OPEN ACCESS Freely available online

PLoS MEDICINE

Essay

The Limits of Reductionism in Medicine: Could Systems Biology Offer an Alternative?

Andrew C. Ahn*, Muneesh Tewari, Chi-Sang Poon, Russell S. Phillips

This is the first in a series of two articles that look at the lessons for clinical medicine from systems biology.

Since Descartes and the Renaissance, science, including medicine, has taken a distinct path in its analytical evaluation of the natural world [1,2]. This approach can be described as one of "divide and conquer," and it is rooted in the assumption that complex problems are solvable by dividing them into smaller, simpler, and thus more tractable units. Because the processes are "reduced" into more basic units, this approach has been termed "reductionism" and has been the predominant paradigm of science over the past two centuries. Reductionism pervades the medical sciences and affects the way we diagnose, treat, and prevent diseases. While it has been responsible for tremendous successes in modern medicine, there are limits to reductionism, and an alternative explanation must be sought to complement it.

The alternative explanation that has received much recent attention, due to systems biology, is the systems perspective (Table 1). Rather than dividing a complex problem into its component parts, the systems perspective appreciates the holistic and composite characteristics of a problem and evaluates the problem with the use of computational and mathematical tools. The systems perspective is rooted in the assumption that the forest cannot be explained by studying the trees individually.

In order for a systems perspective to be fully appreciated, however, we must first recognize the reductionist nature of medical science and understand its limitations. For this reason, the first article in this series is dedicated to examining the reductionist approach that pervades medicine and to explaining how a systems approach (as advocated by systems biology) may complement it. In the second article, we aim to provide a more practical discussion of how a systems approach would affect clinical medicine. We hope that these discussions can stimulate further inquiry into the clinical implications of systems principles.

The Essay section contains opinion pieces on topics of broad interest to a general medical audience.

Current Medical Science

While the *implementation* of clinical medicine is systems-oriented, the science of clinical medicine is fundamentally reductionist. This is shown in four prominent practices in medicine: (1) the focus on a singular, dominant factor, (2) emphasis on homeostasis, (3) inexact risk modification, and (4) additive treatments.

Focus on a singular factor. When the human body is viewed as a collection of components, the natural inclination of medicine is to isolate the single factor that is most responsible for the observed behavior. Much like a mechanic who repairs a broken car by locating the defective part, physicians typically treat disease by identifying that isolatable abnormality. Implicit within this practice is the deeply rooted belief that each disease has a potential singular target for medical treatment. For infection, the target is the pathogen; for cancer, it is the tumor; and for gastrointestinal bleeding, it is the bleeding vessel or ulcer.

While the success of this approach is undeniable, it leaves little room for contextual information. A young immuno-compromised man with pneumococcal pneumonia usually gets the same antibiotic treatment as an elderly woman with the same infection. The disease, and not the person affected by it, becomes the central focus. Our contemporary analytical tools are simply not designed to address more complex questions, and, thus, questions such as "how do a person's sleeping habits, diet, living condition, comorbidities, and stress collectively contribute to his/her heart disease?" remain largely unanswered.

Emphasis on homeostasis. For decades, homeostasis has been a vital, guiding principle for medicine. Claude Bernard in 1865 and later Walter B. Cannon popularized this principle, expounding on the body's

Funding: ACA's work on this manuscript was supported by a National Institutes of Health Institutional National Research Service Award, grant T32-AT0051-03. RSP is supported by a National Institutes of Health Mid-Career Investigator Award (K24-AT000589). The contents of this work are solely the responsibility of the authors and do not necessarily represent the official views of the National Center for Complementary Alternative Medicine or the National Institutes of Health. CSP is supported by National Institutes of Health grant R01-HL072849.

Competing Interests: The authors declare that they have no competing interests.

Citation: Ahn AC, Tewari M, Poon CS, Phillips RS (2006) The limits of reductionism in medicine: Could systems biology offer an alternative? PLoS Med 3(6): e208. DOI: 10.1371/journal.pmed.0030208

DOI: 10.1371/journal.pmed.0030208

Abbreviation: MIT, Massachusetts Institute of Technology

Andrew C. Ahn is with the Division for Research and Education in Complementary and Integrative Medical Therapies, Harvard Medical School, Boston, Massachusetts, United States of America; the Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States of America; and the Advanced Study Program, Massachusetts Institute of Technology (MIT), Cambridge, Massachusetts, United States of America. Muneesh Tewari is with the Human Biology Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, United States of America. Chi-Sang Poon is with the Harvard-MIT Division of Health Sciences and Technology, Cambridge, Massachusetts, United States of America, and the Computational and Systems Biology Initiative, MIT, Cambridge, Massachusetts, United States of America. Russell S. Phillips is with the Division for Research and Education in Complementary and Integrative Medical Therapies at Harvard Medical School and the Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States of America.

* To whom correspondence should be addressed. E-mail: aahn@hms.harvard.edu

remarkable ability to maintain stability and constancy in the face of stress [3]. Since then, homeostasis has been incorporated into clinical practice. Illness is defined as a failed homeostatic mechanism, and treatment requires physicians to substitute for this failed mechanism by correcting deviations and placing parameters within normal range. This corrective treatment approach is true for a range of medical conditions, from hypothyroidism to hypokalemia to diabetes.

This interpretation of homeostasis, however, is biased by a reductionist viewpoint in two ways. First, the emphasis on correcting the deviated parameter (e.g., low potassium) belies the importance of systems-wide operations. Either alternate, less intuitive targets may be more effective, or correction of the deviated parameter may itself have harmful system-wide effects. Existing evidence that demonstrates adverse effects of calcium for hypocalcemia [4,5] or blood pressure control for stroke-related hypertension [6] points to the limitations of this homeostasis interpretation as a universal principle.

Secondly, the exclusive focus on normal ranges belies the importance of dynamic stability. Because reductionism often disregards the dynamic interactions between parts, the system is often depicted as a collection of static components. Consequently, emphasis is placed on static stability/normal ranges and not on dynamic stable states, such as oscillatory or chaotic (seemingly random but deterministic) behavior. Circadian rhythms [7] are an example of oscillatory behavior, and complex heart rate variability [8–10] is an example of chaotic behavior. Failure to include these dynamic states in the homeostasis model may lead to treatments that are either ineffective or even detrimental.

Inexact risk modification. Since disease cannot always be predicted with certainty, health professionals must identify and modify risk factors. The common, unidimensional, "one-risk-factor to one-disease" approach used in medical epidemiology, however, has certain limitations.

An example is hypertension, a known risk factor for coronary heart disease. Guidelines suggest pharmacological and lifestyle treatment for individuals with systolic blood pressure greater than 140. This strategy is supported by evidence from the Framingham Study, which showed that men between 35 and 64 years of age with systolic blood pressures greater than 140 were twice as likely to develop heart disease as compared to individuals with systolic blood pressure less than 140 [11]. However, given that nearly 70% of the American population is not affected by hypertension, up to 30% of coronary artery disease develops in individuals with normal blood pressure [11]. Conceivably, a large number of people at small risk may give rise to more cases of disease than a small number of people at high risk. This observation is termed the prevention paradox [12].

To capture these missed cardiac events, the natural recourse is to progressively lower the blood pressure threshold for treatment. Consequently, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure lowered its initial diastolic blood pressure threshold of 105 in 1977 to 90 in 1980, to 85 (for high normal) in 1992, and to 80 (for prehypertension) in 2003. The cost of such a strategy is the unnecessary treatment of individuals who wouldn't have developed coronary disease in the first place. This problem originates from the constraints imposed by a one-risk to one-disease analysis and the inability to work with multiple risk factors and calculate their collective influences. If a more multidimensional analytical method were used, then more precise risk projections for individuals could be devised.

Additive treatments. In reductionism, multiple problems in a system are typically tackled piecemeal. Each problem is partitioned and addressed individually. In coronary artery disease, for example, each known risk factor is addressed individually, whether it be hyperlipidemia or hypertension. The strategy is also extended to coexisting diseases, such as hypothyroidism, diabetes, and coronary artery disease. Each disease is treated individually, as if the treatment of one disorder (such as coronary artery disease) has minimal effects on the treatment of another (such as hypothyroidism). While this approach is easily executable in clinical practice, it neglects the complex interplay between disease and treatment. The assumption is that the results of treatments are additive rather than nonlinear.

Limitations to Current Medical Science

The science underlying our medical practices, from diagnosis to treatment to prevention, is based on the assumption that information about individual parts is sufficient to explain the whole. But there are circumstances in which the complex interplay between parts yields a behavior that cannot be predicted by the investigation of the parts

Table 1. Reductionism versus a Systems-Oriented Perspective

Characteristic	Reductionism	Systems-Oriented Approach
Principle	Behavior of a biological system can be explained by the properties of its constituent parts	Biological systems possess emergent properties that are only possessed by the system as a whole and not by any isolated part of the system
Metaphor	Machine, magic bullet	Network
Approach	One factor is singled out for attention and is given explanatory weight on its own	Many factors are simultaneously evaluated to assess the dynamics of the system
Critical factors	Predictors/associated factors	Time, space, context
Model characteristics	Linear, predictable, frequently deterministic	Non-linear, sensitive to initial conditions, stochastic (probabilistic), chaotic
Medical concepts	Health is normalcy	Health is robustness
	Health is risk reduction	Health is adaptation/plasticity
	Health is homeostasis	Health is homeodynamics

DOI: 10.1371/journal.pmed.0030208.t001

alone. The failure to account for these circumstances is the common denominator for the explanations of why the aforementioned practices are, in many cases, inadequate.

So how should these complexities be addressed? Is there a formal method that can explain how the pieces create the whole? How do we shift our lens from the parts to the system? The answers to these questions may come from a relatively new branch of science called systems biology [13–16]. Systems biology was conceived to address the molecular complexities seen in biological systems. One major impetus for its creation was the human genome project.

Human Genome Project

The completion of the human genome project in 2003, in addition to the development of high-throughput technologies such as DNA array chips, has led scientists to confront a challenge they could not address before; namely, how do genes interact to collectively create a system-wide behavior?

The human genome contains 30,000 to 35,000 genes [17]. Although this number is just five times the number of genes in a unicellular eukaryote (e.g., approximately 6,000 genes in *Saccharomyces cerevisiae*) [18], the human genome encodes for nearly 100 trillion cells in the human body [19]. The richness of information is derived not only in the genes themselves but also in the interaction between genes and between their respective products. The genes encode for messenger RNA, the messenger RNAs encode for proteins, and the proteins act as catalysts or secondary messengers, among other diverse functions. Between each hierarchical level, modifications (e.g., alternative splicing) are made, and at each hierarchical level (e.g., transcription), thousands of molecules interact with other molecules to create a complex regulatory network. What becomes evident from these molecular analyses is that phenotypic traits emerge from the collective action of multiple individual molecules [20]. Therefore, the previous notion that a single genetic mutation is responsible for most phenotypic defects is overly simplistic. Complex diseases such as cancer, asthma, or atherosclerosis cannot generally be explained by a single genetic mutation.

Box 1. Chemotaxis as an Example of Systems Biology's Application

E. coli chemotaxis is an example of systems biology's application (see Figure 1). Chemotaxis is defined as directed motion of a cell toward increasing (or decreasing) concentrations of a particular chemical substance. *E. coli* has been observed to migrate toward areas of higher aspartate concentrations through a series of "runs" and "tumbles." The "runs" are linear paths taken by the bacteria, while the "tumbles" are random rotations that reorient the bacteria. When bacteria reach higher concentrations of aspartate, time spent "running" in proportion to "tumbling" increases—the logic being that if higher concentrations of aspartate are encountered, the bacterium is on the right track and should continue in that direction. If the *E. coli* fails to detect increasing aspartate concentrations, the bacterium eventually exhibits "adaptation," where it returns to the baseline "tumble and run" activities. This ensures that it does not continually head in the wrong direction.

Conventional medical methods have, for more than a decade, been able to identify the enzymes and molecules involved in the chemotactic pathway. Despite this, little was known about how the interactions in this pathway translated to its known chemotactic behavior, namely the ability of *E. coli* to "adapt" in a large range of aspartate concentrations. Spiro, et al. [31] used systems methods in 1997 to provide a mechanistic explanation. They placed the involved enzymes into a mathematical equation (context), considered the relationship between these enzymes (space), and analyzed the activities for each enzyme with the use of computational tools (time). Increased temporal detections of aspartate led to reduced autophosphorylation rate of the aspartate receptor. This effect reduced the tumbling rate and increased the running time. When there was no increased detection of aspartate, methylation of the aspartate receptor occurred, which increased the autophosphorylation rate and caused the *E. coli* to return to prestimulus tumble-and-run activities (adaptation). Importantly, this adaptive behavior occurred at different aspartate concentrations, explaining how *E. coli* does not perpetually exist in an excited state, even at higher aspartate concentrations.

Similar conceptual breakthroughs have been obtained with the use of systems methods in other biological phenomena, such as bacteriophage lysis-lysogeny [32], biological oscillations [33,34], circadian rhythms [35,36], and *Drosophila* development [37–39]. In these situations, the incorporation of context, time, and space into the equation has provided information not otherwise obtained through structural information alone.

Systems Biology: An Introduction

The need to make sense of complex genetic interactions has led some researchers to shift from a component-level to system-level perspective. This novel approach incorporates the technical knowledge obtained from systems engineering, which began with Norbert Weiner's "cybernetics" in 1948 and Ludwig von Bertalanffy's "General Systems Theory" in 1969 [21,22]. The developing fields of chaos theory, nonlinear dynamics, and complex systems science, along with computational science, mathematics, and physics, have also contributed to the analytical armamentarium used by systems analysts.

The intention of applying these theories to biological systems (termed "systems biology") is to understand how properties emerge from the nonlinear interaction of multiple components (Table 2). How does consciousness arise from the interactions between neurons? How do normal cellular functions such as cellular division, cell activation, differentiation, and apoptosis emerge from the interaction of genes? These questions highlight the difficulty of understanding complex biological systems—the moment the lens is directed toward the components of a biological system, the behaviors and properties of the whole system become obscure. Plainly said, one loses sight of the forest for the trees.

Systems biology is an integrative approach that combines theoretical modeling and direct experimentation. Theoretical models provide insights into experimental observations, and experiments can provide data needed for model creation or can confirm or refute model findings. With this integrative approach, it becomes

Table 2. Overview of Systems Biology

Aspect	Description
Definition	Systems biology represents the study of biological systems through the lens of the "whole." It incorporates the dynamic relationships between the "parts."
Predecessor	General systems theory, cybernetics, information theory, molecular biology, and genetics.
Catalyst	Human genome project, molecular high-throughput tools, advances in computer science.
Scientific disciplines	Biology, medicine, physics, mathematics, computer science, engineering, chemistry, statistics.
Sample experiments	*E. coli* chemotaxis [31, 40, 41], bacteriophage lysis-lysogeny [32], biological oscillation [33,42], *Drosophila* development [37–39]
Sample institutes	Institute for Systems Biology (Seattle, Washington, United States of America)
	Computation and Systems Biology Initiative (MIT, Cambridge, Massachusetts, United States of America)
	The Systems Biology Institute (Tokyo, Japan)
	Department of Systems Biology (Harvard Medical School, Boston, Massachusetts, United States of America)
	Institute for Molecular Systems Biology (Zurich, Switzerland)
	The Ottawa Institute for Systems Biology (Ottawa, Canada)

DOI: 10.1371/journal.pmed.0030208.t002

apparent that no single discipline is ideal to address systems biology. Scientists from molecular biology, computational science, engineering, physics, statistics, chemistry, and mathematics need to cooperate in order to explain how the biological whole materializes [23].

While the field of systems biology is young, it has been received with substantial enthusiasm. Many believe that, without a system-level understanding, the benefits of the genomic information cannot be fully realized. The perceived importance of this understanding is reflected in the investments made by major academic and industrial centers within the past few years [24].

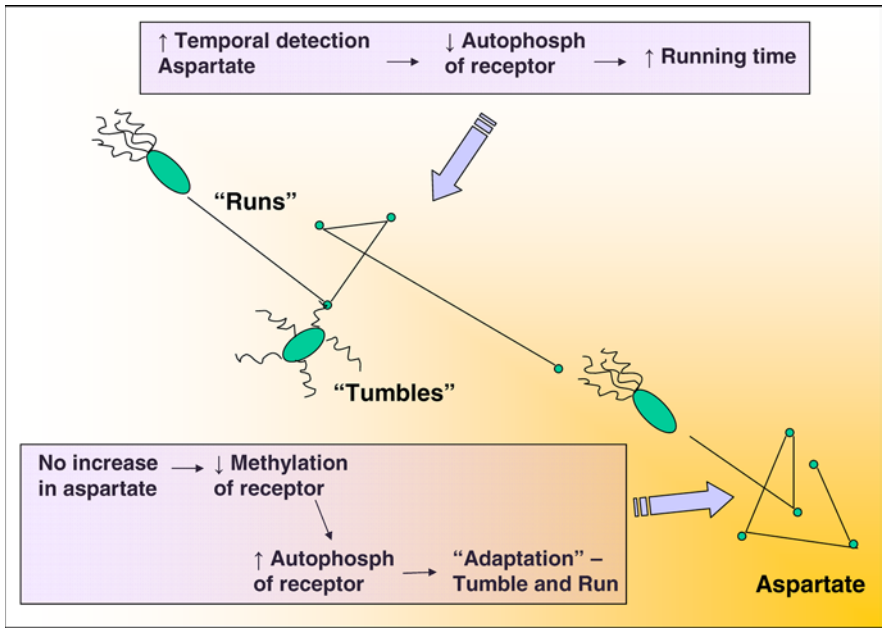
Importance of Context, Space, and Time

How is systems-level understanding achieved? The answer likely lies in the dynamic and changing nature of biological networks. Unlike the static depiction of many wiring network representations, both the molecular concentrations and enzyme activities are continually changing as a result of influences from other molecular substrates. The network is an interactive and dynamic web in which the properties of a single molecule are contingent on its relationship to other molecules and the activities of those other molecules within the network. Therefore, the behavior of the system arises from the active interactions of these biological components. To elicit the system-wide behavior, three factors need to be considered: (1) context, which values the inclusion of all components partaking in a process; (2) time, which considers the changing characteristics of each component; and (3) space, which accounts for the topographic relationships between and among components. Box 1 and Figure 1 show an example of how systems methods—incorporating context, time, and space—allowed researchers to provide a mechanistic explanation for *Escherichia coli* chemotaxis.

The three factors of context, time, and space play a vital role in systems science. Systems biologists consequently use tools such as differential equations, diffusion functions, computational models, and high throughput tools to incorporate one or more of these factors to address a research question. This approach differs from traditional medical methods, where the central focus is elaborating the instantaneous property of a component involved in a disease process. In many medical models, the process of data extraction, such as obtaining serum glucose level or blood pressure, can lead to loss of information on time, space, or context. Systems biologists contend that loss of this information leads to loss of rich information that would otherwise contribute to a better understanding of the systemic and dynamic behavior of the human body.

Systems Biology Concepts

Several concepts have emerged in systems biology to describe properties occurring at the systems level. One prominent concept is robustness, defined as the ability to maintain



DOI: 10.1371/journal.pmed.0030208.g001

Figure 1. *E. coli* Chemotaxis

E. coli has been observed to migrate toward areas of higher aspartate concentrations through a series of "runs" and "tumbles" (see Box 1).
Autophosph, autophosphorylation.

stable functioning despite various perturbations [25,26]. Natural systems specifically demonstrate an uncanny penchant for robustness, which, as many have argued, is necessary for natural systems to survive and procreate [27]. Robustness is attained by five described mechanisms: feedback control, structural stability, redundancy, modularity, and adaptation (see Box 2) [13,28]. Biological systems across all scales, from cells to organisms, rely on a combination of these mechanisms to maintain a semblance of stability. The human body is no exception.

The stability discussed in systems biology is distinct from the stability commonly perceived in clinical medicine. Medical practitioners often picture stability as an unwavering entity such that values are maintained within a specific, confined range. But stability in systems biology is revealed dynamically, and it is the *behavior* of the system rather than the *state* of the system that remains consistent. This dynamic stability can assume many forms, including homeostatic, bistable (having two stable states), oscillatory, or chaotic [29]. Normal biological functions can be classified into one of these dynamic behaviors: for instance, bacteriophage lysis-lysogeny as bistable, circadian rhythms as oscillatory, or heart rate variability as chaotic. This varied perspective of stability is more extensive than the commonly accepted notion of homeostasis and may ultimately influence how treatments are deliberated.

Box 2

Feedback control: Serves to correct deviations and restores the system to its natural behavior.

Structural stability: Explains for the stability that arises from the very nature of the network structure. For instance, the World Wide Web was shown to be resistant to random attacks to Web sites by virtue of its organization [30].

Redundancy: Allows for functionally equivalent units to substitute for one another in the event of a failure.

Modularity: Prevents amplification of a perturbation by dividing function or structure into subunits or modules.

Adaptation: Promotes survival and functioning in a variety of environmental conditions.

Lessons from Systems Biology

The fundamental disconnect that exists between clinical medicine and systems biology largely stems from their disparate worldviews—one focuses on the parts and the other on the systems. As a consequence, the factors of time, space, and context, which are considered vital for a system-level understanding, are not assigned the same level of importance in medicine as they are in systems biology. Moreover, system-level concepts such as robustness, stability, and variability do not have meaningful equivalents in the medical vernacular. The incorporation of such concepts into medicine may help address certain limitations and greatly enhance its therapeutic potential. The second article in this series will explore how systems medicine may be realized in practice. ■

References

1. Lindberg D (1992) The beginnings of western science. Chicago: University of Chicago Press. 474 p.
2. Sweeney K, Kernick D (2002) Clinical evaluation: Constructing a new model for post-normal medicine. J Eval Clin Pract 8: 131–138.
3. Buchman TG (2002) The community of self. Nature 420: 246–251.
4. Zaloga G (1992) Hypocalcemia in critically ill patients. Crit Care Med 20: 251–262.
5. Zaloga G, Sager A, Black K, Prielipp R (1992) Low dose calcium administration increases mortality during septic peritonitis in rates. Circ Shock 37: 226–229.
6. Oliveira-Filho J, Silva S, Trabuco C, Pedreira B, Sousa E, et al. (2003) Detrimental effect of blood pressure reduction in the first 24 hours of acute stroke onset. Neurology 61: 1047–1051.
7. Scheer FA, Czeisler CA (2005) Melatonin, sleep, and circadian rhythms. Sleep Med Rev 9: 5–9.
8. Poon CS, Merrill CK (1997) Decrease of cardiac chaos in congestive heart failure. Nature 389: 492–495.
9. Goldberger A, Amaral L, Hausdorff J, Ivanov P, Peng C (2002) Fractal dynamics in physiology: Alterations with disease and aging. Proc Natl Acad Sci U S A 99 (Suppl 1): 2466–2472.
10. Goldberger A (1996) Non-linear dynamics for clinicians: Chaos theory, fractals, and complexity at the bedside. Lancet 347: 1312–1314.
11. Kannel W (2003) Prevalence and implication of uncontrolled systolic hypertension. Drugs Aging 20: 277–286.
12. Rose G (1994) The strategy of preventive medicine. Oxford: Oxford University Press. 160 p.
13. Kitano H (2002) Looking beyond the details: A rise in system-oriented approaches in genetics and molecular biology. Curr Genet 41: 1–10.
14. Kitano H (2002) Systems biology: A brief overview. Science 295: 1662–1664.
15. Ehrenberg M, Elf J, Aurell E, Sandberg R, Tegner J (2003) Systems biology is taking off. Genome Res 13: 2377–2380.
16. Weston AD, Hood L (2004) Systems biology, proteomics, and the future of health care: Toward predictive, preventative, and personalized medicine. J Proteome Res 3: 179–196.
17. Guttmacher AE, Collins FS (2002) Genomic medicine—A primer. N Engl J Med 347: 1512–1520.
18. Giaever G, Chu A, Ni L, Connelly C, Riles L, et al. (2003) Functional profiling of the *Saccharomyces cerevisiae* genome. Nature 418: 387–391.
19. Chanda SK, Caldwell JS (2003) Fulfilling the promise: Drug discovery in the post-genomic era. Drug Discov Today 8: 168–174.
20. Kauffman S (1993) The origins of order: Self organization and selection in evolution. New York: Oxford University Press. 734 p.
21. Weiner N (1948) Cybernetics (Or control and communication in the animal and the machine). Cambridge (Massachusetts): MIT Press. 212 p.
22. Von Bertalanffy L (1968) General system theory. New York: George Braziller, Inc. 295 p.
23. Hood L (2003 May 15) Leroy Hood expounds the principles, practice and future of systems biology. Drug Discov Today 8: 436–438.
24. Burke A (2003 September 9) Look who's blazing the systems biology trail. Genome Technology: 26–33.
25. Stelling J, Sauer U, Szallasi Z, Doyle FJ III, Doyle J (2004) Robustness of cellular functions. Cell 118: 675–685.
26. Kitano H (2004) Biological robustness. Nat Rev Genet 5: 826–837.
27. Keller E (2000) The century of the gene. Cambridge (Massachusetts): Harvard University Press. 192 p.
28. Ioannou P, Sun J (1995) Robust adaptive control. Upper Saddle River (New Jersey): Prentice Hall. 848 p.
29. Winfree A (2001) The geometry of biological time. 2nd edition. New York: Springer-Verlag. 808 p.
30. Albert R, Jeong H, Barabasi A (2000) Error and attack tolerance of complex networks. Nature 407: 651–654.
31. Spiro P, Parkinson J, Othmer H (1997) A model of excitation and adaptation in bacterial chemotaxis. Proc Natl Acad Sci U S A 94: 7263–7268.
32. Hasty J, Pradines J, Dolnik M, Collins J (2000) Noise-based switches and amplifiers for gene expression. Proc Natl Acad Sci U S A 97: 2075–2080.
33. Elowitz M, Leibler S (2000) A synthetic oscillatory network of transcriptional regulators. Nature 403: 335–338.
34. Atkinson M, Savageau M, Myers J, Ninfa A (2003) Development of genetic circuitry exhibiting toggle switch or oscillatory behavior. Cell 113: 597–607.
35. Ueda H, Hagiwara M, Kitano H (2001) Robust oscillations within the interlocked feedback model of Drosophila circadian rhythm. J Theor Biol 210: 401–406.
36. Barkai N, Leibler S (2000) Circadian clocks limited by noise. Nature 403: 267–268.
37. Houchmandzadeh B, Wieschaus E, Leibler S (2002) Establishment of developmental precision and proportions in the early Drosophila embryo. Nature 415: 798–801.
38. Eldar A, Dorfman R, Weiss D, Ashe H, Shilo B, et al. (2002) Robustness of the BMP morphogen gradient in Drosophila embryonic patterning. Nature 419: 304–308.
39. Jaeger J, Surkova S, Blagov M, Janssens H, Kosman D, et al. (2004) Dynamic control of positional information in the early Drosophila embryo. Nature 430: 368–371.
40. Barkai N, Leibler S (1997) Robustness in simple biochemical networks. Nature 387: 913–917.
41. Alon U, Surette MG, Barkai N, Leibler S (1999) Robustness in bacterial chemotaxis. Nature 397: 168–171.
42. Atkinson MR, Savageau MA, Myers JT, Ninfa AJ (2003) Development of genetic circuitry exhibiting toggle switch or oscillatory behavior in *Escherichia coli*. Cell 113: 597–607.

OPEN ACCESS Freely available online

PLoS MEDICINE

Essay

The Clinical Applications of a Systems Approach

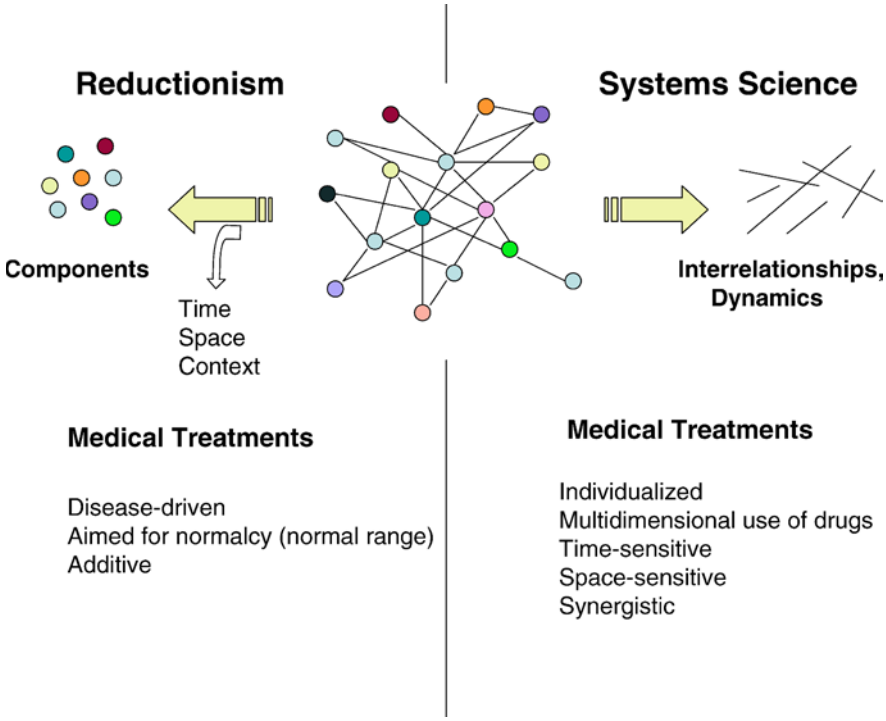
Andrew C. Ahn*, Muneesh Tewari, Chi-Sang Poon, Russell S. Phillips

This is the second in a series of two articles that look at the lessons for clinical medicine from systems biology.

In the first article in this series, we examined the reductionist approach that pervades medicine and explained how a systems approach (as advocated by systems biology) may complement it [1]. In order for a systems perspective to have any practical clinical significance, we must understand when a systems perspective is or is not helpful, and conversely when a reductionist approach is helpful. In addition, we must be able to envision how a systems perspective can be implemented to appreciate the potential benefits derived from its application. In this article, we address these issues and present a practical discussion of systems application to medicine.

Indications for Systems Approach and Reductionism

Reductionism, as a guiding principle, is tremendously helpful and useful. The problem with reductionism stems not from its use but from the wrongful assumption that it is the only solution. Reductionism becomes less effective when the act of dividing a problem into its parts leads to loss of important information about the whole. For instance, a complex machine such as an airplane or a computer may be divided into smaller and smaller fragments, but at some point, the individual parts fail to impart consequential information about the machine's overall function. The primary side effect of a reductionist approach is that the act of reduction (from larger to smaller) disregards component–component interactions and the dynamics that result from them. Therefore, as a general rule, reductionism is less helpful for systems where interactions between components dominate the



DOI: 10.1371/journal.pmed.0030209.g001

Figure 1. Medical Treatments: Reductionism versus Systems Science

Treatment differences stem from divergent problem-solving tactics. Reductionism focuses on components and, in the process, can lose information about time, space, and context. Systems science focuses on the interactions and dynamics and spends less time studying the individual components.

The Essay section contains opinion pieces on topics of broad interest to a general medical audience.

Funding: ACA's work on this manuscript was supported by a National Institutes of Health Institutional National Research Service Award, grant T32-AT0051-03. RSP is supported by a National Institutes of Health Mid-Career Investigator Award (K24-AT000589). The contents of this work are solely the responsibility of the authors and do not necessarily represent the official views of the National Center for Complementary Alternative Medicine or the National Institutes of Health. CSP is supported by National Institutes of Health grant R01-HL072849.

Competing Interests: The authors declare that they have no competing interests.

Citation: Ahn AC, Tewari M, Poon CS, Phillips RS (2006) The clinical applications of a systems approach. PLoS Med 3(7): e209. DOI: 10.1371/journal.pmed.0030209

DOI: 10.1371/journal.pmed.0030209

Andrew C. Ahn is with the Division for Research and Education in Complementary and Integrative Medical Therapies, Harvard Medical School, Boston, Massachusetts, United States of America; the Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States of America; and the Advanced Study Program, Massachusetts Institute of Technology, Cambridge, Massachusetts, United States of America. Muneesh Tewari is with the Human Biology Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, United States of America. Chi-Sang Poon is with the Harvard–Massachusetts Institute of Technology Division of Health Sciences and Technology, Cambridge, Massachusetts, United States of America, and the Computational and Systems Biology Initiative, Massachusetts Institute of Technology, Cambridge, Massachusetts, United States of America. Russell S. Phillips is with the Division for Research and Education in Complementary and Integrative Medical Therapies at Harvard Medical School and the Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States of America.

* To whom correspondence should be addressed. E-mail: aahn@hms.harvard.edu

components themselves in shaping the system-wide behavior (Table 1).

In clinical medicine, complex, chronic diseases such as diabetes, coronary artery disease, or asthma are examples where this rule may apply. In these examples, a single factor is rarely implicated as solely responsible for disease development or presentation. Rather, multiple factors are often identified, and the disease evolves through complex interactions between them. Consequently, a perspective in which the interactions and dynamics are centrally integrated into the analytical methods may be better suited. Systems perspectives, unlike reductionisms, focus on these interrelationships and therefore may be the optimal method for complex chronic diseases.

Where reductionism is helpful, when a systems approach is not, is when one or several components overwhelmingly influence the systems behavior. Diseases such as urinary tract infection, acute appendicitis, or aortic dissection are driven primarily by a single pathology amenable to a specific intervention. Arguably, these conditions would do poorly under a systems approach, where lengthy analysis and comprehensive data acquisition are often required. Reductionism works best when an isolatable problem exists and where a quick and effective solution is needed. For that reason, reductionism may generally be most effective for acute and simple diseases, whereas a systems approach may be most applicable to chronic and complex diseases.

Table 1. Application of Reductionism versus Systems-Oriented Perspective to Medicine

Characteristics	Reductionism	Systems-Oriented Perspective
Optimal	Conditions where one or few components are responsible for the overall behavior of the system	Conditions where interactions between components are responsible for the overall behavior of the system
Disease types	Acute, simple diseases	Chronic, complex diseases
Examples	Urinary tract infection	Diabetes
	Appendicitis	Coronary artery disease
	Aortic aneurysm	Asthma
Theoretical limitations	Disregards component–component interactions and dynamics	Costly in resources and time

DOI: 10.1371/journal.pmed.0030209.t001

The Example of Diabetes

Given that a systems approach is likely applicable to complex chronic diseases, how might it influence the treatment of a complex disease such as diabetes? Research has shown that diabetes is a multidimensional disorder. Factors such as genetics, inflammation [2–7], PPAR-gamma [8], leptin [9], cortisol [10], diet [11], and body mass index, among others, have been implicated in some form with its pathogenesis. The fundamental distinctiveness of systems medicine is not just the recognition that these complex factors are important in disease management, but that they need to be incorporated in some meaningful way to treatment selection and delivery. The primary challenge tackled by systems scientists is the rigorous elucidation of how these multiple variables dynamically interact and how one can apply this understanding to affect the system and achieve a desirable end.

While this approach seems extremely complicated and difficult, the advent of computers and mathematical tools has opened avenues not deemed possible before. For the medical community, the more imminent hurdle may be our inability to envision and thus appreciate the potential benefits derived from the application of a systems approach. To obtain a glimpse of how systems principles will affect medicine, we consider three concepts central to systems medicine that are often overlooked through reductionist approaches: time, space, and context.

Time. Our present diagnosis of diabetes requires two separate documentations of fasting glucose over 6.9 mmol/L or a two-hour oral glucose tolerance test result above 11.1 mmol/L. The criterion relies on a measurement obtained at a single point in time, ideally eight hours after a meal or two hours after a glucose load. The theoretical disadvantage of this definition is that the diagnosis is established much after the underlying abnormality has begun. To use the analogy of a blocked sink—the problem is defined only when the water overflows, despite the fact that the draining problem has occurred some time beforehand. A more sensitive method for detecting a problem may be to evaluate the rate of change in the water level—whether the water level steadily increases with time or whether it fails to decrease in response to a large water input—in other words, to assess the dynamics of the variable of interest.

While this example is a gross oversimplification, it highlights a fundamental tenet of systems medicine, namely, that the dynamics may contain more revealing information about a system than static data alone. To apply this tenet to diabetes, one might assess the likelihood that glucose variability or the change in insulin levels over time may provide useful diagnostic information not otherwise obtained through traditional methods. Some evidence already exists to support this supposition. Healthy individuals show pulsatile insulin secretions of about six- to ten-minute periodic oscillations [12], whereas people with type 2 diabetes have impaired insulin oscillations [13], which also fail to entrain with repeated glucose infusions [14,15]. Interestingly, impaired pulsatile secretions have been detected in metabolically normal yet predisposed individuals (first-degree relatives of people with type 2 diabetes) [16,17], suggesting that these dynamic evaluations may be more sensitive in detecting beta-cell dysfunction than traditional methods [18]. Because of the promise of dynamic analysis in diabetes, many other methods have also been evaluated [19–21].

Because glucose levels are continually regulated through a dynamic balance between glucose-lowering factors (such as insulin) and glucose-elevating factors (such as glucagons, growth hormone, or epinephrine), the manner in which glucose varies over time may reflect the functional health of the relevant metabolic pathways. The premise is that glucose regulatory pathways are inextricably interconnected and that any dysfunction in the pathway is reflected in the glucose/insulin dynamics. The temporal changes of a variable contain hidden, useful information about the overall system. As a consequence, a systems approach to medicine will likely incorporate temporal variability into diagnosis and

treatment in a way that reductionist medicine has never done before.

Space. When chemstick glucose levels are obtained, there is an implicit assumption that the geographic distribution of glucose is uniform: A chemstick in the right finger is equivalent to a chemstick from the left finger or a venous puncture reading from an antecubital region. But glucose, even plasma glucose, possesses spatial differences [22] that are frequently overlooked in clinical practice. The same can be said about insulin injections. Injections in the thigh are often considered just as effective as injections in the abdominal wall, despite evidence indicating that insulin absorption and distribution differ at different sites [23–25]. The problem confronted by clinical medicine is not so much the recognition that these variations occur, but rather the inability to incorporate spatial information into treatment or diagnostic decisions.

In systems theory, spatial variability, much like temporal variability, is valued for its potential to impart system-level information. Analytic tools such as diffusion equations and fluid dynamics are frequently used to evaluate the spatiotemporal patterns of various systems. Consequently, for diabetes, the application of systems principles may promote investigation and enhance understanding of the spatial variations of glucose and insulin within the human body. With proper tools and analytical techniques, we may someday be able to determine where insulin injections are most effective, how bodily glucose distribution can predict risk of diabetes, and how certain foods lead to unhealthy overstimulation of certain susceptible beta-islet cells. The one caveat, however, is that spatial information, such as glucose distribution, is difficult to acquire and may explain why spatial variability of glucose remains largely unexplored. Nevertheless, a systems approach may provide a much-needed conceptual tool for the study of spatial influence in medicine and thus may inform health providers where optimal solutions exist.

Context. One of the principal challenges for medical practitioners will be to curb our instinctive inclination to focus on disease rather than the individual. In diabetes, for instance, we are inclined to focus on the symptom—hyperglycemia—and to deliver treatments aimed directly at lowering glucose. While this approach is highly effective, a systems approach to medicine may redirect our attention away from the elevated glucose per se, toward the contextual milieu that fosters it. Dietary habits, sleeping behavior, immune system, genetics, psychiatric condition, medical comorbidities, and other factors can be systematically integrated into a physician's selection and delivery of treatment. The individual, not the disease, achieves central importance in systems medicine.

However, with a systems perspective, will treatments truly change? How can a patient with diabetes *not* receive glucose-lowering agents? How will "disease" be conceptualized, and will it be defined any differently? Fortunately, studies in systems biology have addressed similar questions and provide two important lessons for clinical medicine: (1) complex diseases may represent many different processes and (2) complex diseases may have varied and sometimes unintuitive treatments.

Systems biology's first lesson for clinical medicine can be derived from the RNA expression profiles of diffuse B cell lymphoma. The lymphoma's genetic profile yielded an unexpected, yet important discovery—namely that for a disorder once considered a single entity, at least three different genetic profiles exist: germinal-center B cell–like, activated B cell–like, and type 3 diffuse large B cell lymphoma [26]. Genetic profiles of other disorders—such as breast cancer [27], non-small-cell lung carcinoma [28], and acute lymphoblastic leukemia [29]—have similarly shown the existence of multiple subtypes. The conceptual breakthrough afforded by these findings is the idea that seemingly single phenotypic entities can have multiple etiologic or pathologic processes. For clinical medicine, this may mean that diseases such as diabetes actually represent many different processes that do not become apparent until the composite factors (i.e., the context) are considered. Therefore, two patients with type 1 diabetes who have identical presentations may nevertheless have different pathogenic processes, and thus should be regarded differently.

The study of diffuse B cell lymphoma also showed that the three identified subtypes have varied prognoses and responsiveness to chemotherapy [26,30,31]. Consequently, systems biology's lesson can be extended one step further, to suggest that not only do different processes exist for a specific disease but that each process should be treated or handled differently. This notion encourages the personalization or individualization of medicine. One patient with type 2 diabetes may respond best to insulin, for example, while another may not. As a corollary to this statement, some patients with diabetes may not require glucose-lowering agents at all, but instead may benefit from a less obvious treatment. The determination of these optimal treatments will rest on the rigorous evaluation of the complex factors inherent in each and every patient.

Systems Medicine in Practice

Systems medicine, as we see, begins to explore medicine beyond linear relationships and single parameters. Systems medicine involves multiple parameters obtained across multiple time points and spatial conditions to achieve a holistic perspective of an individual. The clinical practice that results from this paradigm will

Table 2. Approaching Diabetes within a Systems Perspective

Factor	Systems-Oriented Practice
Time	Assessing temporal variability of insulin or glucose as a means to predict or diagnose diabetes
	Administering insulin at critical time junctures (aside from pre-meal/pre-sleep times)
	Assessing spatial distribution of insulin or glucose as a means to predict or diagnose diabetes
Space	Administering insulin at sites with optimal effect
Context	Using multiple parameters to determine the type of diabetes (beyond types 1 and 2) affecting the patient
	Administering individualized, sometimes unintuitive treatments (e.g., salicylates for certain individuals)

DOI: 10.1371/journal.pmed.0030209.t002

be distinctly different from the status quo, particularly for complex diseases, as shown by our example of diabetes (Table 2). In general, treatments within systems medicine can be characterized by several distinguishing features (Figure 1).

Individualized treatments. Instead of formulating treatments according to disease, a systems clinician may prescribe treatments specifically targeted to individuals and their present conditions.

Minimized interventions. Treatments can deliver the "biggest bang for the buck" so that the least invasive intervention may yield the greatest system-wide benefit, maximize the body's self-healing abilities, and minimize side effects.

Multidimensional uses of medications. Medications may be used for unintended purposes because nonlinear, unintuitive relationships exist between pathogenic factors and disease. In diabetes, for example, evidence suggests the benefits of salicylates for glucose control in certain individuals [32–34].

Time-sensitive treatments. The human body, like most living systems, has cyclical variations that may affect treatment efficacy. To maximize effectiveness, treatments can be delivered at selective times. Cancer chronotherapy is a working example: chemotherapeutic agents given on a timed regimen are more effective than a standard treatment approach [35–37].

Space-sensitive treatments. The efficacy of certain treatments may depend on where the treatment is delivered. Future treatments may be localized to a specific part of the body to maximize system-wide efficacy.

Synergistic treatments. Use of more than one treatment or modality can be given so that the effects are synergistic and not antagonistic or merely additive.

Probabilistic forecasting. The probability of the success or failure of a particular treatment may be calculated specifically for an individual.

Temporary treatments. Chronic treatments may be unnecessary. In systems biology, biological systems are understood to assume certain dynamic states—or "attractor states" [38,39]. Disease may represent certain attractor states, while health may represent others. If so, it is theoretically possible to affect the system dynamics and transform a diseased state to a healthy one through limited interventions [40]. Because these states are effectively stable, chronic treatments may be unnecessary.

These practices and concepts are not new to medical systems. Medical traditions such as traditional Chinese [41], Native American [42], and certain Western medicines have for centuries incorporated these practices in their care of patients, mainly due to the philosophical belief that the world (including humans) is dynamic and interactive. Unlike modern systems medicine, however, human intuition and observation rather than mathematical/computational tools served as the basis for advancing medical knowledge.

Barriers to Systems Medicine

Widespread benefits of systems medicine will not be realized until six key barriers are overcome. First, the network relationships will need to be elaborated in detail. In diabetes, for instance, we lack the in-depth knowledge of how diet, inflammation, PPAR-gamma, genetics, and other factors interrelate and influence each other's behavior. Secondly, a feasible and cost-effective means to acquire comprehensive data will need to be developed. Clinical medicine at the present moment lacks an equal to the DNA array chip that enables numerous parameters to be economically obtained at once. In addition, we lack the means to obtain measures across multiple temporal and spatial conditions without causing patient inconvenience and excessive costs. Third, the optimal balance between too little information and too much information needs to be established. Often, accumulation of information beyond a certain point may contribute to costly expenditures without adding any effective understanding of the system. Fourth, the analytical tools for determining how to affect biological networks and obtain the desired effect need to be perfected. How should we calculate the needed adjustments to our patients' diets to minimize their pancreatic beta-cell loss? The mathematical and computational tools are available but still imperfect. Fifth, the theoretical and experimental methods should be effectively integrated in order for systems science to truly advance. Finally, complex analysis is inherently a long-term, broad-based investment. To investors and researchers accustomed to immediate, predictable results, this consideration may present the greatest barrier, causing many to doubt whether the not-so-apparent benefits merit further financial or temporal commitment.

Despite these challenges, the realization of systems medicine may not be as distant as many may think. Already a computer program called Archimedes has been developed for the complex modeling of diabetes and predicts diabetes-related clinical outcomes with uncanny accuracy [43,44]. Archimedes is just a sample of the many more systems-level programs that will likely emerge within the next five to ten years.

Conclusion

Systems medicine encompasses a broad scope of topics, many of which have been untouched in this two part series. Examples include scaling, stochasticity, attractor states, plasticity, systems definition of health, and many others. The challenges of incorporating systems science into medicine are difficult but not insurmountable. In fact, systems biologists, who deal with thousands of genes and proteins, may arguably be confronted with a much more daunting task. Nevertheless, systems biologists have recognized the necessity of a systems perspective. It is time that physicians, clinical researchers, physiologists, and epidemiologists did the same. The specific task to be faced is the system-level understanding of human health and disease at the organ, organism, and community level. This effort has great potential for the advancement of medicine. ■

References

1. Ahn AC, Tewari M, Poon CS, Phillips RS (2006) The limits of reductionism in medicine: Could systems biology offer an alternative? PLoS Med 3: e208. DOI: 10.1371/journal.pmed.0030208
2. Toni R, Malaguti A, Castorina S, Roti E, Lechan RM (2004) New paradigms in neuroendocrinology: Relationships between obesity, systemic inflammation and the neuroendocrine system. J Endocrinol Invest 27: 182–186.
3. Crook M (2004) Type 2 diabetes mellitus: A disease of the innate immune system? An update. Diabet Med 21: 203–207.
4. Hotamisligil G (2003) Inflammatory pathways and insulin action. Int J Obes Relat Metab Disord 27 (Suppl 3): 53–55.

5. Shoelson SE, Lee J, Yuan M (2003) Inflammation and the IKK beta/I kappa B/NF-kappa B axis in obesity- and diet-induced insulin resistance. Int J Obes Relat Metab Disord 27 (Suppl 3): 49–52.
6. Finegood D (2003) Obesity, inflammation and type II diabetes. Int J Obes Relat Metab Disord 27 (Suppl 3): 4–5.
7. Dandona P, Aljada A, Bandyopadhyay A (2004) Inflammation: The link between insulin resistance, obesity and diabetes. Trends Immunol 25: 4–7.
8. Sugden MC, Holness MJ (2004) Potential role of peroxisome proliferator-activated receptor-alpha in the modulation of glucose-stimulated insulin secretion. Diabetes 53 (Suppl 1): 71–81.
9. Seufert J (2004) Leptin effects on pancreatic beta-cell gene expression and function. Diabetes 53 (Suppl 1): 152–158.
10. Rosmond R (2003) Stress induced disturbances of the HPA axis: A pathway to type 2 diabetes? Med Sci Monit 9: RA35–RA39.
11. Scheen AJ (2003) Pathophysiology of type 2 diabetes. Acta Clin Belg 58: 335–341.
12. Schmitz O, Brock B, Hollingdal M, Juhl CB, Porksen N (2002) High-frequency insulin pulsatility and type 2 diabetes: From physiology and pathophysiology to clinical pharmacology. Diabetes Metab 28: 4S14–4S20.
13. Sturis J, Polonsky KS, Shapiro ET, Blackman JD, O'Meara NM, et al. (1992) Abnormalities in the ultradian oscillations of insulin secretion and glucose levels in type 2 (non-insulin-dependent) diabetic patients. Diabetologia 35: 681–689.
14. Mao CS, Berman N, Roberts K, Ipp E (1999) Glucose entrainment of high-frequency plasma insulin oscillations in control and type 2 diabetic subjects. Diabetes 48: 714–721.
15. Hollingdal M, Juhl CB, Pincus SM, Sturis J, Veldhuis JD, et al. (2000) Failure of physiological plasma glucose excursions to entrain high-frequency pulsatile insulin secretion in type 2 diabetes. Diabetes 49: 1334–1340.
16. O'Rahilly S, Turner RC, Matthews DR (1988) Impaired pulsatile secretion of insulin in relatives of patients with non-insulin-dependent diabetes. N Engl J Med 318: 1225–1230.
17. Schmitz O, Porksen N, Nyholm B, Skjaerbaek C, Butler PC, et al. (1997) Disorderly and nonstationary insulin secretion in relatives of patients with NIDDM. Am J Physiol 272: E218–E226.
18. Porksen N, Hollingdal M, Juhl C, Butler P, Veldhuis JD, et al. (2002) Pulsatile insulin secretion: Detection, regulation, and role in diabetes. Diabetes 51 (Suppl 1): 245–254.
19. Topp B, Promislow K, deVries G, Miura RM, Finegood DT (2000) A model of beta-cell mass, insulin, and glucose kinetics: Pathways to diabetes. J Theor Biol 206: 605–619.
20. Holt TA (2002) A chaotic model for tight diabetes control. Diabet Med 19: 274–278.
21. Kroll MH (1999) Biological variation of glucose and insulin includes a deterministic chaotic component. Biosystems 50: 189–201.
22. Stahl M, Brandslund I (2003) Measurement of glucose content in plasma from capillary blood in diagnosis of diabetes mellitus. Scand J Clin Lab Invest 63: 431–440.
23. Witt MF, White NH, Santiago JV (1983) Roles of site and timing of the morning insulin injection in type 1 diabetes. J Pediatr 103: 528–533.
24. Berger M, Cuppers HJ, Hegner H, Jorgens V, Berchtold P (1982) Absorption kinetics and biologic effects of subcutaneously injected insulin preparations. Diabetes Care 5: 77–91.
25. ter Braak EW, Woodworth JR, Bianchi R, Cerimele B, Erkelens DW, et al. (1996) Injection site effects on the pharmacokinetics and glucodynamics of insulin lispro and regular insulin. Diabetes Care 19: 1437–1440.
26. Rosenwald A, Wright G, Chan WC, Connors JM, Campo E, et al. (2002) The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 346: 1937–1947.
27. Zhang DH, Salto-Tellez M, Chiu LL, Shen L, Koay ES (2003) Tissue microarray study for classification of breast tumors. Life Sci 73: 3189–3199.
28. Au NH, Cheang M, Huntsman DG, Yorida E, Coldman A, et al. (2004) Evaluation of immunohistochemical markers in non-small cell lung cancer by unsupervised hierarchical clustering analysis: A tissue microarray study of 284 cases and 18 markers. J Pathol 204: 101–109.
29. Mancini M, Scappaticci D, Cimino G, Nanni M, Derme V, et al. (2005) A comprehensive genetic classification of adult acute lymphoblastic leukemia (ALL): Analysis of the GIMEMA 0496 protocol. Blood 105: 3434–3441.
30. Rosenwald A, Staudt LM (2003) Gene expression profiling of diffuse large B-cell lymphoma. Leuk Lymphoma 44 (Suppl 3): 41–47.
31. Wright G, Tan B, Rosenwald A, Hurt EH, Wiestner A (2003) A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. Proc Natl Acad Sci U S A 100: 9991–9996.
32. Hundal RS, Petersen KF, Mayerson AB, Randhawa PS, Inzucchi S, et al. (2002) Mechanism by which high-dose aspirin improves glucose metabolism in type 2 diabetes. J Clin Invest 109: 1321–1326.
33. Giugliano D, Ceriello A, Saccomanno F, Quatraro A, Paolisso G, et al. (1985) Effects of salicylate, tolbutamide, and prostaglandin E2 on insulin responses to glucose in noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab 61: 160–166.
34. Baron SH (1982) Salicylates as hypoglycemic agents. Diabetes Care 5: 64–71.
35. Canaple L, Kakizawa T, Laudet V (2003) The days and nights of cancer cells. Cancer Res 63: 7545–7552.
36. Fu L, Lee CC (2003) The circadian clock: Pacemaker and tumour suppressor. Nat Rev Cancer 3: 350–361.
37. Mormont MC, Levi F (2003) Cancer chronotherapy: Principles, applications, and perspectives. Cancer 97: 155–169.
38. Huang S (2001) Genomics, complexity and drug discovery: Insights from Boolean network models of cellular regulation. Pharmacogenomics 2: 203–222.
39. Kauffman S (1993) The origins of order: Self organization and selection in evolution. New York: Oxford University Press. 734 p.
40. Lopes da Silva F, Blanes W, Kalitzin SN, Parra J, Suffczynski P, et al. (2003) Epilepsies as dynamical diseases of brain systems: Basic models of the transition between normal and epileptic activity. Epilepsia 44 (Suppl 12): 72–83.
41. Nisbett RE, Peng K, Choi I, Norenzayan A (2001) Culture and systems of thought: Holistic versus analytic cognition. Psychol Rev 108: 291–310.
42. Lewton EL, Bydone V (2000) Identity and healing in three Navajo religious traditions: Sa'ah naaghai bik'eh hozh [symbol: see text]. Med Anthropol Q 14: 476–497.
43. Schlessinger L, Eddy DM (2002) Archimedes: A new model for simulating health care systems—The mathematical formulation. J Biomed Inform 35: 37–50.
44. Eddy DM, Schlessinger L (2003) Archimedes: A trial-validated model of diabetes. Diabetes Care 26: 3093–3101.