NewsBytes

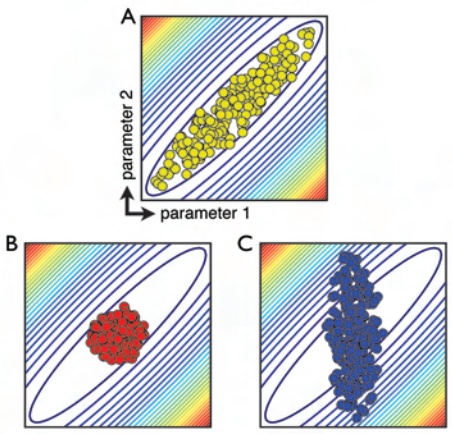
"Sloppy" Systems Biology

Systems biologists seek to model many complex biological interactions all at once. Typically, they input tens or even hundreds of variables to produce predictions about a system—for example, how a cell might react to an environmental signal, or how an animal might respond to a drug. But, researchers have now found, many systems models are strikingly vulnerable to even small changes in the variables, according to a recent analysis of 17 such simulations.

"This pattern we see is universal," says **Ryan Gutenkunst, PhD**, who performed the research under **James Sethna, PhD**, a professor of physics at Cornell University. "It's common among all these models." The work was published in *PLoS Computational Biology* in October 2007.

Typically, modelers scan the literature or perform experiments to define the parameters of a system. But, Gutenkunst notes, such experimental data might not reflect biological reality. For example, an enzyme may function differently in a test tube than it does in a cell. And although scientists knew some models were sensitive to parameter variation, the extent of the problem was elusive.

To test how well models deal with varying parameters, Gutenkunst and his colleagues collected 17 systems biology models, including the yeast cell cycle, circadian rhythms, and others, from the literature and an online database. All 17 examples were vulnerable to producing inaccurate predictions when parameters changed only a small amount. Gutenkunst and his co-authors say this means the models are "sloppy," which doesn't necessarily mean bad. "Sloppy's a descriptive word for the fact that there's all this wiggle room," he says.



In these diagrams of model input, the best predictions result when the input parameters (colored points) are within the central ellipse. The red points in (B) represent what happens when all parameters are measured accurately. In (C), the blue points show how the predictions can become inaccurate when even one parameter is off. In (A), working backward from real data to constrain parameters results in all of the yellow points staying within the ellipse, where predictions are most trustworthy. Courtesy of Ryan Gutenkunst.

The traditional approach to modeling is akin to basic arithmetic: If every number on the left-hand side of an equation (i.e., the parameters) is known, then the answer (the prediction) is calculable. Gutenkunst and his co-authors support an alternative more like algebra: There are unknown variables on the left-hand side, but using a known answer on the right, it's possible to work backwards to define them.

"You can still get good useful predictions out of these models," Gutenkunst says. He suggests plugging in real-life information—the right-hand side of the equation—and searching for parameters that give the correct result. For example, modelers could use experimental data on how yeast grow to determine what parameters will work on the left-hand side of their cell-cycle equation. The researchers found that even if they can't define the parameters precisely, they still get useful predictions.

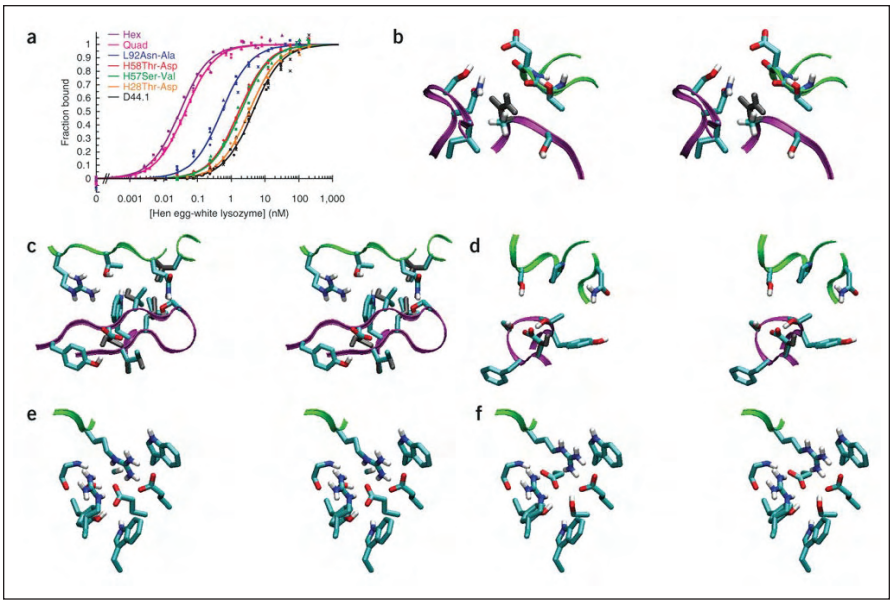
While the algebra approach to modeling is not new, the notion that "sloppiness" pervades biological modeling will apply to many researchers, says **Nathan Price, PhD**, a systems biologist at the University of Illinois at Urbana-Champaign. "What they argue is that it's not even very worthwhile to try to know all these parameters in advance," Price says. "It's a very broad message."

—By Amber Dance, PhD

"Sloppy is a descriptive word for the fact that there's all this wiggle room," says Ryan Gutenkunst.

Turning Therapeutic Antibodies into Better Drugs

The word "antibody" conjures images of our bodies fighting off bacteria and viruses. But because they can latch onto their targets with great precision, antibodies are also used to treat non-infectious diseases such as cancer. Researchers at Massachusetts Institute of Technology have now designed a computer algorithm that manipulates antibodies to predict which forms will bind their targets more tightly. These predictions are then confirmed in



The high specificity of antibodies makes them valuable as drugs, but the conventional process of developing antibody-based drugs is tedious. MIT's new computational approach identifies all possible amino-acid changes in a particular antibody, such as D44.1 (depicted above), predicts the binding strengths of any introduced mutations (a), and models the structures of these mutations (b – f). With this approach, researchers can design a customized antibody that binds more tightly to its target. Courtesy of Bruce Tidor. Reprinted by permission from Macmillan Publishers Ltd: Nature Biotechnology 25, 1171-1176 (2007).

the laboratory. The group's work could lead to significantly improved antibody-based drug design.

"Part of the effectiveness of an antibody-based drug is related to how tightly it binds its target," explains **Bruce Tidor, PhD**, professor of biological engineering and computer science at MIT. He co-authored the work with **K. Dane Wittrup, PhD**, professor of chemical engineering and bio-engineering at MIT, and **Shaun Lippow, PhD**, the paper's lead author and a joint graduate student of both Tidor and Wittrup at the time the work was done. The research was published in the October issue of *Nature Biotechnology*.

Like all proteins, antibodies aren't rigid; they are more like Play-Doh than wooden building blocks. It doesn't take much to affect an antibody's shape. For example, substituting any of the amino acids strung together in a protein chain may alter its final folded shape markedly. Such changes, in turn, impact how strongly the antibodies bind to other molecules.

The biggest challenge in antibody-based drug design has been tweaking amino acid sequences to obtain that 'just-so' fit with the target. Traditional methods miss many possible amino-acid changes that might make the altered antibody bind more tightly. MIT's approach, combining computational structure analysis and experimental lab chemistry, may provide the missing link.

The computer algorithm works by first modeling the physical interactions that make a particular antibody latch onto its target. It then rapidly identifies all possible amino-acid substitutions for that antibody and calculates which of those changes will tighten binding. Researchers can introduce mutations that improve antibody function but might never arise naturally or with conventional techniques, and they can predict the effectiveness of these mutations.

The researchers experimentally verified their model on a drug called cetuximab (trade name Erbitux®, used to treat colorectal cancer). With guidance from the computer program, they synthesized a new version that binds 10 times more strongly to its target, a molecule called epidermal growth factor receptor. They also created a revised version of an antibody (D44.1) that is useful in laboratory experiments. It has a 140-fold improvement in binding affinity.

"This represents an interactive collaboration between calculation and experiment," says Tidor. "The ability to have tight feedback cycles between predictions and testing was essential to our success in this work."

Janna Wehrle, PhD, program director of the biophysics branch at the National Institute of General Medical Sciences, is enthusiastic about the new model. "Dr. Tidor and his team have developed a method that will allow much of the design work to be done on the computer, saving months or years in the lab," she says.

—By Alissa Poh

Protein Structure Prediction: Getting it Right

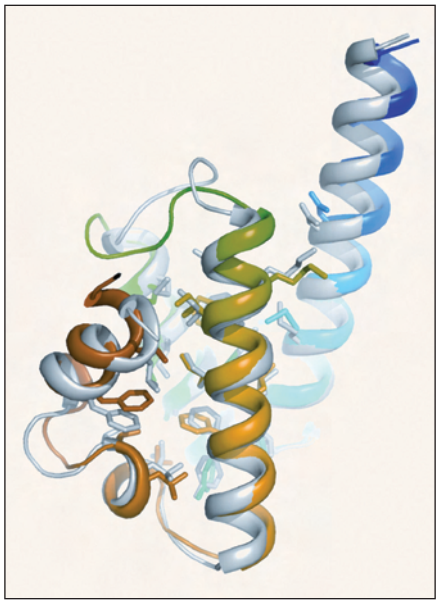
When nature folds an amino acid sequence into a protein, it usually knows that just one conformation is the right one. But when a computer tries to do the same thing, it often predicts multiple possible shapes. Now, a team of scientists at the University of Washington, led by biochemistry professor **David Baker, PhD**, have made a significant advance toward predicting which of the multiple structures is correct. They also accurately predicted a small protein's structure without relying on X-ray crystallography.

To predict a protein's structure, researchers must find the arrangement of the individual amino acids that represents the lowest energy form. It's kind of like gravity, notes Baker. "If you drop a ball on a hill, it rolls to the bottom of the hill." For proteins, that spot represents the most settled overall shape, a compact blob of amino acids linked into helices and sheets. In the past, it was hard to figure out when a predicted structure truly reached its lowest possible energy, not just an intermediate step. "If you

"I crunch for Rosetta because I believe in this project wholeheartedly," says blogger Antony Magnus.

drop a ball on a bumpy landscape, it may get stuck in a [higher] valley," Baker says.

For a number of years, the Baker team's primary tool for predicting protein structures has been Rosetta@Home, a program that relies on a staggering amount of computing power. "We employ the computers of about 150,000 volunteers," Baker says. Volunteers install Rosetta@Home on their computers. It runs like a screen saver while the computer is otherwise idle. The program calculates many possible structures for an amino-acid chain and sends promising structures to the researchers. A central computer then searches for the lowest-energy structure, in which the chain curls up most comfortably.



Using Rosetta@Home, a program that runs on the personal computers of 150,000 volunteers worldwide, David Baker's team predicted the structure of a 112-amino-acid protein from scratch. The predicted structure (gray) closely mimics the true protein structure (in color).

His team's new research, published online in *Nature* on October 14, 2007, describes a major refinement to Rosetta@Home that searches for a way out of "energy valleys." The team fine-tuned how Rosetta analyzes the toughest protein sections. If the program consistently predicts the same folded shape, the answer is probably correct. But when Rosetta churns out many different solutions, the program now recalculates those error-prone regions in search of the lowest possible energies—and more robust final shapes.

The refined method makes it easier to get useful data from traditional protein-structure experiments, in which researchers blast X-rays at protein crystals. Baker's lab also used the method to predict an accurate structure for a small protein (112 amino acids) with no X-ray data, an achievement noted in a *Nature* commentary as "a real breakthrough."

The new research is "a significant milestone in the development of methods to model protein structure from amino-acid sequence," comments **John Moult, D. Phil.**, a professor of computational biology and biophysics at the Center for Advanced Research in Biotechnology in Maryland.

Rosetta@Home's clan around the world savors the success. As volunteer **Antony Magnus** wrote in an online message board: "I crunch for Rosetta because I believe in this project wholeheartedly." Volunteers interested in participating in Rosetta@home can sign up at boinc.bakerlab.org/rosetta.

—By Erin Digitale, PhD

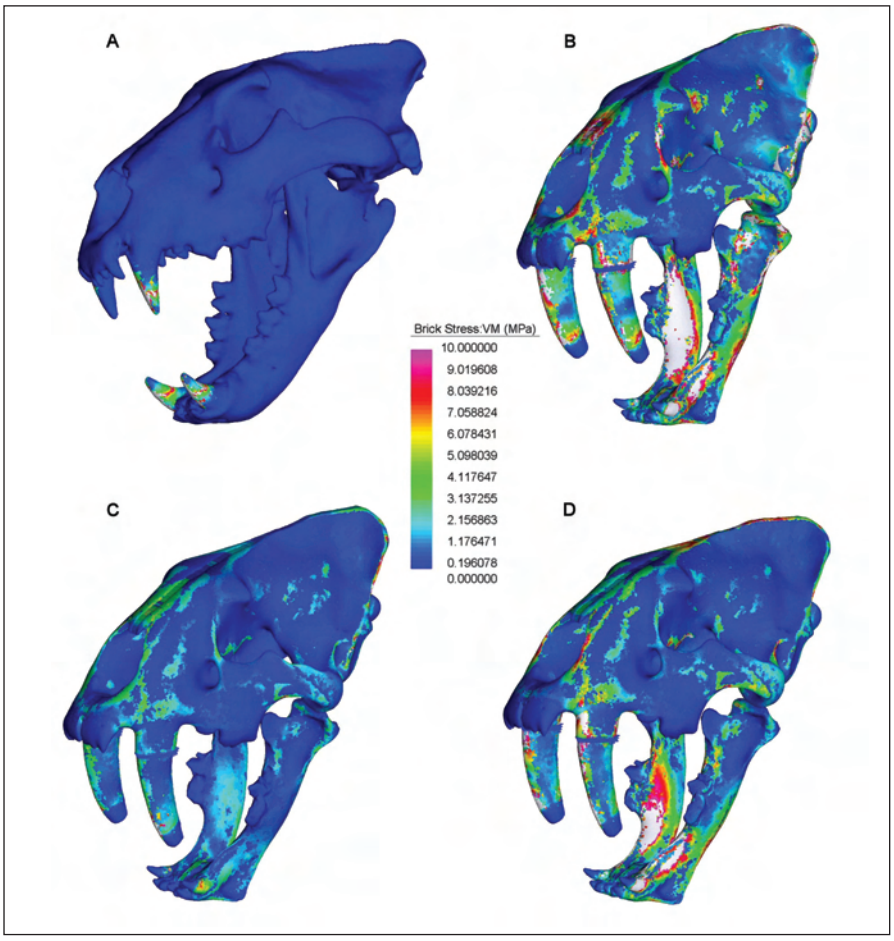
Extinct Sabercat Brought to Life

Wildlife biologists can watch a lion stalk its prey, but paleontologists must examine fossils to understand how the extinct saber-toothed cat hunted. Researchers now have modeled an American sabercat's skull with software designed for stress testing in engineering, building the highest resolution vertebrate animal model to date. They found that the sabercat's massive teeth belied a surprisingly weak bite.

On a computer, "you can crash test a biological design," says **Colin McHenry**, a doctoral candidate at the University of Newcastle, and lead author of the work. His team built a virtual sabercat skull that could display the effects of stress down to cubic millimeter resolution. Stress resistance indicates how hard the cat could bite and which muscles contributed the most force. The study appeared in the October 9, 2007 issue of the *Proceedings of the National Academy of Sciences*.

Despite more than 150 years spent studying sabercats, scientists have yet to agree on the animal's biting power and the relative importance of head and neck muscles. In recent years, researchers have turned to computer simulations to reconstruct the musculature of extinct animals. They use the finite element method (FEM), a system originally designed to test aeronautical designs under stress. Until now, FEM studies featured animal skulls modeled as though bone has the same strength and density throughout—which it doesn't. And they didn't account for moving jaws.

To create a more lifelike simulation, McHenry's team used a standard medical imaging technology, computed tomography, to build high-resolution FEM models of sabercat and (for comparison) lion skulls. The individual elements that make up this 3D model mimicked realistic bits of bone with different strengths. The team then added musculature, estimating the sabercat's muscle sizes and strengths from the skull's geometry. After subjecting both



A high-resolution model of a lion's skull (A) shows little stress compared to a model of an American sabercat skull (B) when researchers apply lateral forces to simulate thrashing prey. Twisting forces (C) and forces pulling forward on the canine teeth (D) also illustrate the stresses a sabercat might have encountered while killing animals. Courtesy of Colin McHenry.

models (sabercat and lion) to the forces of struggling prey and the pull of the animal's own muscles, they mapped the resulting stresses.

The sabercat skull generally handled forces poorly, while the lion skull took them like a tank. The researchers concluded that the sabercat didn't land powerful bites, and that the jaw muscles may have required help from the neck muscles to puncture prey. These results support existing arguments that sabercats killed with piercing canine tooth bites, but there was still debate about the bite force, says McHenry. The sabercat probably bit one-third as hard as a comparably sized lion, the team concluded.

The next step is to account for the way bone responds to pressure from different directions, a method called anisotropic modeling, says **Lior Horesh, PhD**, a post-doctoral research fellow in Emory University's department of mathematics and computer science. Horesh calls the team's research "one good step forward."

McHenry and his colleagues soon will apply FEM modeling to biomedical questions, including mechanical evaluation of surgical planning procedures and stress-testing of prosthetic devices. "I think the medical community can learn a lot from paleontologists and biologists," he says.

—By Hayley Rutger

Center of Mass Controls Balance

Bumped from behind, a person may step forward to avoid falling. Perhaps her arms fly out as well. To the untrained eye, these movements seem like the result of the brain controlling individual nerve and muscle reflexes. Yet an elegant new model of balance control suggests the brain only cares about one thing: the body's center of mass. This possibility, modeled for the first time, could help rehabilitation experts design better treatments to suit the specific needs of each balance-impaired patient.

"People had theories about the center of mass being important, but they hadn't actually demonstrated in a causal sense that it was critical," says **Lena Ting, PhD**, assistant professor of biomedical engineering at Georgia Institute of Technology and Emory University and co-author of the work published in the October 2007 issue of *Nature Neuroscience*. "We've shown that the nervous system controls the arms and legs to regulate center of mass motion."

Neuroscientists have tested a variety of hypotheses such as whether balance originates from motions of the head or the ankle. But these hypotheses have not consistently predicted which muscles would spring into action when a person loses balance. Ting's previous experiments found that the only way to foretell muscle reaction accurately was to monitor the direction of the fall, not individual joint angles. This suggested that the body's reflexes during a fall involve a higher level of control: If the center of mass is off-kilter, the nervous system will act to bring it back to balance.

To explore this idea in action, the researchers placed cats on a moving platform that made them lose their balance. The team also induced sensory damage in the cats that triggered balance-control problems. A computer simulation created by the researchers accurately predicted the reactions of the cats' muscles based on the motions of their centers of mass.

In addition, the cats with sensory damage regained balance within a few days. They used different sensory pathways to do the same balancing tasks, resulting in unique patterns of muscle activity. While these muscular adjustments were clinically "abnormal," they were close to optimum for the balancing task at hand. This result should earn notice from balance rehabilitation professionals, Ting says; they now have an accurate, unique goal toward which they can aim each patient's rehabilitation efforts.

Biomedical engineer Lena Ting (right) prepares to measure how a volunteer's muscles react when her balance is disturbed by a moving platform. Courtesy of Georgia Institute of Technology.

Ting's group has provided an attractive, simple model of posture control, says **Fay Horak, PhD**, a senior scientist at the Neurological Sciences Institute of the Oregon Health & Science University. "The big implication is that something this complicated, that involves many, many joints and muscles, could be controlled by the nervous system regulating a single parameter," she says.

Horak believes researchers need more data before applying Ting's results to humans with balance disorders. Ting concurs, noting that her team has started using the moving platform to test human balance reactions.

—By Jane Liaw

A Model of Epstein—Barr Virus

During our lives, most of us will come in contact with the Epstein-Barr virus, commonly known as that bane of teenagers, infectious mononucleosis. Now, a new simulation mimics the virus's infection cycle on the tonsils, shedding some light on how the infection spreads.

"The actual biology is so complicated," says **David Thorley-Lawson, PhD**, professor of pathology at Tufts University who co-leads the project with **Karen Duca, PhD**, a biophysicist formerly at the Virginia Bioinformatics Institute (now at Kwame Nkrumah University, Ghana). "But what we got out of the simulation looks remarkably like a real infection." They and others developed the Pathogen Simulation (PathSim) model published in the October 2007 issue of *PLoS Pathogens*.

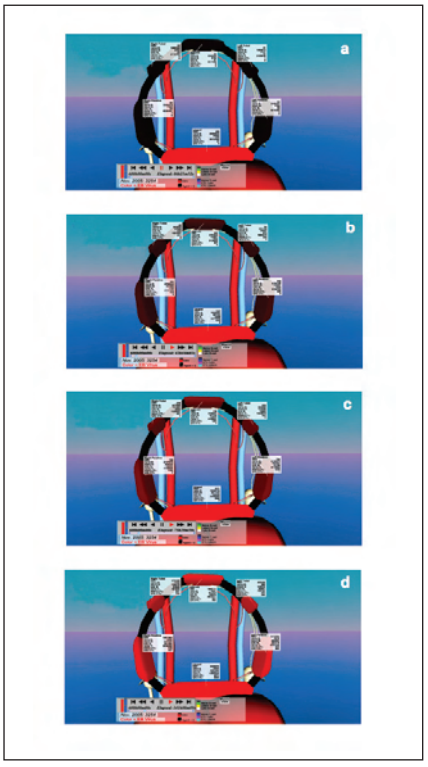
The potential benefits of modeling infection seem endless. Scientists can raise the viral load in ways that would be unethical in humans; and insight into the dynamics of infection could lead to novel therapies. But the question remains: Do the models truly replicate how infection spreads in the body?

Until now, most computer modeling only reproduced general properties of the immune system, or involved the use of differential equations to provide more specific insights, such as with some HIV models. Using a well-studied virus like Epstein-Barr as a guide, Thorley-Lawson and colleagues believed they could create a model that rivaled the sophistication of HIV models while remaining comprehensible to nonspecialists.

"One of the main goals was to have models that biologists could look at and say, 'Oh, I get that,'" says Thorley-Lawson. To accomplish this goal, the researchers created a ring of tonsils—the point of attack for Epstein-Barr virus—on a virtual grid.

During the simulation, the virus infected cells at about the same rate it does in a person. "This suggests we're not missing huge parts of the biology," says **Michael Shapiro, PhD**, co-lead author and lecturer in pathology at Tufts.

Already, the model has helped explain a clinical puzzle. Several years ago, Thorley-Lawson and his team found that when Epstein-Barr causes infection *in vivo*, only 0.5 to 1.0 percent of the host's B cells—key sentinels of the immune system—replicate the virus. At the time, the researchers didn't know why that replication rate was so low.



The PathSim model predicts that infection begins on the lingual tonsil (at the base of the ring) and spreads evenly (increasing red color) to the other tonsils through the bloodstream, instead of spreading through the ring directly from one tonsil to the next. Courtesy of David Thorley-Lawson.

When an almost identical proportion of the model's B cells were active at the same stage in PathSim, Thorley-Lawson and his colleagues increased the number of B cells replicating the virtual virus to see what would happen. This tinkering "killed" the virus's host by overwhelming it with infected B cells. According to PathSim, the virus has honed in on the speediest possible replication rate while still keeping its host alive—thus ensuring its further spread.

"This is a very nice first step," says **Alan Perelson, PhD**, a biophysicist at Los Alamos National Laboratory. He acknowledges that as PathSim becomes more complex, it will rely on more biological assumptions. Still, he says, "The model looks like it's driving some new experimentation."

—By John Cannon

A Digital Human Could Advance Medicine

Science and medicine have fractured the human body into pieces: the cardiovascular system, the immune system, the endocrine system. Now a European initiative seeks to put the jigsaw puzzle back together by developing a computer model of a complete human being. The Virtual Physiological Human (VPH) would encompass all the knowledge we've gathered, from genetic interactions to systems biology, into one integrated digital package.

"If you thought the genome project was big work, this is probably a million times more complicated," says Marco Viceconti of the Virtual Physiological Human.

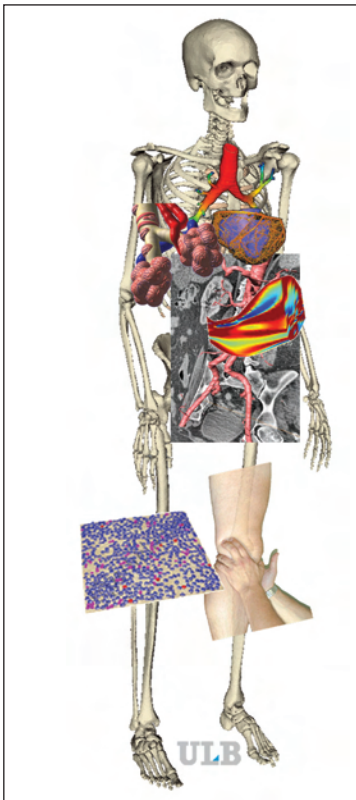
"If you thought the genome project was big work, this is probably a million times more complicated," says **Marco Viceconti, PhD**, scientific officer of the Strategy for The EuroPhysiome (STEP), a coalition of leaders from research, industry, and clinical practice who hope to create the virtual human. "This is not something you will ever finish."

In recent years other groups have begun digital modeling of various human processes, including two other worldwide projects to assemble our physiome—a complete description of human physiology. To prevent fragmentation, all projects are communicating under an umbrella organization called the World Integrative Research Initiative. They will share technology and computer infrastructure, and will agree on common terminology.

Researchers in the VPH initiative, funded by the European Commission, plan to build the virtual human piecemeal by linking each model as it's created. A brain aneurysm model is already under way. If clinicians could predict which aneurysms are unlikely to rupture, they might avoid unnecessary brain surgeries. Scientists working on the project (called @neurIST) are gathering genetic and metabolic data from patients with aneurysms, which they will feed into a computer model to develop a predictive algorithm.

Candidates for other initial projects include disease models for diabetes and osteoporosis. The European Commission is running an evaluation process to select projects for funding starting in early 2008.

It may take at least a decade before a complete virtual human exists, but Viceconti hopes some pioneering applications such as the aneurysm model will soon deliver benefits. An early goal is reducing the costs and risks of drug development by first testing drugs on a virtual patient to gauge harmful side effects. Eventually, physicians could use the virtual human for better diagnosis and treatment by programming it with a patient's specific data, yielding a unique assessment of how certain drugs might affect him or her.



The Virtual Physiological Human will integrate digital modeling at all levels—genetic, cellular, tissues, organs, and systems—into one complete package that will be useful in medicine and research. Courtesy of Serge Van Sint Jan, Université Libre de Bruxelles.

"There's a very strong focus in the EuroPhysiome on modeling for clinical applications," says **Peter Hunter, PhD**, director of the Bioengineering Institute at the University of Auckland and representative of the IUPS Physiome Project, one of the other international physiome initiatives. He sees the EuroPhysiome as complementary to his project.

A strong spirit of international collaboration will help the EuroPhysiome succeed, says Viceconti. "This is definitely a team science exercise."

—By Madolyn Bowman Rogers, PhD

Virtual Genomic Scans with Real Data

Trying to find the genetic causes of a human disease requires lots of data. These days, researchers scan the genomes of people who do and don't have a particular disease and look for genome-wide associations between a particular disease and a gene or genes. But they'd like to know if their findings are statistically valid. Moreover, the variety of disease models currently in use have led to debates over which work best. Now, researchers have developed a new tool that they hope will help resolve these issues and will also work with any genotyping platform in use. Their software generates large simulated populations using present-day genetic information from specific populations.

"The main challenge is working out how you draw from real data to mimic what you expect to happen in a disease model situation," says **Fred Wright, PhD**, a biostatistician at the University of North Carolina and senior author of a study published online in September 2007 in the journal *Bioinformatics*. "Because of that, we developed a method that's simple, almost dumb, in the way it approaches it."

Current statistical simulations either work backward to generate genetic "histories" that might give rise to present-day forms, or else they go forward, simulating genetic data from the distant past until the present day.

To present a more accurate simulation grounded in real data, Wright's method—called HAP-SAMPLE—now offers a third option: using data from a real population to generate a large sample set against which genes of interest can be checked. Because the data already contain realistic historic mutations, there's no need to let the population evolve (developing new mutations) over time. Instead, HAP-SAMPLE generates simulated populations solely by meiosis and its associated crossovers—it's that simple.

The real genetic data is supplied by HapMap, an international database that catalogs 10 million common genetic variations (single nucleotide polymorphisms or "SNPs") within three populations—Caucasian European, Chinese /Japanese, and Nigerian.

HAP-SAMPLE is potentially valuable to researchers who have identified a possible gene-disease association and want to see how it would play out in a larger population. For example, would the same SNP still be a significant contributor to the disease of interest in a larger population? By comparing the resulting simulated data against known SNPs, they can figure out how good their statistical methods are.

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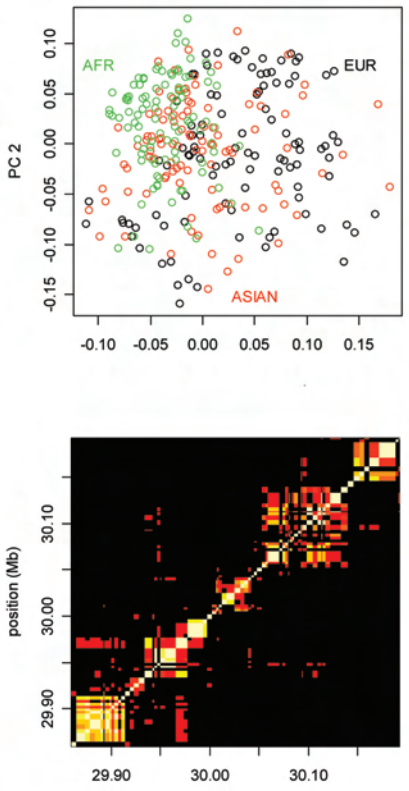
"HAP-SAMPLE is great because it takes real data as the template for the simulation," says **Marylyn Ritchie, PhD**, a computational geneticist at Vanderbilt University, whose lab developed a complementary simulation tool. Still, she adds, HAP-SAMPLE's usefulness is limited by HapMap's small chromosome pool: Fewer than 400 people represent the three populations. For some researchers, having a real data template might not overcome the problem of limited population size, Ritchie cautions.

"What they're asking for is just a broader population base," Wright responds. His team does plan to augment HAP-SAMPLE soon with updates from other genetic databases.

—By Massie Santos Ballon



HAP-SAMPLE simulations accurately reflect population ancestry and how often different SNPs are inherited together. At the top, we see that for the disease gene in question, three distinct populations (AFR= Nigerian samples; EUR= Caucasian European samples, ASIAN= Chinese/Japanese samples) are only mildly different from one another. The heatmap at bottom plots SNPs against one another based on their chromosomal positions. Areas of brightness (white is strongest) indicate SNPs that are likely to be co-inherited in the Caucasian European data. Courtesy of Fred Wright.

Homing in on the Minimum Genome

Scientists have long wondered how many genes are necessary to support life. This knowledge could be used to construct new forms of artificial life to efficiently produce better biofuels or drugs.

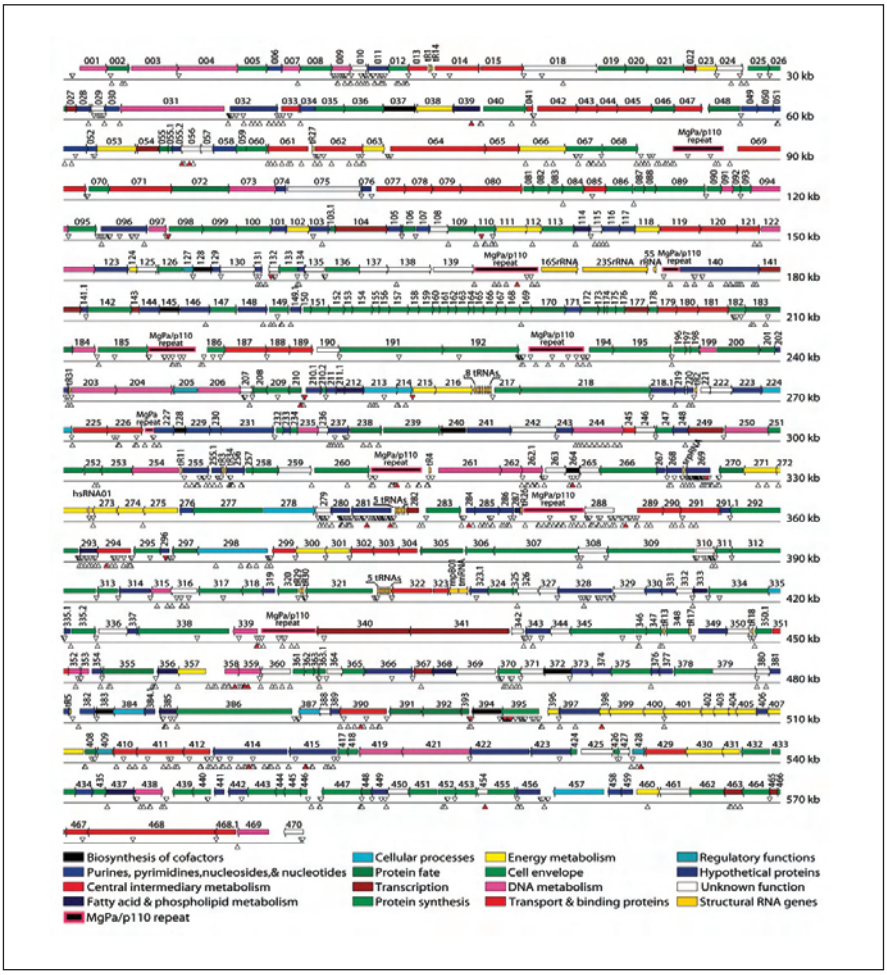
Now, computer scientists are using hypothetical synthetic bacteria to screen out inessential genes as a way to home in on the "minimum genome." The remnants, they hope, should make good candidates for synthesizing artificial organisms and reduce the number of costly experiments required to achieve that goal.

"If your hypothetical organism does not survive the simulation, the chances are high that it would not survive in reality," says **Roberto Marangoni, PhD**, professor of bioinformatics at the University of Pisa and senior author of the study in the September issue of *PLoS Computational Biology*.

Scientists plan to build the minimum genome by culling unnecessary genes from *Mycoplasma genitalium*, a bacterium with one of the smallest known genomes. At just 521 genes, *Mycoplasma's* genome is about one fiftieth the size of the human genome. In an earlier attempt to find an "essential" set of genetic instructions (published in 2006), **J. Craig Venter, PhD**, of the J. Craig Venter Institute, and his colleagues shaved that number from 521 to 382 by disrupting each gene one at a time. They excluded from their hypothetical minimum genome all the genes whose disruption did not kill the bacteria.

Eventually, if lab scientists try to build artificial life from scratch, testing potential minimum genomes would be a time-consuming and expensive trial-and-error process. Researchers will need a way to increase the chances of hitting the right set of genes on an early try, Marangoni says.

To address that problem, Marangoni and his team created a computer simulation to test the viability of theoretical bacteria with a variety of possible minimum genomes. They gathered all chemical reactions known to take place inside *Mycoplasma* and ran recurring simulations of all of these reactions, assuming different sets of genes were present. The team looked for genomes that, over the course of many repeated reactions, produced a life-friendly balance of the reaction products in the cell. The simulations of some virtual creatures resulted in wildly fluctuating chemical levels, or levels that bottomed out almost immediately—conditions that would not sustain actual life.



Scientists hope to create synthetic organisms using the minimal gene set possible to sustain life. They plan to base this minimum genome on that of the bacteria* Mycoplasma genitalium*, which has a paltry set of 521 genes. In this graphic, each of* Mycoplasma*'s genes is a colored bar. Courtesy of Hamilton Smith and John Glass, J. Craig Venter Institute.

Some previously proposed minimum genomes failed this test. These creatures' energy supplies went to zero very quickly, Marangoni says, which is probably what "killed" them.

Marangoni's work is promising, but not the final word, says **Arcady Mushegian, PhD**, director of bioinformatics at the Stowers Institute for Medical Research, "There will have to be more computer estimates of genes and how they fit together in the metabolic puzzle," he says. "And of course ultimately the actual organism should be engineered."

—By Rachel Tompa, PhD

Simulating a Scaffold for Bone Growth

Designing a scaffold, the internal structure that helps patients regenerate bone, is a delicate balancing act. The scaffold must be strong enough to protect the injury, porous enough to allow nutrients to pass through, and fast-dissolving enough to make room for new tissue. Now, using a 3-D computer model, scientists have simulated stem cells growing within a scaffold to predict which combination of these properties will produce the most bone.

"It's the first 3-D computational work that takes account of stem cells" in scaffold design, says senior author **Patrick J. Prendergast, PhD**, a professor of bioengineering at the University of Dublin, Trinity College.

Patients rely on scaffolds to support bone regeneration after surgeries such as bone grafts, cartilage repair, or tumor removal that requires bone to be cut away. Most scaffolds are either made of gels, which tend to be weak, or stiffer materials such as coral, which may not completely dissolve. In the past, scientists evaluated scaffold materials by testing them on animals. At the same time, computational biologists devised algorithms predicting how a patient's stem cells might differentiate into new types of tissue during healing. But until now, no one had simulated the scaffold alongside the stem cells as a way of improving scaffold design.

Prendergast's group created a 3-D computer lattice model of a scaffold, then planted "seeds" inside the lattice to represent the patient's stem cells. In their simulations, the cells multiplied, spread, and eventually transformed into bone, cartilage, or connective tissue depending on the strain and fluid pressure affecting each cell.

"It's the first 3-D computational work that takes account of stem cells" in scaffold design, says Patrick J. Prendergast.

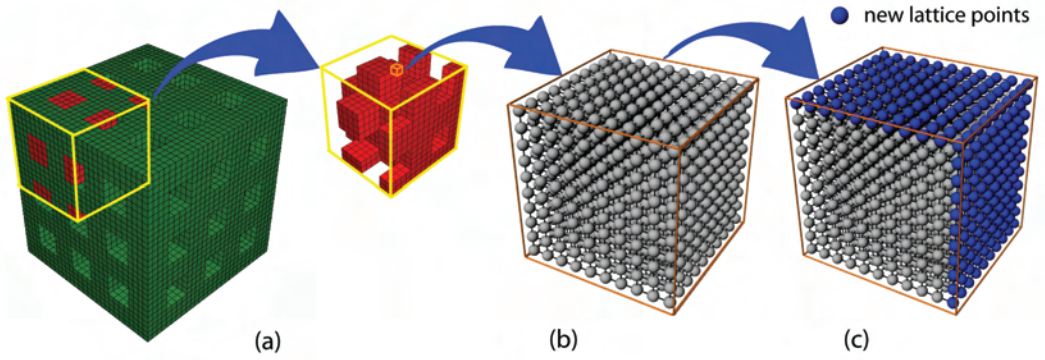
Meanwhile, the program tracked the progress of the scaffold as it slowly dissolved and became more porous, clearing room for new tissue. The scientists tried various combinations of scaffold properties and tested the system under high and low load-bearing conditions to simulate injuries in different parts of the body. A leg bone, for instance, bears more load than an arm bone and might heal differently.

The researchers found that the scaffold only works if it has the right balance of pore size and disintegration rate. If both are too high, "It won't be long before the whole thing dissolves away," says Prendergast. They also found that the load on the area changes how scaffolds perform, suggesting that scaffold designers should tailor their materials for specific patients and body parts. The work appears in the December 2007 issue of *Biomaterials*.

Studying the interplay between cells and synthetic materials is promising because most people focus on only one, says **Christopher Jacobs, PhD**, director of the Cell and Molecular Biomechanics Laboratory at Stanford University. "I think that's a very creative concept," he says. The work needs to be verified with further experiments, says Jacobs, but could potentially direct the design of better scaffolds that both offer enough support and dissolve completely into the body.

Toward that end, Prendergast and his colleagues plan to simulate blood vessels growing in scaffolds, which can affect bone regeneration.

—By Roberta Kwok □



Granulation tissue (red), a mixture of tissue matrix and cells that develops early in wound healing, fills a bone regeneration scaffold (green) that's 50 percent porous. Zooming into small portions of the tissue, we see a lattice (grey) containing stem cells, which multiply and develop into new tissue (blue) that replaces the dissolving scaffold. Courtesy of Damien P. Byrne. This article was published in Biomaterials, Volume 28, Damien P. Byrne, Damien Lacroix, Josep A. Plannel, Daniel J. Kelly, Patrick J. Prendergast, "Simulation of tissue differentiation in a scaffold as a function of porosity, Young's modulus and dissolution rate: Application of mechanobiological models in tissue engineering," p. 5544-5554, Copyright Elsevier (2007).