Chapter 9
Systems Health: A Transition from Disease Management Toward Health Promotion

Li Shen, Benchen Ye, Huimin Sun, Yuxin Lin, Herman van Wietmarschen, and Bairong Shen

Abstract To date, most of the chronic diseases such as cancer, cardiovascular disease, and diabetes, are the leading cause of death. Current strategies toward disease treatment, e.g., risk prediction and target therapy, still have limitations for precision medicine due to the dynamic and complex nature of health. Interactions among genetics, lifestyle, and surrounding environments have nonnegligible effects on disease evolution. Thus a transition in health-care area is urgently needed to address the hysteresis of diagnosis and stabilize the increasing health-care costs. In this chapter, we explored new insights in the field of health promotion and introduced the integration of systems theories with health science and clinical practice. On the basis of systems biology and systems medicine, a novel concept called "systems health" was comprehensively advocated. Two types of bioinformatics models, i.e., causal loop diagram and quantitative model, were selected as examples for further illumination. Translational applications of these models in systems health were sequentially discussed. Moreover, we highlighted the bridging of ancient and modern views toward health and put forward a proposition for citizen science and citizen empowerment in health promotion.

Keywords Systems health • Systems biology • Complexity • Critical transitions

L. Shen • B. Ye • Y. Lin • B. Shen (✉)
Center for Systems Biology, Soochow University, No.1 Shizi Street, Suzhou, Jiangsu 215006, China
e-mail: bairong.shen@suda.edu.cn

H. Sun
Collaborative Innovation Center of Sustainable Forestry in Southern China of Jiangsu Province, Nanjing Forestry University, Nanjing 210037, China

H. van Wietmarschen (✉)
Louis Bolk Institute, 3972, LA, Driebergen, The Netherlands
e-mail: H.vanWietmarschen@Louisbolk.nl

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9.1 Introduction

Over the last several decades, the pace of life is rapidly increasing. A modern lifestyle is often characterized by demanding jobs, families in which both parents work and care for children and other family members, and a busy social life. Attempts to sustain this kind of lifestyle are often accompanied by stress [1], late work hours, sleep problems [2], no time to cook, unhealthy diet [3], and too little exercise [4]. As the population ages, the amount of people suffering from lifestyle-related diseases such as cardiovascular disease, cancer, diabetes, COPD, and Alzheimer is soaring [5]. Unhealthy lifestyle combined with an aging population results in an increasing demand on health-care resources. Unfortunately, the current health-care system is failing to respond appropriately to meet this demand, resulting in high health-care cost in many countries, especially in developing countries. Scientists and doctors are working on several strategies in order to relieve the current pressure on the health-care system. However, health-care professionals themselves as well as medical students count among the highest numbers of burnout cases showing an inability to regulate their own stress levels adequately [6].

One strategy is further improving disease management. In 1996, Dr. Robert S. Epstein and Dr. Louis M. Sherwood clearly put forward the definition of disease management that disease management refers to the use of an explicit systematic population-based approach to identify persons at risk, intervene with specific programs of care, and measure clinical outcomes [7]. Since then, disease management has become an effective way for medical care. Doctors give patients advice on how to manage a chronic disease like diabetes and hypertension. Patients learn to take responsibility for understanding how to take care of themselves. They work together to avoid potential problems and exacerbation, or worsening, of their health problem. This was a quite effective approach, which increases patient satisfaction and improves their quality of life. However, there is no evidence that the primary goal of disease management, controlling health-care costs, is actually reached [8–10].

Another strategy developed in past decades is targeted therapy for complex diseases [11]. This brought chemical drug therapy into a new age. One main reason for this change is that single-target therapy can effectively relieve the side effect which usually appears in traditional broad-spectrum chemical drug therapy. Based on a large amount of OMICS data generated in recent years, as well as the rapid development of computer technology, bioinformatics, and cheminformatics, computer-aided drug design (CADD) has become an efficient tool for novel specific drug design for corresponding targets [12]. More and more novel single-target drugs have been designed and have been commercialized. However, for more than 80 % of the diseases, there is still no effective therapy currently.

Most of the medical care programs are based on linear thinking. The disease management and single-target therapy mentioned above are good examples for this. One of the reasons that these strategies are not optimal for treating chronic diseases is that these strategies lack a consideration of the holistic nature of human beings.

Most chronic diseases are complex lifestyle-related conditions resulting from a disturbance in a combination of biological, psychological, social, spiritual, and environmental factors [13]. An optimal strategy for managing chronic diseases should therefore consider biology, psychology, and social environment together. More holistic approaches, sometimes called systems medicine approaches, have increasingly been developed and applied in the area of medicine over the last 10 years [14]. This has provided traditional medicine with new insights and guides us entering a new era of medical care. In recent years, more and more evidence is showing that our current health-care strategies have reached a tripping point. We need a shift from disease management toward existing knowledge, tools, and technology for health promotion. The aim of this review is to explore new insights in the area of health promotion and to introduce the integration of systems thinking with health-care science and clinical practice.

9.2 Complexity and Health

Here we divide the concept of health network into two parts, i.e., inner body network and environment network, for clear discussion. Our body can be considered as a complex system consisting various organs and units connected into one another. There is a widespread existence of self-regulating and adaptability mechanism at all levels and all part of the body. The interaction and mutual effect between related items can maintain the stability of human body vital signs and maintain the life activities of the body. One key reason why human body can deal with various external factors effectively is that our body is a dynamic system. Here we take 100K Wellness Project as an example. In 2014, Dr. Leroy Hood brought forward a new medical project in order to further promote P4 medicine [14, 15] (Fig. 9.1). The idea of this project is to take 100,000 well patients to carry out a detailed data collection in genomic, proteomic, metabolic, epigenetic, and phenotypic levels through examining patients' blood, saliva, stool, and other physiological and psychological factors. Only when every index in this examination stays in a reasonable range can patients present healthy situations. This project enhances the importance of precision medicine, and at the same time, it reflects the significance of system dynamic balance in human health. But there are two major drawbacks of this approach. The first one is the lack of measurements at various time-points and therefore a lack of insight into the changes of the system over time and the relationships between various changes over time. The second drawback is the limitation to the consideration of the inner body system only. For health promotion, we cannot ignore our surrounding environment (Fig. 9.2), such as our families, communities, workspace, as well as personal lifestyle. All of them are linked together. For example, if one person's friends and colleagues have positive lifestyle and willing to share with you, your lifestyle will be naturally changed over time. One's lifestyle plays a key role in personal health. Besides our social environment effects, natural environment effects also should be taken into account. Relevant

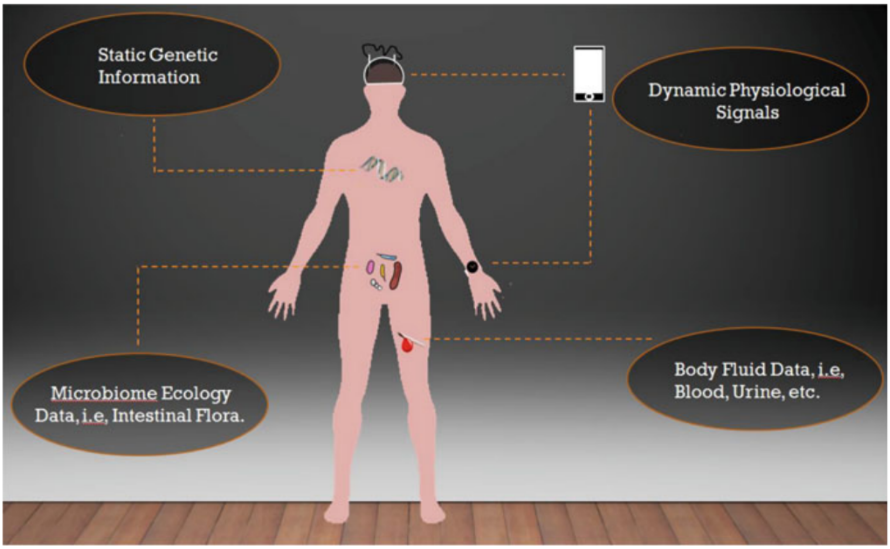

Fig. 9.1 The paradigm of personal examination in 100K Wellness Project

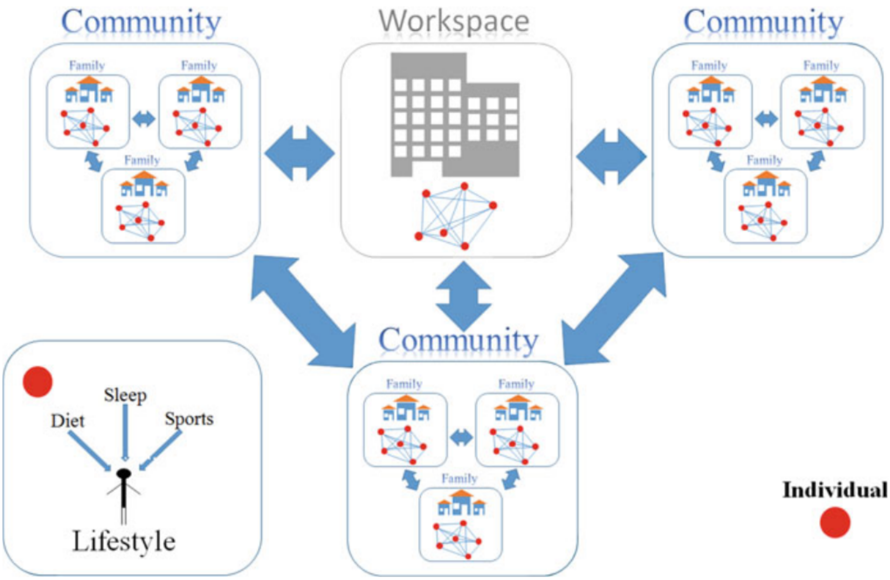

Fig. 9.2 Health emerges from interactions within and between nested systems, i.e., families, communities, and workspace. The *red points* here represent individuals in these systems

researches have shown that many diseases, especially vector-borne diseases, are strongly associated with climate change [16]. Luis Fernando Chaves et al. found that cutaneous leishmaniasis, an emergent disease with increasing number of patients in the Americas, has a dynamic link with local climate cycles [17]. Researches in dengue fever, West Nile fever, and malaria also got the similar results and further support the linkage between disease and natural environment [18–21].

Complexity science offers methods to observe the dynamics of systems, as well as trajectories of changes within the dynamics [22]. It appears that lifestyle is developed over time into very stable habit patterns, which can be healthy patterns or patterns resulting in disease [23–25]. These habit patterns emerge from upbringing, role models, peer groups, social environment, and other factors [26]. This is one of the reasons that an unhealthy diet is so hard to change, despite large amounts of books about healthy diets [27]. Complexity science also shows that an unhealthy stable system might be changed into a healthier stable system through specific triggers. One well-known trigger is a life-changing event such as receiving a diagnosis of a life-threatening disease. Experiences from health coaches and patients indicate that during those times in life, people are suddenly realizing that they might have to change their lifestyle and are more open to make those changes. Complexity science offers theories and methods for studying such emerging habit patterns as well as critical transitions between various stable states of a system [28, 29].

9.3 From Systems Biology to Systems Health

In traditional biology research, biologists tend to specialize into fields covering limited parts of the human body even as small as individual cell systems, individual proteins, or individual metabolites. Even though our understanding of the mechanisms of biological processes and organ functions has increased, the importance of generating knowledge about the function of the human body as a whole is often overlooked by biologists and delegated to other fields of science such as philosophy, psychology, and sociology. Dr. Norbert Wiener, the founder of cybernetics, wanted to find out a new approach that could explain these processes in a holistic way. In 1948, he innovatively put forward an idea to illuminate complex bio-systems at a whole systems level [30]. Since then a new word called "biocybernetics" has been created, which is the predecessor of systems biology.

The aim of systems biology is to understand biological systems at a system level (Fig. 9.3). In other words, scientists investigate the components, structure, and dynamics of cellular and organismal function instead of the characteristics of isolated parts of a cell or organism [31]. Furthermore, systems biology develops tools, techniques, and models to predict the results brought about by stimulations of a living system combined with possible interferences from the outside environment. Based on systems theory, scientists and clinicians are able to develop holistic treatment strategies to complement simple molecular-targeted therapies. More and more systems theories are being applied to solve difficult medical issues and improve health care [32, 33]. This movement toward the implementation of systems

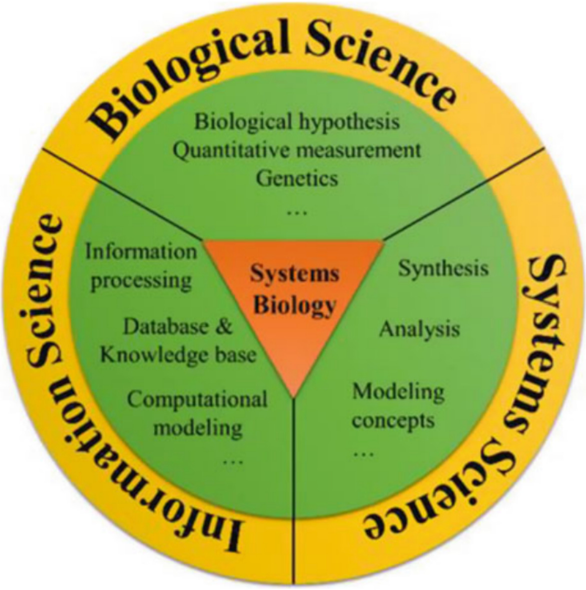

Fig. 9.3 A schematic overview of the concept of systems biology. Generally it covers three research fields: biological science, information science, and systems science

thinking and systems biology into the medical and health-care arena drives the development of what we call systems health, a biopsychosociospiritual approach toward health and healing [34]. An emerging field in systems medicine is the development of optimal healing environments, which are designed to optimize the environment in which patients are healing [35–37].

9.3.1 Network Biology

One of the science areas that is crucial for studying and understanding patterns of relationships is network biology [38]. Network biology arose from a merging of network theory, mathematics, and biology. In systems biology, network biology is commonly used to study changes in gene regulatory and protein interaction networks but also to explore relationships between social, psychological, environmental, and biological factors [39]. In other words, network biology reveals a phenomenon that relations among these items sometimes are more important than objects.

One example is the use of network biology to understand microRNA-mRNA interactions. MicroRNA (miRNA) is a small noncoding RNA containing 22–23 nucleotides. The first miRNA which was reported to play a role in gene regulation was found in 1993. Lee et al. noticed that a *Caenorhabditis elegans* gene, lin-4, which controls diverse postembryonic cell lineages, represses the expression of its target gene line-14 instead of encoding a protein [40]. Since then, an increasing number of researches have focused on human miRNA discovery, and considerable details are now known about their biogenesis [41]. Till now, more than 2,500 miRNAs have been annotated in humans [42–45], and in a recent study, miRNAs have been demonstrated to be effective biomarkers for complex diseases [46–48]. Based on this interaction, a human miRNA-mRNA regulation network has been built to further investigate the relationship among microRNAs and regulated genes. We can map those aberrant expressed genes or miRNAs onto this network to find out their relationships, helping us better understand the complex mechanisms [49].

9.3.2 Measuring Systems Health

Based on systems biology, systems thinking, as well as health theories, "systems health" was coined as a new frame of thinking about health as a dynamic complex system of relationships [34]. The concept of systems health challenges the manner in which health is currently assessed and monitored. Nowadays, measurement is mostly related to the absence of health or a disease state. For instance, cholesterol levels are measured in blood to detect hypertension, blood sugar levels are measured to indicate diabetes, and inflammatory markers are measured to detect inflammation or infections. However, these measurements do not tell much about the healthy state of the human system. Plenty of researches showed that health is not so much a state as an ability to adapt in the face of the challenges of life [50–52]. Measuring health therefore requires dynamic measurements to capture this ability to adapt this resilience. Furthermore, to capture a broad picture of someone's health, not only biological factors should be measured but psychological, social, and spiritual factors as well. This requires an ability to integrate data from various sources and methods to analyze this data as a whole [53, 54].

9.3.3 Systems Health Models

Mathematical and physical models are especially suitable to study the dynamics of systems, and there has been an increasing interest in such models in the field of systems biology over the last two decades [55]. Models are interesting for several reasons. First of all, systems health models can be used to increase understanding of how health emerges from relationships; it can help to raise health awareness. Furthermore, semiquantitative models can be used for clinical decision support, and quantitative models can be developed to study trigger points for behavior change. In the following section, we will mainly explore the first and third examples to further illuminate the value of systems health models.

9.3.3.1 Causal Loop Diagrams to Promote Health Awareness

Today, the majority of information about health and disease reaches people through social media, newspapers, magazines, television talking, websites, and social networking sites. However, there are many conflicting views on what is healthy and what is not. There are views on how to treat certain conditions and many sources of individual experiences with diseases and treatment options. This amount of information causes a lot of confusion for the majority of people because there is little integration of all the information into a coherent view on health. There is a great need for tools and methodologies to integrate the dynamics and the multitude of interacting factors related to health in a comprehensible way that can be used to generate health awareness [56–59].

Systems dynamics is a field of research which provides specific methods to describe causal relationships between factors into a model structure and provide options for simulating the dynamics involved in health and disease. An example of a causal loop diagram is shown in Fig. 9.4, a practical method to show causal relationships [60]. The systems health causal loop diagram shown in Fig. 9.4 was built by the Netherlands Organization for Applied Scientific Research (TNO) and discussed in a recent publication [34]. A large amount of expert knowledge was collected during focus group sessions form scientists in different research fields such as nutrition science, systems biology, computational modeling, and public health, to better understand the cross-domain relationships and to investigate the dynamical interactions between these domains in an integrated way. Another

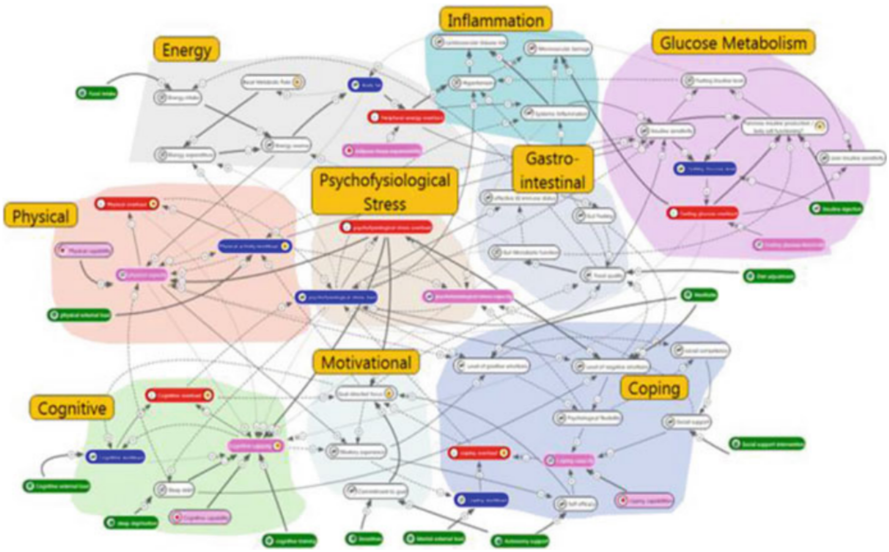

Fig. 9.4 The causal loop diagram related to biopsychosocial health built by TNO to simulate intervention dynamics. Different domains are modularized in it. They are energy, inflammation, glucose metabolism, gastrointestinal, coping, motivational, cognitive, and physical [34]

example of a causal loop diagram application to health is from Jaimie McGlashan et al. [61]. In their research, they used network analysis combined with a causal loop diagram to find out the drivers of childhood obesity. Based on this, the researchers found keywords which were frequently discussed when it comes to children obesity, such as “Advertising/Sponsorship of Fast and Processed Food,” “Level of Physical Activity,” and “Participation in Sports.” The feedback loops and reinforcing loops in the model help to connect different domains, from which the relationships between these phrases can be clarified and new insights about children obesity were generated. The examples above show that the causal loop diagram can be suitable tool for non-research people to better understand complex diseases in our life, enrich their knowledge in relevant fields, and further increase their health awareness (Fig. 9.4).

9.3.3.2 Quantitative Models to Discover Trigger Points for Behavior Change

Traditional mathematical modeling in biology research was usually used to inform and explain complex biological functions and processes and to understand the interactions between individuals through dynamic network based on gene expression and signaling pathways [62–64]. Generally these models are built based on theory and experimental observations. However, due to their small scales and the wile variations among individuals, plus the size of data storage which is rapidly increased, large-scale quantitative models are becoming increasingly necessary. Today, with the remarkable development of research technologies, a number of novel models have emerged, which allow us to assess the articulation of the changes of genes, proteins, and metabolites more comprehensively [65]. There is an obvious phenomenon that quantitative models are extending its application. In recent years, more and more quantitative models have been applied into clinical trials [66, 67], making a transition from fundamental research to medical application.

In order to illuminate quantitative models in more detail, here we select two investigations as examples. First is Marten Scheffer and his colleagues’ work [68–70]. They developed a probabilistic model to compute the probability of symptom changes in major depression. The main formulas show as below:

$$A_i^t = \sum_{j=1}^{J} W_{ij} X_j^{t-1}$$

$$P\left(X_i^t = 1\right) = \frac{1}{1 + e^{\left(b_i - A_i^t\right)}}$$

Before developing this model, the authors made three assumptions: (1) symptoms (X_i) can be on two conditions: active (1) or inactive (0), (2) symptom activation occurs (t) over time, and (3) symptom i and j are connected with each other in the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPUD) data. Here, the first formula A_i^t means total activation function. It represents that the total amount of activation symptom i receives at time t is the weighted (W) summation of all the neighboring symptoms X at time t-1. The second formula is the probability of the activation of symptom i at time t. It depends on the difference between the threshold they estimated from VATSPUD data and A_t^i. The smaller the $\left|\left(b_i - A_i^t\right)\right|$ is, the more possible symptom i will be active at time t. This is an intraindividual, symptoms-based model which develops over time. It gives a strong support to clinical doctors on major depression progression prediction and identification as it offers specified evaluation indexes that doctors are able to find out the trigger points and then distinguish different stages more easily.

The other good example for quantitative model application is Megan Sherwood et al.'s work [71]. They used meta-analytic and statistical approaches to examine the schizophrenia patients' response profile to clozapine, protracting a time course of symptom change. The formula they set is as below:

$$\text{Expected BPRS Item Score} = \beta_0 + \beta_1{}^*W + \beta_2{}^*W^2.$$

Here the W represents week number. $ß_0$, $ß_1$, and $ß_2$ are the coefficients they get from the regression analysis [72]. Through this model, they identified the range of weeks that distinguished different responses to clozapine. A supervising finding is that clozapine shows response in an early stage and the magnitude of it is somewhat larger than other antipsychotic drugs.

Meta-analysis approaches are pretty common in current clinical research [73–75]. But this is just an epitome of quantitative models. In other words, quantitative models have a great potential in medical application [76]. With huge amounts of medical data support, the demand for more accurate, more deep-level, and more complex models is growing [77]. With this method tend to mature, people are able to monitor their health systems in real time in the foreseeable future, which is an important object of systems health.

9.4 Bridging Ancient and Modern Views on Health

As Western medicine is struggling to move away from disease fighting toward health promotion [78], many traditional medicine systems are designed to promote health. In traditional Chinese medicine, a doctor who had to treat diseases was considered to be ordinary, whereas a doctor who treated the spirit or prevented diseases from occurring was considered an excellent expert. For ages TCM doctors were paid for the amount of healthy people in his care, which is a very different business model from the Western one, which pays for treatments [79]. Therefore there are many reasons to learn from traditional healing systems, not only for discovering new treatment options but also for discovering ways to maintain health and even discover government structures that promote health [80, 81].

One of the challenges for the integration of traditional healing systems and Western medicine is the poetic terminology that is often used in traditional healing systems. Concepts such as qi, prana, meridians, and chakras are often frowned upon by Western trained doctors and scientists because these concepts do not fit in their current thinking paradigm. Over the last several decades, attempts have been made to translate concepts and ideas from Chinese medicine and Ayurveda to Western scientific thinking using systems biology [82, 83]. Several studies have been conducted to discover subtypes of chronic diseases such as rheumatoid arthritis, diabetes, and metabolic syndrome, based on TCM diagnostic patterns [84–86]. Moreover, these subtypes were related to biological pathways and mechanisms well known in Western science, opening up opportunities to use these subtypes in clinical practice [87]. One of the big challenges in translating Chinese medicine diagnosis is the inconsistency that is often encountered among various TCM doctors [88, 89]. Therefore various research groups are working on standardizing symptom patterns with questionnaires [90–92]. This type of research shows that it is possible to build a bridge between Western science and medicine and traditional healing systems.

9.5 Transition Toward Citizen Science and Citizen Empowerment

Over the past years, there is a rapid development of tools and devices to measure your own health, as well as apps to store and analyze health data [93]. People are going to have much more data and information about their own health. Interestingly, a lot of this data is related to symptoms that are frequently experienced by individuals. Ecological momentary assessment is a new area of research focusing on capturing symptom data in a simple manner but within the context of daily life [94]. Novel data analysis methods are being developed to analyze this type of personal health data, allowing an individual to monitor the effects of self-chosen interventions on health [95]. More advanced data analysis methods have been developed to predict changes in the dynamics of symptom patterns for migraine and depression, allowing a timely prediction of a migraine attack [96] or a depression episode [69]. Symptom patterns commonly used in traditional healing systems can be very interesting for such self-monitoring approaches. The patterns can be used to distinguish between types of migraine, depression, or stress and can, for example, be used to direct people toward effective dietary interventions [97].

Health data is going to be owned more and more by the individual instead of health institutes. Currently, individuals start organizing themselves in health data cooperatives, independent organizations that are responsible for protecting the privacy of the participants and can mediate in contributing the data to scientific projects [98]. A famous example is PatientsLikeMe, a network with over 500,000 patients donating data toward hundreds of scientific projects [99]. Furthermore, it functions as a social network which people use to communicate personal experiences with drugs, treatments, and lifestyle interventions, helping others in their personal journeys toward health and well-being. Community platforms such as PatientsLikeMe stimulate empowerment of patients and empowerment of entire communities to participate in health promotion and scientific research [100]. It actually allows people to create health [101]. A systems approach toward health and disease is essential for such communities, as it integrates all the aspects that are relevant for the life of a patient and citizen. It will help with the integration of biological, psychological, social, and environmental health measurements and guide citizens toward relevant interventions to sustain a healthy life.

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References

1. McEwen BS (2012) Brain on stress: how the social environment gets under the skin. Proc Natl Acad Sci U S A 109(Suppl 2):17180–17185
2. Irish LA et al (2015) The role of sleep hygiene in promoting public health: a review of empirical evidence. Sleep Med Rev 22:23–36
3. Lustig RH (2006) The ‘skinny’ on childhood obesity: how our western environment starves kids’ brains. Pediatr Ann 35(12):898–902. 905–7
4. Kohl HW 3rd et al (2012) The pandemic of physical inactivity: global action for public health. Lancet 380(9838):294–305
5. Yach D et al (2004) The global burden of chronic diseases: overcoming impediments to prevention and control. JAMA 291(21):2616–2622
6. Dyrbye LN et al (2010) Burnout and serious thoughts of dropping out of medical school: a multi-institutional study. Acad Med 85(1):94–102
7. Epstein RS, Sherwood LM (1996) From outcomes research to disease management: a guide for the perplexed. Ann Intern Med 124(9):832–837
8. Mattke S, Seid M, Ma S (2007) Evidence for the effect of disease management: is $1 billion a year a good investment? Am J Manag Care 13(12):670–676
9. McCall N, Cromwell J (2011) Results of the medicare health support disease-management pilot program. N Engl J Med 365(18):1704–1712
10. Dewan NA et al (2011) Economic evaluation of a disease management program for chronic obstructive pulmonary disease. COPD 8(3):153–159
11. Gerber DE (2008) Targeted therapies: a new generation of cancer treatments. Am Fam Physician 77(3):311–319
12. Seoane JA et al (2013) Biomedical data integration in computational drug design and bioinformatics. Curr Comput Aided Drug Des 9(1):108–117
13. Wahlqvist ML (2014) Ecosystem health disorders – changing perspectives in clinical medicine and nutrition. Asia Pac J Clin Nutr 23(1):1–15
14. Flores M et al (2013) P4 medicine: how systems medicine will transform the healthcare sector and society. Perinat Med 10(6):565–576

15. Hood L, Lovejoy JC, Price ND (2015) Integrating big data and actionable health coaching to optimize wellness. BMC Med 13:4
16. Grasso M et al (2012) The health effects of climate change: a survey of recent quantitative research. Int J Environ Res Publ Health 9(5):1523–1547
17. Chaves LF, Pascual M (2006) Climate cycles and forecasts of cutaneous leishmaniasis, a nonstationary vector-borne disease. PLoS Med 3(8):e295
18. Akter R et al (2017) Joint effects of climate variability and socioecological factors on dengue transmission: epidemiological evidence. Trop Med Int Health 22(6):656–669
19. Samy AM et al (2016) Climate change influences on the global potential distribution of the mosquito Culex quinquefasciatus, vector of West Nile virus and lymphatic filariasis. PLoS One 11(10):e0163863
20. Ferrao JL, Mendes JM, Painho M (2017) Modelling the influence of climate on malaria occurrence in Chimoio municipality. Mozambique Parasit Vectors 10(1):260
21. Ivanescu L et al (2016) Climate change is increasing the risk of the reemergence of malaria in Romania. Biomed Res Int 2016:8560519
22. Holland JH (2006) Studying complex adaptive systems. J Syst Sci Complex 19(1):1–8
23. (1983) Health promotion: alcohol and drug misuse prevention. Publ Health Rep. Suppl: p 116–32
24. Leung DY et al (2016) Hardcore smoking after comprehensive smoke-free legislation and health warnings on cigarette packets in Hong Kong. Public Health 132:50–56
25. Schane RE, Glantz SA, Ling PM (2009) Social smoking implications for public health, clinical practice, and intervention research. Am J Prev Med 37(2):124–131
26. McEwen BS, Getz L (2013) Lifetime experiences, the brain and personalized medicine: an integrative perspective. Metabolism 62(Suppl 1):S20–S26
27. Adam TC, Epel ES (2007) Stress, eating and the reward system. Physiol Behav 91 (4):449–458
28. Jayasinghe S (2012) Complexity science to conceptualize health and disease: is it relevant to clinical medicine? Mayo Clin Proc 87(4):314–319
29. Scheffer M et al (2012) Anticipating critical transitions. Science 338(6105):344–348
30. Wiener N (1948) Cybernetics. Sci Am 179(5):14–18
31. Kitano H (2002) Systems biology: a brief overview. Science 295(5560):1662–1664
32. Liu ET, Kuznetsov VA, Miller LD (2006) In the pursuit of complexity: systems medicine in cancer biology. Cancer Cell 9(4):245–247
33. Haase T et al (2016) Systems medicine as an emerging tool for cardiovascular genetics. Front Cardiovasc Med 3:27
34. van Wietmarschen HA, Wortelboer HM, van der Greef J (2016) Grip on health: a complex systems approach to transform health care. J Eval Clin Pract
35. Jonas WB, Chez RA (2004) Toward optimal healing environments in health care. J Altern Complement Med 10(Suppl 1):S1–S6
36. Freedman MR, Stern JS (2004) The role of optimal healing environments in the management of childhood obesity. J Altern Complement Med 10(Suppl 1):S231–S244
37. Schweitzer M, Gilpin L, Frampton S (2004) Healing spaces: elements of environmental design that make an impact on health. J Altern Complement Med 10(Suppl 1):S71–S83
38. Barabasi AL, Gulbahce N, Loscalzo J (2011) Network medicine: a network-based approach to human disease. Nat Rev Genet 12(1):56–68
39. Lucas M, Laplaze L, Bennett MJ (2011) Plant systems biology: network matters. Plant Cell Environ 34(4):535–553
40. Lee RC, Feinbaum RL, Ambros V (1993) The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 75(5):843–854
41. Lin S, Gregory RI (2015) MicroRNA biogenesis pathways in cancer. Nat Rev Cancer 15 (6):321–333
42. Hsu SD et al (2011) miRTarBase: a database curates experimentally validated microRNA-target interactions. Nucleic Acids Res 39(Database issue):D163–D169

43. Xiao F et al (2009) miRecords: an integrated resource for microRNA-target interactions. Nucleic Acids Res 37(Database issue):D105–D110
44. Kozomara A, Griffiths-Jones S (2014) miRBase: annotating high confidence microRNAs using deep sequencing data. Nucleic Acids Res 42(Database issue):D68–D73
45. Rennie W et al (2014) STarMir: a web server for prediction of microRNA binding sites. Nucleic Acids Res 42(Web Server issue):W114–W118
46. Shen L et al (2016) Knowledge-guided bioinformatics model for identifying autism spectrum disorder diagnostic MicroRNA biomarkers. Sci Rep 6:39663
47. Hayes J, Peruzzi PP, Lawler S (2014) MicroRNAs in cancer: biomarkers, functions and therapy. Trends Mol Med 20(8):460–469
48. de Boer HC et al (2013) Aspirin treatment hampers the use of plasma microRNA-126 as a biomarker for the progression of vascular disease. Eur Heart J 34(44):3451–3457
49. Li Y, Zhang Z (2015) Computational biology in microRNA. Wiley Interdiscip Rev RNA 6 (4):435–452
50. Huber M et al (2011) How should we define health? BMJ 343:d4163
51. Ryff CD, Singer BH, Dienberg Love G (2004) Positive health: connecting well-being with biology. Philos Trans R Soc Lond Ser B Biol Sci 359(1449):1383–1394
52. Ryff C et al (2012) Varieties of resilience in MIDUS. Soc Personal Psychol Compass 6 (11):792–806
53. Adourian A et al (2008) Correlation network analysis for data integration and biomarker selection. Mol BioSyst 4(3):249–259
54. Derous D et al (2015) Network-based integration of molecular and physiological data elucidates regulatory mechanisms underlying adaptation to high-fat diet. Genes Nutr 10 (4):470
55. Posada D (2008) jModelTest: phylogenetic model averaging. Mol Biol Evol 25 (7):1253–1256
56. Lan TS et al (2014) An investigation of factors affecting elementary school students' BMI values based on the system dynamics modeling. Comput Math Methods Med 2014:575424
57. Pere D (2017) Building physician competency in lifestyle medicine: a model for health improvement. Am J Prev Med 52(2):260–261
58. Mechanick JI, Zhao S, Garvey WT (2016) The adipokine-cardiovascular-lifestyle network: translation to clinical practice. J Am Coll Cardiol 68(16):1785–1803
59. Homer JB, Hirsch GB (2006) System dynamics modeling for public health: background and opportunities. Am J Publ Health 96(3):452–458
60. Goh YM et al (2012) Dynamics of safety performance and culture: a group model building approach. Accid Anal Prev 48:118–125
61. McGlashan J et al (2016) Quantifying a systems map: network analysis of a childhood obesity causal loop diagram. PLoS One 11(10):e0165459
62. Umulis DM et al (2010) Organism-scale modeling of early drosophila patterning via bone morphogenetic proteins. Dev Cell 18(2):260–274
63. Jaeger J et al (2004) Dynamic control of positional information in the early drosophila embryo. Nature 430(6997):368–371
64. Fakhouri WD et al (2010) Deciphering a transcriptional regulatory code: modeling short-range repression in the drosophila embryo. Mol Syst Biol 6:341
65. Kurz FT et al (2017) Network dynamics: quantitative analysis of complex behavior in metabolism, organelles, and cells, from experiments to models and back. Wiley Interdiscip Rev Syst Biol Med 9(1):e1352
66. Garcia-Martin A, Fernandez-Golfin C, Zamorano-Gomez JL (2014) New quantitative model of aortic valve in PreTAVI patients. Rev Esp Cardiol (Engl Ed) 67(6):488
67. Hongwei W et al (2010) Nonspecific biochemical changes under different health statuses and a quantitative model based on biological markers to evaluate systemic function in humans. Clin Lab 56(5–6):223–225

68. Cramer AO et al (2016) Major depression as a complex dynamic system. PLoS One 11(12): e0167490
69. van de Leemput IA et al (2014) Critical slowing down as early warning for the onset and termination of depression. Proc Natl Acad Sci U S A 111(1):87–92
70. Wichers M et al (2014) Reply to Bos and de Jonge: between-subject data do provide first empirical support for critical slowing down in depression. Proc Natl Acad Sci U S A 111(10): E879
71. Sherwood M, Thornton AE, Honer WG (2012) A quantitative review of the profile and time course of symptom change in schizophrenia treated with clozapine. J Psychopharmacol 26 (9):1175–1184
72. Sherwood M, Thornton AE, Honer WG (2006) A meta-analysis of profile and time-course of symptom change in acute schizophrenia treated with atypical antipsychotics. Int J Neuropsychopharmacol 9(3):357–366
73. Ratheesh A et al (2017) A systematic review and meta-analysis of prospective transition from major depression to bipolar disorder. Acta Psychiatr Scand 135(4):273–284
74. Fusar-Poli P et al (2012) Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Arch Gen Psychiatry 69(3):220–229
75. Schumacher M, Rucker G, Schwarzer G (2014) Meta-analysis and the surgeon general's report on smoking and health. N Engl J Med 370(2):186–188
76. Swanson KR, True LD, Murray JD (2003) On the use of quantitative modeling to help understand prostate-specific antigen dynamics and other medical problems. Am J Clin Pathol 119(1):14–17
77. Issa NT, Byers SW, Dakshanamurthy S (2014) Big data: the next frontier for innovation in therapeutics and healthcare. Expert Rev Clin Pharmacol 7(3):293–298
78. Lindstrom B, Eriksson M (2005) Salutogenesis. J Epidemiol Community Health 59 (6):440–442
79. Zhang C et al (2016) Integration of Chinese medicine with western medicine could lead to future medicine: molecular module medicine. Chin J Integr Med 22(4):243–250
80. Roberti di Sarsina P, Alivia M, Guadagni P (2012) Traditional, complementary and alternative medical systems and their contribution to personalisation, prediction and prevention in medicine-person-centred medicine. EPMA J 3(1):15
81. Verhoef MJ et al (2005) Complementary and alternative medicine whole systems research: beyond identification of inadequacies of the RCT. Complement Ther Med 13(3):206–212
82. Scheid V (2014) Convergent lines of descent: symptoms, patterns, constellations, and the emergent interface of systems biology and Chinese medicine. East Asian Sci Technol Soc 8 (1):107–139
83. Mukherjee PK, Venkatesh P, Ponnusankar S (2010) Ethnopharmacology and integrative medicine – let the history tell the future. J Ayurveda Integr Med 1(2):100–109
84. van Wietmarschen HA et al (2012) Characterization of rheumatoid arthritis subtypes using symptom profiles, clinical chemistry and metabolomics measurements. PLoS One 7(9): e44331
85. van Wietmarschen H et al (2009) Systems biology guided by Chinese medicine reveals new markers for sub-typing rheumatoid arthritis patients. J Clin Rheumatol 15(7):330–337
86. Wei H et al (2012) Urine metabolomics combined with the personalized diagnosis guided by Chinese medicine reveals subtypes of pre-diabetes. Mol BioSyst 8(5):1482–1491
87. Schroen Y et al (2015) Bridging the seen and the unseen: a systems pharmacology view of herbal medicine. Science 350(6262):S66–S69
88. Coeytaux RR et al (2006) Variability in the diagnosis and point selection for persons with frequent headache by traditional Chinese medicine acupuncturists. J Altern Complement Med 12(9):863–872
89. Zhang GG et al (2005) Variability in the traditional Chinese medicine (TCM) diagnoses and herbal prescriptions provided by three TCM practitioners for 40 patients with rheumatoid arthritis. J Altern Complement Med 11(3):415–421

90. Tan S et al (2005) Traditional Chinese medicine based subgrouping of irritable bowel syndrome patients. Am J Chin Med 33(3):365–379
91. Gadau M et al (2016) TCM pattern questionnaire for lateral elbow pain: development of an instrument via a Delphi process. Evid Based Complement Altern Med 2016:7034759
92. Fu TC et al (2016) Validation of a new simple scale to measure symptoms in heart failure from traditional Chinese medicine view: a cross-sectional questionnaire study. BMC Complement Altern Med 16:342
93. Ernsting C et al (2017) Using smartphones and health apps to change and manage health behaviors: a population-based survey. J Med Internet Res 19(4):e101
94. Bos FM, Schoevers RA, Aan het Rot M (2015) Experience sampling and ecological momentary assessment studies in psychopharmacology: a systematic review. Eur Neuropsychopharmacol 25(11):1853–1864
95. Maes IH et al (2015) Measuring health-related quality of life by experiences: the experience sampling method. Value Health 18(1):44–51
96. Dahlem MA et al (2015) Understanding migraine using dynamic network biomarkers. Cephalalgia 35(7):627–630
97. Schroen Y et al (2014) East is east and west is west, and never the twain shall meet? Science 346(6216):S10–S12
98. Hafen E, Kossmann D, Brand A (2014) Health data cooperatives – citizen empowerment. Methods Inf Med 53(2):82–86
99. Frost J, Massagli M (2009) PatientsLikeMe the case for a data-centered patient community and how ALS patients use the community to inform treatment decisions and manage pulmonary health. Chron Respir Dis 6(4):225–229
100. Den Broeder L et al (2016) Citizen science for public health. Health Promot Int
101. Cloninger CR (2013) Person-centered health promotion in chronic disease. Int J Pers Cent Med 3(1):5–12