model the relationship between these new vital signs and the physiological signals we can measure from the body. A fundamental question for us is "how can we get accurate information from the body in a way users will love?" Given that users won't wear twenty different devices, we work to build a single system that delivers value on multiple fronts from the same piece of effort. Finally, we recognize that continuous body monitoring is providing data that science and medicine haven't seen before. We are working to build systems that take advantage of these increasingly large data streams both to better help the consumer and to increase our knowledge of health, physiology, and human behavior.

The SenseWear system and its applications are a first step toward a vision of the future of healthcare that enables users to manage their health and care for their bodies anywhere they choose to do so. The future of healthcare is happening today.

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Chapter 50: How Can We Avoid Individual and Inter-generational Medical Errors?

Renata G. Bushko, M.S.
Director, Future of Health Technology Institute, Hopkinton, MA, USA

Abstract

Errorless, invisible, continuous and infrastructure-free healthcare should become our goal. In order to achieve that goal, we need to rapidly move from current episodic and emergency-driven "healthcare delivery system" to an intelligent and extelligent health environment. That requires introduction of distributed affective Intelligent Caring Creatures (ICCs) consisting of healthons. Healthons are tools combining prevention with diagnosis and treatment based on continuous monitoring and analyzing of vital signs and biochemistry. Unlike humans, who posses only two or three dimensions of thinking, healthons can assure errorless health because of their adaptability, flexibility, and multidimensional reasoning capability. ICCs can do "the right thing" based on (1) state-of-art medical knowledge, (2) data about emotional, physiological, and genetic state of a consumer and (3) moral values of a consumer. The transition to the intelligent health environment based on ICCs requires the solutions to many currently unsolved healthcare problems. This paper lists the unsolved problems (by analogy to mathematical unsolved problems list) and explains why errorless healthcare with bionic hugs and no need for quality control is possible.

1. Errorless, Invisible, Continuous and Infrastructure-free Healthcare

A concept of errorless healthcare is based on the broad definition of an error:

Definition 1: Individual Error

Error occurs when we could have had a positive impact on person's life assuming current state of medical science, knowledge and resources but we fail to do so.

Definition 2: Inter-generational Error

Error occurs if we could have had positive impact on populations' health but we failed to achieve that because of inappropriate allocation of resources.

E.g. If we invested in nonomedicine the day that Dr. Eric Drexler described it, we could be saving lives with much more advanced nanorobots today. If we, as a society, decide to delay research on postponing aging or common sense knowledge representation, we may create an inter-generational error that costs us millions of lives.

It is not enough to set a goal to reduce the number of medical errors, which is what happens with many improvements programs. These medical errors must be eliminated. We strive for errorless space missions. The same should happen in health care. The life of an astronaut is equally important as the life of any other person.

The invisible feature of new healthcare means that it is handled in an unobtrusive way that does not disturb the normal lifestyle of the consumer.

Infrastructure-free and continuous healthcare means that it goes on anywhere and all the time. Healthcare

becomes life-care.

2. Intelligent Caring Creatures and Healthons

Affective Intelligent Caring Creatures (ICCs) are needed to achieve errorless, invisible, continuous and infrastructure-free healthcare, something that is impossible within the current organization of the healthcare system. ICCs consist of "healthons" that consumers carry in their bodies, on their bodies (intelligent health environment) and that are embedded in their homes, offices, cars, plains, furniture and robo-pet assistants (extelligent heath environment). Healthons are tools combining prevention with diagnosis and treatment based on continuous monitoring and analyzing of our vital signs and biochemistry of the body. Healthons in 2050 will be like vitamins or tooth brushes in 2005 – broadly available and used by everyone. There will be one difference, however, because they will be able to talk to each other and, if desired by the consumer, they will be able to explain what is happening with consumer's health at any moment. It is very important that the designers of ICCs include the "explain on human level" feature in the products they produce. Otherwise, we will be left out by the omnipotent machines.

2.1 Examples of Healthons

Memory glasses are a good example of a healthon: a consumer wears them and his/her recognition of people increases 50% without any conscious effort by the consumer. Another example is a nanooptical sensor placed in the brain that can monitor glutamate and that allows for feedback on the progress in the learning in children (glutamate is a neurotransmitter secreted by nerve cells that influences sensory perception, learning and memory).

A Robopet jumping on its elderly owners lap to remind him/her about his/her medication or exercise schedule, an artificial nose extension sensing allergents before they cause negative reaction, or Professor Shioyama's electronic eye translating the visual input into instructions of how to cross the street for the blind, or a second skin (E.g. BodyMedia's bodybugg™ or continuous thermometer) suggesting diet change are also good examples. Artificial red cells that can help us stay underwater for two hours without an oxygen tank or the relational agent that explains the work of other healthons in a virtual medical visit via Nomad-like glasses and realistic OLED display are yet additional examples.

The best example of a healthon that combines diagnosis, therapy and treatment is "surgical injection" developed by Philips Medical Systems: an injectable chemical agent (Apomate) identifies the portion of the heart experiencing the heart attack, and the same agent delivers VasoEndothelial Growth Factor to the region of the heart attack to cause new blood vessels to grow thus repairing the heart non-invasively. Cellular healthons are possible because of fast progress in nanotechnology. One of the examples is nanomolecular tagging technology – molecular bar-coding sys invented by Krasen Dimitri that allows

tagging, identifying, and counting individual molecules.

2.2 Adaptiveness – The Key to Errorless Healthcare

The key attribute that guarantees an errorless health maintenance process is adaptability, which could be achieved by common sense knowledge representation with analogical reasoning engine. Adaptive biomechatronic and nono-biomechatronic ICCs, non-brittle and non-human, will have a better chance of avoiding errors than humans. Investment in the creation of non-brittle ICCs with common sense will generate extensive benefits in healthcare where the compartmentalization and the enormous size of new medical research is prohibiting a single un-aided human mind from being effective.

3. Big Need for Software

In the ICCs era, there will be no need for healthcare quality control, but instead a great need for software quality control. Everything from nonomolecular devices in our bodies to relational agents explaining to us nanorobot's actions will contain software programs. Intelligent Caring Centers (equivalent to current hospitals but without patients because of infrastructure-free healthcare organization) will reprogram and upgrade Intelligent Caring Creatures. Intelligent Caring Centers will be run by healthmaticians (mathematicians that serve human health) and NURSES (New Unified Resource Systems Engineers) who also take care of healthon allocation according to the medical needs and the ethical convictions of the population. Significant investment in software development methodologies is needed to conquer the software bottleneck and to make sure that we can take advantage of all newly available hardware. Healthmaticians and NURSES must remember to include the "explain on human level" feature in all ICCs – even those who can program themselves based on the experience they have had. These learning ICCs can self correct, and some of them can set their own goals. Because of that, healthmaticians developed an "Emotion in Motion" engine that can indirectly influence ICCs to set humanitarian goals.

4. Deriving Dynamics from Medical Data - the Key to Errorless Healthcare

We cannot currently derive the dynamics of the system from data about our body and genes. There is a better chance that machines can do that before we – mere humans – can. This is what medical science is trying to do "manually," using previous experience, isolated data points, and a lot of guessing. It is like trying to find an ant in a 5000 square-foot house.

What if we have all possible data about the way our body functions gathered by wearable or implantable devices? Does it change much? Yes – but only if we can reason on the data and derive dynamics of the phenomena that manifested itself by that data

Intelligent Caring Creatures and healthmaticians have a better chance of inferring the dynamics that need to be understood than human physicians. Humans can only process comfortably

in three dimensions while computers can see an infinite number of dimensions. We will need to trust the distributed network of Intelligent Caring Creatures and NURSES who built the medical intelligence into our external environment. The time that it takes t accept the fact that machines decide about the healthcare process will determine the time that it takes to achieve errorless healthcare.

5. Talking to Our Cells – Nanocommunication

What if we had a digital model of a human including the functioning of each and every cell? What if a wearable computing paradigm applied to each and every cell? Cells would be making a decision to "wear" the nanomonitor or not; to undergo nanosurgery or not; to die or not. Cells would be reporting to organs and to their owners (us) about the probability of a mutation that may cause a problem (e.g. cancer) later on. Or should we forget about reporting all together – why waste the time doing that – let's give our cells the power to fix themselves and to communicate only with other cells that perform related functions. This would mean invisible healthcare – similar to the invisible disease creation process. Real-time electrical detection of single viruses is already possible – we are moving in the right direction. We are also moving rapidly from the era of robotic surgery to nanosurgery. A high-speed ultrasensitive bar-coding system for identifying individual molecules by NanoString Technologies gets us closer to knowing ourselves on a cellular level and talking to our cells.

6. Bionic Hugs – Unlimited Supply of Care – Remote Presence

Errorless, infrastructure-free healthcare could be possible with an army of bionic helpers – a type of specialized Intelligent Caring Creatures who replace current nursing and are made available in any amount to all who need physical or emotional help. From a simple handshake to a sophisticated dialog, bionic intelligent caring creatures will be able to help.

Bionic pets will play an important role too. The human need for affection and friendship will be fulfilled even for those who cannot care for a real pet. Robo-pets will also serve medical roles – gathering data about the consumer and reminding about healthy behaviors and disease management routine in chronic conditions. With robotic-pets encouraging an active lifestyle, childhood obesity will be a long forgotten history.

7. Extelligent Adaptable Environment

Most of us will still have a chance to live in an extelligent environment that will change depending on the emotional and physical state of the consumer. With the use of OLED wall-sized programmable displays wirelessly communicating with body sensors, it will soon be possible to design healing environments that are so much underutilized. For example, a patient who loves outdoors but has to stay immobile for some time could program his room as a tent with

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windows showing pine forest and wind moving the branches and an occasional blue bird's call. The walls could also be self-programmable based on diaries from the past describing most positive energizing experiences.

Objects that we use in every day life will talk to each other, to the walls, cabinets, our second skin and nanorobots inside our bodies. They will be working together to create the most favorable living environment for each of us.

8. Remote Presence and Trust in Invisible Healthcare

Physical and virtual remote presence will extend to unthinkable proportions. What if a new type of a human/machine doctor – "doctoron" could care for 100 patients with the similar disease at the same time? Of course, that would be needed only if consumer chooses to know each and every step of the care process. Most consumers will choose to lead a normal, uninterrupted life style instead of checking on the doctoron's decisions. It will be more and more so within our capability to extend our life spans indefinitely. There will be no need to double-check our human/machine doctorons or even use them. Most people will delegate control to their cells directly.

Just like computers are used in mathematical proofs (computer performs tasks that are not possible to be verified by humans), they will be also used this way in healthcare – without us understanding each and every step of the reasoning and computation behind a decision. But we need to be in control – we need to understand qualitatively what is happening and our biggest current responsibility as human beings is to make sure that it will happen – that new brave human/machine systems will be able and will be willing to share their findings with us human beings.

9. Getting There – Example of Turning Existing Infrastructure into HealthStructure

Before we all wear body monitors in the form of second skin, we would all be healthier if we could get a quick medical checkup while pumping gasoline at the gas station. Our blood pressure at least should be measured every time we stop at the gas station and we should also be checked for sleepiness and alcohol level (breathalyzers) to determine if we should continue driving. Falling asleep at the wheel causes a large percentage of accidents. We could imagine facilities for those who need to take a nap or rest (Sleeping chambers) right at the gas stations.

10. Unsolved Health Problems

By analogy to mathematics where there is always a list of unsolved problems to guide the young generation of mathematicians, Future of Health Technology Institute conducted an "unsolved health problems" survey in 2003-5. The results are listed in the table below. All survey participants were also asked to state what will we gain if we solve that problem and what will we lose if we do not solve it. Solving these problems will get us closer to errorless, invisible healthcare with bionic hugs and no need for quality control.

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Table 1. Unsolved Health Problems – Based on HFTI's Unsolved Problems Survey 2003-5

Unsolved Problem	What will we gain if we solve this problem?	What will we lose if we do not solve this problem?
Lack of clean water in much of developing world.	Reduced (especially child) mortality rates.	Lives
Lack of drugs resulting from human genome.	Cures for previously untreatable, fatal illnesses.	Funding for genetic research
Really effective interfaces with human users.	Efficiency	Usability
Significant (in magnitude) replacement of human professionals by machines.	Enormous increase in efficacy/ productivity and better "results"/ outcomes.	Status quo
Translation from the Laboratory to the Bedside: many innovations seem to never to get past the "proof of concept demo" phase.	We may see more of these projects make a difference in clinical treatment.	We will waste a lot of our intellectual capital on projects that don't make it to the bedside.
Lack of tools to build causal models that integrate all pieces of medical and process information; information systems that can help us to integrate all information into causal models, test the models against available information, and help us do thought experiments to devise new hypothesis to test.	If we are able to overcome the problems of how to build, interpret and validate what will often be massively underspecified models of physiological systems, then we will be able to accelerate the process of discovery.	We will continue to build an increasingly fragmented knowledge base and many important discoveries will not get translated into useful understanding.
Independent nanorobots with smart software controls.	Stop disease before it develops.	Lives.
Anticipating human and system failures so that processes can be devised to prevent these failures.	We will be better able to optimize the care we can give with the clinical advances we have in hand.	Medical errors will continue to limit our ability to give the best care possible with the current clinical knowledge.
Structured capture of clinical data (history, physical examination, progress notes, procedure reports, discharge summaries.	Increased formal encoding of phenotype information to enable research, clinical care, decision support, etc.	We will continue the present process of having this information unavailable. Some could be captured through natural language processing techniques, but structured data capture also encourages more discipline and thoroughness in recording, and provides more opportunity for timely decision support.

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Personal longitudinal integrated health record.	This will foster improved continuity of care, access to relevant information to care providers, better decision making, decreased errors (e.g., overlooking an allergy or ordering of a medication conflicting with another), and the ability to track a patient's care over time, issue reminders, recommendations for improved health, etc.	We will continue the present process of fragmented, incomplete, inefficient management of episodes of care without ever having a complete picture of the health status of a patient.
Comprehensive structured population health data bases.	This will provide the ability to do analyses of screening tests, genome-phenotype correlation, outcomes analyses, technology assessments, and clinical prediction/prognosis.	Continued current state of limited comparability and size of datasets.
Application of cutting edge technologies for Primary Prevention i.e. implanted calorie counter/blood sugar monitor with beeper or such for weight loss, nicotine or drug aversion implants etc to give ongoing feedback and stimulus for behavior change. The simple low cost pedometer is a good example, but perhaps taken to a higher level or personalized monitoring.	Decrease in incidence of chronic illness and money spend for chronic illness, care and improved quality of life.	Individual quality of life and economic stability in health care costs as current population ages with chronic illnesses due to behavior factors.
Cost benefit ratio analysis of health technologies.	Truly beneficial and cost effective health technology applications.	Increasing personal and 3rd party costs for marginal efficacy - "technology for technology sake".
Inadequate distribution of current technologies, based on geography, income etc.	Equity in world health.	Continued Inequitable distribution which may eventually be the death of us all i.e. SARS AIDS etc. spreading world wide without available monitoring and prevention measure

Lack of coordination. This problem crosses all applications of technology, whether business, aerospace, or medical. In medicine, the cost of mistakes is already too high.	A specific example of positive coordination among medical systems includes the sharing of patient information among pharmaceutical and patient records so that errors in prescriptions, both in hospital and out of hospital are reduced, if not eliminated. But also that same mechanism of sharing, can provide a uniform source of information across many platforms, many software systems, so that validation and cross checking among the different systems may be simplified and when errors are detected, more easily tracked.	If we do not attack the problem of coordination, we risk additional sources of error, loss of our ability to track errors, and loss of time, not to mention increases in medical error and possible law suits.
Lack of recognition that not all medical problems can be solved with "more technology"... sometimes, "LO TECH", is a more cost effective and patient friendly. E.g., providing access to meditation classes can reduce the cost of medication for chronic medical conditions such as high blood pressure and pain management.	Reduce patient load, empower patients, create first steps in the cultural shift to one where patients begin to take an ACTIVE rather than PASSIVE role in their own health.	Continuing on the path we are on is no longer an option. Health insurance costs are not going down. Not only are Americans uninsured they are also underinsured.
Effective use of media such as TV and the internet to raise awareness and engage the average consumer into healthcare. Make being healthy "trendy"; make it "attractive". This requires administrators to make this a line item in the budgets, a non-technical issue, but implementation is technical.	It will take time to help consumers reach for self care in their medicine cabinets rather than pills, but eventually we can hope to see an improvement in the overall health of human race reducing the costs of chronic conditions and the incidence of health problems.	We will continue to see the deterioration of health status. The cost of insurance, and the cost of Hi-tech healthcare need to be offset by low tech, such as dietary habits, practice of meditation, and so on.
Regenerative Medicine: ability to apply stem cells to address regenerative medicine.	Find cures for millions that suffer and sometimes die prematurely from degenerative illnesses.	Billions of dollars spent on unpromising therapy as well as incalculable human misery.
Background noise in biological agent detection system.	Ability to rapidly detect pathogens to isolate populations from further exposure.	Millions of lives lost to infectious disease epidemics that may be able to be curbed with early detection.

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Growing new Telomeres from stem cells.	Potentially slow down the aging process.	Immortality
100% Electronic infrastructure for medical records.	Greater portability of data, greater collation of data for research, longitudinal tracking of health information, and potential reduction in medical errors.	Privacy lapses, consumer apprehension.
Wide-spread mobile computing in medical care.	Instant access to reference and clinical information, greater evidence-based healthcare.	Application in well-funded vs. poorly-funded settings; physician resistance and lack of acceptance of new computing technology.
Personal understanding of preventative health lifestyles.	Lower heath costs and better quality of life.	Unbounded cost of health care.
Adequate pricing of health care	Reduction of serious ethical problems in health care pricing.	Lost market pressure for improved health care costs with monies being extracted for drugs and procedures no care and health.
Inpatient medical error as the third leading cause of death. Medication error is the largest subcomponent and by itself is the fourth leading cause of death. 60% of medication error is caused by physician ordering and 30% is caused by nurse administration.	Eliminate of a substantial portion of 220,000 unnecessary inpatient deaths per year and millions of persons maimed or incapacitated in some way. Elimination of a portion of about 1M unnecessary outpatient deaths. Elimination of about half of patient visits and hospitalization by proper disease management.	220,000 unnecessary inpatients deaths and millions of outpatient deaths and disabilities. About $500 Billion in unnecessary healthcare costs.
Outpatient medical error (even higher than inpatient error, perhaps by an order of magnitude)	Human Lives	See Above
Disease management errors - the iceberg of which medical error is the visible tip. E.g., many unnecessary amputations on diabetics performed every year in the U.S., caused by improper follow-up.	Human Lives	See Above
Bringing the bio-med hypothesis builders and the tech developers closer (educational challenge).	Fast progress and better penetration of innovations into practice.	Slow progress

A reliable protein/proteomics database for NORMAL human serum. (Surprisingly, from the many decades doctors have looked for signs of disease in the blood, the normal constituents--proteins-in blood are very poorly known, both qualitatively and quantitatively. Before we can exploit nanotech & high throughput methods, we really must get a handle on what the range of normal proteins is in peripheral blood).	Human Lives – Reduction in unnecessary anxiety about "symptoms" that are part of normal variation not a sign of disease.	Lack of individualized biochemistry understanding and treatment.
Expediting tech transfer from lab to clinic (administrative, governmental challenge).	Reduction in suffering.	Wasted human effort.
Finding the genetic basis of the telomerase-independent telomere extension seen in about 10% of human cancers.	We'll be able to control telomerase-independent cancers (including half of all sarcomas, for example) by gene therapy in the same way that we will be able to control telomerase-dependent cancers by gene therapy against the telomerase genes.	We will fail to give people longer healthy life spans and reverse aging in order to reverse aging comprehensively enough to keep people alive and healthy for a few decades more than now, which will be enough to let us improve the therapies further and keep us alive indefinitely.
Making the 13 protein-coding mitochondrial genes work when placed in the nucleus.	We'll be able to ignore the accumulation of mitochondrial mutations during aging, because they will be harmless -- the proteins that are made from the mitochondrial DNA will be made from nuclear copies of the genes so the mitochondria will still work.	We will fail to give people longer healthy life spans. See Above
Finding microbial enzymes to break down the cholesterol analogues that cause atherosclerosis and maybe Alzheimer's disease.	We'll be able to treat all major diseases that are caused by the accumulation of garbage inside cells. That includes atherosclerosis, macular degeneration and probably most types of neurodegeneration.	We will fail to give people longer healthy life spans. See Above.
Lack of machines with common sense that could take care of us	Well cared for population. Increased health status of the population.	Worldwide healthcare crisis due to lack of care givers. Unnecessary suffering.

Lack of comprehensive working easy to use framework for performance evaluation of adaptive complex systems.	Faster progress towards errorless healthcare.	Slow progress towards errorless healthcare.
Maintaining long-term engagement between users and health dialog systems (caring machines), especially crucial for chronic disease management systems in which we need people to use the system regularly for the rest of their lives.	Increased speed of acceptance of caring machines.	No good communication between people and caring machines.
Encoding of behavioral medicine concepts and theories into shareable computational ontologies, to support information sharing and re-use.	Exponential growth of the use and utilization of the caring machines.	Limited use of caring machines.

9. Conclusions

Utilizing Intelligent Caring Creatures (ICCs) to achieve errorless healthcare requires departure from thinking that the only entity that can justify a medical action is an un-aided human being. Once we are ready to delegate management of our health to ICCs we need to make sure that they are able and willing to explain their multidimensional reasoning. Compiling a list of "unsolved problems" helps moving towards errorless healthcare. It would be useful to have awards system for solving currently unsolved healthcare problems to make healthcare errorless, invisible, infrastructure-free and continuous sooner – to enter a healthon era. The Worldwide Marathon for Health: Healthon Initiative initiated by FHTI will start that process.

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Chapter 51: Thought to Computer Communication

Kevin Warwick
Professor of Cybernetics, Department of Cybernetics, University of Reading, UK

Abstract

This paper describes some of the implant experimentation presently underway. The basic approach taken is introduced and general techniques are explained. Achievements already attained are summarized and short term plans are expanded. Potential results, as they could impact on healthcare and related issues, are thrown into the arena. The author speculates 'a little' on what might be achieved in the future with implant technology.

1. Introduction

Let's start with a few basics. Humans are, for the most part, successful at being humans. As Homo Sapiens we have though been around for only 100,000 years or so, which is a very brief time span in comparison with many other creatures. Just as Big Macs relate to gourmet food so humans relate to life on earth. But the moving hand of evolution points to the future. Some creatures adapt, surviving or even becoming more successful, those that don't will, almost surely, die out. Even the Big Mac, as we know it now, will not last for ever.

It is possible that humans will slowly change, to utilize more effectively the technical world we are creating. The consequences of not adapting at all are potentially horrific. Could we really end up with machines, far more intelligent than ourselves, becoming the dominant 'life' form on earth? An alternative is for humans to e-volve, to technically upgrade the human form by linking much more closely humans with technology. In science fiction terms this means we will become Cyborgs – part human, part machine.

But what sort of an upgrade are we looking at for humans? It may be that spare arms and legs become the order of the day, but unless we are all going to become Inspector Gadget look alikes, with corkscrew fingers and propeller heads, it is difficult to see where this will get us. No, clearly it is not a physical upgrade where the rewards are greatest, it is a mental one. In fact healthcare problem number one in this new technological world, in that most physical aspects of the human body are rapidly becoming redundant. Some people, as a result, become obese, whilst others take regular, enforced, exercise. What is to be done with physical bodies that are no longer required to perform as they used to, yet are living much longer is indeed a pertinent question. But I will not attempt to answer it here.

Even though humans have been in their way, fairly successful on earth, we are extremely limited in what we can do and how we perform. Clearly we have physical limitations. In the last few centuries in particular we have employed technology to improve our capabilities. So we can lift heavy

loads, dig tunnels, accurately and rapidly repeat a mundane task, communicate instantly around the world and fly.

Even though humans have been in their way, fairly successful on earth, we are extremely limited in what we can do and how we perform. Clearly we have physical limitations. In the last few centuries in particular we have employed technology to improve our capabilities. So we can lift heavy loads, dig tunnels, accurately and rapidly repeat a mundane task, communicate instantly around the world and fly.

But what are the possibilities for humans to be upgraded to cyborgs to take on board some of these abilities? Could it be possible for ourselves, in cyborg form, to understand the world in many dimensions, by linking our human brain directly with a computer brain? Could we then directly tap into the phenomenal math and memory performance of the computer. What's the use of the human brain remembering things or learning math when the computer brain can do those tasks much better? Whilst human brains will, on their own, evolve relatively slowly, perhaps by gradually expanding over generations; could it be possible for us to bring about a form of designer evolution by connecting computer brains, with near-infinite potential, to our own.

Our senses also might be directly upgraded. Is it possible, for example, for us to take on board x-ray, infrared and ultrasonic signals? Could these be fed directly to our brains? What then would the world feel and look like to a cyborg who senses it also in terms of ultra violet and ultrasonic signals, and comprehends it in 8-dimensions? Surely this would completely change our understanding of the world; what we believe to be possible and what not.

2. Self-Experimentation

In the fall of 1998 I had a silicon chip transponder surgically implanted in my left arm, with this in position the main computer in the Cybernetics building at the University of Reading was able to monitor my movements. Essentially at various doorways large coils of wire within the door frame provided a low power radio frequency signal which energized the small coil within the transponder. This in turn provided an electric current enabling the transponder's silicon chips to transmit a unique signal to the computer, identifying me.

Signals were, in this way, transmitted to/from the computer and inside my body. To demonstrate some of the capabilities, a voice box by the entrance welcomed my arrival each morning with "Hello Professor Warwick", the door to my lab opened as I approached and the computer was aware of what time I entered a room and when I left. It switched on lights for me, automatically, as appropriate. The experiment having been a success, 9 days after its insertion, the implant was removed.

Since that time we have been working on the next step of our

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research program, a new implant. The operation to put it in position is tentatively scheduled for September 2001, almost exactly 3 years after the previous experiment. Once again the target area is my left arm, just above the elbow. This time however a direct connection will be made with the nerve fibers running up the center of my arm. Electronic signals on the nerve fibers will be picked up and transmitted to a computer, rather like tapping into a telephone conversation. Signals will though also be received from the computer, and played down onto the nervous fibers.

The nerve fibers in the upper arm link the brain to the hand and they carry a variety of signals. In one direction signals from the brain cause movement and dexterity in the hand, whilst in the opposite direction sensory data from touch or pressure is passed. Also apparent are a number of body state signals concerned with temperature, blood flow and the like, along with physical emotional signals such as anger, shock and excitement. Signals relating to pain are also sent via this route. So at any instant in time the nerve fibers carry a very mixed collection. Some people might regard many signals as noise, but this is not really the case at all, as every signal is important. This said, if you are investigating movement then signals relating to anger or pain could be deemed to be noise as they do not directly relate to the study at hand. One thing is apparent however and that is, in the upper arm the nerve fibers are rather like a Freeway in that most of them directly link the brain and hand, with very few turn offs. It is therefore a good place to investigate a nervous system implant if, as a scientist, you are not yet ready to have one positioned in your brain.

Apart from a direct connection onto the nervous fibers, the implant will contain a transmitter, a receiver and some local signal processing and conditioning. The implant will merely be providing an interface between the nervous fibers and the computer, it will not be carrying out any signal understanding itself.

We wish to look at a range of signals. Firstly a series of movement experiments will be conducted. The signals which cause particular fingers to move will be recorded in the computer and then played back again in an attempt to recreate the movement as closely as possible. Secondly signals from an ultrasonic sensor will be directly played down onto the fibers and I will visually learn when objects are close by and when not, thereby relating visually to the signals on my nervous system. We will see if I can directly sense objects close by. Hopefully the movement experiments will contribute to research in that area whilst extrasensory signals could be immediately useful as an alternative sense for people who are blind.

Then come experiments more into the unknown. Pain, anger and shock signals will all be stimulated as much as possible and recorded on the computer, even excitement. The relevant signals will then be played

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back down again onto the nervous fibers. Will my brain indicate any of the original feelings? This is what we wish to find out. Could it be possible to initiate the feeling of pain electronically? If so perhaps we can send in equalizing signals instead, to counteract the effects of pain in an individual. Can we electronically cause excitement, happiness and so on? If so we are looking at the potential world of e-medicine.

3. Communication

As long as the experiments go well with my implant in place, my wife Irena will join me by having her own implant. What we wish to look at then is communication from one person's nervous system to the other. Potentially across the internet. So the signals from my own nervous system will be played down onto Irena's nervous system and nice versa. Both implants will be positioned at roughly the same point in our upper left arms.

Obviously movement signals will be of interest. When I move my left index finger and the electronic signals that achieve that are played down onto Irena's nervous system, will it achieve anything like the same movement in her hand? When she feels pain in one finger, due perhaps to excessive pressure, will I feel the same sort of pain? Indeed is it roughly the same in men and women? If she gets excited (as in the presence of an attractive young man), what will I feel when the associated signals appear on my nervous system?

We hope to have time to look at phobias and fears. Irena is extremely frightened of spiders. I would like to experience those feelings, to an extent at least. I am scared of being high up in a building. Can we arrange for one of us to be in the UK and the other in the USA – perhaps I can be in the Empire State Building. What will Irena feel when signals from my own nervous system in that situation appear on hers, as she is sitting quietly?

Clearly these experiments are only a start of person to person communication by means of direct nervous system signaling. At this stage we have very little idea as to how far we will be able to take it. Could it be possible in the future, with implants directly positioned in the brain to communicate in the same sort of way. Could we send our thoughts to a computer? Could we think to each other? Could we communicate by thought signals alone? Obviously we will not be able to go that far with our own next experiment. It will be merely a step on the way.

4. Medicine

It is worth remembering that the human brain is an electrochemical entity. In the western world we have, till now, largely concerned ourselves with the chemical aspects of the brain. Chemicals are employed for a number of reasons – to ease a headache, to prevent pregnancy, to help get to sleep or, in the case of coffee, to help wake us up and perform better in examinations. Could anything like the same sort of effects be realized, fairly

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easily, electronically? If so the potential for e-medicine is enormous. Perhaps electronic signals could be used to provide a viable alternative to cigarettes, without some of the side effects. Indeed electronic signals have already been successfully used to combat the effects of both Parkinson's disease and Alzheimer's disease.

We must however remain rather wary in opening up this field. Just as electronic signals might potentially be used for their positive medicinal effects, they might similarly be used for individuals to get high on a daily, electronic pick-me-up? The field of cybernetics is perhaps just around the corner.

5. Supporting Cases

Much research work is being carried out presently by various research groups around the world which directly supports and influences our own work. For example as recently as 1997 a group at the University of Tokyo attracted a microprocessor directly to the motor neurons of a cockroach, which carried the computing power around as a back pack. Signals from the microprocessor were then used to drive the cockroach around in a planned route. No matter what the cockroach might have itself wanted.

Meanwhile in 1999 it was reported that John Chapin at the MCP Hahnemann School of Medicine in Philadelphia and Miguel Nicolelis at Duke University had implanted electrodes into rats' brains. Initially the rats were taught to pull a lever in order to get a ratty treat. However the implants were positioned such that the rats merely had to think about pulling the lever and these signals, when transmitted to the computer, were enough to cause the treat to be electronically released. Interestingly the rats soon learned that they didn't have to actually pull the lever, merely thinking about it was sufficient. As far as humans are concerned, several groups are experimenting with computers linked to the nervous system. Ross Davis' team at the Neural Engineering Clinic in Augusta, Maine have been developing technology to attempt to treat patients whose central nervous system has been damaged by an accident or a disease such as multiple sclerosis. They have obtained excellent results in regaining muscle control by means of computer generated (as opposed to brain generated) signals.

Perhaps the most stunning research so far though is that carried out by Philip Kennedy and his team at Emory University in Atlanta. There they have implanted an electrode directly into the brain of a paralyzed war veteran, Johnny Ray. He is paralyzed from the neck down and hence cannot control or move any part of his body below that point. A functional MRI scan was used to detect brain activity when Johnny was asked to think about moving his arms and hands. The implant was positioned in an area of the brain seen to be active under such circumstance.

With the implant in place Johnny was able to move a cursor around on a

computer screen thereby spelling out words and constructing sentences, merely by thinking about it. The electronic signals in his brain which relate to thoughts, about certain movements, are transmitted to the computer by a radio signal in a similar way to our own implants. What is incredible though is that not only can Johnny, in this way, communicate by means of his thoughts alone but also that his working brain has actually readjusted to its newly found power. His own neurons have grown into, and strengthened the link with, the implant.

6. Cybernetics

All of this research is very much at the heart of what cybernetics (a term originated by Norbert Wiener of MIT) is all about: humans and technology acting together as an overall system. One key element of this is consideration of the human brain as just another, albeit extremely important, physical organ in the human body. The human brain has no magical properties over and above its physical working. A brain's consciousness is merely a function of its operation, it is not some remote entity that exists elsewhere in the ether. Thoughts are merely as a result of particular states of the brain, dependant on a set of electrochemical signals in the brain at that time.

On average a human brain has, something like, 100 billion individual cells. It is a complex network, each cell connecting with thousands of others to produce its own operation. It is extremely difficult, at the present time, to unravel and hope to fully understand its actual operation. It is certainly not a parallel processing device however.

The range of capabilities of, and intelligence associated with, humans is dependent on our brain cells and the way they are connected together. However if we enable implants to link our brain directly with a computer then anything that computer can connect to could potentially operate for us. Not only could doors open and lights switch on automatically, as they did even for my first implant, but we might be able to drive a car or fly a plane merely by thinking about it. I feel that once some rudimentary trials have been carried out we would rapidly learn how to expand our abilities and operate the whole system more effectively.

But communicating from brain to computer and ultimately from human brain to human brain, in terms of thought signals alone opens up new questions. Why would we need to speak? Will language and the culture as we now know it, disappear completely or will it still have a small role to play, perhaps in the development of babies. As humans evolve to this new level so telephones become obsolete. If we communicate by thoughts perhaps we will become less open and learn to control our feelings and emotions more. Indeed a simple evolutionary step would suggest that those who could better control their feelings might be more likely to succeed in the new world.

7. Immediate Uses

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Implant technology does though offer some more immediate potential uses. Dependent on the position of an implant, certain body states can be measured, or inferred, e.g. blood pressure, temperature and pulse. The relevant values can then be transmitted to a computer which gives an overall conditional indicator. Whilst this could be useful for athletes and other sports people, it would have a direct impact in patients undergoing constant monitoring. In these cases electrodes repeatedly placed on the skin surface can cause deep sores and much bleeding after a while. The implant alternative is, I feel, worthy of investigation.

But the real potential appears when brain implants are considered. Computer based machines are rapidly becoming more intelligent, perhaps in a complementary way to humans. Linking a human brain to such technology, creating a cyborg seems to be a natural way ahead, simply upgrading the human form. In most cases though the computer brain would not be operating in stand alone, but rather would be part of a network, with mixed intelligence and capabilities. The question then needs to be asked as to how the human fits into that. In that way a cyborg would not be an individual but would themselves be a node on the network. Away from the network your capabilities are limited to the poor performance of humans, connected into the network and you are merely part of a considerably greater whole.

With my first implant it did not take long before I mentally considered the implant to be part of my body, part of me. However the computer was linked to the implant, hence it was linked to me. We were not separate, yet complemented each other. When the implant was removed, on the one hand I felt relieved that any potential medical problems, such as infection, were behind me, however I also felt that I had lost a friend, in that myself and the computer were not longer an item!

With the new implant including a nervous system connection, such feelings of affinity can only get stronger. When brain links are involved they will be stronger still. As a cyborg would you have the same morals and ethics as those of a human? I would think not. Sure the cyborg started in human form and hence human values probably play a part, however I would guess that as a cyborg it would be cyborg morals and ethics that would be in evidence.

8. The Future

We must be careful as we investigate further into the use of implants. Until now they have been mainly for helping out something in the human body that is not functioning correctly, as is the case with a heart pacemaker or a cochlea implant. However implants in general open up the possibility of giving humans extra capabilities. In the short term this may mean we can think about repairing, to a certain extent at least, a nervous system break, and hence get people moving again. Possibly we'll also be able to bring about extra senses and apply complex

electronic signals to help both physical and mental illnesses.

When we link human brains and computer brains together though, we are going a stage further. By creating such mental cyborgs we are doing something more. We will change the basic nature of ourselves. We will give ourselves much more powerful means of communication, and the ability to think about problems in many dimensions. Those without an implant, i.e. those that remain as mere humans, will become very sorry individuals unable to compete. They will, roughly speaking, occupy the position that chimpanzees are in today.

If you were to ask me whether I would wish myself to go for the unknown and unchartered cyborg future, I do not have to think twice to answer. No way, under any circumstances do I want to belong to a chimpanzee-like sub species. It's a cyborg life for me.

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Chapter 52: Of Mice and Men: Brain Cultured in the Laboratory Linked to a Physical Robot Body

Kevin Warwick
Professor of Cybernetics, School of Systems Engineering, University of Reading, UK

Abstract

In this chapter we consider a distinct example of the link between biology and technology, with particular reference to the brain. We look at the example of a brain cultured in the laboratory which is then linked to a physical robot body. The overall entity therefore consists of a physical robot body controlled by a purely biological brain. The entire system provides a wonderful base for the study of the fundamental features of diseases such as strokes and Alzheimer's disease, as well as allowing for a basic investigation into the mechanisms for neural signal transfer.

1. Introduction

The intelligent controlling mechanism of a typical mobile robot is usually a computer system. Research is however now ongoing in which biological neuronal networks are being cultured and trained to act as the brain of a real world robot – either replacing or operating with a computer system. Studying such neuronal systems can give an insight into biological neural structures and has immediate medical implications. The principal aim of the research described here is to assess the learning capacity of dissociated cultured neuronal networks. This has been approached by the creation of a hybrid system incorporating closed loop control of a mobile robot solely by a dissociated culture of neurons. The human brain is a complex computational platform. Studying how the brain processes and encodes information in living animals [4] can be technically problematic as access is limited by the skin, skull and the sheer number of neurons present in the brain. Moreover, whole animal approaches capable of recording the activity of individual neurons or small populations thereof are limited by the invasive nature of such techniques. For these reasons laboratory cultured neurons grown on a planar array of non-invasive electrodes provide an attractive alternative possibility. It rapidly processes a plethora of information, is adaptable to noise and is tolerant to faults. Recently, progress has been made towards the integration of biological components (such as neurons) and electronic components. These technologies are beginning to blur the distinction between the synthetic and the organic. Reger et.al. [1] demonstrated that it was possible to use the brain of a lamprey in order to control the trajectory of a robot whilst others are beginning to control creatures such as cockroaches [2] and rats [3] as if they were robots. Studying how the brain processes and encodes information in living animals [4] can be technically problematic as access is limited by the skin, skull and the sheer number of neurons present in the brain. Moreover, whole animal approaches capable of recording the activity of individual neurons or small populations thereof are limited by the invasive nature of such techniques. For

these reasons laboratory cultured neurons grown on a planar array of non-invasive electrodes provide an attractive alternative possibility.

Recent research has focussed on culturing networks of some tens of thousands of brain cells grown in vitro [5]. These cultures are created by dissociating the neurons found in cortical tissue using enzymes and then culturing them in a specialised chamber by providing suitable environmental conditions and nutrients. The base of the chamber itself is composed of an array of multiple electrodes (a multi electrode array – MEA) providing an electrical interface to the neuronal culture [6,7,8,9]. The neurons in such cultures spontaneously begin to grow and branch out and, even without external stimulation, begin to re-connect with nearby neurons and commence both chemical and electrical communication. This propensity to spontaneously connect and communicate demonstrates an innate tendency to network; studies of neural cultures of this type suggest that they mature in around a month [10,11]. The neuronal cultures themselves form a monolayer over the electrode array on the base of the chamber making them extremely amenable to optical microscopy and accessible to both physical and chemical manipulation [9].

The multi-electrode array enables the voltages to be recorded from each electrode, allowing the detection of the action potential firing of neurons near to each electrode as voltage spikes representative of charge transfer within the electrode's recording horizon. Using spike sorting algorithms [12] it is then possible to separate the firing of multiple individual neurons, or small groups, from a single electrode. With multiple electrodes a picture of the global neuronal activity of the entire culture can be pieced together. It is also possible to electrically stimulate any of the multiple electrodes in order to induce neural activity. The multi-electrode array therefore forms a functional and non-destructive bi-directional interface with the cultured neurons.

The objective of the project described here is to investigate the use of cultured neurons for the control of mobile robots and as a result to investigate some fundamental aspects of brain activity – especially those associated with memory.

For the purpose of this research, it is necessary that the disembodied cell culture is provided with embodiment, since a dissociated cell culture growing in isolation and receiving no sensory input is unlikely to develop much useful operation since sensory input significantly affects neuronal connectivity and is involved in the development of meaningful relationships necessary for useful processing. In particular, the use of rodent primary dissociated cultured neuronal networks for the control of mobile robots is a novel approach to discovering the computational capabilities of biological networks [13].

Typically, in vitro neuronal cultures consist of many thousands of neurons. As a result signals generated by them are highly variable and multi-dimensional. In order to extract from such data components the features of

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interest which are representative of the network's overall state, appropriate pre-processing and dimensionality reduction techniques must be applied. The signal processing involved can be broken down into two discrete areas: 'culture to robot', an output machine learning procedure processing recorded neuronal activity and 'robot to culture', an input mapping process, from sensor to stimulus.

Several schemes reported in the literature have thus far been constructed in order to investigate the capacity of hybrid systems. Notably, Shkolnik created a very interesting control scheme for a simulated robot [14]. Two channels of a Multi Electrode Array (MEA) were selected for stimulation and a signal consisting of a +/-600mV, 400µs biphasic pulse was delivered at varying intervals. The concept of information coding was formed by testing the effect of electrically inducing neuronal excitation with a given time delay called the Inter-Probe Interval (IPI) between two stimulus probes. This technique gives rise to a characteristic response curve which forms the basis for deciding the robot's direction of movement using simple commands (forward, backward, left and right).

Other groups meanwhile used a simulated rat [15] which moved inside a four-wall environment including barrier objects, or physical robots such as 'Koala' and 'Khepera' robots [16]. The latter were employed in a sort of embodiment experiment wherein one of the robots (the Koala) attempted to maintain a constant distance from the other which moved under random control. It was reported that the Koala robot managed to successfully approach the Khepera and maintain a fixed distance from it [15]. It is important to stress here that inherent firing actions of the culture were sent to a computer which then made a decision (in a binary sense) as to what action the Koala should take. The culture itself was not directly controlling the Koala through a feedback loop and no learning action was reportedly exploited. Although this research stands as a landmark, it is these features that are both critical in the study described here.

In a well publicized experiment, DeMarse and Dockendorf investigated the computational capacity of cultured networks by introducing the idea of implementing the results in a "real-life" problem, in this case that of controlling a simulated aircraft's flight path (e.g. altitude and roll adjustments) [17]. Meanwhile recent developments have focused on the application of learning techniques in neuronal cultures. Shahaf and Marom [18] were one of the first groups to achieve desired discrete output computations by applying a simple form of supervised learning to randomly connected neuronal cultures. More recently, Bull & Uroukov [19] successfully applied a Learning Classifier System to manipulate cells into responding in pre-defined ways to electrical input signals. However, both of these cases indicated successful results in only about one third of their experiments, indicating the underlying complexity and vulnerability of the networks, along with apparent difficulties in achieving repeatability. Such work also highlights the

importance of understanding key functional and effective connectivity features within the cultures. Clearly this will assist in attempting to perform learning schemes, but it should not be seen as a prerequisite. The importance of experimentation through adaptive feedback control cannot be stressed more clearly.

It is clear that even at such an early stage, such embodiments (real or virtual) have a prevailing role in the study of biological learning mechanisms. The physical and simulated robots proposed here provide the starting point for creating a proof-of-concept control loop around the neuronal culture and a basic platform for future - more specific - reinforcement learning experiments. As the fundamental problem is the coupling of the robot's goals to the culture's input output mapping, the design of the robot's architecture discussed in this paper emphasises the need for flexibility and the use of machine learning techniques in search of such coupling.

The main point to stress here is that each cultured network, when embodied, acts as a neural experimental test bed. Hence, with such a foundation in place, it is possible to investigate effects on the culture of electrical and chemical stimulation alongside external/ environmental effects – this means that the representation of memories and how the culture deals with neural death in certain regions can be investigated.

2. Culture Preparation

In order to realise the cultured neural network, this firstly involves the removal of the neural cortex from the fetus of a rat. Enzymes are then applied to disconnect the neurons from each other. A thin layer of these disassociated neurones is subsequently smoothed out onto a Multi Electrode Array which sits in a nutrient rich bath. Every couple of days this bath needs to be refreshed in order to not only provide a food source for the culture but also to flush away any waste material.

Once they have been laid out on the array the neurones start to reconnect – indeed even within the first 24 hours such new connections are clearly visible under the microscope. These can be regarded initially as mere projections forming into axons and dendrites, making connections between neighbouring neurones. By the time the culture is almost one week old electrical activity can be witnessed to appear relatively structured and pattern forming in what is, by that time, a densely connected matrix of axons and dendrites.

ted matrix of axons and dendrites. Neuron firing can sometimes appear, from external inspection, to be initiated at random, resulting in signals (action potentials) pulsing through the network. In many cases a large bunch of neurones will fire spontaneously, something which is referred to as bursting. Exactly what these bursts are is not completely known however some see them as being the result of sensory deprivation, to be quelled by the embodiment of the culture, providing it with sensory input [24].

During its lifetime, which presently is typically up to a maximum of three months, the culture must be housed in an incubator which maintains a

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constant body temperature under relatively sterile conditions. A smaller version of this is then employed as a temporary base for the culture when it is required for it to communicate bidirectionally with its robot body. Once a test run has been completed (typically taking an hour or so), then the culture is returned to its incubator home.

3. Closing the Loop

The overall system is constructed with a closed-loop, modular architecture in mind. Neuronal networks exhibit spatiotemporal patterns with millisecond precision [16], the processing of which necessitates a very rapid response from neurophysiological recording and robot control systems. The software developed for this project runs on Linux-based workstations communicating over the ethernet via fast server-client modules, thus providing the necessary speed and flexibility required when working with biological systems..

The study of cultured biological neurones has in recent years been greatly facilitated by commercially available Multi Electrode Array systems. These consist of a glass specimen chamber lined with an 8x8 array of electrodes as shown in Figure 1.

A standard MEA measures 49 mm x 49 mm x 1 mm and its electrodes provide a bidirectional link between the culture and the rest of the system. The associated data acquisition hardware includes the head-stage (MEA connecting interface), a 60 channel amplifier (1200x gain; 10-3200Hz bandpass filter), a stimulus generator and a data acquisition card

Figure 1, a) An MC200/30iR-gr MEA, showing the 30 µm electrodes which lead to the electrode column–row arrangement b) Electrode arrays in the centre of the MEA seen under an optical microscope, c) x40 magnification, showing neuronal cells in close proximity with visible extensions and inter-connections.

Figure 2: MEA with culture close to Miabot robot.

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Thus far we have successfully created a modular closed loop system between a (physical) mobile robotic platform and a cultured neuronal network using Multi-Electrode Array (MEA), allowing for bidirectional communication between the culture and the robot. It is estimated that each culture employed consists of 50,000 to 100,000 neurones. The spontaneous electrochemical activity of which is used as input to the robot's actuators (its wheels) and the robot's (ultrasonic) sensor readings are (proportionally) converted into stimulation signals received by the culture, effectively closing the loop.

For the software-hardware/robotic framework we have selected the Miabot (see Fig.2), a commercially available robotic platform exhibiting very accurate motor encoder precision (~0.5 mm) and speed (~3.5 m/s). Recording and stimulation hardware is controlled via open-source MEABench software[23]. The Miabot is wirelessly controlled via Bluetooth.

The overall closed loop system therefore consists of several modules including the robot, the MEA and stimulating hardware, a directly linked workstation for conducting computationally expensive neuronal data analyses and a separate machine running the robot control interface – a sort of network manager routing signals directly between the culture and the robot body. The modular approach to the problem can be seen in more detail in Figure 3. Client code performs text logging of all important information during an experiment run, which can then be analysed offline. As a sampling frequency of 25 kHz of the culture activity recording demands large network, processing and storage resources, on-the-fly streaming of spike-detected data is the preferred method when investigating real-time closed-loop learning techniques.

Figure 3, Modular Layout of the Robot/MEA System

4. Experimentation

We firstly conducted experiments in a successful closed loop test with a model cell, which is an electronic test circuit equivalent to a passive live culture, i.e. it is a simulation of the culture when acting in an "ideal" way. We then conducted the same experiment with a live culture. In order to do so, initially, an appropriate neuronal pathway within the culture was identified and a suitable stimulus-response electrode pair were chosen prior to the run. The pair was chosen based on the criteria that the response electrode shows minimal spontaneous activity but responds robustly to stimuli (a positive-first biphasic waveform; 600 mV; 100 µs each phase) delivered via the stimulating electrode. The robot followed a forward path within its confines until it reached a wall, at which point the front sonar value dropped below a set threshold

value (approximately 30 cm), triggering a stimulation as shown in Figure 4. If the responding electrode registered activity following the pulse, the robot turned in order to avoid the wall. The robot also turned spontaneously if activity was registered on the response electrode, however the main results of interest were the chain of events: Wall Detection–Stimulation–Response.

The model cell experiment provided a realistic representation of the maximum speed at which the closed loop could respond, dependant subsequently on the "thinking" delay in the response of the culture. Such a study opens up the possibility of investigating response times of different cultures under different conditions and how they might be affected by external influences such as electrical fields and chemical stimulants.

As a follow up closed loop experiment the robot's individual (right and left separately) wheel speeds were controlled via the frequency recorded from the two chosen motor/output electrodes. Meanwhile received sonar information is used to directly control (proportionally) the stimulating frequency of the two sensory/input electrodes. The setup is reminiscent of a simple Braitenberg model [20], however in this case the direct sensor-to-speed control is being decided solely by the cultured network within the overall feedback loop. For comparative purposes the experiment has been performed with both real and simulated robots. Run-times have only been executed for approximately 30 min., which is not typically enough to evoke Long Term Potentiation (LTP) plasticity effects between the stimulating-recording electrode sites [21, 22].

An indication of the robot's typical activity during a simple wall-detection/right turn experiment is shown in Figure 4. The sonar threshold is set at approx. 0.3 cm from a wall, meaning that a stimulation pulse was applied to the culture, via its sensory input, each time this threshold was breached – essentially when the robot approached sufficiently closely to a wall. Yellow vertical bars in Figure 4 indicate electrode firing events - that is signals appearing as responses on the output electrodes from the culture. These events are deemed 'meaningful' only in the case where the time separation between stimulation and response is under 100 ms. In other words the event is a strong indicator that the electric stimulation on the sensory/input electrode subsequently caused a neural response on the motor/output electrode [25].

Figure 4: Sensory-Motor sequence data for the culture (typical of early life).

In Figure 4 the green trace indicates the front sonar value on the physical robot base, giving a direct indication of the closeness of an object (perhaps the wall of the corral) to the robot body. The yellow bars indicate motor responses of the culture. A 'meaningful' event chain would be for example at 1.95 seconds, where

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the sonar value drops below the threshold value (0.3) and a stimulation-response sequence occurs.

Results	Model Cell	Live Culture
Wall -> Stimulation event	100%	100%
Stimulation -> Response event	100%	67%
Total closed loop time	75 ms	200-500 ms
Run time	4 mins	2 mins 40 secs
Meaningful turns	41	22
Spontaneous turns	41	16

Table 1, Basic statistics from the right-turn experiment. 'Closed loop time' refers to the time between wall detection and a response signal witnessed from the culture. 'Meaningful turns' refer to the robot turning due to a wall detection->stimulation->response chain of events.

Table 1 contains typical results from a trial run, firstly with the ideal model cell and secondly with a cultured neural network acting as the sole controlling decision maker for the robot body. If the live culture acted "perfectly", making no mistakes, then the two columns (Model Cell and Live Culture) would be identical. This experiment has 'closed the loop' inclusive of the custom stimulation protocols and has set the basis for the following experiments which will focus on characterising the culture responses and include Machine Learning techniques for performing more complex robot control.

5. Medical Research

Initially the inherent operating characteristics of the cultured neural network have been taken as a start point to enable the physical robot body to respond in an appropriate fashion. The culture then operates over a period of time within the robot body in its corral area. This experimentation can take place for an hour or two every day. Although learning has not, as yet, been an immediate focus of the research, what has been witnessed is that neuronal structures that bring about a satisfactory action tend to strengthen purely through the habitual process being performed (referred to as Hebbian learning). This is mainly an anecdotal observation at this time, which it is wished to formalise and quantify through a detailed analysis using several cultures.

Following the completion of these first phases of the infrastructure setup, a significant research contribution, it is felt, lies in the investigation of electrical and chemical effects on the neural structure and the signalling pathways. Already tests have been carried out to inhibit neural activity by applying restrictive chemicals to regions of the overall structure. The response of the remainder of the structure is then being witnessed as to the effectiveness with which the remaining structure takes on board actions and responses previously manifested in the now dead tissue – how does it learn tasks previously carried out by the now inactive neural pathways.

But the main role that the network will perform is that of memory elicitation. The mobile platform can be taken to various positions and it can be witnessed what happens within the neural pathways at certain instances. Over a period of time the emphasis will be on studying how these pathways

alter and the possibilities of strengthening the pathways for longer term performance. This will be more pertinent as the cell structures age (presently 3 months is about the extreme) – different schemes will be attempted to retain memory elements for as long as possible.

6. Conclusions

The culture preparation techniques employed are constantly being refined and have lead to successful and stable cultures that exhibit both spontaneous and induced spiking/bursting activity.

A stable robotic infrastructure has also been set up, tested and is in place for future machine learning and culture behaviour experiments [26].

There are a number of ways in which the current system will be expanded in the future. It is anticipated that the Miabot may be extended to include additional sensory devices such as extra sonar arrays, mobile cameras and other range-finding hardware such as an on-board infra red sensor. A considerable current limitation is however the battery power supply of an otherwise autonomous robot.

A main future consideration is therefore the inclusion of a powered-floor for the robot's corral, to provide the robot with relative autonomy for a longer period of time. Future work will adapt a Miabot to operate on an in-house powered floor, so the robot can be provided with a constant power supply; this feature is necessary since culture behaviour tests will be carried out for many hours at a time.

Progression of the project will require benchmarking the results obtained from the culture. This behavioural evaluation is likely to provide great insight into the workings of the neuronal network by looking at the culture's performance over a time period in terms of the effects on its neural plasticity.

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Chapter 53: Affective Medicine: Technology with Emotional Intelligence

Rosalind W. Picard, Ph.D.
Director, Affective Computing Research Group, Massachusetts Institute of Technology Media Laboratory, Cambridge, MA, US

Abstract

For a long time people have kept emotions out of the deliberate tools of medicine and science; scientists, physicians, and patients have often felt and sometimes expressed emotion, but no tools could sense, measure, and respond to their affective information. A series of recent studies indicates that emotions, particularly stress, anger, and depression, are important factors with serious and significant implications for health. This paper highlights research at the MIT Media Lab aimed at giving computers the ability to comfortably sense, recognize, and respond to certain aspects of human emotion, especially affective states such as frustration, confusion, interest, stress, anger, and joy. Examples of recently developed systems are shown, including computer systems that are wearable and computers that respond to people with a kind of active listening, empathy, and sympathy. Results are reported for computer recognition of emotion, for teaching affective skills to autistics, and for having computers help users manage emotions such as frustration.

1. Introduction: Frustration, Irritation, Stress and Health

Perhaps the most common emotions people feel in interacting with today's technology are frustration, irritation and other feelings related to stress. We've been doing experiments in our lab where we bring in people, give them a task on the computer that mildly or strongly frustrates them, and measure how they behave. Our aim is to try to teach the computer how to recognize when the user is frustrated, irritated, annoyed, stressed or otherwise in some significant emotional state, and then to equip the computer so that it can do a better job of serving people, ideally not causing them so much stress. It's recently become a joke in the lab when some piece of equipment fails or causes aggravation – "is this one of Picard's affective computing experiments designed to irritate me?"

What could technology do if it could sense that the user is frustrated or otherwise in some unusual emotional state? Could the system change or be changed, so as to reduce frustration in the future, or could it help the user then and there to feel less stress? Our research has focused on both approaches: identifying components of computer interfaces that could be improved by designers, as well as having the computer help users manage strong negative emotions better. This is all part of our effort in "affective computing," computing that relates to, arises from, or deliberately influences emotion [18]. This article will focus the topic further -- on some recent findings about emotion and medicine -- together with examples of new affective technology we are

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developing that has potentially interesting and important implications for health."

Stress is increasingly recognized as a medical problem. A recent Blue Cross Blue Shield survey in New England cited the number one health concern of members in this part of the United States to be stress – rated above cancer, AIDS, high blood pressure, and other medical conditions. Dan Goleman, in Chapter 11 of his book Emotional Intelligence [7], cites a number of studies pointing to important roles in health and medicine for emotions – particularly states of stress, anxiety, chronic anger, and depression. Following are just a few of the examples that he includes:

Stress/distress: Studies of the physical manifestations of stress reveal many measurable changes caused by stress in the human body, influencing not only immune system functioning but also heart rate variability, blood pressure, and other important bodily functions. Several studies have been conducted examining the impact of stress on immunity. For example, Sheldon Cohen, a psychologist at Carnegie-Mellon University exposed people to a cold virus after assessing how much stress they were experiencing in their lives. Of course, a robust immune system usually resists a virus, so mere exposure doesn't mean you will get sick. Cohen found that 27% of the low-stress subjects came down with a cold while 47% of the high-stress people came down with the cold. In another study of married couples who kept daily logs of hassles and upsetting events, a strong pattern emerged: three or four days after an especially intense marital fight or other upset, they came down with a cold or upper-respiratory infection.

Depression: In work cited by James Strain, where 100 patients received bone marrow transplants, a follow-up study was conducted of the 13 who had been depressed vs. the other 87. Of the 13 who had depression, only 1 was alive a year later; of the other 87, 34 were still alive two years later. Another study, by Howard Burton et al., associated early death of dialysis patients with depression: depression was found to be a stronger predictor of death than any medical sign. Similarly, heightened risk of death from heart disease has been correlated with an ongoing sense of despair and hopelessness. The effect of depression on heart attack survivors is as great as that of major medical risks such as left ventricular dysfunction or a history of previous heart attacks.Anger: Dr. Redford Williams at Duke University found that physicians who scored highest on tests of hostility while they were in medical school were seven times as likely to have died by the age of fifty as those who scored low on the hostility tests – their tendency to get angry was found to be a stronger predictor of early death than were factors such as high blood pressure, high cholesterol, and smoking. Findings by Dr. John Barefoot at the University of North Carolina show that scores on a test of hostility

correlate with the extent and severity of coronary artery disease in heart patients undergoing angiography.

The studies above are but a few of the many that reveal emotion to be a measurably important health factor. Note that none of the studies show that emotions cause medical illness – rather they contribute to decreases in immune system functioning and to other physical factors that may significantly prolong or exacerbate an illness. It is fool hink that "positive thinking" or "making yourself happy" can prevent all illness; it is also foolish to continue to think that emotions have no significant effect on health – the truth appears to lie somewhere in the middle, with emotions playing not the only role, but an important measurable role that has typically been ignored.

In the Affective Computing group at MIT, we are particularly interested in the intelligent handling of affective states commonly expressed around computer systems: frustration, confusion, disliking, liking, interest, boredom, fear, distress, and joy. Computers and other forms of technology are interacting with people in more ways than ever before – beyond desktop, laptop, and palmtop, technology is now embedded into appliances, clothing, jewelry, implants, and even pills we can swallow. With all these new forms, technology has the opportunity to detect physical and physiological expressions of many human emotional states. With additional sensing and processing, the expressions of emotional state can be associated with other events – such as what the person is doing when they get angry or stressed, what else is happening in their body concurrent with episodes of depression, (perhaps related to their heart functioning or their physical activity level) or what the interface (if the person is interacting with one) may have just done [19].

The rest of this paper is divided into four areas: (1) Sensors that enable the user to communicate information related to emotion in a way that is physically and psychologically comfortable; (2) Progress in computer recognition of emotion; (3) Tools for helping people learn affective skills, including a system for autistic kids;

Figure 1. Stress is a significant factor in health; it arises in many forms when interacting with technology.

(4) Respectfully handling emotions, such as reducing user frustration.

2. Comfortable Sensing of Signals

Emotions often involve both thinking and feeling – both cognitively experienced events and physical changes in the body. Although there is no technology that can truly read your thoughts, there are a growing number of sensors that can capture various physical manifestations of emotion -- video recordings of facial expressions and posture or gesture changes, microphone recordings of vocal inflection changes, skin-surface sensing of muscle tension, heart-rate variability, skin conductivity, blood-glucose levels, and other bodily changes, and (if invasiveness is allowed), swallow-able or implant-able sensors or means of capturing bodily fluids for analysis. These are just a few of a growing number of possibilities.

Our research efforts include building tools to facilitate multiple forms of emotion sensing, not to force this on anyone, but to allow for a larger space of possibilities for those who want to communicate and better understand affective information. The tools include new hardware and software that we have developed to enable certain machines not only to receive emotional expression, but also to recognize meaningful patterns of emotional expression. In particular, we have integrated several physiological sensors into clothing and jewelry – a blood volume pressure sensor in an earring, skin conductivity in a shoe and a glove, respiration in a sports bra, and more [19] (See some examples in Figure 2). These sensors communicate with new wearable computers that can control peripherals such as a wearable music player/DJ [8] or a wearable camera [10]. For example, the wearable camera system we built saves video based on your arousal response tagging the data not just with the usual time stamp, but also with information about whether or not it was exciting

Figure 2. Emotion influences many changes in the body. These patterns of change can be sensed by various new wear-able or swallow-able technologies.

to you, as indicated by patterns it detects in your skin conductivity [10]. The same system could potentially be modified to detect and communicate health-related variables to you and your physician, perhaps for monitoring and analyzing patterns of stress, anger, or depression.

With any wearable system there are design issues regarding not only what is to be sensed, but also how the sensing system can be made comfortable and robust to noise that arises from activity unrelated to the signal being measured. The key source of noise when measuring emotion from ambulatory patients is artifacts that arise from physical activity. Heart rate, for example, can increase significantly with physical exertion or with sneezing, as well as with anger and other affective states. Inferring the source of a change is easier if you can independently detect the change – such as via context sensors that indicate the person's movement or activity.

One of the physiological sensing systems we built that is robust to motion artifacts is the "Conductor's Jacket," one version of which is shown in Figure 3. This highly expressive wearable system, created by Teresa Marrin, associates patterns of muscle tension and breathing with expressive

Figure 3. The "Conductor's Jacket" used both for gathering physiological changes related to expression and for controlling MIDI output.

Figure 4. Wearable systems can be increasingly hidden in ordinary clothing; their form factor can be modified to not impair social interaction.

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gestures that the conductor uses to shape the music. Seven electromyogram (EMG) and one respiration sensor are included in the version shown here. The EMG's are attached with custom-fit elastics sewn into the shirt, so that they remain snug without strong adhesives, and yet do not move as the arms are moved. This wearable system was designed first to measure how professional and student conductors naturally communicate expressive information to an orchestra. After analyzing real conducting data from six subjects, Marrin found around thirty significant expressive features (largely related to muscle tension changes that signaled interesting musical events) [16]. She has subsequently developed a version of the jacket that transforms natural expressive gestures of the wearer into real-time expressive shaping of MIDI music [17]. A professional conductor, Marrin is currently using the jacket both for live performance and for helping educate student conductors, providing precise feedback on timing, tension, and other important aspects of expressive technique.

In addition to the goal of making wearable sensing devices robust and physically comfortable, we have been concerned about the psychological factor – how do these sensors feel from a personal comfort standpoint and within a social setting? We do not believe there is a one-size-fits-all answer, but rather we find that people like to exercise choices; in many cases, these choices include hiding the sensors, so that they are not visible (although a notable exception was one of the professional conductors we worked with – we took him a sensor jacket with almost everything hidden under the tuxedo, and he asked us to redo it "in red, with the wires in silver on the outside for all to see.") We found that when we integrated sensors with the "lizzy" wearable (Figure 4, at right) that the private eye output display was an impediment to social interaction, and the input device (chording keyboard) took too long for subjects to learn. Consequently we modified a Palm Pilot to serve as an input/output device to the wearable, allowing the Palm to display physiological signals and receive annotations for them. Although a palm device is not hands-free like a heads-up display, it is more comfortable for many people in social settings.

Emotions modulate not only the modes shown in Figure 2, but also many others, including hormone and neurotransmitter levels. The latter are currently not easy to sense without drawing saliva or blood or using other invasive procedures. Presently, none of these procedures provides instantaneous wireless access to the changing levels. However, new implant-able and swallow-able sensors are being developed by many researchers, exploiting strides in nanoscale technology, and giving access to internal bodily signals previously unavailable in real time (e.g., Figure 5, courtesy of Prof. Scott Manalis at MIT) Sometimes, social-psychological concerns such as privacy make one form of sensing preferable to another. For example, although one person might

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be comfortable communicating facial expressions to a computer using a video camera, another might be concerned about the identifying information that the camera would see. In distance learning and in intelligent tutoring systems, there is an opportunity for the student to transmit signals such as confusion or interest in real-time, without having to stop and click on anything that interrupts their attention [22], and without giving away their identity. One means of accomplishing this is via a wearable sensing system designed and built by research assistant Jocelyn Scheirer, the "expression glasses" described in the next section.

Figure 5. New forms of sensing enable real-time wireless readout of internal bodily signals such as temperature or pH.

3. Computer Recognition of Emotional Expression

One of the wearable-computing platforms we built includes a small A-to-D with eight channels for physiological sensing. We have developed algorithms that run on the wearable system, extract features from the physiological signals, and relate these to a deliberately expressed emotion. Short segments of four physiological signals for two emotions are shown in Figure 6. Although the segments here look different for each emotion, this was not always the case; in general, the variations within the same emotion from day to day exceeded the variations in different emotions on the same day. Using a variety of methods of pattern recognition and baselining, we have obtained recent results of 81% recognition accuracy in selecting which of eight emotions was expressed by an actress, given 30 days of data, eight emotions per day, and features of the four signals: respiration, blood volume pressure, skin conductivity, and muscle tension. (See Healey and Picard (1998) and Vyzas and Picard (1999) for details of the data collection and the recognition algorithms [9], [25].) The eight emotions investigated were: neutral, hatred, anger, romantic love, platonic love, joy, and reverence. These are the best known results to date for emotion recognition from physiology, and they lie between machine recognition results of affect from speech and of affect from facial expressions.

It should be noted that these results are for a single user, and they are obtained by a forced selection of one of the eight categories; hence, these results are comparable to recognition results in the early days of speech recognition, when the system was re-trained for each speaker, and it knew that the person was speaking one of eight words, although there could be variation in how the person spoke the words from day to day. Much more work remains to be done to understand individual differences as

well as differences that depend on context – whether developmental, social, or cultural. I expect that, like research in speech recognition, this work will gradually expand to be able to handle speakers from different cultures, of different ages, speaking (or expressing) continuously, in a variety of environments.

Figure 6 (right) shows a computer task and data-gathering system we designed that was intended to induce negative stress and collect data synchronized with the stress-eliciting events [21]. We gave the user a goal with incentive: race through the task as quickly as possible, obtain the best score (a mix of accuracy and efficiency) and win a $100 prize. Along the way, we had the system freeze up as if the mouse was not working, delaying their progress. We continuously measured two physiological signals—skin conductivity and blood volume pressure—then compared patterns in these signals when all was going smoothly vs. during the episodes of unexpected delays. Although we cannot determine whether these episodes corresponded to true feelings of frustration or non-frustration, we did find that in 21 out of 24 subjects, the patterns detected by our Hidden-Markov-Model based approach were able to significantly discriminate these two kinds of episodes [5]. However, the recognition results were still far from perfect, indicating that although this information is helpful, it must be combined with other signals for a more confident decision.

Stress is sometimes a by-product of feelings such as confusion, which a person may choose to communicate by furrowing his or her brow. The furrowing of the muscle can be detected by a camera if lighting and head position is carefully restricted (otherwise current computer vision techniques are inadequate) but these restrictions, coupled with the recording of identity, can make some subjects uncomfortable. An alternative sensor to a camera is a pair of wearable "expression glasses" (Figure 7) that senses changes in facial muscles [22]. These glasses have a small point of contact with the brow, but otherwise are considered by some users to be less obtrusive than a camera in that the

Figure 6. Examples of four physiological signals sensed during different emotional

glasses offer privacy, robustness to lighting changes, and the ability to move around freely without having to stay in a fixed position relative to a camera. The expression glasses can be used *while concentrating* on a task – the wearer does not have to stop and think about how to communicate a facial expression. The glasses can be activated either unconsciously or consciously. People are free to make false expressions, or to have a "poker face" to mask true confusion if they do not want to communicate their true feelings, but if they want to communicate them, the glasses offer a virtually effortless way to do so.

Why wear expression glasses, instead of raising your hand or pushing a button to say you're interested or confused, as was implemented decades earlier [23] by Sheridan and his colleagues? The answer is not that there should be one *or* the other; both kinds of feedback offer advantages. Sometimes people miss the subtlety of this point: affect is continuously communicated while you are doing just about anything. When you pick up a pen, you tend to do so very differently when you are angry vs. when you are joyful. When you watch somebody, your eyes behave differently if you are interested than if you are bored. *As you listen* to a conversation or a lecture, your expression gives the speaker feedback, unless, of course, you put on a poker face. In contrast, if you have to think about pushing a button to communicate your feelings, or to raise your hand to say you're confused, then you have to interrupt your concentration to take such an action. Self-report is important, but it is no substitute for the natural channels of largely non-verbal communication that humans use *concurrently* while engaged in conversation, learning, and other activities. drivers trying to do more than

Figure 7. Expression glasses sense facial muscle changes and detect furrowing of the brow, a signal sometimes used to communicate confusion.

drive. We have conducted experiments measuring the impact of low and high cognitive load tasks on drivers talking over a telephone headset while driving in a simulator. We placed drivers under different load conditions (fast or moderate speed, and fast or slow questioning with simple arithmetic problems like "12 + 14") while otherwise keeping the driving task the same. The drivers were occasionally exposed to signs labeled "brake" or "continue" and were instructed to brake as soon as they saw the brake message. Most drivers braked within 0.7-1.4 seconds after the message; however, there were a number of incidents where braking took place 1.5-3.5 seconds after the brake message, or not at all. In almost all of the latter cases, the subject was talking on the phone. On average, the drivers talking on the phone had reaction times to brake messages that were 10% slower than when they were not on the phone; more importantly, the variance in their braking times was four times higher – suggesting that

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although delayed reactions were infrequent, when delays happened they could be very large and potentially dangerous. The fact that they didn't happen often could furthermore create a false sense of security. Although physiological data gathered in these experiments was limited, our analysis indicated a potential for recognizing patterns that might indicate whether or not a driver was likely to respond with a slowed reaction or not [24].

We are beginning to analyze affect in speech, an area in which humans perform at only about 60% accuracy (on roughly eight emotion categories, when the content of the speech is obscured). Our initial focus is on speech from drivers, taken from the experiment above, examining if the driver's vocal characteristic under different load conditions shows reliable indications of stress [6]. As manufacturers put more gadgets in cars, such as talking navigation systems and restaurant guides or grocery reminders triggered by GPS-sensed location, there is increased potential that the driver might be interrupted at a stressful time that could diminish safety. Another human passenger would be able to sense if the timing was good or not and make a safer decision about interrupting the driver; however, the systems being put into cars are currently oblivious to these factors. If the driver is conversing with one of the car systems, he or she may be distracted at a bad time, compromising safety. We are trying to give the system the ability to sense stress pattern changes in the driver's speech (as well as responsiveness patterns in the driver's behavior, per above) so that the car can be more sensitive to the safety factor.

Our research is developing means of recognition of physiological patterns related to stress in many different natural environments. We have recently moved outside the world of simulators and equipped a car to examine driver behavior features joint with physiological information. One such sensor set-up is shown in Figure 8 (right). In a recent set of experiments we induced stress in a dozen drivers by having them drive around Boston under four stress-eliciting conditions while we recorded electrocardiogram, skin conductivity, respiration, blood-volume pressure, and electromyogram signals, together with video and other information about the driver's behavior and context. Knowing how stressed somebody truly became is hard to assess; therefore, we used three different methods of assessment: self-report of the driver, driving condition (rest, busy city, easy highway, tolls/turn-around), and third-party coding of complexity level based on number of events each minute during the driving situation. Our analysis of patterns of driver physiology, led to an average stress recognition rate of from 89-

Figure 8. Stress was measured from vocal intonation and from driving behavior when drivers were given tasks over a phone headset (left). We designed and integrated a physiological sensing system into a Volvo for measuring bodily signals related to stress among Boston drivers out on the road (right).

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96% accuracy depending on which of three methods was used for labeling the "true" stress level of each subject [11].

An increasing amount of human-human communication takes place through machines. In many cases it would be helpful if the machine would simply facilitate the transmission of affective cues. An example of a system designed to expand human-human communication capabilities via computer is the TouchPhone, developed by Jocelyn Scheirer in our lab (Figure 5). The TouchPhone augments regular voice communication with pressure information indicating how tightly the speaker is holding the phone. For example, if you routinely talk to an elderly parent by phone, this would enable you to not only hear their voice, but also to see how they were holding the phone: Is it the same as most days? Or today does their grip seem weaker, tense, or more fidgety? The pressure is continuously mapped to a color seen by the person on the other side – calibrated to blue if light pressure is applied – and to red if strong pressure. The computer performs no interpretation of this signal; the color signal is simply transmitted to the conversational partner as an additional low bit-rate channel of information.

I met with four of my students for four hours of TouchPhone conversations and the results, while anecdotal, were interesting and were consistent with experiences we have had with other emotion-communication technologies. I found that each of the four students had a nearly unique color pressure pattern, which was distracting until I moved the pattern into my periphery where it became ambient, adding a flavor of background rhythm to the conversation. For one student, the pattern changed very slowly, becoming stable red when I started asking some research questions. I thought nothing of it, because he could have simply been squeezing the phone more tightly by shifting his position. However, even though he knew that I could not tell his feelings from the color, he expressed to me that he wasn't trying to squeeze it tighter at all and he thought it was red because he was stressed about a question I asked him. The student was a non-expressive male engineer who had never revealed such signs of stress to me in the years of conversations we had had prior to this TouchPhone conversation. The technology thus facilitated opening up a greater range of emotional communication – by his choice – it did not impose this, but simply made it easier for him. The color did not give away how any of the students was truly feeling. However, the system provided a new channel of non-verbal communication that, in turn, could and did sometimes open up a new line of verbal communication

Figure 9. System that senses how phone is being held (left.) Examples of intonation changes in annoyed and sad speech (right).

Figure 10. The "ASQ" Computer system shows video clips to autistic kids and prompts them to choose the stuffed dwarf that expresses the emotion appropriate to the video scene. The system senses the child's response and rewards accordingly.

4. Helping Build Human Emotional Skills

Computers just "don't get it" when it comes to practicing many of the social-emotion skills that most of us take for granted. Although autism is a complex disorder, and some of the comments here will not apply to all autistics, there are nonetheless some intriguing characteristics that many autistics share with computers. Both tend to have difficulty with social-emotional cues. Both tend to be poor at generalizing what they learn, and learn best from having huge numbers of examples, patiently provided. Both can be fabulous at certain pattern recognition tasks. Autistics, like computers, also may have very good visual memories. Many autistics have indicated that they like interacting with computers, and some have indicated that communicating on the web "levels the playing field" for them, since emotion communication is limited on the web for everyone.

Because many of the issues we face in giving computers skills of emotional intelligence are similar to those faced by therapists working with autistics, we have begun collaboration with these experts. Current intervention techniques for autistic children suggest that many of them can make progress recognizing and understanding the emotional expressions of people if given lots of examples to learn from and extensive training with these examples.

We have developed a system—"ASQ: Affective Social Quotient"—aimed at helping young autistic children learn to associate emotions with expressions and with situations. The system plays videos of both natural and animated situations giving rise to emotions, and the child interacts with the system by picking up one or more stuffed dwarfs that represent the set of emotions under study, and that wirelessly communicate with the computer. This effort, led by my student Kathi Blocher, has been tested with autistic kids aged 3-7. Within the computer environment, several kids showed an improvement in their ability to recognize emotion [1]. More extensive evaluation is needed in natural environments, but there are already encouraging signs that some of the training is carrying over, such as reports by parents that the kids asked more about emotions at home, and pointed out emotions in their interactions with others. Despite these successes, this work is only one small step; the difficulties in teaching an autistic to appropriately respond to an emotional situation are vast, and we will no doubt face similar difficulties for a long time in trying to teach computers how to respond appropriately.

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5. Respectfully Handling Emotions

Not only do many people feel frustration and distress with technology, but also they show it. A widely publicized 1999 study by Concord Communications in the U.S. found that 84% of help-desk managers surveyed said that users admitted to engaging in "violent and abusive" behavior toward computers. A survey by Mori of 1250 people who work with computers in the UK reported that four out of five of them have seen colleagues hurling abuse at their PC's, while a quarter of users under age 25 admitted to having kicked their computer. It seems that no matter how hard researchers work on perfecting the machine and interface design, frustration still occurs. In fact, even if computers were as smart as people, they would still sometimes frustrate people; the same is true in human-human interaction: even the most intelligent people sometimes frustrate others. Hence, there is a need to address frustration at run-time – detecting it, and responding to it.

This need is particularly important in light of the impact of stress on health, and the important role of computers in increasing interacting with patients. In some cases, patients prefer giving information to a computer instead of to a doctor, even when they know the doctor will see the information: computers can go more slowly if the patient wishes, asking questions at the patient's individual speed, not rushing, not appearing arrogant, offering reassurance and information, while allowing the physician more time to focus on other aspects of human interaction [3] [2]. Also, in some cases, patients have reported more accurate information to computers; those referred for assessment of alcohol-related illnesses admitted to a 42% higher consumption of alcohol when interviewed by computer than when interviewed for the same information by psychiatrists [15].

Suppose that a computer could detect patient stress or frustration with high confidence, or that a person directly reports frustration to the machine so that some kind of response by the machine might be appropriate. How should the computer respond?

Goal:

Reduce user frustration once it has occurred

Strategy:

1. Recognize (with high probability) that the situation may be frustrating, or that the user is showing signs of frustration likely due to the system
2. Is user willing to talk? If so, then Practice a**ctive listening**, with **empathy** and **sympathy, e.g.,**
   "Good to hear it wasn't terribly frustrating"
   "Sorry to hear your experience wasn't better"
   "It sounds like you felt fairly frustrated playing this game. Is that about right?"
   Allow for repair, in case computer has "misunderstood" In extreme cases, the computer may even apologize:
   "This computer apologizes to you for its part in .."
3. Polite social closure

Figure 11: The 2x3 experimental design, comparing the emotion-support agent and two control conditions in both a low-frustration condition and a high-frustration condition.

In developing this system, we avoided language where the computer might refer to itself as "I" or otherwise give any misleading implications of having a "self." The system assesses frustration and interacts with the user through a text dialogue box (with no face, voice, fancy animation or other devices that might provoke anthropomorphism.) The only aspect of the interaction that evokes another person is the use of language, which although cleansed of references to self, nonetheless was made deliberately friendly in tone across all control and test conditions, so that friendliness would not be a factor in this study.

The emotion support agent was tested with 70 users who experienced various levels of frustration upon interacting with a simulated network game [14]. We wanted to measure a strong behavioral indication of frustration, since self-report is notoriously unreliable. Thus we constructed a situation where people were encouraged to do their best while test-playing an easy and boring game, both to show their intelligence, and to win one of two monetary prizes. Half of the subjects were exposed to an especially frustrating situation while they played (simulated network delays, which caused the game to freeze, thereby thwarting their attempt to show their intelligence or win a prize). Afterward, subjects would interact with the agent, which was designed to help them reduce their frustration. Finally, they would have to return to the source of their frustration and engage again with the game, at which point we measured how long they continued to interact with it. Our prediction was based on human-human interaction: if somebody frustrates you, and you are still highly frustrated when you have to go back and interact with them, then you will minimize that interaction; however, if you are no longer feeling frustrated, then you are likely to interact with them longer. The 2x3 experimental design is shown in Figure 6, where thirty-four users played the game in a low-frustration condition, while thirty-six played the same game with simulated delays.

We ran three cases for each of the low and high frustration conditions. The first two cases were controls, text-based friendly interactions having essentially the same length as the emotion-support agent. The first control (*ignore*) just asked about the game, ignoring emotions, and the second control (*vent*) asked about the game, but then asked questions about the person's emotional state and gave them room to vent, with no active listening, empathy or sympathy. After interacting with one of the three (*ignore*, *vent*, or *emotion-support),* each player was required to return to the game, and to play for three minutes,

after which the quit button appeared and they could quit or play up to 20 minutes more. Compared to people in the *ignore* and vent control groups, subjects who interacted with the *emotion-support* agent played significantly longer, behavior indicative of a decrease in frustration. People in the *ignore* and *vent* cases both left quickly, and there was no significant difference between their times of play. We also analyzed the data to see if there were any significant effects with respect to gender, trait arousability, and prior game playing experience; none of these factors were significant. (For more details regarding this system, experiment, and findings, see Klein (1998) [13]).

These results suggest that today's machines can begin to help reduce frustration, even when they are not yet smart enough to identify or fix the cause of the frustration. Our findings further indicate that it takes very little time to help the user reduce stress – the emotion savvy agent took no more time than the two controls, and all of the interactions took around 4-6 minutes. This time included not only addressing the person's feelings, but also asking several questions about the game. In other words, less than a few minutes of addressing the emotion were sufficient to provide a significant behavioral change in the user.

Today, physicians usually have so little time with patients that they feel it is impossible to build rapport and communicate about anything except the most obviously significant medical issues. However, given findings such as those highlighted at the start of this paper, emotional factors such as stress, anxiety, depression, and anger can be highly significant medical factors, even when the patient might not mention them. Although our findings of a computer's ability to reduce stress were only based on one kind of stress-provoking situation, the strong behavioral effect we obtained in just a few minutes of addressing the emotion, suggests that perhaps something significant can be done by physicians to address emotions related to health, even within the limits of a brief office encounter. If a computer in a few minutes can produce a significant behavioral effect, how much more effect could a truly sensitive and caring emotion-savvy person have in the same amount of time?

6. Concluding Remarks

This paper has highlighted several research projects in the MIT Media Lab's Affective Computing Research group. The selected projects are believed to be relevant for future health because they advance the state of the art in physiological sensing, in recognition of emotional signals, in development of emotional skills, and in use of computers to help people manage emotions. Based on the growing number of studies showing that emotions such as anger, anxiety, depression and stress are significant medical factors, helping people better manage these emotions becomes a key form of preventive medicine. As computers assist in gathering information from patients, in helping medical patients communicate with one another and with care-providers,

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and in disseminating information to patients, the need grows for affective intelligence in the computer interface. Patients who have their feelings properly addressed are more likely to leave satisfied, are less likely to return as often, and are less likely to incur legal cost [7]. These effects translate into dollars saved, so that respecting and responding to patients' emotions is good medicine and good business.

Research into the development of affective technologies is relatively new, and many other labs have recently started similar projects, so that it would take a much longer paper to overview all the research in this area. There are also many exciting findings relating affect and cognition, such as those of Isen and colleagues showing a significant impact of a mild positive state on medical decision making – facilitating efficiency and thoroughness in medical diagnostic reasoning [4], with a number of other benefits [12]. Readers who are interested in related work are encouraged to visit the references of the papers cited at the end of this document, which contain over a hundred pointers to related research conducted beyond our lab.

Over the years, scientists have aimed to make machines and technologies that are intelligent and that help people be intelligent. However, they have almost completely neglected the role of emotion in intelligent interaction, leading to an imbalance where emotions are typically ignored. Similarly, emotions have been largely ignored in the general medical community, with the exception of many recent investigations that have measured their impact and found emotion to be a significant factor in health recovery and in disease prevention. I do not wish to see the scale tilted the other way, where machines twitch at every emotional expression, or where physicians treat emotion and not the accompanying medical problems. What is needed is a reasonable balance. The aim of new affective technologies for medicine should be to help medical care givers attend to patients' full health needs – both emotional and non-emotional–in a balanced, respectful and intelligent way.

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Chapter 54: Future of Caring Machines

Timothy Bickmore, Ph.D.
Assistant Professor, College of Computer and Information Science, Northeastern University, Boston, MA, USA
Rosalind W. Picard, Sc.D.
Director, Affective Computing Research Group, MIT Media Laboratory, Cambridge, MA, USA

Abstract

Feeling cared for has profound effects on physiology, cognition and emotional state, and has significant health ramifications whether the source of this feeling is an intimate other, friend or health provider. Unfortunately, not everyone has access to social networks populated with caring individuals or has health providers who are patient, empathic and reliably available when emotional support is needed. Over the last decade, a range of computational artifacts and technologies have been developed that could help fill this unmet need in many peoples' lives. *Caring machines* are technologies that interact with an individual to accomplish a goal while also behaving in ways that give the individual the feeling of being cared for. This chapter presents evidence that these machines can begin to lead to significant health benefits, such as increased adherence to prescribed health behavior change and medication regimens.

1. Introduction

People cannot always get the support that they need. As families become more geographically dispersed and as the population ages, social isolation is becoming more and more prevalent. In addition, even those who are surrounded by people may not always get the comfort, caring and attention they need to thrive. These unmet emotional needs are not just frivolous desires whose neglect is inconsequential; a significant body of research now indicates that addressing an individual's needs for emotional care-taking is essential for maximizing their health and well-being.

Over the last decade, researchers in affective computing—that which relates to, arises from, or deliberately influences emotions [1]—and related disciplines have developed a number of technologies and performed a wide range of experiments that demonstrate that an individual's need for caring could be met (at least partially) by computational artifacts ranging from computer agents to wearable computers to robots.

In this chapter, we first review the literature on human-human and animal-human caring and their known effects on health. We then review the research that has been conducted over the last decade on technology development and experiments that serve to work towards the goal of building machines that people feel care about them. We close with some observations and visions about the possible futures of caring machines

2. Human-Human Caring and Health Implications

Feeling cared for has profound effects on physiology, cognition and emotional state in humans. It plays an especially crucial role in the helping and medical

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professions. According to Levinson, et al, "A growing body of literature suggests that outcomes of care are optimal when physicians address patients' emotional and personal concerns in addition to their biomedical problems. Patient satisfaction, patient adherence, and biological outcomes can be improved with a patient-centered model of care that demonstrates respect and caring for patients" [2].

Social support is the name given to those behaviors that take place within the context of a personal relationship, and that serve to provide aid and assistance. This group of behaviors has been broken down into several subtypes of support including: emotional support (expressions of empathy, trust, esteem, reassurance of worth, affection, attachment, intimacy); instrumental support (material assistance); informational support (giving advice and information); appraisal support (information that is useful for self-evaluation); and social network support (e.g., providing introductions to other people) [3, 4]. Of these, emotional support is the most strongly and consistently associated with health and well-being. For example, a number of studies have demonstrated that emotional support, provided in the context of intimate relationships, increases survival rates among people with severe cardiovascular conditions [5]. The effects of all kinds of social support are primarily a function of the *perception* of support by the one receiving it, rather than the perceptions, intentions or actual behavior of the person providing it [6]. For example, in studies in which both the provider and the recipient of social support were asked about the kinds of support provided in a relationship, the recipient's reports are always the most strongly correlated with the positive effects.

Studies have consistently found a relationship between social isolation and mortality, and this effect is most profound for those individuals who are the most isolated. One study found that older women who lived alone and did not have contact with family or friends had mortality levels three times greater than those who lived with others or had more frequent contact with family and friends [7].

Note that while social support can involve attempts at persuasion (e.g., via informational support), it is fundamentally different from other types of social influence in that it is always provided in a context of caring, trust and respect [4], and thus the technologies that may be involved in artificial caring need to be concerned with a much richer and deeper set of issues than those involved in argumentation or "captology" [8].

2.1. Caring by Health Professionals

There is also a known association between patients' perception of caring by health professionals and patient satisfaction, treatment regimen adherence and outcomes, across a wide range of health disciplines. The most significant empirical support of this phenomenon is in the field of psychotherapy, in which measures of "working alliance" –the trust and belief that the therapist and patient have in each other as

team-members in achieving a desired outcome—show consistently high correlations with successful outcomes [9]. Even in physician-patient interactions, physician empathy for a patient plays a significant role in prescription compliance, and a physician's *lack* of empathy for a patient is the single most frequent source of complaints [10].

However, health professionals cannot provide an individual's primary source of social support. Professionals are rarely available to provide support over long periods of time, and the power differential in the provider-patient relationship may hamper empathic understanding [4]. Additionally, professionals are under significant demands to reduce costs and to see more patients in less time. Time spent with a machine costs significantly less than time with a health professional. As the time that patients interact with machines increases, it is prudent to consider how that interaction can be designed to contribute to helping the patient feel cared for.

2.2. Caring Behavior

There are several human communicative behaviors that are known to elicit the perception of feeling cared for by a person. Although providing any kind of social support can indicate caring, demonstrations of empathy and comforting behavior are perhaps the quintessential examples, and are widely cited in the helping literature as being key in achieving desired outcomes [11, 12]. Other behaviors that can contribute to an impression of caring include social dialogue, self-disclosure, emphasizing commonalities, meta-relational communication (particularly emotional aspects) talking about the past and future together, continuity behaviors (appropriate greetings and farewells and talk about the time spent apart), and reference to mutual knowledge, as well as explicit messages of esteem (see [13] for a summary).

There are also nonverbal behaviors indicative of caring such as facial expressiveness (including displays of concern), head nodding, and tone and timing of speech. Nonverbal "immediacy" behaviors—including close conversational distance, direct body and facial orientation, forward lean, increased and direct gaze, frequent gesturing and postural openness—have been found to project liking for the other and engagement in the interaction, and to be indicative of caring [14].

3. Animal-Human Caring and Health Implications

Pets can also provide a sense of caring and emotional support, and have been found to be correlated with several kinds of beneficial health-related effects, although the specific mechanisms of these effects have not been determined [15]. Candidate mechanisms for the health-related benefits of pet ownership include: the opportunity for people to provide nurturance, since it can increase their self esteem; the ability of pets to provide network support through their role as social catalysts; and their ability to instill a perception of social support in their owners, given that they are always available and reliable,

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nonjudgmental, perceived as caring about and needing their owners, and can provide tactile comfort and recreational distraction from worries.

4. Progress Towards Caring Machines

Although the literature cited above describes the significant positive health effects of perceived caring by humans and pets, these sources of support also have many drawbacks associated with them. First, other people may not be consistently available or reliable to provide support when needed. Human helpers may react negatively if their help is rejected [4]. For older adults, the problem of physical and mental abuse by those who are otherwise supportive is also a real problem [16]. Finally, many individuals may simply not have a network of friends available, or may live in a location in which pets are not allowed. For all these reasons, computer agents that provide people with the perception of feeling cared for may be able to help fill this emotional void in the lives of many individuals.

Before a machine can provide effective emotional support or caring, it is first helpful for the machine to have some idea of what kind of emotions an individual is expressing: Is he upset? Is he pleased? In the following sections we first review the state of the art in sensing human emotional state, then move on to a review of technologies designed to intervene at the appropriate time.

4.1 Technologies for Sensing Human Emotional State

In order to respond in a caring way to people's feelings, it is important first to have a reasonable assessment of what they might be feeling. While there is no instrument that can directly read an individual's feelings, there are a variety of ways that people communicate their feelings to each other (often imperfectly), and these modes of communication are becoming increasingly accessible to machines. These ways range from dialogue and verbal expressions to non-verbal cues such as facial expressions, postural shifts, gestures, and more.

Machine conversational agents are computer characters designed to carry on a dialogue with a person, and this dialogue can help the machine to sense emotional information. While machines remain very limited in their ability to understand most of language, they can already engage successfully in quasi-scripted dialogues about feelings [17-19]. There are times when it is appropriate to overtly ask how somebody is doing, which can lead to disclosure of feelings, e.g.,

"How's it going?"
"Not so great."
"Oh dear. Sorry to hear. Anything I can do to help?" "I don't know, I just feel terrible about ..."

Sometimes feelings are not communicated through *what* is said as much as *how* it is said, e.g. "Good Morning!" can be spoken with genuinely cheery enthusiasm or with annoyance, disdain, and other kinds of inflection that may very clearly contrast the words used. Dialogue systems have a chance to sense the words selected by a person and reason about the associated affect

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[20-22], and also have the opportunity to listen to para-linguistic aspects of speech for indications of a person's feelings [23, 24].

Clearly if there is no dialogue, then speech won't work, and other modes of sensing will be needed. In many medical situations, it is natural to sense aspects of a person's physiology. Physiological information has been shown to carry information that can be used to classify an individual's affective state. Picard, et al, built a recognition system using four physiological signals, which learned patterns for an individual over time, and achieved 81% recognition accuracy classifying one of eight states (anger, joy, sadness, hatred, platonic love, romantic love, reverence, and neutral) that an individual was having [25]. (The person was seated, and deliberately focusing on having each of the eight emotions.)

Figure 1. Klein et al. used simple dialogue boxes to convey the impression of active listening, empathy, and sympathy to frustrated computer users.

Signals such as skin conductance and heart rate variability have also been shown to be indicators of stress in natural situations, e.g., driving in Boston [26], and recently it has been shown that an agent's empathetic responses can influence skin conductance in a way that is associated with decreased stress [27]. Stress and anxiety are increasingly being recognized as common in medical interactions and are also linked to a number of significant health problems; hence, the new ability of empathetic technologies to help reduce stress has many implications for health care. Other forms of affect sensing technologies have been developed for specific environments. Physiological sensors have been put into computer mice [28] and sensors have been put into a chair to sense postural changes related to levels of high or low interest in young learners working with educational software on a computer [29]. There is also lots of research on automated recognition of facial expression and on head gestures to discern states such as "concentrating," "disagreement," "thinking," "unsure," and "interested," [30] all of which could also be helpful to a machine trying to appear more caring by adjusting its responses to those of the person with whom it is interacting. Stronger results can be obtained by combining multiple channels, e.g. face with voice [31] or face with chair, mouse and task [32]. Different kinds of sensing may be more or less natural in different kinds of environments, and confidence that the computer has properly recognized the person's affective state tends to increase with more than one mode of sensing.

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4.2 Technologies for Influencing the Perception of Being Cared For

Once a computer agent has detected that a user is in need of caring, it may engage in some caring behaviors even without detecting the person's state, although knowing more about their state enhances chances of success. There are a wide range of comforting behaviors a computer could use to intervene (as outlined in Section 2.2), with the quintessential example being the expression of empathy. Here, we review some of the systems and studies in which a computer used empathy and other caring behaviors in its interaction with users. Additional examples include the work of Lisetti, et al [33], Paiva, et al [34], and Prendinger, et al [27, 35].

4.2.1 CASPER

One of the earliest empathic agents was the CASPER affect-management system developed by Klein et al. [17, 36], which was demonstrated to provide relief to users experiencing frustration. The system presented a frustrated user with a series of menus (e.g., see three examples in Figure 1) that prompted the user to describe his or her affective state, provided paraphrased feedback, allowed users to repair the computer's assessment and provided empathetic and sympathetic feedback. This agent was found to be significantly better than a venting-only agent (to which users could simply describe how they felt in an open-ended manner without feedback), or an agent that ignored their emotions completely, in relieving frustration, as measured by the length of time users were willing to continue working with a computer after a frustrating experience.

4.2.2 Computers As Social Actors

In their seminal series of studies and resulting book—*The Media Equation*—Cliff Nass and Byron Reeves at Stanford have demonstrated that when computers produce social cues that people respond in fundamentally social ways, even though this reaction is entirely unconscious [37]. In their book, they describe studies that demonstrated the following relational effects:

- Computers that use flattery, or which praise rather than criticize their users are better liked.
- Computers that praise other computers are better liked than computers that praise themselves, and computers that criticize other computers are liked less than computers that criticize themselves.
- Users prefer computers that match them in personality over those that do not (the "similarity attraction" principle).
- Users prefer computers that become more like them over time over those which maintain a consistent level of similarity, even when the resultant similarity is the same.
- Users who are "teamed" with a computer think better of the computer and cooperate more with it than those who are not teamed (the "in-group membership" effect, which can be achieved by simply signifying that the user and computer are part of a team).

Since the Media Equation was published, Reeves and Nass and

their students have continued doing studies within this "Computers As Social Actors" paradigm. Morkes, Kernal and Nass demonstrated that computer agents that use humor are rated as more likable, competent and cooperative than those that do not [38]. Moon demonstrated that a computer that uses a strategy of reciprocal, deepening self-disclosure in its (text-based) conversation with the user will cause the user to rate it as more attractive, divulge more intimate information, and become more likely to buy a product from the computer [39].

In one of their most recent, and relevant, studies in this paradigm, Brave, Nass and Hutchinson compared the use of empathic facial displays and text messages by an embodied computer agent (using images of a person's face with different emotional displays) with self-oriented emotional displays and messages [40]. They found that the empathic agent was given more positive ratings, including likeability and trustworthiness, as well as greater perceived caring and felt support, compared to either an agent that used self-oriented displays and messages or an agent that performed no emotion-oriented behavior.

4.2.3 Mobile System for Sensing and Responding to Stress

Can machine empathy make a positive difference in people's acceptance of a highly interruptive device designed to collect information related to stress? Liu and Picard modified a handheld device (HP IPAQ) to receive signals wirelessly from a set of FitSense sensors for monitoring the heart, foot acceleration, and location context, and to associate this data with what users reported about their stress and how interruptible they were [19]. The device would interrupt people on average a dozen times a day, in order to query for their stress levels and acquire a better understanding of whether or not it was a good time to interrupt. Two versions of the system were built, one designed to be empathetic and one not, and both of which were friendly and polite, and engaged in brief text-only dialogues with the user, for example:

System: Morning, Jane! Do you have a minute?
Jane: Yes
System: You know the drill – feeling stressed?
Jane: It's there – but not the worst.
System: Wish it was better. Hope things start looking up.
System: Thanks so much for all your input.

The above dialogue differed in only one respect in the two conditions: In the empathetic condition all six of the above lines were exchanged. In the non-empathetic condition, the next to last line was omitted by the system. Thus, the empathetic condition took an extra second or two to respond to the user's feelings before thanking the user, while the non-empathetic condition only gave the last line, a polite thank you, in response to the user's statement of her feelings. The presence of an extra empathetic line happened in each interruption during all the days a user interacted with the empathetic system.

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The empathetic system also used a slightly different algorithm to trigger when the interruptions would occur; however, this inadvertently led to the system interrupting people significantly more. Each subject was given each system to use for four days, in counter-balanced order. (Half the subjects used "A" then "B", without us indicating anything about any differences in the two systems, while the other half used "B" then "A".) After the eight days, users chose which one – A or B – that they wanted to use for the next four days. Seven out of ten chose the empathetic system over the control. When asked at the end of each of the first eight days, "about how many times does it seem like the system interrupted you today?" the users significantly underreported the number when using the empathetic system, and not when using the control. Also, at the end of the eight days, those in the group currently using the empathetic system reported a significantly higher desire to continue in the study. While the group of subjects was small, these findings support our intuition that introducing even a single line of empathetic response could have a measurable impact on people's perception of how interruptive a technology is, and on people's desire to keep using the technology.

4.2.4 FitTrack

Evidence that computers can instill a sense of caring comes from a recently completed study on the longitudinal effects of relationship-enhancing behaviors used by a computer agent (a "Relational Agent") on measures of user-computer relationship quality [18, 41, 42]. In this study the agent—named Laura—played the role of an exercise advisor designed to help subjects through a behavior change program, which was designed to increase their physical activity levels. The agent appeared as an embodied conversational agent [43], whose speech and nonverbal behavior (including hand gestures, eye gaze behavior, posture shifts, head nods, proximity and facial expressions) were controlled using the BEAT text-to-embodied speech engine [44] (see Figure 1). Subjects conducted a 5 minute interaction with Laura daily on their home computers for one month, during which Laura provided feedback on their exercise behavior, helped them overcome obstacles to exercise, provided educational content related to exercise, and obtained and followed up on commitments to exercise.

A RELATIONAL version of the agent used all of the caring behaviors described above. For example, if a subject indicated they were not feeling well (and thus unable to exercise), Laura provide appropriate empathetic feedback while exhibiting a concerned facial expression (as in Figure 1). A NON-RELATIONAL version of the agent delivered identical health content but had all caring and relational behaviors removed.

Thirty-three subjects completed the month of interactions with the RELATIONAL subjects with the agent. from the (69%) female agent and twenty-seven completed interactions NON-RELATIONAL Subjects were recruited MIT campus, were mostly students and were 60% (balanced across the two conditions).

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Figure 2. Exercise Advisor Agent

Quantitative Results

In this chapter we only describe results that are particularly relevant to the notion of caring; for a full description see [13]. These results include the following items from the bond subscale of the Working Alliance Inventory, evaluated after four weeks of daily interaction. Subjects in the RELATIONAL condition indicated significantly greater agreement (on 7-point Likert scales) with the following items, compared with subjects in NON-RELATIONAL:

- "I feel that Laura cares about me in her own unique way, even when I do things that she does not approve of." $t(60)=2.39$, $p<.05$
- "I feel that Laura, in her own unique way, is genuinely concerned about my welfare." $t(60)=2.19$, $p<.05$
- "I feel that Laura, in her own unique way, likes me." $t(60)=2.56$, $p<.05$
- "Laura and I trust one another." $t(60)=2.05$, $p<.05$

When asked at the end of the month if they would like to continue working with Laura, subjects in the RELATIONAL condition also responded much more favorably than the NON-RELATIONAL group, $t(57)=2.43$, $p=.009$. This measure is of particular importance since continuing with a treatment program is related to outcome, and desire to continue Treatment is likely to facilitate that result as well.

One behavioral measure related to caring was evaluated. In the closing session, subjects were given a choice of farewell greetings to say goodbye to the agent. Significantly more subjects in the RELATIONAL group (69%) chose the most sentimental farewell ("Take care Laura, I'll miss you." vs. "Bye.") than in the NON-RELATIONAL condition (35%), $t(54)=2.80$, $p=.004$.

Qualitative Feedback

After the experiment we asked subjects about their experiences with Laura. When asked whether they liked the overall concept of conversing with and relating to an animated character, subjects reported strong opinions on both sides of the issue. Representative responses included:

- "It was a really, really great idea to have some kind of animated character because it makes you feel like you're actually talking to a person rather than having words on the computer screen."
- "Personally I detested Laura."
- "I like talking to Laura, especially those little conversations about school, weather, interests, etc. She's very caring. Toward the end, I found myself looking forward to these fresh chats that pop up every now and then. They make Laura so much more like a real person."

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When asked "Do you feel that she really cared about you?", many subjects responded affirmatively but qualified their responses with comments such as:

- Yes, as much as a computer can care."
- "Yea, I think there was an illusion there that she did."
- "As much as it mattered to ... I never forgot that it was a computer program, but you'll notice that I find myself calling her by feminine pronouns rather than calling her an 'it'. So, I definitely remembered that she was a computer program, but I did feel like it was a more personal interaction than that."

Other subjects responded with uncertainty about the concept of Laura "caring":

- "I find 'care' to be a funny term to use with a computer character. I felt like it was helpful to have positive reinforcement, even if it was from a computer character."
- "She's a computer character. I don't know if she cared about me. I don't know if she feels. She's a character and has a role, but I don't know if she has feelings. But, it worked for me and I'm happy."

Finally, there was a group of subjects who answered negatively, emphasizing Laura was a machine.

- "No, not really, because I plugged in a number and she had a script."
- "No. I felt like I was talking to a robot, to a machine."

These responses illustrate a range of user feedback about a system that might evoke feelings of caring – from liking to disliking, from acceptance of the effects to denial of any effects. While clearly the technology did not lead to strong reports of caring in everyone, nonetheless the effect was significant across the group when the caring behaviors were included.

4.2.5. FitTrack for Older Adults

Relational agents may provide an accessible user interface for much of the older adult population, and an especially effective channel for health communication and behavior change interventions. To test this hypothesis, a pilot study was recently conducted to evaluate the acceptance, usability and efficacy of a version of the FitTrack system used by patients from the Geriatric Ambulatory Practice (GAP) at Boston Medical Center, the primary safety net hospital in the Boston area [45, 46].

Several modifications were made to the FitTrack system for older adults including: use of large fonts, a touch-screen interface, and modifications to the dialog content (see Figure 2). A randomized trial compared subjects who interacted with the relational agent daily in their homes for two months (RELATIONAL) with a standard of care control group who were only given pedometers and print materials on the benefits of walking for exercise (CONTROL). The subjects were twenty-two participants recruited into the study based on referrals from the GAP clinic. Participants ranged in age from 62 to 84, were 86% female, and 73% were African American. Seventeen (77%) were overweight or obese, and nineteen (86%) had low reading literacy [47]. Eight (36%) never used a computer before and six (27%) reported having used one only "a few times".

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Figure 3. FitTrack for Older Adults

Comparisons between the RELATIONAL and CONTROL groups on daily recorded pedometer steps were based on generalized estimating equations (GEE) regression models for longitudinal data for increases in mean steps walked per week for each subject. The estimated slope (increase per week in mean weekly steps walked) for the CONTROL group was estimated as 83.9, while the slope for the RELATIONAL group was estimated as 411.1. The difference in slopes is significant ($p = 0.004$). The slope in the control group was not significantly different from 0 ($p = 0.295$), while the slope in the RELATIONAL group showed significant increase in steps over time ($p = 0.001$).

When asked if they liked Laura, RELATIONAL subjects scored this 6.3 on a scale of 1 (not at all) to 7 (very much), and scored their relationship with her a 5.6 on a scale of 1 (complete stranger) to 7 (close friend). When asked if they felt that Laura cared about them, they gave this an average score of 5.9 on a scale of 1 (not at all) to 7 (very much).

When asked if they liked Laura, RELATIONAL subjects scored this 6.3 on a scale of 1 (not at all) to 7 (very much), and scored their relationship with her a 5.6 on a scale of 1 (complete stranger) to 7 (close friend). When asked if they felt that Laura cared about them, they gave this an average score of 5.9 on a scale of 1 (not at all) to 7 (very much).

"By the way that she sound, she sound like she like me."

"I remember one weekend I went to Wareham... You know, I began to feel bad about Laura, stuck in that box."

4.2.5 Caring Robots

Several recent efforts in academia and industry have focused on creating robotic pets for older adults in order to achieve the same beneficial effects found in animal-assisted therapy, namely to decrease stress, anxiety and loneliness and improve mood, e.g. [48]. The "mental commit" robots take the form of cute stuffed animals such as a cat or a harp seal pup, and are designed to foster an attachment with users. One study compared the effects of these robots on older adults in a nursing home with the effects of an identical robot that had a much simpler behavioral repertoire, however no significant differences were found [49]. Although the robot was used in group sessions by the same individuals four days per week for three weeks, and has long-term memory and a reinforcement learning mechanism, it is not possible for it to model a relationship with any particular user

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given that it does not have the ability to discriminate between users. Another study compared the use of a Sony AIBO robotic dog with a stuffed toy dog and a "clothed" AIBO by a group of older adults with severe dementia. This study found that patients actually interacted more with the stuffed toy than either of the AIBOs, but the differences were not significant [50].

There is also an emerging commercial market for robotic dolls targeted at the older adult caretaking market, particularly in Japan. Bandai launched the Primopuel doll in 1999, which is designed to resemble a five-year-old boy who continually asks to be hugged and entertained. Dream Supply released the Snuggling Ifbot in 2004, intended to be a speech-based conversational partner for the elderly. Tomy recently announced the release of the Yumel doll, which also converses with older adults using speech, and assists users in maintaining healthy behaviors such as good sleep hygiene [51]. None of these systems have been reported on as being formally evaluated.

5. The Future

Our machines will undoubtedly continue to improve in their ability to calm, comfort and soothe us, to gain our trust and attachment, and—consequently—to help us in times of sickness and crisis. They may even surpass the ability of many humans to do so, given that they are always available and reliably consistent. In addition, since they can be a persistent part of our lives over many years or even decades, they can have perfect memories of our past history, personal needs, values and aspirations (in human relationships, long-standing intimates are the best source of social support [4]).

Caring machines can certainly make use of more sophisticated techniques in how they address our problems. For example, rather than just offering canned empathetic messages or messages indexed to degree of emotional upset (as in [17, 18, 40]), they can offer comforting messages that are indexed or formulated according to a much more fine-grained set of emotional criteria, such as: extent to which a user's feelings are explicitly acknowledged, elaborated and legitimized; extent to which the messages are centered on the user's emotions (vs. the computer's feelings or the causes of the upset); and whether the empathic messages also contain a cognitively-oriented explanation of the user's emotions or not [52]. These cognitive explanations can also help users re-examine the events that gave rise to their negative emotions in the first place so that they can better cope with the situation.

Of course making people emotionally dependent on their machines has many ethical implications. In addition to the possible malicious use of these machines for manipulation of their users (e.g., see [53]), computer crashes, repairs and upgrades—commonplace events in our current world of computers—suddenly become potentially traumatic events for their users.

Another ethical issue is that this kind of technology may serve to further socially isolate users from other people, even though the potential exists to use the technology to help

bring people together. For example, in the FitTrack study involving older adults, one subject involved her friends in her discussions with Laura, and her friends would often ask her about her ongoing interactions with the character [46]:

> *"I brought my friends up here a couple of times to listen to her. My girlfriend she came upstairs with me and I show it. She say 'what's that?' and I say 'let me show you.' So I talk to her. So every time she talk to me she say 'Did you talk to Laura last night?.'"*

In addition, computer agents can serve in the capacity of match-makers, introducing people to others with similar interests, contacting friends when it thinks someone could use some human social support, and even pro-actively helping someone maintain their social network by reminding them to contact their friends periodically and helping them work through relational problems.

These caring agents will not only reside on our computers, but in our home robots, our mobile devices and in our health care facilities. Caring home health care robots could be used to help users through physical rehabilitation regimens or to bring them their medication, with the warmth and gentle coercion used by a skilled nurse who needs to motivate her patient to take care of themselves. Mobile devices, such as smart phones or PDAs, provide a platform in which caring health interventions can be delivered anytime, anywhere, such as smoking cessation messages at the instant a user gets a craving, or when someone is walking by the stairs on their way to the elevator. Finally, caring machines have obvious uses in our health care facilities, where patients are often ill informed about what is happening to them during hospital or emergency room visits or about proper self care when they return home. Caring agents could provide a persistent comforting presence throughout a hospital stay, answering questions, giving advice and preparing a patient emotionally for diagnoses, procedures, and home care.

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Chapter 55: Cyber-anthropology: A New Study on Human and Technological Co-evolution

Alexander Libin, Ph.D.
Cyber-Anthropology Research, Inc., Georgetown University, Washington, D.C., USA
Elena Libin, Ph.D.
Cyber-Anthropology Research, Inc., Georgetown University, Washington, D.C., USA

Abstract

For the first time cyber-anthropology is defined as a concept and a new field of study aimed at the analysis of person's reciprocal relations with the computer-generated (CG) world evolved as a result of technological progress. In the cyber-era, simulated reality has come to the point of becoming a force that has the potential to transform the human race. Digital beings such as virtual and embodied agents, although not a part of the natural human habitat, have become necessary elements of people's surroundings and life conditions. As a theoretical construct, Cyber-anthropology is concerned with the merger of natural and artificial worlds mediated by the human imagination, as well as compatibility between people and digital life they have created. As an empirical study, Cyber-anthropology deals with the psychophysiology and psychophysics, semantic and semiotics of human engagement with computer-generated reality that is viewed as a Complex Interactive System. Personal competence as a crucial element of any cyber-system underlines the importance of psychological culture in artificial world exploration. A newly developed concept of Psychological Culture is viewed as an essential part of Cyber-anthropology while concentrating on the following core issues: (1) ethical questions, such as whether or not technological tools can be employed to solve human problems; (2) moral consequences of bringing cutting edge technology into our every day life; (3) studies of individual differences regarding psychological competence of technology users through effective vs. ineffective, independent vs. addictive, and active vs. passive dichotomies. Psychological Culture is defined as the study of a person's competence associated with the use of modern technology and individual acceptability of technological innovations. Several crucial dilemmas arise when a human being is engaged in a simulated environment, and artificial agents inhabit a human world. The ultimate goal of Psychological Culture is to provide people with the knowledge necessary for adequate recognition of scientific innovations to overcome obstacles in the process of implementing technology to enhance human well being.

1. Computer-generated reality: a personal touch

Since ancient times people employed their imaginations to model fictitious realities filled with bizarre creatures and strange life forms capable of acting beyond human possibilities. When all the other necessary survival tools were exhausted, people used the power of their minds to gain

the strength of the spirit when fighting unknown diseases or trying to understand unpredictable chains of events. Sometimes, the thin line between the real and imaginary worlds would became blurry or even disappear. The degree of self-immersion into one's own fantasy combined with people's ability to keep up with their actual life requirements would result either in total mal-adaptation or in the re-construction of the existing realities. Modern technological tools have enriched human abilities not only in exploration, but in altering our inner and outer worlds. With the development of digital vehicles for information technologies, we entered a realm never experienced before by the human mind or senses. How do these new experiences fit into the existing methodology of human studies? What are the conceptual frames for analyzing and interpreting a person – cyber-world interaction? Is it possible to predict the outcome of those interactions? Below are defined some primary coordinates of the emerging field of Cyber-anthropology – a theoretical and practical study of human-centered, digitally-based technological systems, their structure, development, and functioning.

1.1. On the crossroad of Anthropology and Cybernetics

A clashing charisma of anthropological studies attracted materialists and idealists, empiricists and methodologists, naturalists and humanitarians. The term 'anthropology' (from Greeks 'anthro-' – a man, and 'logos' – a study) was coined by Aristotle more than 2000 years ago [1], and the new discipline of anthropology was formulated by Kant in 18th century [2] acknowledged the beginning of a science that focused on studying physical, psychological, and cultural trends in human development. The aims of anthropology include the whole range of analyses from cultural artifacts (i.e., archeological method) and diversity of customs and beliefs (i.e., ethnographical method) to the study of human kind's similarity to and divergence from the animal kingdom (i.e., methods of physical anthropology and sociobiology). The body of knowledge about human life phenomenology was greatly expanded by the explorations of philosophical, structural, psychological and semiotic anthropology (see Table 1). However, regardless of the scientific paradigm underlying the investigation of a particular aspect of human – world interactions, anthropological analysis strived to search for the answers to the two inter-related questions posed by our very existence*: How do human beings transcend themselves in their own experience?,* and*: How do people actually behave?*
[3].

Over the last twenty centuries, the systematic study of *Homo sapiens*, specifically their physical, psychological, and socio-cultural functioning, went through numerous transformations. The recent one is associated with the rise of highly technological systems based upon electronic "brains" and digitally originated behaviors. In such hybrids, a person appears as a human agent who performs a peripheral or –

sometimes – a central role in the complex system functioning. A concentrated view on the essence of relationships between artificial and living systems was formulated by Norbert Wiener in 1948 in a concept named cybernetics (from Greek *kybernet*(es) or steer(-s) man) [4]. Cybernetics is viewed as a science of control processes in organic, and technological, mechanical and electronic systems. Cybernetic principles are employed by psychology for exploring the phenomena of artificial intelligence and emotion-like behaviors, by social sciences for studying effective management, and by engineering for analyzing the optimizing possibilities of technology-based processes.

Both worlds – human and artificial – came to existence as a result of evolution: socio–biological or technological respectively. The development of two independent subjects of study – anthropological and technological – brought to life a new field of Cyber-anthropology. Its dual nature is an adequate systematic method for studying this hybrid phenomenon – the cyber world.

1.2 Cyber-anthropology: Human world through the prism of technology

The definition of the new phenomenon is unavoidably multi-semantic, for it has to account for the methodology and the epistemology of the variety of analyzed experiences, as well as their theoretical and practical implications. Bearing this in mind, we would like to present a unified framework that combines various meanings – or, rather, dimensions for the analysis – of the emerging field named Cyber-anthropology (see Table 1):

Table 1. Definitive classification of Cyber-anthropology

Anthropological models of man	Cyber-anthropology elements		
	Focus of the computer-mediated analysis	Subject of Cyber-anthropology study	Related cyber-phenomena
Physical anthropology/ Cognitive anthropology	Reconstruction of human beings via virtual representations	Archeological and evolutionary aspects of human physical representations through the historical and geographic prospective	Digital reconstruction of human's predecessors, their behavior, and associated artifacts
Ethnographical anthropology Social anthropology	Analysis of computer-mediated social interactions	Social manifestation of interactions between humans and virtual agents	Virtual heritage and Internet culture.

Philosophical anthropology	Methodological analysis of computer-generated phenomena such as presence and immersion	Reflection on human existence into digital world	Sense of immersion and presence produced by person's engagement in virtual reality or virtual communications
Structural anthropology/ Semiotic anthropology	Structural analysis of semantic and semiotic of digital artifacts	Functioning of digital symbols	Imaginary, virtual, and embodied personages; digital folklore; myths of computer era
Psychological anthropology	Study of compatibility between human and technology	Psycho-physiological, psychological, and social effects produced by human – computer interactions	Digital self and virtual identity; cyborg-dilemma; psychological aspects of people-robot co-existence

Cyber-anthropology for the first time is defined as a concept and a new field of study aimed at the analysis of human reciprocal relations with the computer-generated (CG) world which have evolved as a result of technological progress. In the cyber-era, simulated reality has come to the point of becoming a force that has the potential to transform the human race. Digital beings such as virtual and embodied agents, although not a part of the natural human habitat, have become necessary elements of people's surroundings and life conditions. As a theoretical construct, Cyber-anthropology is concerned with the merger of natural and artificial worlds mediated by human imagination, as well as the compatibility between people and the virtual and embodied forms of digital life they have created. As an empirical study, Cyber-anthropology deals with the psychophysiology and psychophysics, semantic and semiotics of human engagement with computer-generated reality viewed as a Complex Interactive System [5].

2. Cyber-anthropology as a science of differentiation between living and artificial complex interactive systems

The importance of the notion that speaks to distinctions in origin, structure and ultimate goals of living and non-living, inanimate, artificial systems has been emphasized by many authors. The founder of differential psychology and inventor of the IQ (Intelligence Quotient) hypothesis, William Stern, pointed out that the biggest methodological mistake is to apply mechanistic interpretation to the analysis of '*a person*', which transforms it into '*a thing*' by eliminating a certain psychological component from the epistemological and

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phenomenological analysis [6][7]. A differing criteria, based upon the '*closed vs. open*' dichotomy, was offered by von Bertalanffy, a creator of the modern systematic approach, to distinguish between *non-living, closed* and *living, open complex* systems [8].

A study of the principles of mental representation revealed the fundamental role of tactile-kinesthetic gestalts in forming a hierarchical structure not only of sensory-motor, but emotional and cognitive mental phenomena [9]. Only the neuronal core of an open living system is able to produce tactile-kinesthetic sensation unavailable in the artificial systems. The latter is based exclusively upon information exchange in the form of electric impulses, which lie at the foundation of electronic-originated phenomenology. No matter how complex the system is and how high the level of the system's internal or external interactivity is, the ability of living beings to transform non-transitive physical properties of an object into the internal sensation through the tactile-kinesthetic mechanism [9], remains a major criteria that differentiates between natural and artificial phenomena, mental and virtual representations, real and unreal experiences.

It is notable that a concept of complexity brings two vitally significant components into the cyber-anthropological approach – the non-linear nature of examining phenomena and its interactive nature. Perhaps because interactivity is a main characteristic of the brain [10], mental functioning [9] and human development in general [11], an interactive nature of cyber-applications makes them natural - like part of our physical and social environment. On the other hand, having human personality as a main element in person–cyber-world interactions emphasizes the key role of psychological knowledge in understanding the character of cyber-anthropological models. In 1930, Vygotsky rightfully suggested that a study of psychological systems focuses rather on the analyses of relations between different functions and modifications of these relations over time, than on changes within each function and their structure [12].

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3. Practical applications of Cyber-anthropology

The artifacts produced by digital technologies form the subject for experimental and applied Cyber-anthropology research. Primary classification of computer-generated phenomena sheds some light on the practical agenda of Cyber-anthropology,, which includes an examination of:

A. *Cyber-space*, including: 1) computer-mediated communication such as Internet, Email, Chat groups, Virtual communities, 2) World Wide Web as a mediated form of immediate social contacts, 3) cyber-culture

B. *Virtual environments* as part of 1) VR-based application (i.e., database representations, cyber-therapy products), 2) video games, and 3) virtual projection of digital structures

C. *Digital representation* or reconstruction of real experiences associated with 1) living beings such as humans – ancient in case of traditional physical anthropology and archeology, or modern in case of virtual medicine, and 2) material objects (i.e., virtual heritage or modern architecture)

D. *Human-computer* interactions as constellation of psychological and ergonomic factors including multi-modal interfaces

E. *Embodied agents* in the form of interactive robotic creatures with artificial intelligence and sensory feedback, e.g., lifelike robots imitating living beings, humanoids, etc.

The first three sub-groups (A-C) are organized in a class of virtual phenomena, the fourth group is structured as a transitional class combining both virtual and embodied elements, and, finally, the last group (E) presents a newly emerged class of embodied agents – a materialized form of digital activity. Cyber-anthropological studies of person – robot interactions are carryied out in two modes recognized as *Robotic Psychology* and *Robotherapy*. Robotic psychology focuses on the compatibility between humans and robots [13], while Robotherapy concentrates on using interactive robots as therapeutic agents for people with psychological problems or limited physical, cognitive, or emotional resources [14][15].

4. First research priorities from the Cyber-anthropologist's point of view

Although traditional approach has proved the effectiveness of the formula 'All's well that ends well', a more important rule at the beginning of new ventures (ought to sound like) sound like: "It's better to start well. ". Presented below is a brief schema for the Cyber-anthropology research necessary to establish a systematic techno-knowledge [16] about the field:

- Emotional experiences triggered by both virtual and embodied digital interactions;
- Criteria of differentiation between real and imaginary worlds
- Symbolic meaning of computer-mediated interactions and digitally-generated experiences
- Stereotypes and myths about the origins and functioning of cyber-reality

- Psychological and psycho-physiological effects produced by person interactions with virtual and embodied agents
- The nature of presence and immersion

Classification of cyber-phenomena based on tactile-kinesthetic and visio-geometrical gestalts and related studies on multi-modal interfaces

Finally, the concept of Psychological Culture deserves a special attention in Cyber-anthropology study program.

5. Psychological Culture as a subject for Cyber-anthropology studies

- Exploring advantages and disadvantages of human-cyberworld co-existence;
- Understanding the psychological specifics of interactions between persons and their artificial partner (i.e., virtual or embodied agent) on all levels: sensory-motor, emotional, cognitive, behavioral and social;
- Studying how the rich diversity of our personalities justifies a broad variety of environments and agents;
- Searching for possible solutions of moral dilemmas stemming from human-technology interactions;
- Providing people with knowledge required for the further virtual space expansion and effective person–artificial agent collaboration.

First of all, Psychological Culture concentrates on ethical questions such as whether or not technological tools can be employed to solve human problems. The next important issue relates to the study of the moral consequences of bringing cutting edge technology into our every day life. The third core question involves a study of individual differences with relation to psychological competence of technology users through effective vs. ineffective, independent vs. addictive, active vs. passive dichotomies.

Among the main topics that catch the attention of psychological culture researchers are such questions as *`Why does one person maintain a lifestyle independent from modern technologies while others develop technology (TV, computer, internet etc.) addictions?`*, *`What are the psychological parameters that can predict effective or ineffective technology usage? `*, and *`How technology can help people cope with their problems without putting an extra burden on them?`*

In sum, Psychological Culture studies the extensive range of psychological aspects of technology–mediated communication that arise on the merge of artificial and human worlds.

6. Technology–mediated solutions for human problems

In recent decades, the merger of artificial and human worlds has shown its promising results. Many researchers, engineers, and practitioners have already proven the productivity of technological applications in such areas as health, education, therapy and entertainment. In particular, exploration of virtual reality advantages known as `immersion` and `sense of presence` promoted a creation of original VR-based methods of psychological therapy. A new approach named Cybertherapy [17] showed

effectiveness of VR-applications employed for treating psychological disorders including phobias (i.e., fear of flying, agoraphobia, etc.), social anxiety, different kinds of addiction (i.e., gambling, tobacco addiction), and cognitive and emotional deficits (i.e., autism, attention deficit hyperactivity disorder, sensory disintegration, etc.). Computer-generated reality has proven to be a useful therapeutic tool for a wide variety of populations such as children and the elderly, persons with physical and mental disabilities, and people who live both in home environment and clinical settings.

Success of early VR-based therapeutic interventions has inspired designers to further investigate the potential of artificial tools to provide real-life benefits. This is a vivid example of mutually advantageous collaboration between technology and psychology.

Another promising technological application concerns the development of embodied digital agents or interactive robots. The contemporary world of robotics is inhabited by a broad variety of artificial creatures designed for the purpose of helping people with special needs to overcome their limitations and enrich their quality of life. Nowadays, robotic creatures are used as mediators in the treatment of mood disorders, loneliness and depression, and as rehabilitation aids. The concept of an artificial partner [5] places person-robot interactions into a psychological, rather than a technological, context. Beneficial features of robots as human companions lie at the foundation of a new field of study named Robotic psychology and Robotherapy [13], [14]. Even so, interactive robots serve as therapeutic agents or stimulating companions, the effectiveness of people's communication with their artificial partners depends on their compatibility. Therefore, the robot's design should take into an account a whole range of both psychological and ergonomic parameters. This means performing a comprehensive analysis of human differences that underlie preferences in communication mode or intensity of interactions, degree of emotional or tactile stimulation, and the specifics of personal needs that are essential for maintaining effective person–robot compatibility.

tive person–robot compatibility. Obviously, the broad diversity of people's personalities justifies the creation of a wide variety of virtual and embodied agents. Since a person is the central part of technology-mediated communication, human factors define the adequacy and effectiveness of the process' organization per se. An outcome of computer-mediated interactions depends on two inter-related issues:

- whether or not the person's individuality matches the specifics of artificial environment or agent;
- the level of the person's psychological culture based upon an understanding of the role and place technology takes in human life.

7. Moral dilemmas of human engagement with the artificial world

Without doubt, exciting virtual reality (VR) and robotics' applications have enriched science and engineering,

industry and public service, medicine and entertainment, psychology and psychiatry, education and therapy. Technological agents positively influence the quality of human life by bringing accessibility and comfort, inspiration and enjoyment. Computerized tools have greatly expanded the human capability to visualize desires, materialize images, and observe the hidden processes. However, several crucial dilemmas arise when a human being is engaged in the simulated environment, and artificial agents inhabit the human world.

7.1. Virtual Presence vs. Reality Absence

Cyber-phenomenon known as 'presence' is a subjective sense of being in a virtual environment. Sheridan defines presence as 'sensory information generated only by and within a computer...a feeling of being present in an environment other than the one that person is actually in' [18]. Visual, auditory and haptic sensations produced by virtual reality applications are a part of an artificially simulated environment, otherwise known as artificially simulated illusions, which allow persons to experience 'presence'. Artificially triggered senses of presence may create positive, though illusory, experiences (i.e., VR-based treatment of phobias), or create false experiences resulting in a new chain of real problems (i.e., MUD-addiction based on false identity). One of the main psychological problems and moral dilemmas associated with the phenomena of presence stems from the person's inability to distinguish between real and artificial words. Individual inability to understand that those two worlds are not identical, but different, creates a barrier for implementing the achievements of engineering science. Psychological culture aims at studying the nature of simulated illusions and elaborating criteria for experiencing the sense of presence without side effects.

7.2. Coping With Difficulties vs. Escaping From Life

Technological applications provide people with new tools for coping with life's difficulties.

The level of individual psychological culture or psychological competence depends on understanding the meaning of technological progress for one's own life. If used appropriately, artificial reality expands human possibilities and enhances quality of life. However, there is much evidence of using technological innovations as an excuse to escape from real life problems into an illusory world. Psychological Culture is aimed at studying the criteria of differentiation between technology–mediated coping and defensive strategies. Coping strategies are defined as cognitive, emotional, and behavioral efforts *directed toward resolving an experiencing difficulty*. Defensive strategies are cognitive, emotional and behavioral efforts *directed away from actual problem solving* [19].

7.3. Assistance vs. Substitute

The next main task of Psychological Culture is to bring awareness to an individual as well as social consciousness about the value of both technology–mediated assistance and human support. Neither artificial reality nor any of its superlative products

may serve as a replacement for genuine human relationships. Lack of psychological competence necessary for the adequate use of technical innovations in our daily life leads to various side effects, such as computer dependence, mixed identities resulting from rejection of real self in favor to the virtual persona, replacing human communications with electronic message exchanges and interpersonal relationships with person–machine interactions.

In particular, the moral dilemma of 'assistance vs. substitute' stressed in the use of robotic creatures for therapeutic purposes. The most important concern many researchers and practitioners pose is that robots would become a substitute for human caregivers [20], [21]. This is true for any kind of robotic assistance. For instance, the use of robotic pets poses a question: *'Are robotic pets designed with the intention of replacing our favorite cats and dogs?'* This dilemma requires special attention from psychological culture research. When a robotic creature is employed in therapeutic practice, it is necessary for a therapist to keep in mind that any state-of-the-art robot is only a technological tool. The use of technological innovations establishes special requirements for psychological culture of the therapist or professional caregiver. It is especially important to not delegate a therapist's function to a robot. Humanistic robotherapy considers innovative technological tools as an additional resource essential to human care, but not the other way around. Robotherapy cannot be interpreted as an excuse for a therapist to avoid responsibility or deprive caretakers from human assistance. Effective technology–mediated health intervention of any kind is based upon conscious preference of technological means viewed as a way to improve human assistance while providing compassionate professional treatment [22].

Thus, a concept of Psychological Culture based upon an idea that human engagement with an artificial world is not an escape from reality and an excuse to avoid life's challenges, but an opportunity to expand coping resources.

8. Conclusion.

Cyber-anthropology can be defined as a study of how humans are influenced by the artificial world produced by the technological evolution. In a broad sense, Cyber-anthropology is the science of investigating physiological, psychological, and socio-cultural phenomena that occur as a result of interactions between human mind–body systems and artificial computer–generated reality.

To gain benefits from cyberspace exploration, as well as from interactions with virtual and embodied agents, one needs to employ a systematic analysis of psychophysiology and psychophysics, semantic and semiotics of human–artificial world co–existence. Cyber-anthropology, while studying a complexity of person–machine interactions, employs principles of Psychological Culture. The ultimate goal of the new approach is to provide people with the knowledge necessary for adequate recognition of scientific innovations to overcome obstacles in

the process of implementing technology to enhance human well–being.

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Chapter 56: Potential of Using Computer Technology to Support and Augment Psychotherapeutic Interventions in Hospitals, Communities and Homes

Marina U. Bers, Ph.D.*
Assistant Professor, Eliot-Pearson Department of Child Development, Tufts University, Medford, MA, US
Joseph Gonzalez-Heydrich, M.D.
Assistant Professor of Psychiatry, Harvard Medical School & Medical Director, Outpatient Psychiatry Programs, Children's Hospital, Boston, MA, US
David Ray DeMaso, M.D.
Associate Professor of Psychiatry, Harvard Medical School & Associate Psychiatrist-in-Chief, Children's Hospital, Boston, MA, US

Abstract

This chapter explores the potential of using computer technology to support and augment psychotherapeutic interventions in hospitals, communities and homes. We describe two applications piloted at Children's Hospital Boston. The first pilot explored how patients with pediatric heart disease used the Storytelling Agent Generation Environment (SAGE) computer program to create interactive storytellers and share their personal stories. The second involved youngsters on hemodialysis for end stage renal disease using the Zora graphical multi-user environment to create a virtual city and form a therapeutic virtual community. In this chapter we show how computer technology can be used to help patients explore their identity, cope with their illness and provide mutual support and interaction. We also present design recommendations for future interventions of this kind.

1. Introduction

Advances in medical care have greatly increased the life expectancy of children and adolescents suffering from a myriad of physical illnesses. Despite these advances, many youngsters must continue to contend with a chronic physical illness and ongoing treatment [1, 2]. It has been recognized that enhancing adaptive coping strategies improves health outcomes and resiliency in many patients. Interventions that provide information, facilitate expression of feelings, and allow mutual support are important components of psychoeducational interventions that have been found to be useful. In addition there is an emerging recognition that both emotional and physical benefit can be gained through the development, expression, and understanding of an individual's personal narrative or "story" of a physical illness [3]. Personal narratives often include how a physical illness has changed or not changed who they are, their relationships and life choices, and "what it means to them."

Parallel to these psychotherapeutic developments in the support of physically ill patients, computer technologies have evolved that facilitate mutual support networks, the exploration of the self, and the development of personal narratives. The recent increase of home pages,

chat-spaces, virtual worlds, multi-user environments and Internet-based role-playing games are "real world" examples of these technologies. Turkle [4] suggests that the "Internet has become a significant social laboratory for experimenting with the constructions and re-constructions of self that characterize postmodern life." Despite these technologic advances the challenge remains of how to design environments that leverage the characteristic of the computer to purposefully support explorations about identity that can lead to therapeutic personal narratives and better mutual support.

Identity construction environments [5] can serve this purpose. They are designed following the philosophy of constructionism [6] that asserts that people learn best when engaged in creating meaningful projects that they can reflect upon and share with others. Therefore identity construction environments enable children to design their meaningful computational projects to explore their sense of self. In this chapter we present two examples of identity construction environments, SAGE and Zora. SAGE enables children to design interactive storytellers, while Zora provides them with tools to create a virtual city. This chapter describes the use of these two identity construction environments in Children's Hospital Boston.

2. SAGE: Telling Stories With An Interactive Soft Rabbit

SAGE (Storytelling Agent Generation Environment) is an identity construction environment that supports the creation of individualized "wise or sage storytellers" by children. It was developed at the MIT Media Laboratory in Cambridge, Massachusetts to help children "play out" what is happening in their lives by telling and listening to stories. In order to encourage child's emotional engagement, the wise storyteller's assistant was embodied in an interactive stuffed animal (rabbit) — a *soft interface*. With SAGE, children became the designers as well as users of their creations. Thus, SAGE supported two modes of interaction. In the first mode, children share their personal stories with a wise sage, and his rabbit assistant, who "listen" and then offer a relevant tale in response. In the second mode, children can add to the collection of wise sages by designing their own storyteller for themselves and others to interact with. They then write stories for their sage to tell [7].

In order to support children in creating their own characters, a visual programming language was developed to design and program: (1) the scripts that are used by the storyteller, (2) the conversational structure or flow of the interaction, (3) the body behaviors of the interactive toy, which behaves as the pet assistant of the storyteller, and (4) the database of tales that are offered in response by the character. SAGE also has multimedia capabilities allowing children to record their own stories and to draw their own characters. SAGE was designed to focus on creating stories and storytellers that invite reflection about the child's inner world.

SAGE seeks cognitive and emotional engagement. Hence, the decision to embed the assistant of the sage storytellers in a programmable interactive stuffed animal (see figure 1). The stuffed animal is capable of some of the types of nonverbal behaviors that humans use to indicate engagement and which are commonly found in conversational narratives between people (i.e., the rabbit moves as the children converse with it). In design mode, children are able to decide on the toy's communicative behaviors as well as the different personalities it might have.

Figure 1: Interactive programmable stuffed rabbit

3. Stories From The Heart

Patients admitted on the hospital's cardiology ward (ages 7 to 16) were asked to use the SAGE to tell their stories and to create interactive characters. Informed consent was obtained from all families as part of a larger project by the authors to understand and promote family coping with cardiac illness, hospitalizations, and invasive medical procedures. The aim of this project was to explore the feasibility of physically ill children to use SAGE as well as its usefulness and safety in the hospital setting.

To engage hospitalized youngsters in the project, we created special characters for SAGE that could tell stories relevant to the medical environment. This began with "Mrs. Needle" who was a cartoon-type character that engaged children around the common child fears of "needles or pokes." This character used humor as a way to "break the ice" with these children. These characters proved quite successful as evidence by the creation of new hospital characters, e.g., "Mr. Tape", by the children themselves. Interestingly hospital professionals even created their own characters, e.g., "Mr. Squeeze".

The following are two examples of how two patients used the system to write stories of their medical experiences.

- Lisa created a character (herself) called "Sadly Alone." The character asks the user, "Are you feeling sad?" and then told Lisa a story. In response, Lisa worked on her own story with a close family member. Lisa was gravely ill when working with SAGE wrote the following.

  "My name is Lisa, and I have a problem. I'm 16 years old and I have a real bad heart problem and I am getting ready

to have a heart transplant really soon but the hardest thing is my mother [is very sick] And I have a little brother, so it's so hard to leave them alone so I just stay strong and do what I have to do and if you ever have this kind of problem just stay strong for your family and think of me."

- Samuel is a 13-year-old boy who had had a successful heart transplant. He wrote three stories about this experience and put them together into a trilogy called "The heart transplant dictionary".

  "At first I felt very sick and I had to go into the Emergency room. First I had an IV which I never had before which I was pretty scared about and then I had a blood test on my arm and I never had one of those either which I was very scared about too but the IV was much scarier because I didn't know how much it was going to hurt. And another scary part was a lot of different doctors coming in all the time and that made me nervous because it made me think that there was something very wrong with me [...] but then I got better and I got to go home and I thought that everything will be OK but then I got sick again and I had to go back to the hospital and then they realized that I had to have a heart transplant.

  After my heart transplant I was very sick because my body was rejecting my heart and it made me feel very sick and I had to go in for medicine and get biopsies twice a week where they go through a vein in your neck with a needle and they thread a catheter through and then they scrape a little piece of the heart tissue to see if you have any rejection. Rejection is when your white blood cells do not recognize your heart and think it is some bad virus or disease because it is not your original heart and your white blood cells try to attack your heart. So I kept having rejection [...] so they sent me to [another hospital] to go on a experimental drug [...] and felt better and the new drug is working very well and now I have no heart rejection at all [...]

The following example is from actual SAGE logs of interactions that a 16-year-old patient had with different storytellers (some already existing and others created by the patient). Interaction between the patient (CHILD) and SAGE happens through the keyboard (i.e., typing input and text-to-speech or recorded output.

- This is a log of an interaction between Damian and the rabbit, best friend of "Mrs. Needle."

  CHILD: I guess yes
  SAGE: *Well, Mrs. SAGE: Hi, what is your name?*
  CHILD: Damian
  SAGE: *Welcome, Damian. I am Bunny, the best friend of Mrs. Needle. She hides in the computer because she is a little shy. She thinks that all the kids hate her. So she asked me to talk on her behalf. Is that OK with you?*
  CHILD: yes
  SAGE: *Wonderful, wonderful, Damian! Mrs. Needle is worried because kids scream when they see her. But, have you met Mrs. Needle before?*
  Needle is my best friend and she hides in the computer. Tell me, Damian, how old are you?
  CHILD: 16
  SAGE: *Damian, you are older than me. I wonder if you are you scared of needles as I am ? I hate them, all except my friend Mrs. Needle. What about you?*
  CHILD: They are all right
  SAGE: *As I was telling you, Damian, I am Mrs. Needle's best friend and she asked me to find out why children hate her so much. She thinks that it is because she stings, but she is not sure. What do you think?*
  CHILD: yes no kid is excited to get any needles
  SAGE: *I see Damian ... what else can you tell me about this?*
  CHILD: the kids are afraid of it because it hurts and they don't like it to hurt and I guess that is it
  SAGE: *Well, Damian, let me see if I understand. I am sure that Mrs. Needle is very happy to hear what you have to say.*

Yes no kid is excited to get any needles the kids am afraid of it because it hurts and they don't like it to hurt and you guess that is it. Am I right?
CHILD: yes
SAGE: *Guess what, Damian? Mrs. Needle has a story for you. She is shy but she loves to tell stories. She always says that they have power... Listen to her...*
Ms. Needle's Story: They built me to sting, but that is not all I do. If you were a flower I could water you without hurting you. But you are not, and I am not a water pot. My nose is like a hose or like a straw and my belly has goodies than can help you to heal. When my belly is empty, the goodies are yours and you can feel better. But sometimes it is the other way around. My belly starts completely empty, and then it becomes full with your goodies. You can think of me as a someone that only stings, but I also do good. The problem is that this is not always immediately obvious.
SAGE: *I loved Mrs. Needle's story, but how about you? Does it somehow relate to what you told me before, Damian?*
CHILD: yes it does
SAGE: *I see, Damian, please explain me the connection. I don't get it.*
CHILD: The children don't realize that the stuff can help them, the medicine. SAGE: I see, Damian, you got the power of the story. I am sure my friend Mrs. Needle will be very happy. I wish that you will always have the courage to keep telling and listening to stories. I hope to see you soon....Bye !

- After playing with "Mrs. Needle", Damian decided to create his own character called "Mr. Tape." He created the conversational structure, the scripts that "Mr. Tape" says, and also the stories that he tells. After, he interacted with the character and invited other people in the Cardiac Unit to play with him. This is a saved log of Damian's interaction.

SAGE: *Hi my name is Mr. Tape. What is yours?*
CHILD: Damian
SAGE: *Well hello, Damian, my name is Mr. Tape. I am very sticky, as you probably may know, a lot of children don't like tape because when you have to take it off it hurts. Some kids like me to put me anywhere, like the face, hands, just for fun. Do you like tape?*
CHILD: no
SAGE: *I am sorry, why don't you like me. Does it hurt you?*
CHILD: sometimes, yes
SAGE: *Well, I am good for taping things up that are broken and I come in different kinds. I try to do the best I can with making things back to normal. So, Damian, how old are you?*
CHILD: 16
SAGE: *You are lucky to be able to live that long. My life expectancy is only two to three years. Some people use me up fast and sometimes I am forgotten in the junk drawer. I get pretty lonely in there. Would you like to hear my story?*
CHILD: yes
SAGE: *When I am used as medical tape I am the number 1 user for nurses and doctors. I go on IVs and wrap things up. I am good to write on for the nurses to put on IV medication. You can use me just about everything in the hospital but I am not very sticky for heavier objects. I could be colored on and used for decorations for kids that are very bored. Some people just throw me around and drop me which hurts my feelings, I can't pick them up and drop them, but I thank them for using me as their number one choice. Well it was nice talking to you, maybe you will talk to me again and listen to my story. Bye*

As shown in these examples (as well as many others) youngsters with pediatric heart disease were able to readily use the SAGE to express significant fears and feelings. SAGE proved feasible, safe, and useful. It enabled children to adaptively express emotions through the creation of stories and narratives along with the development of innovative and

interactive characters with whom they could converse. Nevertheless the SAGE did not engage children in sharing their stories with others in a community. When an individual is facing adversity it can be helpful to share one's personal narrative and becoming part of a social network that shares similar concerns. Recognition of SAGE's limitation in developing a supportive community led to the next prototype, Zora.

4. ZORA: Designing And Inhabiting A Virtual City

Zora is a 3D graphical multi-user environment designed at the MIT Media Laboratory [8]. Users build virtual rooms and populate them with objects and characters representing aspects of themselves, program them with storytelling behaviors, and converse with others in real-time through an avatar. Young patients used Zora in the hospital's dialysis unit. These patients form a community because they share a common medical condition and treatment in their end stage renal disease. Yet, at the same time there is little opportunity for social interaction with each other as they are confined to a single bedspace where they are attached to a dialysis machine for several of hours three times each week. The aim of this project was to explore the potential of the Zora identity construction environment to facilitate mutual patient support. In order to investigate this potential, the study examined the feasibility and safety of using the Zora virtual environment in a hospital setting.

Zora is a 3D graphical multi-user environment designed to support the exploration of identity through storytelling and programming. Users can create a virtual city and populate it by designing spaces, objects and interactive characters that can be programmed to engage in interactions with other users. The environment also has a story writing capacity. The name Zora was inspired by one of the cities that Italo Calvino describes in his book *Invisible Cities, "This city is like a honeycomb in whose cells each of us can place the things we want to remember...So the world's most wise people are those who know Zora."* [9].

Users are graphically represented by avatars with the owners' image. Children can visit each other's homes and can communicate in real-time through their avatars via text or gestures. Avatars can gather in the "City Hall" to decide the laws of the virtual city as well as to discuss cases related to community self-government and current controversial news. Users cannot only navigate around the 3D virtual city, but also construct the city's private and public spaces: personal homes, community centers and temples. Temples are shared public spaces that represent cultural traditions or interests. Both personal homes and temples are spatial representations of identity composed by artifacts symbolizing intangible aspects of the self.

Zora is an object-oriented environment, meaning that users can make new objects by cloning existing ones and inheriting its attributes. Objects have the following attributes: 1) presentation attributes, *graphical appearance*

and *motion*; 2) administration attributes, *ownership*, which determines who owns the object and therefore can edit it, and *permissions*, which set if the object can be cloned; and 3) narrative-based attributes, *textual description, stories, values* and *conversations*. Zora is implemented using the Microsoft's Virtual Worlds platform, a development kit for building distributed multi-user environments [10].

5. A Virtual City in the Hemodialysis Unit

During a five months pilot study in the hospital's hemodialysis unit patients had access to a networked computer at their bedside and used it to create their own virtual city (see figure 1). The unit staff was also involved in participating in the study. Informed consent was obtained from all participants.

Figure 1: the Zora computer and the dialysis machine

During this study, participants designed a total of 16 virtual places (see figure 2). Interestingly the hospital staff created 3 spaces including the *Nurse's Room* and the *Temple of Feeling Better* (described by the staff as a place to tell each other ways to cope with hard things). The MIT Medial Laboratory staff created 3 spaces including *the Restaurant*. Patients designed personal homes as well as several common spaces including the *Music Room* and the *Renal Rap* (described by the patients as a virtual space for dialysis patients to get together do fun things).

Figure 2: The Temple of Feeling Better

Participants made a total of 94 objects ranging from pictures of the hospital staff to favorite cartoon characters to video games. Overall, the patients created 14 characters generally cartoon characters that they called "heroes." The values dictionary of the city had 13 values with their definitions, e.g., *"friendship", "doing something positive to help myself or someone else" and "respect" with the definition "people should be aware of what they do to other people's things."*

During the study, the patients created 5 "cases" which are special types of objects representing events or circumstances to be discussed and agreed upon. They require community members to take action to resolve them. For example one case dealt

with setting up the social organization of the virtual city, e.g., "...*someone changed the appearance of my door and I don't understand why*...I would like to suggest as a rule that there is no tampering with other people's stuff..." Participants posted in the bulletin boards 17 messages e.g., "I really liked what you guys have done with the renal rap room". They engaged in interactions with each other more on an asynchronous way than on a real-time way. This is not surprising since not all the participants were in the same dialysis shift and not all of them felt healthy to use Zora at the same time.

6. Feasibility and safety

In order to assess the feasibility and safety of using Zora in a hospital, in the midst of the hemodialysis treatment, participants (both patients and staff) were asked to rate the application using a 7-point Likert scale anchored at one end by "1=not at all" and at the other end by "7=a great deal". Descriptive statistics were calculated for each of these rating scales. Participants were also asked several open-ended questions.*Feasibility*

The patients (n=7) reported that they were very satisfied with Zora (mean = 5.3; standard deviation =1.3) and that they enjoyed very much participating in the experience (mean = 5.7; standard deviation =1.6) (see figure 3). *"It was really nice to have something fun to do at the hospital that could keep my mind off dialysis and that it was not schoolwork, but entertaining"*, said a 15-year-old patient.

Figure 3: Satisfaction of Using Zora

When designing this pilot study there were some doubts about how patients, who are usually tired or sleep during most part of their treatment, would engage with Zora and if they would even use itat all. Zora was found not only feasible to use with patients undergoing hemodialysis treatment,but that was also an enjoyable and positive experience

Hospital staff rated the experience very high (mean = 6.5; standard deviation =0.58) (see figure 3). For example, one staff member noted that being involved with the project helped her learn about the infinite potential of computer applications designed with a structure that might support different forms of therapy. Nurses did not find that Zora interfering with the patient's medical care. On the contrary, they enjoyed seeing their patients using Zora. One of the nurses said: *"I liked it a lot because I noticed that kids could say things in the computer that they might not say face to face and this has a lot of potential. It is a wonderful program for kids who are restricted and limited to the outside world."*

Nurses also enjoyed being involved with different logistical tasks, such as helping kids move the computers around and connect to the Internet. At a personal level, the hospital staff enjoyed the fact that Zora helped them learn new computer skills. They regretted that they could not devote more time to participate in the experience and the lack of a dedicated computer

Safety
Overall, the seven patients reported that Zora was safe (mean = 5.93; standard deviation =1.84) and that participating in the experience was not hurtful (mean = 1.43; standard deviation =1.13). When asked about the safety of using Zora, a 17-year-old replied *"It might be unsafe if you put certain things in your room that younger kids shouldn't see. But that's the whole point with having the [virtual] city hall, where we set the rules and laws for Zora. I don't think it's not safe for kids."* Safety was a significant concern given the multi-user and open-ended nature of Zora and the fact that it runs on the Internet where children could easily find inappropriate content. This patient's response shows the importance of having in Zora as a space for community participation and democratic decision-making. In his perspective it was the patients' responsibility to make Zora a safe space, and not just a matter of obeying a code of behavior imposed by outsiders.

Hospital staff reported that using Zora was safe (mean = 5.63; standard deviation =1.49) and they all agreed that participating in the experience was not hurtful at all (mean = 1; standard deviation =0). One of the nurses said: *"Zora was a safe place and a safe way for patients to get their feelings out. It was an appropriate way to discuss their feelings. Rather than going out an punching a wall they had an opportunity to discuss things and to learn and to ask anything in Zora."* Another staff member agreed but pointed out the importance of supervising what children were doing and saying, in case that intervention from an adult was needed. In the five months that the program was running, there was no need of intervention. However, the community of users was small and they all belonged to the same institution."

7. Exploration of personal identity
identityWhen the study was designed it was hypothesized that patients would use **Zora** to explore their illness as a key component of their identity. We imagined kids would build virtual rooms populated by kidneys, dialysis machines and nurses. However, this did not happen. On the contrary, all of the patients consciously avoided any mentioning of hemodialysis in their virtual rooms. As a 15-year-old said: *"I am already on dialysis and I don't want to put things in my [virtual] room that remind me of dialysis; I don't want to go to other rooms that have that kind of stuff either."* It is not surprising that, when asking kids if participating in Zora helped them gain perspective about their illness, most of them replied that it did not (mean 2.43; standard deviation =2.30).

Children used Zora as a way to escape from the harshness of dialysis, not to think about it. Patients escaped

in two different ways. First, they used their avatars to "move around" the Zora virtual city, while being "tied down" to bed and hooked up to the hemodialysis machine. Patients decided where to go and visit in the virtual city and were able to make decisions regarding how long to stay in the different places. This sense of autonomy and control was one way of escaping the frustrations of dialysis where there is no possibility to move around in a free way, neither to make many choices.

Second, patients escaped the harshness of dialysis by using their rooms to represent aspects of their identity that are usually underplayed during treatment. In general while undergoing hemodialysis, patients spend their time sleeping or watching TV. Their identity is represented by "passive" activities. However, when outside the hospital, like most people of their age, they participate in active endeavors, such as working, going to school or going out with friends. Their image of themselves is not the same inside and outside dialysis. Zora provided a way to bring back the self-image of patients as active agents. It offered a different venue of how to use their extensive time in dialysis in a creative and fun way by engaging in the creation of a personally meaningful project. When asked what she learned during the experience, a 14-year-old said: *"I learned new things about computers, like how to work with pictures and design my room, but I guess that I also learned about myself because I realized the things that I really care about and what my interests are and how to talk to others about that. In my room in Zora I could put both computers and other things I like."*

Since undergoing dialysis was a common factor for all of the participants none of them felt the need to make it explicit in their rooms. Instead they chose to represent other aspects of their identity. For example, Sharon created an Elvis Presley room with animations of the singer performing in the walls while Rina created a horse haven, with stories and pictures of her horse at home. In future studies it might be worth looking at what happens if patients create a Zora city together with kids that do not share their medical condition and treatment. Will they want to highlight the fact that dialysis is part of their identity? Or will they prefer to ignore it? Another question is what would happen if kids were using Zora at home instead of at the hospital. By being removed from the machines, would they use the opportunity to reflect about their experiences?

8. Facilitating mutual patient support and interaction

In order to facilitate mutual patient support and interaction, Zora provided both synchronous and asynchronous ways of communicating and sharing experiences. The patients talked with each other in real-time through their avatars and they also posted messages and wrote stories for their objects and characters.

Patients reported that using Zora helped them make friends or get support from other kids on dialysis in a moderate way (mean = 3.86; standard deviation =2.41). At the same time, they

reported that it greatly helped them to feel more part of a group on dialysis (mean = 4.43; standard deviation =1.62). *"I think that I always was part of the dialysis group but using Zora helped me to get to know the people better because I could talk with them and see their interests, what they like and do not like by going to their virtual homes"*, said a 13 years old patient. Hospital staff perceived that using Zora helped patients a lot to make friends (mean = 4.50; standard deviation =1) and a little less in making them feel part of a group (mean = 3.75; standard deviation =0.5) (see figure 4).

Synchronous Communication: A Private Way to Talk in a Public Space

The hemodialysis unit is a public noisy space where patients are physically together for long periods of time. However, since their beds are far apart from each other, they cannot communicate with each other in a private way. Although the dialysis patients have all the characteristics to form a community, they lack the means to converse while undergoing treatment. Most of the patients particularly liked the fact that Zora provided a good way to communicate with each other in a private way, while undergoing the public event of dialysis. *"I really liked that I could use Zora to talk to other kids who were at a distance. Otherwise I would have to yell across the room. But using Zora was great because others could not eavesdrop on my conversation and I felt more comfortable discussing things. I particularly liked to talk with others about our favorite nurses, without being heard"*, said a 13-year-old patient. On-line conversations were not about dialysis per se, but about favorite video games, movies and activities done during the weekend. Most of the conversations were task-oriented such as helping each other to resolve technical problems and use some of the Zora features.

Asynchronous Communication: A Space to Voice Opinions

Patients used Zora to post messages in each other message boards and to write stories for their objects and characters. This asynchronous way of communicating their feelings was, as one of the nurses noted, *"a way to help patients that weren't on the same shift together to get an understanding of the other patients when visiting their rooms"*.

Asynchronous communication facilitated the creation of a social network by providing a space for patients to voice their opinions, without the burdens of face-to-face and real-time conversation. For example, 17-year-old Larry dropped a case in the "Temple of Feeling Better" in which he complained about the increase of his time on the dialysis machine: "*"I believe that my time on dialysis is too long. Most of the patients are on for only three and half-hours. Maybe you can pull some string and get it cut back. Thank you. Please reply in Caza's room. Leave a message on the bulletin board"*. He attached the value "pity" to the case but did not define it. At first Larry made his case very small and hid it behind other objects in the virtual temple. Only a very skilled Zora user could find it. Meanwhile, one of

the hospital staff noted that Larry was upset and could not talk about what was bothering him. When we pointed out to her the case that he created in the virtual temple, she used it as a jumping board to engage in a conversation with Larry. Shortly after, Larry made his case big and put it in the center of the temple, thus recognizing the legitimacy of his feelings. Later, Larry engaged with Dr. Joe (a physician) in an exchange by leaving messages in each other's rooms and expressed that he was very happy to be able to voice his opinions and be heard.

9. Zora Design Recommendations

A crucial study outcome was to identify not only the positive aspects of Zora, but also problems. This is important to the design of future interventions tailored to the particular needs of this complex real-world setting.

- **Need of a broader community.** In each dialysis session only three patients wereable to connect to Zora at the same time. This was due, on the one hand, to the lack ofcomputers, and in the other hand, to the lack of motivated participants in the required agerange and the difficulties of having a broad patient population feeling up to work at thesame time. Therefore the Zora community logged in on real-time was very small. *"It iskind of lonely in there [Zora] because when you get on there are not many people withyou and it is hard to talk with others",* said a 15-years-old girl. Other patients pointed outthat they felt embarrassed to talk with kids they see everyday about their feelings towardsdialysis. They rather talked anonymously. In the future it might be important to increasethe number of Zora participants such as involving other dialysis units. Another possibilitywould be to extend the experience to a large community by including renal transplantand/or at home dialysis patients.
- **Need of more intervention** Another goal was to observe how patients would useZora on their own and how they would create a participatory community. However, thispatient population requires a lot of direct intervention and guidelines in order to beengaged and motivated in any activity for long periods of time. As the child life specialistnoted *"after a point in time the kids get bored with anything, they want bigger and betterto keep them entertained, and a lot of them just want to sleep... they don't want to doanything because they are not feeling good."* In future experiences it would be helpful todesignate a project coordinator that would propose a tailored syllabus. The creation of asyllabus is a big challenge because, due to their medical treatment, not all the patients canengage in the same type of activities at the same time.
- **The question about dialysis conten**t. All of the patients agreed that they did notwant to encounter in the Zora virtual city any content related to dialysis. They wanted Zorato be a space to escape from dialysis. However, all hospital staff had exactly the opposite o pinion. They thought that Zora would be

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an excellent medium to teach kids about dialysis and to engage them in thinking about the process. For example, one of the social workers suggested the creation of a restaurant because food is a big issue for kids undergoing dialysis. The MIT Media Laboratory staff set up the virtual space and asked patients to create the menus. For our surprise, none of the created menus took in consideration the particular dietary restrictions of this patient population. Following is an excerpt of a conversation that happened in the virtual restaurant

Vitor says 'Washu, do you have any idea about what should we have in the menu?'
Washu says 'shrugs' ll
Vitor says 'What drinks do you think we should have in the menu?'
Washu says 'coffee, tea, ice water, etc....'
Vitor 'Which ones do you like best? '
Washu says 'I like tea with cream and sugar'
Vitor says 'I've never tried that, what about desserts'
Washu says 'ice cream and there is a Chinese dessert that all the nurses love'
Vitor says 'What kind of food do you like?'
Washu says 'I like Chinese food and Italian foods...noodles and fried rice spaghetti and meat balls''
Marina says 'I wonder if there should be a special menu for people on dialysis... what do you think?'
Washu says 'I guess that is helpful to people but I don't like to be reminded that I need different food'

The question is how to create spaces that engage children in learning and talking about dialysis. These spaces should go beyond displaying information produced by professionals. Patients need to take an active role in their creation. For example, they could be the ones who, working together with the professionals, design the virtual rooms to teach visitors about dialysis. For this to succeed it is important that the activity be authentic, namely real visitors should be invited to walk around these rooms and engage in conversations with the patients. For example, visitors can be kids recently diagnosed with end stage renal disease, medical staff, parents of patients, elementary and high school students interested in medicine.

- **Visualizing data.** Patients reported that using Zora did not help them gainperspective or understanding about their illness (mean = 1.86; standard deviation =1.21).At the psychological level, children did not use Zora to talk about dialysis, but as anescape from it. At the physiological level, Zora did not support patients to explore whathappens in their bodies while undergoing dialysis. However, Zora can support both typesof interventions in future experiences. On the one hand, a mental health professional cancoordinate virtual meetings in the same style than therapeutic communities. On the otherhand, the Zora environment can support the collection and display of physiological

dataprovided by the dialysis machines and other medical charts. This data indicates progress inthe treatment as well as the level of compliance between visits. If patients were encouragedto pay with this data in a friendly, creative and educational way they could explore "whatif" possibilities regarding their own health care. And it would allow researchers toinvestigate correlations between engagement with Zora and successful medicalcompliance.

10. Discussion

More and more hospitals are acquiring the means to connect to the Internet. However, connectivity by itself is not enough. We should ask ourselves how can we use the Internet to support therapeutic work already going on in medical facilities. Identity construction environments, such as SAGE and Zora, open up new possibilities for health care. As shown in this chapter, the use of well designed computer technologies to implement well grounded psychotherapeutic interventions is feasible, safe, and useful to patients and staff. Introducing a fun, self-exploratory and community-building computer activity can provide patients with the opportunity to be creative. It help them express themselves and explore aspects of their identity in ways that are generally underplayed and even avoided in the medical setting.
A computer based application that promotes increased coping and resiliency in the face of pediatric illness can make accessible psychotherapeutic interventions that otherwise is only available to those living geographically close to a major pediatric medical center. Identity construction environments such as SAGE and Zora can provide an important opportunity for patients and staff to participate in the process of gaining self-understanding and shared understanding, which are cornerstones to coping and resiliency [11].

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Chapter 57: Therapeutic Robotics for Children with Disabilities: A Case Study

James Drane; Charlotte Safos; and Corinna E. Lathan, PhD
AnthroTronix, Inc., Silver Spring, MD, US

Abstract

The advancement of technology is having a profound effect on enhancing the lives of children with disabilities. As advances in biomedical technology allow research breakthroughs to continue at a steady pace, more and more is being discovered about the nature of different disorders in children. At the same time, partly due to the continuing rapid rate of advancement (and societal acceptance) of robotics technology, researchers, educators, and therapists are exploring the idea that robots might be used as an effective therapeutic and educational tool.

Over the past nine years, AnthroTronix has collaborated extensively with therapists, educators, researchers, parents, and children to uncover the therapeutic and educational benefits of including robotics as part of rehabilitation curriculum for children. As a central part of this effort, the company has worked with its colleagues to develop and refine the CosmoBot system, an interactive robotic toolkit designed to enhance therapy, education, and play for children with disabilities.

1. Introduction

AnthroTronix, Inc., a human factors engineering company founded in 1999, specializes in the development of interfaces that enhance human interaction with the technology around them. The company has developed interface technology to address issues in the health (education and rehabilitation), space, and defense industries. AnthroTronix' projects have been funded by a range of institutions, including the National Institutes of Health (NIH), National Science Foundation (NSF), Department of Education (DoEd), NASA, and the US Army.

Since its founding, AnthroTronix has worked with therapists, educators, parents, researchers, and children to develop a suite of alternative technologies to help children with disabilities. These technologies include CosmoBot, an interactive therapy robot, and Mission Control, a simple 4-button alternative computer interface device. Combined with educational software and wearable robotic interaction sensors, this suite, known as Cosmo's Learning Systems, has been used by numerous children with disabilities in research studies and classroom and home settings.

2. Challenges

Throughout our years of working with therapists and educators, we have encountered some who have been reluctant to accepting robotics as a useful tool for facilitating therapy or educational activities. However, as the general public becomes more and more comfortable with technology, robotics is being embraced as an extremely effective medium for communicating with children in ways that human therapists and educators cannot.

3. Background

3.1 Autism Spectrum Disorder

Autism spectrum disorder (ASD) is characterized by impairments in from one to three aspects of behavior: reciprocal social interaction, communication, and restrictive repetitive behavior. Reciprocal social interaction is the core impairment in all variants and degrees of ASD [7], and may, of itself, be responsible for undermining the child's cognitive, social, and communicative development [2, 3, 4]. The social deficits typically persist throughout the individual's life. Basic sources of satisfaction, such as human relationships, fulfilling work, and independence are beyond the majority of individuals with ASD, including many who are otherwise characterized as "high-functioning" with good verbal skills.

Once considered a rare disorder, ASD is now recognized as a condition that occurs with alarming frequency. A study published in 2003 by the Centers for Disease Control and Prevention [5] reported a prevalence of 3.4/1,000 among children aged 3 to 10. It has been estimated that over 40% of persons diagnosed with an ASD do not have mental retardation [6]; effectively meaning that almost half of the population can be considered "high-functioning."

The value of autism-specific, early educational intervention has long been considered incontrovertible [7, 8], particularly when delivered according to a structured, data-based procedure [9]. A number of tightly controlled studies of specific intervention components, with small numbers of subjects, have contributed to a growing body of knowledge about useful approaches and their potential benefits and limitations [10, 11, 12, 13, 14, 15, 16, 17]. At the same time, there is a need for more knowledge about how to relate specific child characteristics to components of a training package.

3.2 Cerebral Palsy, Brain Injury, and Stroke

Of children with physical disabilities, many require ongoing PT/OT to optimize their movement capabilities in order for them to participate in family, school, and recreational activities. The most common neurological disorders of the brain that impact the physical ability of children are cerebral palsy, brain injury, and stroke.

According to CerebralPalsyFacts.com, "About two children out of every thousand born in this country have some type of cerebral palsy. Studies have shown that at least 5,000 infants and toddlers and 1,200 - 1,500 preschoolers are diagnosed with cerebral palsy each year. In all, approximately 500,000 people in this country have some degree of cerebral palsy" [18]. The incidence of brain injury among school-aged children has been estimated by the Center for Disease Control (CDC) as 90 per 100,000, resulting in the addition of 60,000 children with new brain injuries annually [19]. The incidence of stroke in neonatal children (<1 month of age) has been estimated by the CDC as 1 per 4,000 and for children from 2 months to 18 years as 14.5 per 100,000 [20].

Children with cerebral palsy, brain injury, and stroke have similar physical impairments to movement,

although the sources or causes of the impairments differ. A common impairment that requires PT and/or OT intervention is that of decreased amplitude and strength of voluntary movement in the upper extremities due to neurological involvement in the brain. These physical impairments can impact the child's educational development by interfering with his/her ability to move about and explore their environment, contribute to decreased social interaction and communication, and inhibit access to and interaction with computer or traditional learning tools (e.g., manipulatives such as building blocks, books, writing tools, etc.).

4. Why Use a Robot?

There are significant advantages to using a robot such as CosmoBot instead of software for children's therapy. These advantages are elaborated below. Such data supports the use of physical robots as adjuncts in therapeutic activities.

1) *The ability of a robot to engage the child:* Children have been shown to exhibit a high degree of interest in an interactive robot [21, 22]. Researchers such as Dr. Cynthia Breazeal at the MIT Media Lab have demonstrated the differences between a robot and an animated character in terms of a person's engagement and perceptions of the robot and character. They found that a physical robot was more engaging and rated more highly on the scales of perceptions than an animated character [23, 24]. There are also researchers who are looking at the advantages of a "socially assistive robot" such as CosmoBot that interacts with the environment, exhibits social behavior, and focuses its attention and communication on the user in order to help the user achieve specific goals [25, 26]. Feedback from therapists during the initial phase of our NIH-funded Gestural Interfaces research study indicated that CosmoBot was effective in enabling children to reach not only their traditional PT/OT goals of strength and coordination for example, but also improved the children's attention to their tasks and allowed them to engage in pretend play - important for cognitive develop [27, 28].

2) *The flexibility and expandability of a robot:* Children's software for "play" is generally limited in content and can only engage a child's attention for a limited time. For example, in a software maze, a child may be able to go from point A to point B a few times before they become familiar with the maze and lose interest. Software has limited options to make that maze more engaging to the child. With a robot in the real world, navigating from point A to point B can be expandable to have different concrete goals (e.g., tagging each person in the room, collecting ingredients for a sandwich, stacking blocks). CosmoBot, for example, allows exploration and is unlimited in the ability to use it for creative play therapy. Al Cook's work with Lego Mindstorms robots for unstructured play [29] is a great example of the advantage of a robot over software. Where Mindstorms falls short is in the

ability of the Lego robot (or a remote control toy car) to engage the child in the way that a socially assistive robot can.

3) *Robot as an expandable platform:* Finally, one can envision a robot system such as the CosmoBot system as a platform, analogous to a desktop computer, where new content can be developed to address specific therapy goals and to continually provide motivation for the children to interact with the robot. For example, under our NIH Autism Phase I SBIR grant, we developed Social Activity Modules for children with Autism that make use of the robot's capability to attract and sustain children's attention and interest to foster key reciprocal social behaviors including attending to others, imitation, joint attention, and cooperative play. Our hypothesis is that the Social Activity Modules constituted a novel, engaging, effective mode of delivering social skills training to children with Autism Spectrum Disorder.

5. The CosmoBot System

5.1 User-Centered Design of CosmoBot System

AnthroTronix has incorporated extensive input from a variety of therapists, researchers, educators, parents, and children during the design processes for the current CosmoBot and its two predecessors: JesterBot and CosmoBot version 1 (pictured below in Figure 1). After considering this input, we defined functional requirements that the CosmoBot system should meet in order to be effective. These functional requirements and rationale can be summarized as follows:

- *Target young children* – Need for early intervention
- *Degrees of freedom (DOF)* – Although we do not know the minimal number of DOF needed for a clinically appropriate robot, based on our previous work [30], we hypothesize that CosmoBot's 9 DOF will be sufficient.
- *Anthropomorphic* – Appealing to young children and can somewhat mimic the child
- *Interface* – Accessible to children with disabilities (e.g., alternative to fine motor control operation)
- *Expandable/Programmable* – Needed for longevity and appeal to children of various ages
- *Embedded assessment/Data collection capabilities* – Needed for therapeutic and educational value
- *Therapy value* – Can target a variety of PT/OT goals, and ultimately make the therapist's job easier
- *Educational value* – Activities target cognitive development

Figure 1. a) JesterBot; CosmoBot: b) version 1, c) version 2, d) version 3

The initial robot, JesterBot, whose name reflects a pun of "gestures" and "robot," was a simplistic robot with limited degrees of freedom (DOF). Its arms were able to move up and down and the robot could navigate a room using two wheels.

The first version of CosmoBot became a bit more complex, including a handheld computer (iPaq) in its chest for onboard processing. CosmoBot version 1 could also perform twice the arm movements as JesterBot in addition to moving its head.

Figure 2. Child controlling JesterBot using wearable wrist sensors

After considerable aesthetic and functional redesign, the current CosmoBot was born. The "softer," friendlier feel of this version seemed to be well received by the children. Functionally, the onboard computer was removed and replaced by a Bluetooth link and an electronics board. Range of motion was also increased in CosmoBot's head.

5.2 System Components

The CosmoBot system as a whole primarily consists of the CosmoBot robot and Cosmo's Learning Systems (i.e., Mission Control and Cosmo's Play and Learn Software), which are pictured below. Cosmo's Learning Systems was launched as a commercial product in 2006 by AT KidSystems (an AnthroTronix subsidiary) targeting children developmentally aged 2-8.

Figure 3. The CosmoBot system: a) CosmoBot; b) Mission Control; c) Cosmo's Play and Learn software

AnthroTronix has created gestural interface sensors (both wearable and stationary) that children can use to interact with CosmoBot. The array of sensors is shown in Figure 4 below (from left to right): an adapted standard 4-way joystick, wearable leg sensor, wearable arm sensor, wearable head sensor, wrist extension glove, and pronation-supination sensor with arm restraint brace. The head, arm, and leg sensors, for example, employ accelerometer technology to sense a child's gestures. Threshold levels for all of the sensors can be easily modified in a software program.

Figure 4. CosmoBot gestural interfaces

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6. Pilot Studies with the CosmoBot System

CosmoBot has been involved in six formal research studies, with children with cerebral palsy, autism spectrum disorder (ASD), Down's syndrome, and speech-language delays. The NIH, NSF, and DoEd have funded these studies. The most recent study, funded by the NIH and conducted in 2006 and 2007, explored the efficacy and feasibility of using CosmoBot to improve the social skills of children with ASD.

6.1 NIH Autism Study – Social CosmoBot

6.1.1 Study Description

This "Social CosmoBot" research study was a Phase 1 Small Business Innovation Research (SBIR) study exploring the feasibility of using CosmoBot to address different social skill discrepancies in children on the ASD spectrum. In this first phase, AnthroTronix proposed to develop and test a system integrating a suite of prototype Social Activity Modules and a modified CosmoBot system. The Modules are engaging instructional activities directed at fostering key reciprocal social behaviors that are impaired in children with ASD.

The purpose of integrating the Modules with the robot is to capitalize on CosmoBot's demonstrated capability to attract and sustain children's attention and interest in social activities in which they might not otherwise choose to participate. Modifications to CosmoBot were proposed in order to improve its utility as a tool for instruction and practice in reciprocal social skills; modifications included installation of a camera in CosmoBot's nose, so that manipulating the robot's direction of "gaze" to take in social cues could become part of the explicit activity. Software development was limited to the minimum necessary for running the study, with further development deferred to Phase 2, pending evaluation of the system. We evaluated the modified robot and prototype activities (Modules) with young children diagnosed with an ASD, in order to assess usability and appeal.

The Social CosmoBot study took place at the Neurodevelopmental Center for Young Children (NDCYC) in Crofton, MD, under the supervision of the center's director, Dr. Carole Samango-Sprouse (Ed.D). Table 1 below briefly describes three of the Modules that were tested in the study. Dr. Cheryl Trepagnier, an ASD expert at the Catholic University of America, designed the Modules.

Table 1. Social Activity Modules description (1 example of 6)

Module 2	*Look at that!*
Goals addressed	Joint attention
Activity	Robot attempts to elicit child's attention to target to which he is pointing
Target Response	Child follows robot's point within 1 sec.
Equipment	Two closed boxes that can open under remote control, each with a remotely controlled toy inside. Therapist launches box opening and toy operation when sees that child is looking where the robot indicates.
Procedure	Therapist waits for child to be looking at robot and inputs key stroke to initiate robot's speech and point.

Figure 5. Module 2 – Look at That! focusing on joint attention

Dr. Samango-Sprouse recruited seven children from among clients with an ASD diagnosis. Each child was seen for 8 sessions at the NDCYC. Characteristics of the child participants are listed below in Table 2. Children's scores are reported on the Leiter Brief IQ, an estimate of nonverbal IQ. Since children with ASD are language-impaired, with impairments ranging from minimal to severe, nonverbal IQ is preferable to full-scale IQ tests.

Table 2. Characteristics of children who participated in the feasibility study

Subject Code	Gender	Chron. Age (months) as of 5/1/07	Leiter Brief IQ
SC01*	M	77	123
SC02	M	82	131
SC03	M	59	85
SC04	M	46	NA**
SC05	M	72	83
SC06***	M	73	82
SC07***	F	73	38

*SC01 was very distressed when he arrived for his first session and was withdrawn by his mother. **Leiter not available; WIPPSI-III performance IQ is 79 ***SC06 and SC07 are fraternal twins.

6.1.2 Research Tools Used

- Parent Questionnaires
  - 2 total; 1 pre-study, 1 post-study
- 5-Minute Play Observation
  - Performed by Dr. Trepagnier
- Videotaping
- Observation Sheets
  - Completed by Dr. Trepagnier and AnthroTronix staff
- Software Log Files
  - CosmoBot control software recorded when, with which child, and during which module each CosmoBot action (verbal or movement) occurred.

6.1.3 Outcomes

Tables 3 and 4 below summarize each participant's response to intervention. The baseline assessment and intervention approach is reported for each subject and the post data example highlights a specific outcome observed.

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Table 3. Highlights of participants' responses to intervention

Subj.	Baseline Assessment	Intervention Approach	Post Data
SC02	ASD. Highly cooperative	Partnered with SC03 Therapist needed to find ways to make the Modules adequately challenging for him	As sessions progressed, improved in cooperating with partner to accomplish Modules
SC03	ASD, with mild cognitive delay	Partnered with SC02 Required moderate support for participation	Improved attention to other's behavior (SC02) and positive affect sharing
SC04	ASD with language delay.	Required moderate support for participation participation declined as sessions progressed	Showed gains in attending to faces
SC05	ASD with rigidity and atypical sensory behaviors	Partnered with his mother for all 8 sessions Level of support needed for	Improved in interpreting nonverbal communication, and showed improved flexibility
SC06	ASD with echolalia. Notable for inattentiveness to instructions despite high level of functioning	Partnered with SC07 (fraternal twin) Required little support to participate in Modules	By last session, successfully produced and interpreted communication via facial expression
SC07	ASD with severe communicative impairment and unusual sensory behaviors (mouthing objects)	Partnered with SC06 (fraternal twin) Required high level of support to participate in Modules.	Mother reported that child complied with a verbal request (for imitation) for the first time. Showed improvement in performance of Modules over the 8 sessions. Also gained skill in operating joystick.

Table 4. Summary of qualitative observational data (small "x" indicates some improvement, large "X" indicates marked improvement)

Subject	SC02	SC03	SC04	SC05	SC06	SC07
FUNCTIONAL GOALS:						
1.Gain experience in attending to other's face	x	x	x	x	x	x
2.Improve joint attention	N/A	N/A	**X**	N/A	x	x
3.Increase interest in other's activities	N/A	**X**	x	**X**	x	x
4.Demonstrate positive affect sharing	**X**	**X**	x	**X**	**X**	x
5.Gain experience in taking other's perspective	**X**	**X**	x	x	**X**	x
6.Gain experience in communicating via gesture andfacial expression	x	x	x	**X**	**X**	x
7.Improve cooperation and attention to verbalinstructions	**X**	**X**	**X**	**X**	x	**X**
Parent Questionnaire Social Skills Ratings (Pre-)	35	44	29.5	42	54	0
Parent Questionnaire Social Skills ratings (Post-)	28	48	43	44	60	7
Percent Change	-7%	4%	13.5%	4%	6%	7%

Module 6, "Did we get a lot of points," pictured below in Figure 6, focused on practicing nonverbal communication. This Module consisted of a card game in which one child (in front of CosmoBot's nose camera) was shown either a high or low card. The therapist coached this child as to whether the card was "good" or "bad." The child was then asked to convey to a second child (watching CosmoBot's nose camera video feed)

Figure 6. Module 6 – *Did we get a lot of points?* a) nonverbal facial card interpretation; b) nonverbal thumbs-up card interpretation (on video display)

6.1.4 Next Steps

AnthroTronix intends to apply to continue this research study in order to expand on the Phase 1 research. The end goal of this research is to commercialize a suite of ASD-specific activity modules that help children and their therapists to more effectively achieve their therapy goals.

6.2 NIH Gestural Interfaces Study

AnthroTronix engineers have developed innovative new ways for children with impairments (due to cerebral palsy, brain injury, or stroke) to interact, via body gestures, with technology in their environment (e.g., robots, software games). The end goal of this work is to enhance the PT/OT for these children through allowing them to directly manipulate their environment. Development goals are twofold: 1) to create effective and intuitive gestural interfaces for children w/ impairments and 2) to integrate CosmoBot with another therapeutic robotic device, Roamer-Too, to create a new robotic tool that leverages the interaction capabilities of both components. The gestural interfaces are being designed to work with and expand the capabilities of the CosmoBot system. In addition to developing these physical gestural interface devices, effort is being applied to developing specific content for the CosmoBot system to maximize its utility for PT/OT, specifically focusing on upper extremity movement (UEM) in these young children. These efforts are being conducted as part of an NIH-funded Phase 2 SBIR project entitled "Use of Gestural Interface and Robotics Technology to Facilitate Motor Development and Functional Mobility."

6.2.1 Gestural Interfaces

Figure 7. Child interacting with CosmoBot via wearable sensor at Mt. Washington Pediatric Hospital

In Phase 1 of this project, we performed a technical feasibility study using gestural interface technology and interactive robotics (the CosmoBot system) to facilitate motor development and functional mobility of children with a wide range of physical disabilities. Clinical testing of the CosmoBot system was conducted with six children at the Mount Washington Pediatric Hospital in Cheverly, MD. Outcomes are summarized in Table 5 below.

Table 5. Phase 1 Gestural interfaces study outcomes

Efficacy	Increased improved UE strength in 4 children	Improved coordination in 3 children	Increased attention to task in 4 children	Improvement in activities of daily living in 3 children
Motivation for Children	Each child engaged in pretend play with CosmoBot (CB) in every session over 4 months	Each child asked for technology during each	No child claimed boredom or did not want to use CB in therapy	Other therapists in clinic used CB as reward for many children during SLP & OT
Therapist's Ease of Use	Technology robust & easy to use	Technology needed repair once over 4-month period	CB gives therapist ability to keep sessions new & fun during 4 months	Therapist saw high motivation when using CB for each child, leaving more time for therapy & less coaxing child

Table 6. Additional Phase 1 study outcomes

Name	Child A	Child B	Child C	Child D	Child E	Child F
Age	10	5	5	4	6	8
Developmental Age	6 1/2	4	4 1/2	4	6	2 1/2
Diagnosis all subjects diagnosed w/ CP; entry provides more details & other diagnoses	L hemi-plegia	s. quadri-plegia	s diplegia & R hemi-plegia	s. quadri-plegia	s. R hemi-plegia	s. diplegia & ADHD
Difficulty focusing attention on therapy tasks?	N	Y	Y	N	Y	Y
FUNCTIONAL GOALS:						
Improve ADLs: tying shoes, fasten belts & buttons	x				x	

Edited by: **Renata G. Bushko** - bushko@fhti.org
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Improve ball skills (throwing, catching)	x					
Increase ability to walk farther than 20 steps using walker		x				
Increase ability to independently dress & maintain hygiene			x			
Improve sitting independently				x		
Sit in chair & lift arm over head without falling over				x		
Control joystick on power wheelchair				x		
Improve functional use of upper extremity				x		x
STRENGTH/COORDINATION/RANGE OF MOTION (ROM) GOALS—to increase:						
supination ROM	x			x		
wrist ROM	x			x		x
bilateral coordination	x		x			
shoulder ROM		x	x	x		x
Upper extremity strength		x	x	x	x	x
Elbow ROM				x		x
SENSORS USED: (see Section 10 for details on sensors)						
Supination/ pronation brace	x		x			
Wrist extension glove	x		x	x	x	x
Wearable arm sensors		x				
Wearable leg sensors				x	x	
Joystick		x		x	x	x
Mission Control buttons	x	x	x	x	x	x

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The innovation research being undertaken in Phase 2 is to further develop and evaluate the use of gestural interface and interactive robotics to treat young children with motor control and functional mobility impairments due to cerebral palsy, brain injury, or stroke.

6.2.2 CosmoBot and Roamer-Too

Through a partnership with Valiant Technology, Ltd., whose team has developed an easy-to-program robotic platform called the Roamer-Too, AnthroTronix is working to create a new CosmoBot product that combines CosmoBot and Roamer-Too (see Figure 8), implementing the Roamer-Too platform as CosmoBot's base. Initial clinical testing of the prototype system began in the fall of 2008. This CosmoBot is also being used in our formal study with children with physical impairments at the Mayo Clinic in Rochester, MN.

Figure 8. CosmoBot version 3 (with integrated Roamer-Too base)

7 Conclusions

Clinical research studies using the CosmoBot system repeatedly demonstrate the effectiveness of both using a robot (in general) and leveraging the CosmoBot character with children with disabilities. Phase 1 of our NIH Autism study demonstrated that (1) children found the robot motivating and engaging, (2) children participated in the instructional activities, and (3) they demonstrated acquisition of the skills being taught. Results from the initial phase of our NIH Gestural Interfaces study (see Table 5 above) also suggest that CosmoBot is effective, both as (1) a therapeutic intervention tool for targeting goals of increased strength, coordination, and range of motion, with the ultimate goal of improving function, and (2) a motivation for children to participate in therapy. Further research is currently underway (NIH Gestural Interfaces, Phase 2) to systematically and objectively evaluate these metrics in a controlled manner, over a considerable amount of time.

However, further development will be needed to mold CosmoBot into a commercial version available to therapists everywhere. And while we look forward, the field of interactive robotics continues to grow and robotics technology continues to improve and become more available. Basic human-robot interaction is now easier and less expensive to achieve than ever before, with objective data collection included in the package! It is therefore ever so critical that the

disabilities community expand its leverage of the incredible therapeutic potential of robots like CosmoBot.

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Chapter 58: Future of Anti-addiction Vaccines

Thomas R. Kosten, M.D.
Professor of Psychiatry and Medicine, Yale University School of Medicine, New Heaven, CT, US

Abstract

The medical rational for using anti-drug antibodies in the serum as a treatment is to reduce drug levels in the brain and to bind drug before it enters the brain. Drugs of abuse are small molecules that can readily cross the blood brain barrier, while antibodies are larger molecules that cannot get into the brain. Thus, any drug that is bound to antibody also cannot cross the blood brain barrier and cannot enter the brain. Active anti-drug vaccines stimulate the body to makes its own antibodies, but the small size of abused drugs prevents them from stimulating an immune response. Thus, individuals do not ordinarily produce antibodies to abused drugs, and vaccines to stimulate antibodies are made by chemically linking these abused drugs to toxins such as cholera toxin. Alternatively, passive immunotherapy uses monoclonal antibodies that are generated in a laboratory and then administered via intravenous injection. Antibodies can be used to treat drug overdose; to reduce drug use relapse; or to protect certain at risk populations who have not yet become drug dependent. The advantages of anti-addiction vaccines are that antibodies target the drug, not the drug's sites of action in the brain and antibody binding inactivates the drug. These vaccines can complement behavioral and other medical therapies with minimal side effects and are not addictive like some chemical agonists. Technology advances in manufacturing and delivery systems will improve future anti-addiction vaccines, but social acceptance of anti-addiction vaccines will depend on substance abuse program staff and the families of substance abusers, who have some values that oppose medical solutions to addictive diseases and view addictions as moral problems.

1. Introduction

Nearly 200 years ago Jenner first used vaccination (active immunization) for the prevention and treatment of human disease, and over these 200 years only clean water may have provided a greater impact on worldwide public health. By stimulating an immune response to disease-related organisms vaccines have prevented illness or death in millions of individuals each year. Immunizations generate protective antibodies in the body fluids, which act as an early surveillance system to block or reduce the effects of an invading organism or substance, such as a toxin. Antibodies are continually produced and broken down (metabolized and inactivated) in the body. The most common type of antibody (IgG) has a half-life in blood of about 3 weeks [1]. That is, about half of the antibody produced on day 1 is eliminated by day 21. Blood levels of antibody after vaccination are maintained because new antibody is continually produced. After passive immunization with monoclonal antibodies, a steady decline in

antibody level with a half-life of about 3 weeks is expected, so that repeated antibody doses every few months would probably be needed to maintain antibody levels in blood. Recently, we have begun to conceptualize abused drug as toxins that might also be treated and perhaps even prevented from developing into the disease of addiction by using immunotherapy.

Several advances in immunotherapy allowed us to consider manufacturing anti-addiction vaccines [2]. An early use of immunotherapy involved polyclonal antibodies in the form of specific immune serum to treat infectious diseases. These antisera effectively treated pneumonia and tetanus, but a serious adverse side effect was serum sickness, an allergic reaction resulting from the administration of animal antisera to humans. Thus, these animal antisera could only be used as a last treatment option. Later, human donors were immunized and human immune globulin collected for treatment, and these are still used to treat hepatitis B, tetanus and Varicella zoster. We can now produce monoclonal antibodies, which can be produced by large scale manufacturing techniques, without the use of animals or animal proteins and without the risk of transmitting human infectious agents such as HIV and hepatitis viruses.

2. What are anti-addiction vaccines?

The medical rational for using anti-drug antibodies in the serum as a treatment is to reduce drug levels in the brain and to bind drug before it enters the brain. Many small molecules such as drugs of abuse (molecular weights of 200-300 Daltons) can readily cross the blood brain barrier while larger molecules such as antibodies (molecular weights of about 150,000 Daltons) cannot [3]. Thus any drug that is bound to antibody also cannot cross the blood brain barrier and cannot enter the brain. In animals, immunotherapy reduces drug distribution to brain within the first few minutes after a single drug dose by up to 80% [4, 5]. This is important because the rewarding effects of drugs are also greatest in the first few minutes after a dose. Thus, the drug binds to the antibody, and the rewarding or medically harmful effects of the drug are reduced or blocked. Because these therapies target only the drug, they are potentially safer than treatment with small molecule medications, which bind directly to important receptor systems in the brain and other organs.

Immunotherapies for drug abuse can be either active or passive. Active immunizations use drug vaccines to stimulate the body to makes its own antibodies and to create a long-term immunological memory for a more rapid future response to vaccine. An important consideration in this approach is that the small size of abused drugs prevents them from stimulating an immune response. Thus, individuals do not ordinarily produce antibodies to abused drugs, and even after effective vaccination continued drug use does not make more antibodies. This lack of immune stimulation by the abused drug alone contrasts with infectious disease vaccines where expose to the

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infectious agent will itself trigger a strong immunological response in a person who has been vaccinated and markedly increase the production of new antibodies. Like standard infectious disease vaccination, antibodies are not produced until several weeks after these active immunizations. Passive immunotherapy uses monoclonal antibodies that are generated in a laboratory and then administered via intravenous injection. In this case more antibody can be administered and the protection can be immediate, but it only lasts until the antibody is cleared and there is no immunological memory against the abused drug.

2.1 Active anti-addiction vaccination

In active immunotherapy, the drug of abuse (called a hapten) is chemically coupled to an antigenic protein carrier like cholera toxin, and this combination is then used as a vaccine. Vaccines are currently being tested in humans for cocaine and nicotine [6, 7]. Because stimulation of an immune response requires multiple interactions on the surface of an antibody forming B lymphocyte, a single, small drug molecule (like cocaine or nicotine) cannot produce cross-linking of cell surface antibodies on a B cell to activate it to produce more antibodies. For this reason, drug haptens must be irreversibly bound to their large protein carriers for use as vaccines. The molecular orientation and spacing of the drug haptens on the protein surface are critical factors that scientists must control for an optimal immune response. Thus, the antibody response will not increase if a vaccinated individual uses the abused drug, itself, and only the circulating antibody at the time of drug use will be protective. Because cross-linking of surface antibody on B cells is required to stimulate antibody production, the same drug hapten-protein vaccine must be used for making more antibody, called boosting the immune response, when the antibody levels fall to relatively low levels typically 4 to 6 months after the original vaccination series is completed. Periodic boosting with the vaccine is required to keep serum antibody levels high. The actual serum level of antibody is affected by the quality of the drug-protein vaccine, the dose of the vaccine, the frequency of vaccinations, the time interval between immunizations, and poorly understood genetic variations among individuals. Based on results from prior vaccine regimens it is anticipated that the immune response will not be adequate for at least 3-6 weeks after the start of vaccination, and booster immunizations will be required every 4-6 months to maintain a sufficient level of drug-specific antibodies. Improper timing of vaccinations could result in a poor response or a significant reduction in the amount of circulating antibody. Thus, the timing and duration of vaccinations will need to be carefully coordinated with patient needs and other medical interventions like counseling or behavioral modification programs

2.2 Passive monoclonal anti-addiction immunotherapy

Passive immunotherapy does not vaccinate an individual to stimulate his/her antibody response, but administers pre-formed anti-drug antibodies to the

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person. This antibody medication could be polyclonal serum from an individual who has been vaccinated against a drug of abuse. However, a monoclonal antibody could be made with high affinity for a specific abused drug and be either a chimeric monoclonal comprised of 34% mouse protein and 66% human protein, a humanized monoclonal comprised of >90% human protein, or a fully human antibody. Currently, advanced biotechnological techniques have produced FDA-approved monoclonal antibodies for ten therapeutic and one prophylactic indication. For example, Synagis® is a monoclonal antibody approved for the prevention of serious lower respiratory disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. This antibody is administered before and then monthly throughout the RSV season to maintain protective circulating antibody levels. Thus, passive immunotherapy with monoclonal is being successfully applied in a variety of medical areas and is beginning to be applied in chemical addictions.

Another technological development for monoclonal therapy has been new ways to make specific immunotherapies in relatively short periods of 12 to 18 months rather than the typical 15 years required for bringing a new medication to market [8-13]. These immunotherapies can be genetically engineered as new abused drugs are detected by emergency room admissions of overdoses, by police seizures from illicit drug dealers or by other early indicators of a new "designer drug" of abuse. Applying this technology to the immunotherapy of addictions would allow us to match the rapid proliferation of newly abused substances with an early-response system that can quickly treat new addictive disorders and potentially stop their epidemic spread. A similar rapid technology probably can be developed for developing the much less expensive active vaccines, since the initial development of both cocaine and nicotine vaccines has suggested that several carrier proteins derived from various bacterial toxins can be effectively coupled to drugs of abuse [7]. Extending this technology to other currently abused substances such as marijuana, amphetamine or ecstasy, as well as to new generations of "designer drugs" of abuse will be a tremendous opportunity to have new pharmacotherapies rapidly available before experimental abuse of a new substance develops into an epidemic.

3. How might anti-addiction vaccines be used in the future?

3.1 Three clinical applications of anti-addiction immunotherapies

Antibodies could potentially be used in drug abuse treatment for three clinical applications: to treat drug overdose; to reduce drug use relapse; or to protect certain at risk populations who have not yet become drug dependent [14]. Adolescent children of cocaine dependent parents might illustrate this third application. If these adolescents begin using cocaine, then preventative vaccination might be considered to protect these adolescents from becoming cocaine dependent with all its severe implications for psychosocial

as well as developmental complications. Other special populations such as fetuses of drug abusing mothers might also warrant protective immunotherapy of the mother to prevent fetal exposure to the abused drug. Vaccination could potentially be used in all of these situations, except for drug overdose, where only monoclonals will be suitable, because the effect of the therapy must be rapid and cannot be delayed for several weeks. Monoclonal therapy might also be modified for special uses such as overdose. For example, antibody fragments, of a size that would be cleared by the kidney, could be used to treat overdose so that not only would the antibody bind the drug and lower the amount in the brain, but also, the drug-antibody complexes would be cleared quickly from the body. Depending on the particular setting, a combination of vaccination and monoclonal antibody therapy could be administered. In a drug abuse protection or relapse setting, where one would like to have significant antibody present over a long period of time, one could envision administering a loading dose of a monoclonal antibody along with active immunization (vaccination) with periodic repeat booster doses of vaccine to maintain the desired serum antibody concentrations. This combined approach of using active (vaccination) and passive (monoclonal) antibody therapy takes advantage of the relatively low cost of vaccination for long-term protection and the immediate efficacy of more costly monoclonal therapy. Monoclonal therapy can also be simply given repeatedly every couple of months. For example, Remicade® is given at 0, 2 and 6 weeks as a loading dose and then every 8 weeks thereafter for the treatment of rheumatoid arthritis. In summary, flexible combinations of vaccination and monoclonal immunotherapies can address a range of therapeutic challenges in the addictions, and the models for using immunotherapies are already being applied in other medical disorders.

3.2 Addressing current immunotherapy limitations

While current immunotherapies have potential limitations, most of them can be addressed. Some of these limitations are technological, but others are challenges from the systems of medical care delivery and from social consequences of these therapies. Technological limitations differ for vaccines and monoclonals. One limitation for monoclonal antibodies involves their production, which is time-consuming and expensive. Furthermore, the development of a high affinity monoclonal anti-drug antibody is sometimes difficult to achieve. This discovery process of selecting an appropriate monoclonal antibody among the thousands that can be produced will led itself to high throughput screening, which has been very effectively applied to many aspects of the drug discovery process for small molecules such as antibiotics. The technological challenges for vaccinations include the inadequate antibody response in some individuals. When an individual makes insufficient antibodies, then the blockade of the illicit drug will be ineffective or quite weak and easily overridden by

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increasing the amount of drug used. While biotechnology advances may address many biological reasons for such inadequate antibody responses, adherence rates for a wide range of treatment regimens have been far from perfect. For cocaine treatments lasting only 3 months dropout rates range from 15% to 79%, with an overall rate of 48% [15]. Adherence may be a particular problem for completing a series of three to five initial vaccinations over 2 to 3 months or for obtaining later booster vaccinations in substance abusers. Insuring behavioral adherence will require other social strategies beyond this paper, but are critical for the overall success of any anti-addiction vaccine program. However, a more optimistic view is provided in a recent intervention targeting over a thousand heroin addicts in Italy, 88% completed a full six-month hepatitis B vaccine series [16]. So high compliance is possible even in heavy drug-using populations.

Predicting who will develop adequate responses will be improved substantially as we develop better understanding of the genetic determinants of these responses. Individuals showing low antibody responses might then be treated more broadly for this relative immuno-deficiency by variations in gene transplantation and perhaps infusions of appropriate T and B type white blood cells to generate antibody responses, as well as being given cytokines and other small proteins that enhance immune responses. The importance of such treatments for their immune system is not simply to treat their inability to adequately respond to these anti-addiction vaccines, but also their diminished ability to fight a broad range of potential immune challenges such as infectious agents and large protein toxins. Improving vaccines by better adjuvants than the alum ones currently used, as well as by using concurrent cytokine treatments to enhance the antibody response are other potential technological fixes to these challenges of individuals' inadequate responses to immune stimulation. Vaccinations also may not produce antibodies in a timely fashion for proper integration with other medical interventions (e.g., drug overdose). For overdoses, the obvious solution will be to develop monoclonal antibodies for passive use. For other applications, where such a rapid response is not essential, concurrent cytokine administration and sustained release formulations may accelerate the antibody response. Oral or even intranasal administration rather than injections of the vaccines may be another technological improvement for addictions like nicotine that sometimes are viewed more as lifestyle issues rather than immediately life threatening diseases.

3.3 Unexpected social consequences of anti-addiction vaccines

Because in some cases the drugs of abuse are closely related in structure to either neurochemicals or approved medications (e.g., nicotine replacement therapy for cigarette smoking), it is possible that the therapies could lead to unexpected adverse reactions or reduced effectiveness of other medications. This drug interaction is easily tested, however, and extremely specific because of the specificity of

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antibodies. Thus, this potential problem will be easily detected and of a very limited duration, since vaccines and monoclonals only maintain sufficiently high antibody levels to produce such effects for about 3 to 4 months without booster vaccination or re-infusion of the monoclonal. The duration of efficacy after an initial course of vaccination or active immunotherapy also raises ethical considerations about stigmatization, because of the potential for long-lasting immunologic memory to serve as a marker of past immunization for years or even a lifetime. Monoclonal antibodies, however, have a finite life span and several months following treatment would no longer be detectable.

Immunotherapies like all long-acting blockers also have special risks, because large amounts of drug could override the beneficial effects of immunotherapy. Effectiveness of the blockade will also decrease over time, but not at a predictable rate in a particular individual. Blockades that are completely effective either immediately from a monoclonal or progressively from a vaccine will both become progressively ineffective. As the level of blocking wanes over time following administration, there is no obvious signal to the patient that the blocking effects have diminished after weeks or months of sustained blockade. Toward the end of the â€œeffectiveâ€ duration of blockade the patient may ingest a relatively large amount of drug that previously had produced minimal effects, but now results in an overdose. Furthermore, immunotherapies will not reduce drug craving, and craving may increase as the blockade becomes weaker and the drug abuser feels a partial or delayed drug effect. This enhanced craving due to partial blockade when a modest amount of drug is used coupled with the diminished blockade of toxicities may enhance accidental overdose risk.

The success of any blockade strategy also assumes that the drug's pharmacological effects primarily drive drug use, but these effects are not the sole motive for drug use. In adolescents drug use may be a form of defiant behavior and attenuating the primary reinforcing effects of an abused substance such as tobacco or marijuana smoking may not deter the substance use. Furthermore, some harm stems from behaviors associated with drug use itself or from substances mixed in with the reinforcing drug that is blocked [17]. Those potential harms would be exacerbated if users sought to override immunotherapies' partial blocking by taking more of the drug or taking it more frequently. For example, the risk of lung cancer from cigarette smoke will be enhanced by greater use. Even if a vaccine intercepts the harmful effects of nicotine, tar and other carcinogen exposures will increase and damage the esophagus and lungs.

A related effect of relatively potent risk reduction strategies is increased engagement in these risky activities. Existing data support this unfortunate effect of risk reduction strategies. Smokers compensate for filters and low-tar tobacco by smoking more cigarettes, inhaling more deeply, or blocking the filter vents [18, 19]. Similarly, Katz et al. [20] report that

the percentage of San Francisco men who report unprotected anal sex increased from 24 percent to 45 percent between 1994 and 1999. The authors present correlations and anecdotal evidence linking this increase in risky sex to reduced fears of HIV since the advent of HAART, which can effectively treat AIDS. A survey reported by Ostrow et al. [21] also shows a correlation between unsafe sex and perceptions that HAART reduces the harmful consequences of HIV infection. In both these cases, some of the safety gains brought about by a reduction in the probability of harm given unsafe conduct have been offset by increases in the probability of that conduct

For illicit drugs, adverse consequences of attempting to override the vaccines could extend beyond the drug user to other people, if immunotherapies increased the demand for drugs from drug dealers and black markets [17]. For example, crime committed by users to get money to buy drugs and conflict related to drug transactions, (e.g., disputes among dealers over drug money) account for more than 2/3 of drug-related crime. If immunotherapies increased market demand, they could yield a net increase in drug-related crime and violence.

3.4 Summary of advantages for future anti-addiction vaccines

In spite of these various limitations, both active and passive immunotherapies have several major advantages over other approaches to treating drug dependence. 1. The antibodies target the drug, not the drug's sites of action in the brain. 2. The binding of drug to antibody inactivates the drug. 3. The antibody can be highly specific for the drug and/or the drug class. 4. These immunotherapies can complement conventional therapies (like behavioral modification) for a more comprehensive medical approach. 5. The use of immunotherapy would not necessarily preclude the use of chemical agonists or antagonists for the brain receptors or transporters involved in the actions of the abused drug. An important exception is the combined use of a nicotine agonist therapy and anti-nicotine antibodies, although nicotine agonist therapy can be used during active vaccination without interfering with antibody production. 6. Immunotherapy has a different pattern and generally minimal side effects compared to treatment with chemical agonists or antagonists. 7. The antibodies are not addictive like some chemical agonists.

4. What technological advances might be made in immunotherapies?

Technology advances in manufacturing and delivery systems will improve future anti-addiction vaccines, as indicated above through several examples. Perhaps the most important will be a marked increase in the speed for discovering and bringing new treatments to market for abused substances, as new abused drugs constantly evolve and are spread among the youth of the world. Related advances will increase the stability and longevity of antibody blood levels and produce combination vaccines and monoclonal antibodies to simultaneously treat a variety

of abused drugs. Delivery systems for vaccines can be improved. Current multiple injections can be converted to single injections in sustained release formulations to improve peak antibody levels and sustain those levels more effectively. Injections also can be converted to oral and intranasal administration forms. As our understanding of cytokines and other immune modulators improves, we will be able to add adjuvant agents to the basic vaccines that will markedly reduce the time for antibody production from several weeks to possibly several days. These adjuvants will also increase the peak antibody response and prolong the duration of these responses thereby enabling less frequent boosters. Monoclonal antibodies will be produced in more efficient plant-based systems rather than the significantly more expensive microbial incubator vats that now produce these molecularly engineered proteins.

5. Facilitating adoption of technology in alcohol and drug treatment services

Progress in the development of medications for the treatment of drug dependence will lead to little application of these therapies, if drug abuse treatment practitioners and programs are not ready, willing, and able to embrace medication technologies. Six broad sets of barriers to the diffusion and adoption of emerging technologies in drug abuse treatment settings were identified in the Institute of Medicine's [22] analysis of the linkages between research and practice:

- Structure – small programs with limited resources may be unable to afford the medical staff and training required to fully utilize medications;
- Financing – the multiple funding streams that support drug treatment may have unique rules and may not provide coverage for new therapies including medications;
- Education and training – in many programs training for staff relies more heavily on an apprenticeship (experiential training) emphasizing traditional approaches rather than the more theoretical and cosmopolitan perspective found in graduate education;
- Stigma – ignorance and prejudice about drug abuse contributes to inadequate training in graduate programs and medical schools, inhibits the construction and location of facilities, and reduces investments in technology development;
- Lack of knowledge about technology transfer – a lack of systematic research on the adoption of technology in drug abuse treatment settings slows the development of more effective dissemination strategies;
- Policy – local, state and federal policies sometimes restrict the types of services available and the individuals who receive those services.

These six issues that slow diffusion of any new medical therapy into substance abuse treatment may be complicated due to several unintended behavioral consequences of anti-addiction vaccines. These consequences can be divided into four potentially negative scenarios. 1. Users can attempt to override the therapy with larger doses. 2. One drug whose effects have not been blocked

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can substitute for another drug whose effects have been blocked. For example, amphetamine substituted for cocaine in a stimulant abuser taking a cocaine vaccine. 3. There may be an increased incidence and/or prevalence of drug use because of a perception of less risk involved with drug initiation. 4. Drug sellers losing sales may adopt aggressive actions in an attempt to move into new markets. All of these scenarios emphasize how the intended recipients of intelligent health environments can defeat the benefits of these new technologies through unintended uses and distortions of technologies and their goals.

These six issues that slow diffusion of any new medical therapy into substance abuse treatment may be complicated due to several unintended behavioral consequences of anti-addiction vaccines. These consequences can be divided into four potentially negative scenarios. 1. Users can attempt to override the therapy with larger doses. 2. One drug whose effects have not been blocked can substitute for another drug whose effects have been blocked. For example, amphetamine substituted for cocaine in a stimulant abuser taking a cocaine vaccine. 3. There may be an increased incidence and/or prevalence of drug use because of a perception of less risk involved with drug initiation. 4. Drug sellers losing sales may adopt aggressive actions in an attempt to move into new markets. All of these scenarios emphasize how the intended recipients of intelligent health environments can defeat the benefits of these new technologies through unintended uses and distortions of technologies and their goals.

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Chapter 59: Future of Addiction Treatment: Enhancing the Human Experience and Creating a Fix for the Future

David H. Gustafson, Ph.D.
Research Professor of Industrial Engineering and Director of the Network for Improvement of Addiction Treatment, University of Wisconsin, Madison, WI, USA
Tara E. Palesh
University of Wisconsin, Madison, WI, USA
Rosalind W. Picard, Sc.D.
Director, Affective Computing Research Group, MIT Media Laboratory, Cambridge, MA, USA
Paul E. Plsek
Paul E. Plsek & Associates, Inc., USA
Lynne Maher, RGN, BSc Hons, MBA
Head of Innovation & Acting Director for Improvement, NHS Modernisation Agency, London, UK
Victor A. Capoccia Ph.D.
Senior Program Officer The Robert Wood Johnson Foundation, Princeton, NJ, USA

Abstract

The country's system of providing treatment for people struggling with addiction requires a fundamental overhaul. To address these daunting problems, a group of experts from outside the addiction field met in an intensive retreat and envisioned a new future for addiction treatment that would use the latest available technology. Retreat leaders employed creative techniques to help free up thinking beyond incremental improvement ideas. Current and former addicts or alcoholics and family members also attended the retreat to provide the panelists with a real-world understanding of their lives. Through this process, the panelists generated eight idea categories that visualized future treatments for addiction using technology. They were: (1) Integrated System and Record; (2) Monitoring/ Treatment; (3) Virtual Experiences; (4) Treatment Access and "One Stop Shop; (5) Networks; (6) Tailored Media Campaigns; (7) Diagnostic Tools; and (8) Help for Family. Two stories illustrate how these ideas could help a heroin addict and an alcoholic. The sponsors plan another meeting to bring these visionary concepts closer to real application.

1. Introduction

It is the year 2020 in a large city. Scattered along the city's streets are booths that resemble the old public telephone booths that have long disappeared from the urban landscape. These booths cover a wide variety of health topics and people can talk to "virtual" counselors at the touch of a screen. Maria, a heroin addict, has passed these new public health booths a few times—perhaps on her way to rendezvous with her drug dealer. Today, she pauses for a closer look. Maria's boyfriend beat her up a few days before and she ended up in the emergency room. She is worried about her health.

At the booth, Maria enters some information about her background including telling the system that she is in her 20s. Then the booth's screen filled with an image of a young woman about Maria's age. The woman is friendly and draws Maria in with her

easy-going manner. The young woman, who is a "virtual" substance abuse counselor named "Selene," talks about the difficulty of heroin addiction and says that she can help Maria through the process of quitting drugs. In fact, Maria can get started towards recovery today by stopping in any booth to talk to her virtually. Selene will be waiting for her. Maria pauses to listen. This public health booth, where heroin addicts would be able to speak to a virtual substance abuse counselor, is just one way that technology may be able to provide critical support in some of the daunting problems facing this country's substance abuse treatment system. While many effective drug and alcohol treatment programs exist, they serve only a small fraction of those in need. According to the 2002 National Survey on Drug Use and Health, only 15% of an estimated 22.8 million addicts in the United States receive treatment. For every person who has been able to control this disease countless others are far less successful.

The Robert Wood Johnson Foundation (RWJF) supports research projects that focus on treating people with addiction disease. Two of the authors (Gustafson and Palesh) served in the national program office for the RWJF's Paths to Recovery Program, a program with a sister relationship to a federal government program called Strengthening Treatment, Access and Retention. The program was designed to improve administrative processes that prevent addicts from accessing and then staying in treatment. The program demonstrated substantial reductions in waiting time to receive treatment and in numbers of clients dropping out of treatment.

Even so, it quickly became apparent that improving the existing system would not substantially improve addiction treatment. The current system is not sustainable. Counselor salary levels are so low that it is difficult to prevent counselors from leaving the field for jobs that offer higher pay. Substantial increases in funding are unlikely in the foreseeable future. Yet the demand for services is almost certain to grow. The foundations of addiction treatment need to be rethought to take full advantage of the technology that is available today and that will be available in the future. With this in mind, RWJF funded a project to bring together creative thinkers in fields outside addiction to envision a new system that could effectively treat people struggling with addiction. The resulting ideas offer insights not only into the future of substance abuse, but in how to tap into the creative process to find solutions to some of the most daunting problems facing the health care system today.

2. The Creative Process

One of the difficulties in envisioning a new system of health care is that people doing the envisioning are often part of the system that is not working. When people are steeped in a current structure, it is daunting to think creatively about a new way of providing services. To remedy this ongoing problem, staff at Paths to Recovery looked for creative thinkers outside of the addiction field. The staff invited a small group of internationally

respected experts in other fields to design an innovative and effective addiction treatment system. The experts represented fields such as nanotechnology, robotics, biomedical engineering, genetics, neurobiology, artificial intelligence, bio-informatics, social psychology, collaborative technologies and pharmacology. Facilitators had a few key criteria for those they wanted to invite. They needed people who:

- Had a sound grasp of the technology that will be ready for use by 2020
- Were not be encumbered by knowledge of the current system for treatment addiction
- Were creative, collaborative and communicative In addition to the outside experts, the group included addiction experts and consumers of services (recovering addicts and alcoholics and family members) to provide a clear picture of the treatment system today. The consumers of addiction treatment services were vital to this project. They provided a first-hand, vivid portrait of their lives and their needs. In all, 28 experts gathered for an intense two-day retreat in November 2004 to envision a new substance abuse treatment system for alcoholics and heroin addicts.

Members of the expert panel

Futurists

- **Timothy Baker**-University of Wisconsin, clinical psychology.
- **Rena Bizios**-Rennesselaer Polytechnic Institute, biomedical engineering.
- **Patricia Brennan**-University of Wisconsin, nursing informatics.
- **Renata Bushko**-healthcare futurist.
- **Noshir Contractor**-University of Illinois, communication networks.
- **Juan de Pablo**-University of Wisconsin, nanotechnology.
- **BJ Fogg**-tanford University, medical-informatics.
- **David Gustafson**-University of Wisconsin, medical informatics/technology innovation.
- **Thomas Kosten**-Yale University, pharmacology.
- **Dean Lea**-organizational development consultant.
- **Lynne Maher**-British National Health Service, Modernisation Agency
- **Jesper Olsson**-Swedish Federation of County Councils, medical-informatics.
- **Tara Palesh**-University of Wisconsin, systems engineering
- **Rosalind Picard**-Massachusetts Institute of Technology, human computer interfaces
- **Paul Plsek**, author and developer of DirectedCreativity
- **Victor Strecher**–University of Michigan, communications science
- **Peter Szolovits**–Massachusetts Institute of Technology, decision and computer science.
- **Sheila Wang** – social psychology.

Addiction Experts

- **Bret Shaw**–communication science.
- **Maria Levis-Peralta**–community activist.
- **Tom McLellan**–addiction services research.
- **Kristin Schubert**–Robert Wood Johnson Foundation, genetics.
- **Elaine Cassidy**–Robert Wood Johnson Foundation, evaluation.
- **Victor Capoccia**–Robert Wood Johnson Foundation, addiction treatment
- **Dwayne Proctor**–Robert Wood Johnson Foundation, communications systems.
- **George**, recovering alcoholic
- **James**, recovering heroin addict
- Belle, mother of a current heroin addict

3. Logistics

Coordinators paid close attention to the details of the meeting's location and ambience to help make the experience as positive as possible for the participants. A poor location or any unexpected travel inconvenience could have a severe impact on the creative thinking of the entire group. Planners chose a site that reflected the meeting's goals. It was a facility outside of Chicago in a location that was both

relaxing and boasted the latest technology. The facility had ponds and streams with paths for walking as well as an extensive exercise facility, good food and easily accessible Internet connections throughout. Participants were provided with limousines to the facility and a cell phone number of a meeting organizer should any problems arise. With these preliminary arrangements, even the small glitches that did occur were addressed quickly. All of the participants arrived feeling well taken care of and ready to work.

To help the expert panel prepare for the retreat, facilitators developed a package for those who wanted more information on addiction prior to their arrival. Facilitators sent a copy of *Hooked: Five Addicts Challenge Our Misguided Drug Rehab System* by Lonny Shavelson to each panel member. They also sent fact sheets about addiction and its treatment and stories of addicts and their families told in flow charts. However, the retreat did not hinge on panelists having done any background reading on addiction. Facilitators just asked the panelists to bring their creativity to the meeting and arrive on time.

4. Meeting

The first day of the meeting, facilitators gave participants their charge: to design an addiction treatment system that would involve no humans. They told participants that in the year 2020 all of the substance abuse treatment professionals had been killed by a virus. Addicts and their families would have to obtain help primarily through technology. This charge freed up thinking beyond incremental improvement ideas such as more training programs, more counselors, more clinics and more funding.

While facilitators felt that it was not important (and even counter productive) to understand the addiction treatment system of today, it was essential to understand how it feels to be an addict and the family member of an addict. One of the facilitators encouraged the development of a set of stories that described the life experiences of addicts and their family members. Another facilitator who had personal experience with addiction treatment (she is the daughter of an alcoholic) developed a prototype of a story. Instead of a story narrative, she wrote a flowchart. It was a concise, easy to follow format to present a large amount of information quickly. More important, it was an innovative way to break down the experience while highlighting key events and aspects of the disease. The team used that approach to develop three other flow charts that told the story of someone affected by addiction. Facilitators identified a recovering heroin addict from an inner-city ghetto (James), a recovering alcoholic CEO (George), and the mother of a 21 year-old current heroin addict (Belle).

4.1 Day 1

The morning of the first day of the meeting, a facilitator presented each of the flow charts. The consumers whose story was told in the flow charts were in the room. Provided with a rapid but detailed version of each consumer's life, the panel asked

consumers questions about anything they did not understand or wanted more details about. Panelists said they found it powerful to have the four consumers depicted in the flow charts available to clarify any misconceptions and share more of their experiences. In fact, the question and answer phase was so useful that it took much longer than anticipated as panelists became deeply involved in the lives of their new "customers." The presentation of the flow charts and the in depth discussion they fostered encompassed the entire morning session rather than just a portion of it. However, during that time panelists were already placing ideas on post-it notes for future use (which had not been planned until the afternoon).

After lunch, the panel transitioned into the idea generation phase. The planning group had assembled a collection of creative thinking tools to prepare for the meeting. The idea generation tools were based on the "directed creativity" concepts of attention, escape, and movement. Innovative ideas are more likely to emerge in a group when people focus *attention* on something that they do not normally focus on, *escape* the current ways of thinking about the issue, and encourage free-wheeling mental *movement* to capture all ideas without censorship.[1 2 3] For example, in the *Future Tinkertoys*™ tool, leaders helped generate escape and attention by asking participants to identify attitudes, technologies, and devices that they expect to be commonplace in the year 2020. Ideas came in such a torrent that facilitators wrote furiously just to try and keep up. Participants often built upon one another's ideas—a demonstration that the panel was becoming comfortable with the notion of creative thinking and were working well together as a group. With that exercise as a start to future thinking the facilitators randomly assigned panelists to one of the four tables in the room. Each consumer joined a table so that they could answer any questions that arose during idea generation. Facilitators asked panel members to create as many ideas as possible related to the future treatment of addiction. The four groups began with simply throwing out ideas among themselves and then writing them all down. As expected, each of the four groups had a different method to generate ideas. The facilitators moved around the room reading the ideas and marking the ones that would need further explanation. In all the four groups generated 268 ideas. Facilitators compiled the ideas into an Excel sheet for further analysis. By the end of the first day, participants had begun to see a network of knowledge forming to focus on the future treatment of addiction.

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Daughter wanted to go to different school.
Daughter admitted drug use, marajuana
Felt daughter was close to failing out, convinced different school would help
Daughter gets license and older boyfriend is a bad influence
Daughter was holding down a good job
Drug Assessment for Daughter
Sent Daughter to Alternative School
Problems with Daughter Continue
Daughter said using. Urine analysis said no drug use
School was much smaller
"Did not know it was drugs, I thought I would recognize it"
Found pipe
"I did not know what was going on", looked to professionals for help
Daughter lost touch with good friends, which made me worry
Daughter began breaking curfew and I discovered she was sneaking out
I was suspicious and began more open discussions
Daughter went to a Counselor
Asked Pediatrician for depression assessment
Locked her out once
"Powerless", tried to set rules. She would break them. Did not know what factors were to blame… there were so many
Only made her angry
Counselor was not helpful
He said: "Not necessary"
1996
1997
Belle - Part 2

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Belle - Part 3

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Belle - Part 5

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Chapter 60: The Future of Information Technology for Health in Developing Countries

Scott C. Ratzan, MD, MPA, MA
Senior Technical Advisor, Global Bureau at the U.S. Agency for International Development
& Editor, Journal of Health Communication,International Perspectives
Maria I. Busquets, MA
Chief of the Communication, Management and Training Division in the Population, Health
and Nutrition Center at the U.S. Agency for International Development.

Abstract

What is the future of communication technology for health in developing countries? This chapter sets out to answer this question by first considering the background and potential of information technology, identifying some of the issues and trends in communication, and finally following with some challenges and opportunities of how communication technologies can make a difference in health in developing countries. Past research has shown that communication can contribute to all aspects of population, health, and nutrition programs and is relevant in a number of contexts. Some of the trends in using information technology can be classified in the following categories: competition, cognitive-based presentations, comprehensive translation, convergence, and culture. Challenges include finding a way to include the South in the exchange of ideas and information. In addition, reaching a consensus on worldwide quality standards will not be easy. Yet, beyond these challenges, there are many opportunities being created for international development agencies to increase their capacity for impact.

1. Introduction

During a visit to India in March 2000, President Clinton watched a woman enter a village health center, call up a web page on the computer, and get information on how to care for her baby. This baby will live a longer life than her mother, mostly because of 20th Century public health advances and the new technological potential of the 21st Century.

Unfortunately, it is a rare occurrence for a woman in a developing country to have access to the Internet. The hopes for progress in technologies present ongoing challenges in access, quality, and equity. In fact, over half of the women in the world have never made a phone call. In Africa, which has a population of 700 million, fewer than one million people had access to the Internet in 1998, and of this number 80 percent were in South Africa. Among the other 20 percent the ratio of people who have access to the Internet to those who do not is 1 to 5000, in the United States or Europe the ratio is 1 to 6.5.

The woman in India in the example above is an anomaly as many villages still lack a working telephone. The new information technologies potentials is concomitant with the divide in the access to learning opportunities: 885 million people in the world are illiterate, and two-

thirds of them are women. More than half of these adults lives in India and China, another one quarter in seven other nations in Sub-Saharan Africa and South Asia. Yet, information and communication technologies are often the hopeful solution to end these inequities, particularly among those who are poor and isolated in developing countries.[1]

A search of PubMed in December 2000 yielded 6,692 citations containing "Internet." The number is growing by at least eight per day. But of course, this is disproportionate with developing countries. Fewer than 0.1 percent of these articles are related to developing countries, despite the fact that developing countries represent over 25 percent of the scientists in the world. Similarly, a study of Medline looking back at 1992-96 showed the British Medical Journal (BMJ) had only 0.4 percent of the publications mentioning developing countries, the Lancet 0.6 percent, and the New England Journal of Medicine 0.05 percent. When you look at content and language on the Internet, the statistics are sobering—for example, only .02 percent of the Internet content comes from Sub-Saharan Africa, and while content in several languages has risen in recent years, English is still the predominant language used on the Internet.

With such a daunting challenge, we ought to answer the important question: What is the future of communication technology for health in developing countries?

To answer this question, we will first describe the background and potential of information technology (IT), some of the issues and trends in communication, and follow with some ideas of challenges as well as opportunities of how communication technologies can make a difference in health in developing countries.

While we read each day about HIV/AIDS, cancer, and emerging diseases, there has still been great progress in public health globally. Last century in both developed and developing countries, there has been a 25-year increase in life expectancy, the most rapid improvement in history. Much of the success is not due to better drugs, surgery, and diagnosis. Almost all the improvement has been the result of public health: surveillance, sanitation, nutrition, changing lifestyles, etc.

Public health actually is a field that principally focuses on the transfer and exchange of information: data collection, surveillance, information transmission, and communication. The new communication technologies have great application in public health practice.

2. Background

Recent advances in information and communication technology provide an unprecedented means of overcoming two of the root causes of extreme poverty—ignorance and isolation. The opportunity to communicate public health information and expand the flow of ideas and data coming from the South will allow for a horizontal two-way dialogue that will contribute to new opportunities to communicate public health information not available before.

Effective use of communication technology can benefit personal and public health. Past research has

shown that communication can contribute to all aspects of population, health, and nutrition programs and is relevant in a number of contexts, including (1) individual's exposure to, search for, and use of health information; (2) the collection, dissemination, and utilization of individual and population health risk information (often termed risk communication); (3) individual's adherence to clinical recommendations and regimens; (4) the construction of public health policies, messages, and campaigns; (5) health provider-patient relations; (6) creation of "health as we know it" through popular culture and mass media transmission; and (7) the agenda-setting phenomenon of prioritizing public health and health care system developments. Most of the usage of communication technology has focussed on the first few areas

Most people today think of IT as electronic mail, Internet World Wide Web sites, and interactive CD-ROMs. These are just a few of the many new communication media that provide unprecedented global access to people and information.

The landmark ideals of Marshall McLuhan represent a challenge for those of us using IT: McLuhan accurately predicted that "the new electronic interdependence recreates the world in an image of a global village."[2] Already, we have evolved communication from broadcast to multicatch, but IT is more than just the web. IT now includes the ideas of demassification—narrowcasting information to the end user, interactivity, a true exchange of information, asynchonicity, the ability to communicate whenever with our "real time" interaction, and mechanomorphism of multimedia to include all the senses (except smell at this juncture) into the communication experience.

Despite the potential of communication technology, we must be mindful. While globalization has the potential to bring people together and to provide them with tools to advance their social and economic well being and their health, it poses great risks. There is a dark side to IT: the fact that some can use it to create a "digital divide." We must be particularly concerned about Internet access for under-served populations and opportunities for girl's and women's participation in the digital information.

3. Trends

We have five basic C's that help us describe the future trends in using information technology in development:

- Competition
- Cognitive-based presentations
- Comprehensive translation
- Convergence
- Culture

These areas are creating uncharted territory as the new media evolves

Competition—The answer to the question who's knowledge and whose information will become more complex. While there are media conglomerates and publishers that have a monopoly on communication of "knowledge" in our scientific and medical journals, this will change. Researchers and scientists have begun to bypass print journals and put research directly on the web.

Cognitive-based presentations—Powerful new cognitive formats will

evolve; as this happens, the traditional format of Abstract, Introduction, Methods, Discussion, and Results could become extinct. One new format may create a new language not just for computer programmers, but consumers. A "Hypertext Comic Book" to teach children how to spot landmines in Mozambique or a Nursing School Midwifery Curriculum in Kenya that enhances by iconic "cognitive" paradigms can allow a user to point and click to icons for medical knowledge. For information or medical knowledge, the Uniform Medical Language System may evolve into cognitively based formats that maximize interactivity, hyperlinks, and memory.

Comprehension translation—Most books appear in only print format; one size fits all. The IT future allows people to indicate their backgrounds, education level, language preference, and interest with software to individually tailor a translation to maximize comprehension. These Intelligent Agents will create a digital document for an epidemiologist that will be different for a physician in Canada or traditional healer in Haiti. Translation software will evolve that can adapt for dialects, aphorisms, and other specific linguistic markers

Convergence—The convergence of media (computers, telephones, television, radio, video, print, and audio) and the emergence of the Internet create a nearly ubiquitous networked communication infrastructure. The potential of this cannot be underestimated. Networking can be used for many purposes in public health, from creating support groups of persons trying to quit smoking to "action alert" networks for advocacy purposes. We are already seeing the creation of online communities amongst scientists, teachers, and Ministers of Health. A group of mid-level health professionals in Francophone Africa is, for the first time ever, able to share information, compare experiences, and "speak" with other professionals with similar problems.

Electronic communication can also be used for public health interventions to persuade the general public or policy makers, such as through health education, social marketing, or advocacy. Because of the capacity to segment audiences, electronic communication can be used to develop health education and behavioral change materials for specific populations (e.g., smokers, non-English speakers).

Convergence will also bring scientists to "push" new information into the world via Internet delivery. Convergence will also take place as the distinctions between the latest scientific findings, lectures, journals, and books become blurred. Schools, books, and lessons will have information days old, rather than years or decades old.

Culture—There is a problem of acculturating individuals to new technologies. Repetition has induced attitudinal change by familiarizing people with, in this case, technology through repeated exposure. Yet, the use of IT can in fact develop an information generation. This generation can change governance and policymaking. One way processes and vertical organizations will be vestiges of the 20th Century. On the

Internet, interactivity will prevail; policies and research may benefit from early feedback from users. A culture of passivity on the part of the users also may ensue. People may merely access and download information, treating the Internet as an online health library. But as they spend more time on the Internet, gain access to different sites, and notice consistencies and contradictions, critical thinking ought to emerge as people pose their own questions and apply their own knowledge. Health policymakers and researchers should exploit such opportunities for interaction with users.

The health impact of interactivity, customization, cultural diversity, and enhanced multimedia is just beginning to be explored. Yet, already, interactive health communication technologies are being used to exchange information, facilitate informed decision-making, promote healthy behaviors, enhance peer and emotional support, promote self-care, manage demand for health services, and support clinical care.

4. Current Initiatives

Through a U.S. Inter-Agency Agreement launched by President Clinton in late 1998, the Internet for Economic Development (IED) Initiative seeks to empower developing countries to develop and use the Internet to boost their economies, gain access to knowledge and foster the free flow of ideas. Through this initiative, USAID Missions have supported the development of community telecenters in Ghana, Guatemala, and Haiti; and the use of the Internet for Mayan-language education.

Efforts are underway throughout the world to develop integrated national and global health information infrastructures to support health improvements. In the United States, the National Committee on Vital and Health Statistics (NCVHS) seeks to develop a system that links surveillance systems, information sources, and establishes communication linkages (on emerging and reemerging diseases).

The infrastructure makes it possible for people not only to use health information designed by others, but also to create resources to manage their own health and to influence the health of their communities. For example, community groups could use computers to gain access to survey information, health indicators, disease surveillance, and access about the quality of life in their neighborhoods and apply this information to create an action plan to present to local elected and public health officials. Information is a critical element of informed participation and decision-making, and appropriate, quality information and support services for all are empowering and democratic.

At the Millennium Assembly of the United Nations in September 2000, the right of universal access to information and communication services was discussed as a new component of the UN's principles and conventions on human rights and development. When John Chambers of Cisco and Carly Fiorina of HP joined sixty-five other CEOs in June 2000, they discussed how to make IT more accessible to the world's poor. When the G8 held their meeting in Tokyo last July, they focused on the crossroads of

development and IT, and in an unprecedented move, invited developing country and civil society representatives to join the Dot Force. When they meet again in 2001 in Genoa, progress towards eliminating the digital divide will again be discussed. President Bill Clinton recently held a panel discussion on the Digital Divide in Health, Education, and Technology. The common theme was the "the global divide giving way to a global connection."

Rhetoric has given way to action. For example, the United Nations has begun `Health InterNetwork,â€ which is designed to improve public health around the globe by providing health information using Internet technologies. It links scientists in over 30 countries to the leading scientific journals, databases and discussion groups.

Under the Leland Initiative, USAID is implementing agreements with more than 20 Sub-Saharan African nations to enhance Internet connectivity and use in a competitive policy environment. Now that through the efforts of many, African countries are connected to the Internet, the Leland Initiative is supporting broadband connectivity to secondary cities and towns in select countries such as Guinea and Uganda. In addition, private and public activities are beginning to provide access to the Internet, especially through community access points, for the world's population presently without such access by the end of 2004.

In Africa, there are hundreds of initiatives developed by donor agencies—some intended to increase access to these technologies in remote areas by establishing "waystations" (resource centers that provide access to health information on CD Roms and online) and others dedicated to increasing the use of these technologies in specific areas like health and agriculture.

5. Challenges

Widespread availability and use of interactive health communication and telehealth applications create several serious challenges. One is related to the debate on whose information and knowledge appears on the Internet or on a CD-ROM. Knowledge from the "North" will need to make space for the ideas, experiences, and information stemming from other cultures and experiences. Anyone that has tried to cull through the clutter of the web will understand the challenge of creating usable content, especially content applicable to the health needs in the developing world. There are also risks associated with consumers use of poor quality health information to make decisions.

Concerns are growing about the Web making available large amounts of information that may be misleading, inaccurate, or inappropriate, which may put consumers at unnecessary risk. Although many health professionals agree that the Internet is a boon for consumers because they have easier access to much more information than before, these professionals are concerned that poor quality of a lot of information on the Web will undermine informed decision-making. These concerns are driving the development of a quality standards agenda to help health professionals and consumers

find reliable Web sites and health information on the Internet.

Reaching a consensus on worldwide quality standards will not be easy. The process will most certainly move us away from the more academic and traditional quality standards that were created by the North for the North. Finally, even if we were all connected with affordable access and quality information, illiteracy and lack of computer skills remain a considerable hurdle.

6. Opportunities

The vision of new technologies cannot be underestimated. The power of technology has been described as revolutionary, and the Organization for Economic Cooperation and Development has written of a new, knowledge-based economy.

Opportunities are many—the Internet is a one trillion dollar technical infrastructure and, in theory, available to anyone; it's global and borderless with new business and development applications and models coming in from all directions; open when needed—24 hours a day—which means time zones are no longer a barrier; it's changed the way we conduct work, recreation, and even love!; and keeping it all together is *information*—it's the glue, the value-added—that keeps us coming back for more.

The information revolution can be an equalizer. Chat rooms around the world have recently been furiously debating what is a false dichotomy of computers and technology on the one hand, and health, food, and basic services on the other. It's not an either/or debate but a two-track approach to revolutionizing the way we do business.

Recognizing the challenges we face (outlined earlier), IT can still be harnessed to empower individuals and reinvent governments, promote electronic commerce, and expand access to information. In the development arena, IT has numerous applications.

International Development Agencies can use the new technologies to reinforce and modify present forms of technical assistance. Interactive multimedia training courses are being used to provide opportunities for individual and group interactions. CD-ROMs accommodate a wide range of learning styles, and their use seems to be increasing user's overall level of learning including improved engagement and retention of information.

Electronic training is becoming a reality—and big business. Hybrid CD-ROM/Web solutions are used when connectivity is a challenge. Start-up costs often appear to make electronic delivery of training appear costly in comparison to face-to-face training. However, given the large number of healthcare providers requiring training, electronic training could be very cost effective.

Virtual consultancy, where no one travels, is highly possible. Several pilot studies are already underway.

Collaborative research can take place online, as can data analysis. It is possible to do online team planning with members of the team at different points of the compass. Even real-time

epidemiology is possible online.

Isolated communities can have access to online, accurate, up-to-date, quality health care information from local sources or the world's largest medical library, the National Library of Medicine at the National Institutes of Health. The MedlinePlus service provides access to extensive information about specific diseases and conditions, and has links to consumer health information, dictionaries, lists of hospitals and physicians, health information in other languages, and clinical trials.

CD-ROMs and desktop publishing offer university libraries advantages, and even African University libraries are increasingly connected to the Internet. Digital libraries are changing the work and, indeed, the idea of the library. Increasingly, it appears that scientific publishing will be available online.

Additional applications include virtual "toolkits" including communication strategic planning software, international drug price indicator guides, web courses on infection prevention, Instant Messenger for real-time training, Cyber Cafés, community forum message boards, multi-media idea bank on condoms, Technology Assisted Learning Centers, and a database of free photos.

There are numerous possibilities, almost all of which are presently 'under-exploited' in international health and development. And these possibilities will be much more attractive and valuable with the acceleration of online interactive video technology. What has become clear to the authors is that waiting for technology stability is a losing tactic.

An equally important concept to consider is the indirect impact of ICT. Many of the populations that international development agencies work with do not have access to the Internet and most likely never will. These populations receive the benefits of ICT, but it is especially hard for the public to perceive. The Famine Early Warning System[4] (FEWS) in Africa was designed to utilize high technology means to provide advance warning of the development of famine conditions. It was designed to allow acquisition and stockpiling of food in advance of market shortages. Thus the success of FEWS is marked by lower costs of food and fewer food shortages. Yet not only do most of the beneficiaries of FEWS not have direct personal access to its technology or any ICT technology, but they are not aware of the ICT benefits they receive.[5]

The new technologies provide many potential ways through the above and many others to expand the opportunities of international development agencies to maximize their impact on health concerns.

a. The technologies are built on interaction;
b. They are inclusive—allowing the quick identification of a range of information on an issue and the choice of the information most relevant to the setting;
c. The information and knowledge can come from a range of perspectives and countries;
d. They are flexible—when the information changes it can be updated very quickly; and
e. The new technologies operate at scale.[6]

Recent discussion of the future with

technology leaders in Silicon Valley and Virginia's 270 Corridor found that no one can predict which of the new technologies (or the infinite number of upcoming developments) will go mainstream. Just as Napster [recently] and the world-wide web [5 years ago] were hugely surprising in their rapid growth and use, the future is also very difficult to foresee. Some of the possible areas mentioned by the experts were:

- Wireless—continued rapid expansion of wireless access and technology (e.g., Palm Pilot, RIM, information pager networks, cell phones and WAP) with the implication of being able to access information and interact from potentially anywhere, at good speed, and not restricted by land-line capacity.
- Personalization—automated processes so that you 'pull' down the information that you want to see, not the information that the web sites are pushing at you, which provides rapid information on the most recent trends, data, and experience relevant to your work and restricts the necessity for long searches on many sites. Essentially, you take control.
- Video—will move ahead in leaps and bounds. VBIC already offers a guaranteed lip-synch online video facility—training, conferences, one-to-one calls, etc.—at U.S. $0.05 per minute. Virtual meetings could replace some travel because quality and cost are getting that good.
- Voice recognition--no typing: train your computer to recognize your voice. This software is developing very quickly and could result in better efficiencies.
- Data mining—the ability to sift through and manipulate (i.e., try to connect different variables and cross-reference topics) large quantities of information in a vary short time. This would really help information overload issues and lead to better, more targeted analysis.

Finally, in the midst of this technology revolution, we must:

- ensure women have equitable access to the benefits of telecommunications and are not disadvantaged by sector reform and industry changes;
- design and provide telecommunications technologies and services which take into account women's needs and requirements; and increase women's participation in all levels of the telecommunications sector. [7]

7. Conclusions

Even if the woman in the village at the beginning of this chapter gets access to the Internet, she will not necessarily be able to use the information to improve her child's health because as it is often said, trying to get information from the Internet is like drinking from a firehose, you don't even know what the source of water is.

The future will have more quality information provided by web sites but, realistically, only a few branded, highly

credible sites will emerge (competition and convergence). Despite retrieving accurate information, the woman in the village still has to decide if the information is relevant to her situation. This hopefully will become unnecessary as more data would be generated and shared in a decentralized network linking knowledge in the developing countries, creating a so-called South to South dialogue.
Hopefully the future Medline will reference and share a number of journals from developing countries. The Internet can converge with gateways to become a Global HealthLine. The problem is complex, and possible explanations range from the difficulties encountered by researchers in developing countries in gaining funding for research)only 10 percent of funding is spent studying problems relevant to developing countries) to the existence of "ethnocentrism at its worst" in biomedical publishing circles. But now, with the availability of publishing software that can be coupled with powerful Internet search engines, it is possible for authors or local scientific societies to bypass traditional avenues of scientific publishing. They can post their research directly on their own web sites or, for example, on web sites that focus on international health or on general health and clinical research web sites like Pubmed Central or other electronic servers operated by biomedical journals.

Wireless is likely to be the principal means to access the Internet. The second billion people on the planet who access the Internet will not access it through a personal computer, but rather through wireless devices. This is facilitated by the development of less expensive technology and ease of usage coupled with a rising sense among people all over the world that they are entitled to participate openly in their government and society. Greater mobility in using the technology will be made possible through the use of pocket sized wireless devices such as Internet enabled mobile phones. Extensive tailoring of the volume and style of presentation of information can already be done using hypertext and multimedia links. This can convert any material to accessible formats that cater for different audiences.

To ensure that the envisioned future does not remain merely commercial hype, a systematic effort should be made to exploit the advances of information and communication technologies for use in developing countries. As has been described, many efforts are already being made to bring these technologies to developing countries. The long list of initiatives is impressive but how successful have their efforts been to work synergistically?

In terms of health, attention would be best directed to improving access to accurate and relevant information. Credible agencies or organizations that provide evidence based health information can increase the speed with which users are able to download information by constructing mirror or replica sites in different geographical areas. For example, the European Union funds the web site of Scientists for Health and Research for Development (www.shared.de/sharedhome.html). This web site lists

potential donors, ongoing projects, and resources available to researchers in developing countries or their partners in the developed world. Medical journals that have their own web sites can follow the lead of the BMJ and provide free access to their articles.

The relevance of information can be improved partly by increasing the visibility of health research from developing countries. Technical assistance in designing web sites could be provided, preferably through the creation of templates to be easily adapted by different users. Alternatively, some agencies might offer to host other organizations on their web sites, absorbing the costs of developing and maintaining the sites. For example, Kabissa (www.kabissa.org/index.html) provides low cost domain hosting for non-profit, non-governmental organizations in Africa, including the Network on Equity in Health in Southern Africa (www.equinet.org.zw), a network of research, non-governmental, and health sector organizations seeking to influence health policy in southern Africa.

The development community is going through the same struggle as many small private sector businesses. Many tend to take small steps, especially senior management. But major shifts are warranted. It is absolutely critical to move from viewing IT as a tool to viewing it as a transformer. From the gigabytes and megahertz discussions of high end computing to low end computing such as the $10 hand held device recently developed by computer science students at MIT. From the Western perspective of desktop computers in every household to wireless and satellites. The creation and use of Web Sites should also embrace change. It is critical to move from "talking at" to "listening to" and from "brochure ware" to assessing and serving customer needs. Finally, the most often overlooked shift—the movement towards changing what's behind the web sites—the people, the processes, and the corporate cultures.

As the disparities between the information have and have-nots increase (not only between countries, but also within countries), so too do inequities in health status. Consequently, there is a great urgency to act. The new global disease threats must be addressed not only with medical means, they must be complemented by efforts to enhance literacy, economic development, and the like—what Nobel Laureate Amartya Sen has called "support led strategies". Such strategies can include communication technologies to focus on lengthening the factors that make economic development possible, of which education, health, and the empowerment of women are central components.

There are many success stories combining community effort and social mobilization to build on. Among the most promising are programs for community-based literacy education, complemented by significant social mobilization efforts using role models with high credibility from the local and national arenas, such as figures from the media and the entertainment industry.

Ideally, education could evolve just

like this edited volume on the future of health so that "virtual centers," or collaboratories, where the expertise is drawn from many locations can be integrated. These do not need to be from the North or developed countries. Special consideration with new media technologies should address access issues for underserved, minority, and disabled populations. Opportunities with new communication technologies can integrate new research methodologies and approaches to respond to the swift pace of change inherent in the communication revolution. Ideally, a new connectivity can foster relationships with other public health agencies, advocacy groups, non-governmental and support organizations to the private sector.

Finally, there is an opportunity to advance a leadership position not only in publications and media channels along with the hospital, health care facility, and academic health center, but also in using communication technology for health in the private and public sector. Systematic agenda setting in keeping appropriate health issues on the political agenda in general could be of great value. This is where highly credible organizations, such as the World Health Organization, or professional organizations and governmental agencies could be most powerful by providing accurate, trustworthy data for public consumption. Developing health leadership could be the most important communication advance.

Could there be a future when people throughout the world can elicit accurate, up-to-date interpretation of study results that translates"health as we know" into real-life daily activities? Could we communicate well enough to individuals so that we develop health â€œnews you can use"? There are no longer technological barriers to such ideas.

While many are optimistic that we will do the right thing and create a new health as is "ought to be," health as "we know it" today might prevail—a world with disparities of income, health, and human rights, and environmental justice. Humankind often advances with market forces suggesting we have the right to just do it, rather than just doing the right thing. While we have identified the latest frontier as cyberspace, our ability to reach people for profit supercedes promulgation as a species. Perhaps, we are now at a crossroads in the third millennium. Nearly fifty years ago, there was a different warning: "Science, which now offers us a golden age with one hand, offers at the same time with the other the doom we have built up inch by inch since the Stone Age and the dawn of any human annals. My faith is in the high progressive destiny of man."

While Winston Churchill warned of the nuclear age, I also suggest a warning of the communication age. We must empower the individual to access information with appropriate interactive health communication to enhance his/her decision-making.

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Julia Royal / Strategies for Positive Outcomes: Can Information Technology Make a Difference in Health in Africa in World Health Strategy" eBook, www.Futureofhealth.org (Ed.) Renata G. Bushko, FHTI, 2016. Strategy for the Future of Health (Ed.) Renata G. Bushko, IOS Press 2009

Chapter 61: Strategies for Positive Outcomes: Can Information Technology Make a Difference in Health in Africa

Julia Royall
Chief, International Programs US National Library of Medicine

Abstract

This chapter looks to the future through the prism of pilot projects well in progress at the time of this writing: use of a malaria electronic tutorial in Mifumi village, development of a mental health electronic tutorial in northern Uganda, and development of an electronic health management system at Tororo Hospital. Each demonstrates a strategy, rooted in African soil, whose ultimate objective is to improve health through IT and medical informatics. The projects connect users, health professionals, and decision-makers, bringing together interdisciplinary teams. These projects all seek to address the question: Can an information and communication technology (ICT) intervention make a difference in morbidity and mortality in African settings? The findings indicate that not only can these interventions be implemented but can be enhanced with community collaboration, making a positive outcome in terms of community adaptation more likely. Finally, this chapter proposes a health informatics center, a Menlo Park for innovation and entrepreneurship in East Africa in which new ICT inventions and interventions for better health can be created from around the region.

1. Background

In 1992, a small satellite in a low earth orbit quietly delivered the first electronic version of a medical journal article in sub-Saharan Africa. Published in the *New England Journal of Medicine*, the article concluded that "treatment with vitamin A reduces morbidity and mortality in measles, and all children with severe measles should be given vitamin A supplements." [1]
At the time, measles persisted as a common killer of children in developing countries, and vitamin A was readily available almost everywhere. Results of this research which had been carried out in Africa, however, had not reached African doctors who could have used it to save lives. The delivery of the medical journal article in sub-Saharan Africa provided a symbolic gesture, bringing home information that had belonged there all along. When the antenna on the ground picked up the signal of the satellite above, it officially brought down the article from the sky to the computer in the ground station in Nairobi.

Mission accomplished, right? Wrong! As difficult as it was to get all the technology to work properly to accomplish this simple exchange, the challenge of access had just begun. The article had been delivered into a void. The technology succeeded - the first electronic delivery of a medical journal article in sub-Saharan Africa - but the transfer of bits, as yet, had no meaning [2].

This small but significant event raises a major question regarding the challenges of using technology to achieve positive outcomes in health.

Edited by: **Renata G. Bushko** - bushko@fhti.org
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Today, ubiquitous cell phones in African cities reach even remote areas. On a continent where infrastructures of transport and access to information remain often undependable or unreliable, the cell phone network acts as a superglue keeping people connected – with each other, with the price of coffee beans, or with relatives continents and oceans away.

2. Use of Electronic Tutorials

2.1 An electronic tutorial on malaria informs patients in Mifumi village.

From ivory tower to village health center and back: an interactive tutorial on malaria, combining expertise from the U.S. National Library of Medicine's MedlinePlus with Makerere University Faculty of Medicine in Uganda to focus on tropical disease in developing country contexts. [3]

Nurse Sister Gorretti is a seasoned professional who runs the Health Center in Mifumi village, about 45 minutes along a road through the bush outside of Tororo in Eastern Uganda. She drives to work on a motorcycle. Her approach is caring but no-nonsense, and beneath her unflappable demeanor, one can occasionally catch a glimpse of a warm smile. Gorretti is a remarkable blend of the fortitude and expertise required to run a Center which treats large numbers of mostly women, children, and babies, many with malaria. The surrounding area is highly malarious with water standing in ditches and bogs. Bednets have been distributed in the past with no effect whatsoever on the morbidity and mortality of this major killer of children under five.

Figure 1: Sister Gorretti in Health Center in Mifumi Village. (Photo: Julia Royall)

Oceans away, the National Library of Medicine (NLM) remains committed to reaching the consumer or end user, no matter what the location of the user, through its popular and widely used database MedlinePlus [4]. In 2005, NLM brought together the existing machine of MedlinePlus with medical school faculty and students at Makerere University Faculty of Medicine, which had recently implemented a case-based curriculum. The challenge was to leverage the delivery platform of MedlinePlus and to work tirelessly with two teams of players from the US and Uganda to reach a successful local outcome that could be shared internationally.

This project creates another layer of health care education in the field and in the medical school, connecting those two worlds in ways whereby each can inform the other. The project leverages existing methodologies such as MedlinePlus and the concept of health information for consumers, to create a new product for an African context, bringing together local health

and language experts and a respected university with the cultural context and artists who can reflect that particular context through their use of imagery.

Figure 2. "What is Malaria?" A page from Luganda version of NLM MedlinePlus Africa Tutorial on Malaria. (Artwork by Kenneth Nek)

Figure 3. Cultural Considerations in Image Creation: it is a common belief that mangoes cause malaria. From NLM MedlinePlus Africa Tutorial on Malaria. (Artwork by Kenneth Nek)

As the medical students field tested the first tutorial they created on malaria, they witnessed tangible results of their success through the integration of the messages of the tutorial with the life of the village, for example villagers cleaning up areas of

Figure 4. Translation of Tutorial into Local Languages in Uganda.

Figure 5. Instruction in the Preparation and Use of Bednets in Mifumi Village.(Photo: William Lubega)

their yards which had previously been breeding grounds for mosquitoes. The testing, in turn, increased their desire for working in the field as "agents of change."

Students, health workers and staffs of clinics can now use the tutorials in both electronic, on computer, CD, or radio, and hard copy formats, as booklet and poster versions, to educate the general public. Through the Community Based Education and Service Program (COBES) at the medical school, students have taken the lead in the distribution of these materials to district health offices, local health centers, youth centers, trading centers, churches, NGOs, and schools in twenty districts.

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Figure 6. Students Nixon Niyonzima, Brian Sseruyombya, and Ronald Kiweewa Take the "Information Intervention"on Malaria Prevention and Treatment to Mifumi Village. (Photo: William Lubega)

Figure 7. Artist Kenneth Nek with Malaria Tutorial Posters on Wall of Mifumi Health Center. (Photo: Julia Royall)

ATION SOURCES

you get information about malaria? (can tick more than one)

Friends ☑ Healthworkers ☐ Health center ☑ Doctor ☐ Nurse sister
onal healer ☐ Drug shop ☑ Radio ☐ Television ☐ Newspaper ☐ Posters

trust the information you get? Yes ☑ No ☐

hy not? Because it helps her to survive.

you ever changed your behavior based on information? If yes, give example.

Yes
- the future would has been fragile.
- Sleeps under a net.

Figure 10. Baseline Survey of Knowledge about Malaria in Mifumi Village 2008. (Photo: Julia Royall)

Figure 8. Mifumi Health Worker Prepares to Use Booklets and Posters in the Field. (Photo: Julia Royall)

Figure 9. The Author with a Mother in Mufumi Health Center as She Uses the Electronic Version of the Tutorial. (Photo: Daniel Hama)

Medical students from Makerere University, Moi University in Kenya, and visitors from Israel complete short residencies at the Mifumi Health Center. The project proves to be an innovative way of supporting the enthusiasm of medical students as well as engaging the interest of the people in the village. Makerere medical students have carried out a baseline survey of over 100 respondents on the community's knowledge about malaria. This survey has been analyzed and will be critical in determining whether an information intervention in electronic and hard copy formats can make a difference in the morbidity and mortality of malaria in this community.

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Figure 11. Ronald Kiweewa, 4th Year Medical Student at Makerere University Talking with Children about Malaria Prevention in Mifumi Village. (Photo: William Lubega)

Figure 13. Bernard, Using Tutorial Booklet, for Educational Outreach at Mifumi Health Center. (Photo: Julia Royall)

Says Nurse Sister Gorretti: *"When we played the CD for them, after that we actually stopped and asked them, have you got any message from what you have just heard, they really say yes. And then when we ask them some few questions that they say the voodoo is not asking, or would not have asked. They say that it helps us to know that they have understood and at the same time they are practicing what they are actually listening to and then whatever was*

Figure 12. Women with Malaria Posters in Mifumi Village. (Photo: William Lubega)

Figure 14. Bernard Guides a Patient through the Malaria Tutorial. (Photo: Daniel Hama)

not said from the CD, they request to know from us in detail. Yes....
"Once you see something, then you believe in it more than if you are told. When you physically see something really happening with your own eyes, you learn from it more than when I tell you. When you see something you really believe in it. And it is very close because it really affects you. You really get it deep in you. It is very possible that you can change behavior from that.....
"They (the patients) were proud that they were learning to do something and they

were very happy with what was produced from the screen. A poster they also see and learn from, but from the screen as they were pressing (the arrows), they were also learning, and they felt that they were doing it themselves....
"It is possible that you can change a life. You can make that change to have a better healthy life." [5]

2.2 Development of a Mental Health Electronic Tutorial in War Torn Northern Uganda.

In the stunning first light in Gulu, the epicenter of more than twenty years of conflict in Northern Uganda, I imagine the nightly pilgrimages made not so long ago by children, escaping the dangers in their villages. Death, rape, mutilation, destruction, and displacement. Their migration would begin as a trickle in late afternoon then turn into a human wave of thousands, sleeping in doorways, on mats, in streets. The kids would carry a few possessions; at times, one could glimpse a small bluebook for schoolwork. [6]

Here, at a new medical school, founded in 2004, I meet with another team of enthusiastic medical students mentored by a dedicated faculty. The dean wants to create an NLM MedlinePlus African tutorial on mental health with a focus on teens [7].

At the mental health unit of the Gulu district hospital, 9,600 cases of mental illness were reported in 2006 and 2007, with more than 4,400 cases reported in the past four months, according to officials. The conditions include post-traumatic stress disorder or PTSD, depression, epilepsy, alcohol abuse, acute psychotic disorders, and chronic psychosis.

Figure 15. Sister Gorretti with Staff and Patients at Mifumi Health Center. (Photo: Daniel Hama)

According to the New Vision, a national newspaper, a recent survey conducted by a team of British and Uganda psychiatrists concluded that the rate of PTSD was higher in northern Uganda than in most other places in the world. For example, out of 1,200 adults assessed by mental health doctors in Amuru and Gulu districts in 2006, 54% were suffering from PTSD. Researchers also found that 67% of the respondents had depression. Health workers report the preponderance of alcoholism with accompanying high levels of suicide, attempted suicide, and depression. Can the use of an information intervention affect the prevalence of mental illness?

Information Intervention for Mental Health in Northern Uganda is a collaborative project of Gulu Medical School, Saturday Vision and Rupiny newspapers, and the U.S. National Library of Medicine (NLM) to encourage community action in management and prevention of mental illness.

As a result of over two decades of war and massive displacement of people, the Gulu Medical School finds itself in the midst of a region plagued by serious issues of mental health. Creating a tutorial provides a "next step" intervention to follow a mental health survey recently carried out in the district by medical students. The mental health problems emerging from the analysis of the survey results will form the basis for the text of the tutorial. Suicide and alcohol abuse rates in the North of Uganda are high, and many students report difficulties at home. Experiencing the effects of years of war only recently turned to peace, and massive displacement of people, the Gulu Medical School has decided to tackle the mental health problems of the region.

Saturday Vision is well known for its successful outreach to young people, engaging them in dynamic interaction through contests and work with teachers. Their process comprises working with the marketing and editorial team to create a manual for schools, briefing teachers, holding focus groups, advertising contests, sending contest guidelines to schools, receiving entries, and publishing the weekly winners with a team of judges awarding final prizes in a formal ceremony. Rupiny is a regional weekly newspaper of New Vision whose reporters are committed to regular coverage of health issues.

Gulu Medical School and the Saturday Vision will work together to create the MedlinePlus African tutorial on mental health, a unique educational tool with a focus on teens ages 12-16 and 17-20. Gulu Medical School will provide the text of the tutorial, based on their recent survey analysis, setting forth four mental health conditions which can be prevented or managed. The medical students will translate the text into Luo, a local language, and will test it for clarity and accessibility as part of their field work.

Using the text, Saturday Vision will meet with their marketing team and then reach teachers, for briefing on the project, and young people in these two age brackets, for focus groups. At this point, there may be a need for Gulu Medical School to provide some revisions, edits, or clarifications.

When the text is set, Saturday Vision and Rupiny will advertise the contest in the paper and accept entries from teens for artwork to illustrate the text. On a weekly basis, entries will be selected for publication with the name of the student, name of the teacher who most helped him or her, age, and the name and location of school. A panel comprising a psychiatrist, a pediatrician, and an artist, from the North or well-versed in the issues of the North, will choose the final selections of artwork for the tutorial. The winners will be announced and awarded prizes at a ceremony. The complete tutorial, including winning entries and text, will be published as a part of the Saturday Vision.

The MedlinePlus African Tutorial on Mental Health will receive regional distribution through Rupiny, national distribution through the Saturday Vision, and electronic interactive international distribution online through NLM's MedlinePlus African Tutorials. An easy to use booklet version of the tutorial with a Teacher's Guide will be

published by New Vision as part of the project and distributed to teachers throughout the North of Uganda.

The evaluation component will be built into the project from the beginning during the initial briefing with teachers and focus groups with students. Teachers and students will be asked what they believe will be successful outcomes. Based on these responses, they will then assess whether or not these outcomes were achieved by the conclusion of the project.

This project presents an excellent opportunity for researchers at Gulu Medical School to further their knowledge about mental health in the region and develop innovative ways of prevention and management. The project could eventually provide a model for use in other settings suffering the effects of war trauma.

3. A prototype electronic health management information system (eHMIS) at Tororo Hospital.

Radiating a youthful presence despite his experienced leadership, Simon Ndira stands in front of a group of staff at Tororo Hospital. He is not an outside expert but was born here and is now back, having spent ten years in Europe working in Internet security in the private sector. His undergraduate degree came from the University of Heidelberg where he is currently completing his PhD. He is at Tororo Hospital to launch Phase 2 of the eHMIS project. It is the end of the day for the weary hospital staff, but they have stayed for the meeting. Simon demonstrates impressive technical skills, managerial knowledge, and vision. He recounts the beginning of the project in 2003 in the mother and child health department with its aim to provide timely, available, and accurate information. The latter has been a problem.

NLM enabled the project to extend to other parts of the hospital. Simon makes sure that the project is not merely a technical exercise but a way to use health systems to save lives. He mentions that there will be many challenges – organizational, managerial, evaluative, social, and cultural. The second phase will focus on accuracy – capturing data correctly and dealing with the ever present challenges mentioned by the group -- power shortage and understaffing. To address the power shortage, Simon says they will work with management to stabilize power through a generator; for the understaffing issue, it may be necessary to reanalyze the workflow and use volunteers. He also talks about the ability of the system to accommodate flags, inter-messaging, and a PDA interface in which treatment can be entered in real time.

The hospital networks with a computer at every critical point. Staff trains on the eHMIS application as well as computer basics, and reports now generate automatically, eliminating paperwork as much as possible.

Soon, the system will be turned over completely to the staff with Simon on standby if needed. This period marks the beginning of the research phase, in which the impact of monitoring, evaluation, and improvement on technical and nontechnical issues affecting the

application will be assessed. Simon and his team will make corrections and measure accuracy. All staff will have access to the reporting module and will be able to make their own analyses. All will engage in the research of what works, what does not, and how to problem solve.

Tororo Hospital will be the first hospital in Uganda and one of the first in the region with an eHMIS [8]. When everything is up and running, the question to be answered will be whether or not the health system functions better electronically, without paper.

It is one thing to continue producing small interventions which are shown to make a difference. It is another to set up a mechanism which promotes development and implementation of innovative solutions on an ongoing basis, connecting human capital and infrastructure with extant agencies whose mission is to improve health.

4. A Menlo Park for 21st Century in East Africa: Promoting Innovation and Entrepreneurship in Health.

In Uganda as well as East Africa, there is no link among medical students post-graduation, their field experiences while in school, and the district health offices and Ministry of Health. In an effort to build on the positive experiences of young people who want to make a difference and engage mentors from a variety of disciplines who have much to offer, the concept for the Center is a web which can draw together creative minds of all ages to make a difference in health in a district, a country, a region.

4.1 Can a health informatics center for research and outreach, focusing on innovation, incubation, and invention, support individual creativity and connect it with health and IT infrastructure?

The potential site for the Health Informatics Center for Research and Outreach in East Africa sits high on a hill, overlooking Lake Victoria. One can easily envision the center as a launch pad for new thinking, new ideas and new ways to connect. The Center may provide an African oriented engine for change, as it links medical students, health professionals, the arts and humanities, business and academic communities, with district health offices.

The purpose of the Center is to provide a base for research, training, development, demonstration, and dissemination of innovative uses of electronic information technology resources to serve positive health outcomes in Uganda and in East Africa in general. An ICT incubator devoted to health does not currently exist in Uganda or East Africa. It will serve as an extension of and an ongoing link among Ugandan medical schools and schools of public health, including Makerere, Mbarara, and Gulu, and the communities of Uganda through the Ministry of Health, District Health Offices, and the Uganda Council of Science and Technology. This bridge does not currently exist in Uganda or East Africa.

The Center's approach brings together interdisciplinary teams to

address issues and challenges in the field of health. Team members come from the fields of medicine, information technology, library science, public health, agriculture, veterinary science, computer science, social science, anthropology, management, business, and the arts. These project teams and experts from a variety of disciplines engage in processes of innovation and implementation of health solutions in Uganda with potential solutions as straightforward as a planning session for a month's work in a village or as complex as a design for cyberinfrastructure to support health care delivery in country. The Center will focus on how information technology resources can support and inform each phase of the research cycle – from the identification of an initial area of interest, population and relationship of variables, to a study plan and research proposal, to actual implementation, reporting, publication, and presentation.

Beyond these traditional phases, the Center will go further in using IT to provide interventions that can alter the morbidity and mortality in a particular village or district with the successful translation and implementation of this research in the field. The research itself will be conducted in the rural communities at sites used for Community Based Education and Service (COBES) programs of the medical schools in Uganda.

The Center will serve as a nexus for the creation of culturally appropriate health communication tools, which are community based and created locally by physicians, artists, health workers, and students – as in the case of MedlinePlus African tutorials [9]. Away from the chaos of the city, the Center will provide a restful and creative setting for discussion, strategic information sharing, and planning to support interdisciplinary, systems oriented approaches. Work at the Center will focus on developing innovations to enhance health care and disease prevention in Uganda and East Africa.

4.2 Purpose of the Center

For students and medical schools, the Center will build on and extend the successful Problem-Based Learning Curriculum and COBES Programs so that communities benefit directly over the long term. The Center will provide a link between the Faculties of Medicine and Public Health and the community on an ongoing basis through involvement by students (COBES), doctors (COBES alumni), researchers, and librarians. It will also provide positive, supported experiences in rural areas for students and young practitioners so that they are encouraged to practice in those areas. Finally, and most important, the Center will train future leadership in the medical and health community, and build local capacity and leadership in medicine, research, informatics and public health for Uganda and East Africa.

4.3 Center Components and Programs

The Center's objectives and activities would comprise four components:

1)To build local capacity in Health Informatics by hosting intense one week hands-on Health Informatics Workshops. Entry to these

workshops would be competitive, and they could be taught by international experts in the field. Interested candidates from the East African Region will be eligible to apply.

2) To strengthen Community Based Education and Service programs by encouraging student initiated outreach projects. These projects will require modest funding and will be awarded competitively to projects from medical students at Makerere University in Central and Southern Uganda, Mbarara Medical School in Western Uganda, Gulu Medical School in Northern Uganda, and at Mifumi village outside of Tororo in Eastern Uganda. The projects will be generated and implemented during the medical students' residencies in the field. They will focus on further research and implementation. As part of this program, students will be mentored in all phases of project management [10].

3) To provide infrastructure for ICT in health by working with MTN and UTL, two large telecommunication service providers in Uganda. The Center could become a technical and programmatic focal point for the expansion of broadband EASSy, East African Submarine Cable System [11] now under construction, so that it supports demonstration ICT projects which may have national or regional value. This infrastructure can provide underlying support for online courses, telemedicine, and access to electronic health resources.

4 To support continuous professional development in rural districts by hosting special seminars and courses in training or idea/concept development: generated by the center or on request by medical schools, ministry, districts, or outside organizations; to investigate Continuing Medical Education (CME) and Evidence-based Medicine (EBM) development as well as use of Global Distance Learning Center (GDLN), to include programs for nurses, clinical officers, paramedicals, and health management.

Each program will need to meet criteria as articulated in the Center's purpose and approach. Each program will be evaluated by the program's organizational sponsors and directors at its conclusion or at regular intervals. Together with program collaborators, the Center will use these reports and evaluations to monitor the impact of the Center and carry out longitudinal tracking

5. Conclusions

Information Communication Technology has come a long way since those early days of low earth orbit satellites. Technological infrastructure can now carry the article on Vitamin A to the medical library or to the researchers, clinicians, or health workers who compose the human infrastructure. But despite significant advances, the challenge remains the same: how can the media best carry the message in a way which results in behavior change for better health. The latter, of course, requires inspiration, perspiration, passion, invention, reinvention, and long term commitment of those intermediaries working in the field.

This chapter offers examples of imaginative problem-solving and communication strategies as the human infrastructure seeks to engage Ugandans in taking charge of their health and becoming catalysts for change. The Health Informatics Center is a potential locus for internetworking the threads of human and technical infrastructure with the needs of the surrounding society. In the words of an Ethiopian proverb, "When spider webs unite, they can tie up a lion."

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Videos

Big Questions in the Future of Health - Overview
Consumer Empowerment Era - Self-care
Big Data and Analytics in Health
Future of Brain's Health
From Artificial Intelligence to Intelligent Health
Future of Drugs and Pharmacology
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