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Dynamical systems approaches to personalized medicine

Jacob D Davis^{1,3}, Carla M Kumbale^{1,2,3}, Qiang Zhang², Eberhard O Voit¹

¹Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, 950 Atlantic Drive, Atlanta, GA 30332, United States

²Department of Environmental Health, Rollins School of Public Health, Emory University, 1518 Clifton Rd, NE, Atlanta, GA 30322, United States

Abstract

The complexity of the human body is a major roadblock to diagnosis and treatment of disease. Individuals may be diagnosed with the same disease but exhibit different biomarker profiles or physiological changes and, importantly, they may respond differently to the same risk factors and the same treatment. There is no doubt that computational methods of data analysis and interpretation must be developed for medicine to evolve from the traditional population-based approaches to personalized treatment strategies. We discuss how computational systems biology is contributing to this current evolution.

Introduction

It is difficult to pinpoint the true beginnings of systems biology. Over two millennia ago, Hippocrates already pondered the wholeness of organisms and Aristotle discussed phenomena like synergism that lead to emerging properties in complex systems. More recent roots can clearly be seen in the work of physiologists in the 18th and 19th Centuries and in the molecular biology of the 20th Century. Early pioneers like Claude Bernard, Alfred Lotka, and Ludwig von Bertalanffy were, without doubt, systems biologists in spirit, even though the term *systems biology* was introduced much later by Mihajlo Mesarovic in 1968. The foundations of modern systems biology followed shortly, advanced by pioneers like Richard Bellman, Robert Rosen, Nicolas Rashevsky, Reinhart Heinrich, and Michael Savageau. With the first human genome sequenced at the turn of the millennium, the ‘new’ field of systems biology moved forcefully into the limelight of biology. Several books on systems biology entered the market in short order (e.g. in Refs. [1–7,8•]). Importantly, systems biology offered an alternative to the traditional reductionist approach [9,10] and was exuberantly hailed ‘the future of medicine’ [11], the ‘enabling force’ [12] and a ‘strong driver’ for personalized medicine [13].

The roles of reductionism and systems biology actually form an interesting Yin and Yang. On the one hand, systems biology proposes an approach that is conceptually opposite to

Corresponding authors: Zhang, Qiang (qiang.zhang@emory.edu), Voit, Eberhard O (eberhard.voit@bme.gatech.edu).

³Equal contributions.

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reductionism. On the other hand, systems biology absolutely depends on reductionistic research, as it needs the details of molecular inventories for the reconstruction of systems. Expressed differently, the perspective of systems biology is diametrically different from reductionism, but it cannot be achieved without a very detailed understanding of the biological parts, which reductionism offers.

The rationale for proposing systemic approaches was and continues to be the enormous complexity of the human body and, specifically, the frequent observation that diseases like breast cancer can exhibit rather different manifestations among individuals that cause the same drug to be effective in some patients but not in others [14]. Our genomes differ by approximately six million bases, which in combination permit an enormous range of possible disease patterns. This repertoire of differences is further augmented by variations in lifestyle, diet, and environmental exposures, which all affect well-being and can lead to persistent epigenetic differences [15•]. Given this complexity, it seems that the only truly valid control for distinguishing health and disease is an individual's own healthy baseline [16].

Only computational methods have the capacity to handle this variety and complexity. While acknowledging the daunting challenges facing personalized medicine, Weston and Hood [17] proffered that “systems biology ... will catalyze fundamental changes in the future of health care” and that it “will have a major role in creating a predictive, preventative, and personalized approach to medicine.” Kitano [11] confidently predicted: “Although the road ahead is long and winding, it leads to a future where biology and medicine are transformed into precision engineering.”

Systems biology of health and disease

The field of systems biology can naturally be divided into experimental and computational subdisciplines. Of course, these two branches are intimately interwoven with each other, as computational systems biology (CSB) critically depends on measurements, whose coverage and accuracy have a direct bearing on the value of computational models. At the same time, models often suggest novel hypotheses, which are to be tested experimentally.

Experimental systems biology (ESB) is best exemplified with the various –omics approaches, which have enormously changed the way biological research is executed and applied to medicine, although not always without caveats [18•]. In particular, the vast repertoire of new tools accompanying ESB permits personalized diagnosis and prognosis for the efficacy of treatments, based on biomarker profiles (e.g. in Refs. [19,20]).

A beautiful illustration is a study on childhood acute lymphoblastic leukemia (ALL), for which chemotherapy can normally have a long-term disease-free survival rate of about 80%. But what about the remaining 20%? Microarray and *in vitro* cell-killing assays with leukemia cells from cohorts of pre-treatment patients revealed between 20 and 45 differentially expressed genes that were associated with single-drug resistance or cross-resistance [21]. By measuring these prognostic transcriptomic signatures in an independent cohort of young ALL patients, responders and non-responders to drug treatment could be

predicted with high accuracy [22]. Numerous other biomarker studies, based on different –omics analyses, have spawned new translational and clinical research and resulted in classifications of patient cohorts with respect to treatment efficacy. An introductory review of methods focusing on –omics, multi-omics [23], and even ‘integrative personal –omics profiles’ can be found in Ref. [12].

Computational systems biology (CSB) contains two some-what overlapping areas. The first uses machine learning and artificial intelligence to identify statistical patterns in large datasets, which typically consist of complex, nonlinear associations between subgroups of data and disease diagnosis, prognosis, and optimal therapeutics [24,25]. However, despite extensive research and increasing numbers of applications, machine learning approaches by themselves are insufficient. A major caveat is the lack of mechanistic connections between input features and predicted outcomes. As a result, the models can be limited in adaptations to new data types and for making predictions regarding data obtained under new conditions. Overcoming these limitations requires dynamic modeling approaches whose goal it is to be causal and mechanistically explanatory, at least to some degree. These dynamic approaches are the focus of the second area of CSB and the prime topic of this article.

Health and disease as features of dynamical systems

In dynamical systems theory, health and disease may be viewed as *stable attractors*. They are typically steady states (fixed points) in a high-dimensional molecular and physiological space, but may also consist of stable limit cycles, such as circadian rhythms, or even chaotic attractors. Homeostasis is viewed as the state of optimal health. This attractor is stable, at least for some time, as the human body uses complex systems of regulatory feedback and feedforward mechanisms to regain homeostasis after moderate perturbations, such as changes in diet or mild environmental exposures. Disease represents an alternate, suboptimal attractor, which typically is also stable. The migration from health to disease may be gradual, but may also be abrupt or even manifest as the loss of chaotic, yet healthy features, for instance in heart and brain rhythms, which has been identified as an early sign of aging, frailty, or general system failure [26].

Differences between health and disease are typically assumed to map onto altered parameter profiles rather than altered system topologies, because one would expect the fundamental physiological mechanisms to be retained throughout a disease, even though some of their characteristics might change. For instance, important pathways are seldom entirely destroyed by (mild) disease, but their activity may be altered. Even so, differential parameter profiles for health and disease may include values of zero for some rates or other features, which may be due to a gene mutation leading to loss of function, and because these parameters represent particular system structures, the corresponding processes operating in healthy individuals may cease to exist in disease. Because uncounted shifts away from a healthy parameter profile are possible, individuals might migrate from health toward any number of personal disease states, as it is indeed observed [14,16]. Some of these disease states may have the same phenotype but respond differently to treatment.

A natural implementation of a shift from health to disease is a dynamic model of all pertinent components of the health state. Such a model is constructed based on known information, which is almost always a reflection of ‘normal averages’ from human or animal populations. To personalize the model for an individual, as many pertinent parameters as feasible are obtained from this individual and substituted for the corresponding average parameters. This basic strategy was proposed in the context of dynamic models some while ago [14,27]. The personalized model renders it possible to translate parameter changes into mechanisms of disease [28•], explore root causes of disease [29], design disease simulators [30] and assess alternate treatment options [31].

One class of dynamic models that already had a tangible impact on personalized medicine consists of physiologically-based pharmacokinetic (PBPK) models. Since their infancy, these models had been used for extrapolations from animals to humans (cf. [5]), but recent applications have focused on the personalization of disease PBPK models (e.g. in Refs. [32••,33,34,35,36]) through parameter value adjustments.

One must acknowledge in this context that the identification of suitable parameter values is almost always a challenge in modeling, and this challenge is magnified for any types of personalized models, because all parameter values should ideally come from the same person. In addition, a single parameter may not be directly measurable as it might reflect a collection of many interacting processes. For instance, a parameter may represent the overall trend of a process, but not a single, measurable detail. The issue is furthermore related to the choice of variables, which in some cases are aggregate representatives of a subsystem. For instance, some intermediary metabolites and reactions may not seem to be necessary, but their omission could be detrimental to the model if they had additional, unknown roles. Taken together, there is a delicate balance between the complexity and simplicity of a model, which influences model and parameter choices.

It is often implicitly assumed that migrating away from homeostasis is continuous and smooth, but there is no guarantee. Dynamical systems theory offers various modalities for capturing abrupt switches or tipping points through bifurcations. One generic mechanism is a positive feedback that propels the system to a different state when a critical threshold is crossed [37]. A simple illustration is a bistable system with a high stable (health) and a low stable (disease) steady state, with an unstable steady state in between (Figure 1). If a signal or exposure parameter crosses a critical point, the system moves over the unstable state and jumps from health to disease or *vice versa*.

Somewhat more complicated threshold behaviors are discussed in the field of catastrophe theory, which offers seven ‘elementary’ types of abrupt behaviors. An intuitive illustration is a buckling beam that bends under pressure and snaps back when the pressure is removed, but suddenly breaks if the pressure exceeds some threshold [38]. As an extension, one might think of material fatigue, where a structure can tolerate stresses, but only a limited number of times. It is easy to see the analogy to a healthy person who tolerates adverse effects, such as parasite attacks or environmental exposures, but only up to a point. As a different type of change, a dynamic system may lose its stable steady state and start oscillating persistently.

In the simplest case, the parameter threshold where such a switch happens is known as a Hopf bifurcation. A medical example is the onset of tremors.

Bistable and catastrophic systems often have hard thresholds where the system dynamics changes dramatically. This fact is important, because even small perturbations in a parameter at the threshold or tipping point propel the system from one state into the other, possibly moving erratically back and forth many times. One guard against such stochastic *flickering* [39] of this type is the heterogeneity and connectivity of components within a system: groups of sufficiently heterogeneous, loosely connected components tend to change gradually, whereas homogeneous, tightly connected components tend to resist change up to a certain degree but then change abruptly [37]. In fact, the tolerance of homogeneous systems to repeated small perturbations may give the wrong impression of strong resilience.

Protection against undue jumps between two stable states is also afforded by a phenomenon called *hysteresis*. As sketched in Figure 2, a hysteretic system has steady states (Y-axis) that depend on the strength of a signal, exposure or other parameter (X-axis). The high and low steady states, which are stable, form overlapping lines (green, red) that are connected by a line of unstable states (blue). Instead of a single tipping point, such a system has a buffer domain (grey) within which its behavior does not change abruptly. In this domain, the system can operate around two states: Depending on its recent history, it operates either on the upper or on the lower branch of stable steady states, as long as it does not cross the boundaries of the buffer domain. An interesting special case emerges when the numerical settings of the correspond to a hysteresis diagram with a buffer domain that crosses the Y-axis (Figure 2b); this situation permits a jump from the upper (health) to the lower (disease) branch but not *vice versa* and thus represents an irreversible disease (see also Refs. [5,40,41]).

In reality, systems are exposed to numerous signals or inputs, possibly leading to high-dimensional hysteretic systems. A two-input system is visualized in Figure 3 and could be interpreted as a two-hit cancer model [42], where one carcinogen or exposure of moderate strength is tolerated without immediate consequence, but a second, independent exposure leads to cancer. Interestingly, as the system approaches and transcends the buffer domain (in either direction), the real part of at least one eigenvalue moves toward 0, indicating the impending loss of stability. Because the inverses of eigenvalues are measures of time scales in the system, the eigenvalue approaching zero also indicates that the responses of the system become sluggish [43,44]. In particular, the return from a perturbation to the optimal state within the health manifold (green and yellow) becomes slower, thereby increasing the chances of falling onto the disease manifold (red), due to some additional, possibly stochastic effect. From a more positive viewpoint, this sluggishness may serve as a possible warning sign and diagnostic tool for predicting an imminent, abrupt change [12].

Of course, health and disease are not static but change over time. To capture these trends, it would be ideal to establish models with personalized parameter profiles at many time points, thereby creating high-dimensional time series that correspond to personalized health trajectories. To interpret such a trajectory, it is necessary to classify all states into ‘(more or less) healthy’ and ‘(mildly or severely) diseased.’ Because states close to the optimal health

profile are still normal, it is useful to replace the point of optimal health with a high-dimensional product of normal health intervals. Furthermore recognizing that combinations of extreme values of these intervals are often detrimental to health, the unique health state becomes a *health simplex*, which is surrounded by one or more simplexes of different disease severity (Figure 4) [45]. Within this conceptual framework, a personal health history corresponds to a trajectory migrating through these nested simplexes. If validated, such a personalized trajectory will even allow future health predictions with some reliability.

Traditionally, health predictions for at-risk subpopulations are made with epidemiological models, such as the linear-logistic and Cox's proportional hazard model. At first glance, these seem to be very different, if not entirely incompatible with the dynamic models introduced here. However, these epidemiological models can be derived as direct properties of general dynamic disease models at their steady states [46].

Conclusions

The past decade has witnessed enormous advancements in analytical technologies for personal sensing, including wearable devices that track activities and vital signs [47•]. Combined with imaging and -omics profiling, the type, quantity, and quality of information-rich data that can be collected from a single individual is unprecedented. Eventually these data will hold the key to personalized medicine, that is, to predicting disease outcomes, devising individualized treatments, and understanding why the same disease manifests differently among individuals and why some drugs work for some patients but not others. The sheer enormity of biological information mandates computational methods of analysis that first filter true signals from noise and extract patterns associated specifically with a disease through machine learning and secondly convert these association patterns into dynamic models that permit explorations and simulations of disease, treatment, and future health trajectories that are not possible in any other way. These two complementary CSB approaches mutually feed into each other through mechanistic model-based feature engineering that expands feature repertoires and through developing machine learning-based dynamic models [48•,49•].

The challenges are great, but systems biology has taken the first steps toward addressing them. It is now necessary to push forward and to educate the next generation of researchers who can transform medicine into precision engineering [11,50•].

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Figure 1.

Vector field of a two-variable system with two stable steady states (green dots), one unstable steady state (yellow dot) and two saddle points (orange dots). Depending on the (non-steady-state) starting position, the system approaches one or the other stable steady state. An invisible line, the separatrix (dashed line) separates the basins of attraction for the two stable states. A trajectory starting at a non-negative position on the X-axis approaches the lower saddle point (orange dot). The green and blue lines are nullclines, while the red lines display examples of trajectories from various initial points toward a steady state, given a set of initial conditions.

Figure 2.

Diagrams of hysteretic systems. **(a)** The system has stable high (green) and low (red) steady states (Y-axis) that depend on the strength of a signal, exposure or other parameter (X-axis). The steady states form overlapping lines that are connected by a line of unstable steady states (blue). If the system operates close to point ① it will remain close to this state even if the signal on the X-axis is increased (green arrow), as long as it does not cross the right border of the buffer domain (grey). Similarly, if the system operates close to ② it will remain at some close-by state, even if the signal is reduced (red arrow). **(b)** A horizontal shift of the signal-response curve can lead to a situation where the system cannot recover from disease.

Figure 3.

Two-dimensional hysteretic system. The state of optimal health is located at the top of the green domain, for exposures $E1$ and $E2 = 0$. As a consequence of exposures, the homeostatic state moves away from the optimum into the yellow part of the manifold and may eventually drop (down-arrows) onto the disease manifold (red). A sufficient reduction in exposure allows a recovery back up onto the health manifold (up-arrows). The green/yellow and red parts of the surface are connected by unstable, medically unrealizable states (blue).

Figure 4.

Health and disease manifest as biomarkers inside or outside normal ranges. **(a)** Health corresponds to biomarkers within their normal ranges (yellow), with the optimum (green) somewhere close to the center. **(b)** Combinations of extreme values even within the normal ranges of individual biomarkers are often detrimental; cutting them off (black lines) leads to a health simplex. **(c)** The health simplex is surrounded by one or more simplexes of different disease severity. Any personalized health trajectory (curved arrow) eventually traverses some or all of these simplexes. **(d)** Health and disease simplexes in three dimensions.