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A Systems-Theoretical Framework for Health and Disease:

Inflammation and preconditioning from an abstract modeling point of view

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Abstract

Modern advances in molecular biology have produced enormous amounts of data characterizing physiological and disease states in cells and organisms. While bioinformatics has facilitated the organizing and mining of these data, it is the task of systems biology to merge the available information into dynamic, explanatory and predictive models. This article takes a step into this direction. It proposes a conceptual approach toward formalizing health and disease and illustrates it in the context of inflammation and preconditioning. Instead of defining health and disease states, the emphasis is on simplexes in a high-dimensional biomarker space. These simplexes are bounded by physiological constraints and permit the quantitative characterization of personalized health trajectories, health risk profiles that change with age, and the efficacy of different treatment options. The article mainly focuses on concepts but also briefly describes how the proposed concepts might be formulated rigorously within a mathematical framework.

Keywords

Disease; Health; Inflammation; Modeling; Preconditioning; Simplex; Systems Analysis

Introduction

Throughout its history, mankind has been fascinated with human health and disease, and arguably the vast majority of biological research has been motivated directly or indirectly by the goal of retaining, regaining, or improving health. Recent advances in the natural and computational sciences have made it possible to study health and disease with a new and powerful arsenal of molecular and computational tools, and the enormous potential of these tools has focused the spotlight on the possibility of predicting health processes and personalizing treatment. NIH Director Dr. Elias A. Zerhouni told a Congressional Subcommittee in April of 2006: “We can now clearly envision an era when the treatment paradigm of medicine will increasingly become more predictive, personalized and preemptive. We will strike disease before it strikes us with the hope of greatly reducing overall costs to society.”

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The vision of personal health risk predictions and individualized treatment regimens has its support in the enormous growth in information that has been achieved through the combination of traditional, crisply focused biology with the more recent comprehensive, high-throughput methods of data generation. The result of this combination has been a flood of data, and it is often implicitly assumed that the amassing of biomedical data will enable us to reach the goal of the “3 Ps” of prediction, personalization and preemption. Bioinformaticians have admirably managed the flood of data and made methods available for information mining and data driven analysis. However, data and their management alone will be insufficient for a comprehensive understanding of how cells or organisms function and which molecular or physiological changes might lead from health to disease. The reasons for the remaining gap in understanding are manifold and include the facts that the human brain cannot comprehend large numbers of concurrent processes, that control of these processes is usually distributed throughout several spatial and temporal scales, and that biological systems may respond in drastically different ways if they operate either below or above some invisible thresholds, whose characteristics are buried deeply in the structure and regulation of the systems: Only a small amount of additional sun exposure can turn tanning into a sunburn. These ubiquitous threshold characteristics are driven by complicated combinations of numerical features among the system components, such as concentrations, process rates and control signal strengths, and preclude reliable, unaided cause-and-effect argumentation.

A promising approach toward closing the gap in understanding is the construction of integrative mathematical and computational models. With advances in hardware and software as well as in systems analytical methods, these models are on the brink of becoming sufficiently accurate and comprehensive to yield deep insights into specific disease processes and eventually to facilitate the transition from treatments based on average disease scores toward personalized treatments [1]. While the current models have not yet reached this point, their potential and utility are clearly visible on the horizon [2]. Under this premise, this article shows how models can aid our thinking about health and disease beyond the observation that one state is “normal” and other states are abnormal or diseased. Specifically, we will define health and disease simplexes, which represent the multi-factorial nature of health and disease and permit the characterization of interpersonal variability, genetic predisposition, life style choices, risk assessments, the investigation of reversible and irreversible trajectories from health to disease and back, and for assessments of alternative treatment strategies. The article formalizes these concepts mathematically in the language of Biochemical Systems Theory [3;4], which has been used in the past for a variety of analyses of biomedical systems (*e.g.*, [5;6]) and disease processes (*e.g.*, [7;8;9;10]) and also provided the first objective rationale for Cox's proportional hazard model and the linear-logistic disease risk model of epidemiology [11].

Inflammation and preconditioning will be used throughout the article as a specific illustration of the abstract concepts. Inflammation constitutes an intriguing dynamic and tightly regulated systemic state, which may lead to drastically different outcomes. On one hand, inflammation is needed for infections to heal and for the prevention of ongoing losses of healthy tissue after injury. On the other hand, local inflammation may spread and ultimately result in sepsis and systemic inflammatory response syndrome, SIRS. As a specific example, patients with multiple injuries often have a positive outcome if they quickly gain homeostasis of their inflammatory mediators, because dominance of the pro-inflammatory potential typically leads to systemic inflammatory response syndrome, while dominance of the anti-inflammatory mediators may trigger “immunoparalysis” and septic complications [12;13]. Which of these responses actually occurs depends on numerous physiological characteristics of the patient, including his or her medical history and any preconditioning from earlier inflammation stimuli.

The body's initial and long-term inflammatory responses are manifold and include transport of plasma and leukocytes from the blood into the injured tissues, biochemical signaling

cascades, and the mobilization of cytokines, such as interleukins. These and other physiological characteristics, along with the individual body's specific responses, are parts of a dynamic, autoregulatory system that we are only slowly beginning to understand [14;15;16]. The complexity of this system suggests that outcome predictions would greatly benefit from mathematical and computational modeling (e.g., [5;6;16;17;18;19]).

Health and Disease Conceptualized as Simplexes

Many authors have discussed the future role of systems biology in predictive, personalized, and preemptive health. In most cases, this role has been seen in amassing data from multiple microarrays, which are ideally to be combined with information from other levels, such as proteomic or metabolic abundances, or with knowledge of diverse interactions among proteins or between proteins and DNA. While this information is very valuable, its integration requires methods of functional and dynamical data analysis and, thus, the employment of mathematical models. These models must capture the large numbers of biological components and their dynamic interactions over short time periods—as well as life-time horizons—and allow us to merge data and information into a functional context of health and disease. The approach proposed here takes a small step into this direction. It is quite generic and neither focuses on particular mathematical representations nor on specific diseases or disease risks, although inflammation is used as an illustrative application. Instead, the aim is a conceptual, systematic framework that allows thinking about health and disease in a general fashion and permits systematic definitions of disease processes, personalized health risk, biomarkers, disease trajectories, and other related phenomena.

It is difficult to define 'health' outside negative definitions like the 'absence of disease.' Health is often implicitly seen as the "normal state" of the organism, but such a definition is limiting because it precludes interpersonal variability and excludes healthy individuals who are apparently abnormal in some physiological aspects. An alternative that generalizes a health state is a *health simplex*.

Consider biological markers, including concentrations of key metabolites, gene expression levels, the oxidative state of a cell, a voltage potential, the degree of arterial blockage or any other measurable quantities that are relevant in the classification between health and disease. Generically, these markers play roles in a system that consists of dependent variables X_i , X_j , ... and processes v_{ij} that connect X_i and X_j and are the dynamic drivers of the system. The processes are functions of the dependent variables, which change in response to the state of the system, and also of independent variables Z_i that reflect a person's biological make-up and could represent gene alleles, enzymes, or other drivers of physiological or pathological functioning. Over short time periods of minutes, hours, or even days, the Z_i are usually quasi constant. However, over a horizon of several months or years, their values may change. Such slow changes are associated with aging or with chronic diseases and may be reversible or irreversible. It is also possible that the Z_i change very fast, and even in a discrete fashion, as it happens in acute diseases. Particularly fast changes are seen in the body's response to injury, where the abundances of biochemical mediators, such as TNF, interleukins, and sphingolipids begin changing almost immediately after injury (e.g., [1;13;20;21;22]).

Of course, the human body contains thousands of dependent and independent variables, which renders it useful to reduce this large space to the space of relevant physiological features involved in the specific disease of interest (cf., [18;23]). In some cases, this reduction may be substantial. For instance, if an injury or disease is localized or relatively minor, it may be assumed that features characterizing many of the major organs, muscles and bones are relatively unaffected and within their normal ranges. In other cases, the reducibility may be minor. Paradigm examples are severe trauma, multi-organ failure, and metastatic cancer, where

the disease specific subspace may not be much smaller than the entire feature space. Even in these cases, many features, such as the person's genetic predisposition are not changed by the disease.

In the reduced feature space, each dimension refers to a variable that is a candidate contributor to the disease. It is common practice to call such a feature a *biomarker*, which is defined as a “characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” [24]. Although there is often no distinction made between causative and purely symptomatic biomarkers, we will use this terminology in the following, supposing that the biomarkers of interest, if outside their normal ranges, are causative disease drivers. The definition of the disease subspace thus consists of two components, namely the identification of those biomarkers that are to be included and the characterization of the boundaries of this subspace. The identification of causative biomarkers will certainly change throughout the foreseeable future, because new biomarkers are detected with high frequency. At the same time, many biomarkers later turn out to be false positives, or it is recognized that only certain combinations of alleged biomarkers are of significance. Furthermore, it is not always clear at present whether biomarkers only exhibit a statistically significant association with a disease pattern or whether they are truly causative. If they are not causative, but only symptomatic, they may be useful for diagnostics, but they do not have to be included in the feature space. This role of each biomarker is a matter of biological and medical investigation and is expected to change as we learn more about a particular disease process. The advantage of creating disease feature spaces with mathematical methods is that these methods easily scale up, whereas the unaided human brain is quickly overwhelmed, especially if biomarkers are of relevance only in specific numerical combinations. Because the significance of biomarkers is related to their normal ranges, biomarker identification and the characterization of boundaries of the feature space are interdependent. They will be discussed next.

In line with clinical practice, each biomarker is assigned a normal range, which accounts for interpersonal variations among healthy individuals (Fig. 1). If two biomarkers are considered simultaneously, the product of these ranges is at first a rectangle. However, it is to be expected that some extreme combinations of biomarkers are inconsistent with health. If so, the corners of the rectangle are truncated, thus leading to a polygon. In higher dimensions, this polygon becomes a simplex, which we call the health simplex (Fig. 2).

The locations of the simplex faces are independent of any individual, because they are determined by human physiology. As a first approximation, the faces are given by the “normal” ranges for all biomarkers, as well as unhealthy interdependencies that are discovered through clinical and epidemiological observations. To determine the boundaries, future clinical observations or epidemiological data should minimize averaging and be evaluated as multivariate combinations of biomarkers, risk factors and the associate health or disease status.

While the boundaries of the true health simplex in an idealized world are dictated by biochemistry and physiology, and independent of any person, their actual definition will require enormous biomedical effort. It is to be expected that, barring wrong findings or interpretations of data, the development of the health simplex will resemble the creation of a sculpture out of raw rock, which occurs gradually and exhibits increasingly finer detail. The health simplex assumed to be valid now is given as the mathematical product of the known, allegedly normal biomarker ranges. The future will refine the current definition in two ways. It will greatly increase the dimensionality of this simplex and it will reveal non-orthogonal faces that correspond to harmful interactions among biomarkers. The actual completion of the simplex must be expected to take a very long time. However, even if the full simplex will not be available for some while, it will be feasible much sooner to construct lower-dimensional, unrefined

simplexes that focus on one particular disease and assume biomarkers in all other dimensions to be irrelevant or within their normal ranges.

Disease states may be defined with respect to a specific disease or generically with respect to any disease. These states are characterized by certain profiles of biomarkers that fall outside the normal ranges. Thus, the health simplex is surrounded by a larger simplex of “transient unhealthiness,” which includes conditions like fever, dehydration, slightly increased cytokine levels, and other temporary illnesses. This simplex, in turn, is surrounded by a disease simplex and a permorbidity simplex, outside which all states are fatal. Thus, health and various disease states form nested simplexes.* Some distances between subsequent simplexes may be short, others long. These distances are a measure of the severity of the disease.

The concept of simplexes renders it evident why a single biomarker may not be sufficiently informative, because its impact depends on other variables. Specifically, suppose a score above ϑ for biomarker x is considered an indicator of disease (Fig. 4). Two individuals P_1 and P_2 may have the same score ($x_1 = x_2 > \vartheta$), but it is possible that Person 1 is healthy because P_1 resides within the health simplex (with coordinates x_1, y_1, z_1), while Person 2 has the disease, because P_2 's coordinates (x_2, y_2, z_2) fall outside the health simplex. In P_2 's case, biomarker x and its threshold ϑ are considered valuable, while the case of P_1 is categorized as a false positive. Note that the inability of biomarker x to distinguish between health and disease is not due to poor diagnostic quality or an inaccurate determination of ϑ , but to the role of the (possibly unknown) biomarkers y and z ; clearly it is easy to construct cases where these biomarkers fail to classify correctly if considered without x .

The introduction of simplexes may be seen as an extension of a large body of work that has been trying to predict health outcome from sets of biomarkers. As a good example in the context of inflammation, Rixen *et al.* [15;25] proposed a “multidimensional physiologic hyperspace” of relevant biomarkers, in which certain areas correspond to different inflammatory responses. The hyperspace serves as the basis for a quantitative severity stratification scheme for critically ill post-trauma patients, called the *Physiologic State Classification (PSSC)* system. After clustering of the original 17 physiological features, PSSC leads to a reduced state space characterized by the nature and magnitude of the inflammatory mediator responses of Tumor Necrosis Factor (TNF) and interleukins IL-1, IL-6, IL-8. These are crucial indicators, because they can have a variety of functions in the inflammatory response [15;26] and, for instance, alter blood flow and lead to the accumulation of immune cells [14]. Within the reduced biomarker space, an individual patient is not compared to “normal values” in a healthy population, but instead to a comparable reference group of recovering trauma patients. Patients with positive and negative outcomes after trauma are clustered, and the results are used in a logistic regression model that allows more accurate outcome predictions than had been possible before. In the context of the high-dimensional simplexes described here, Rixen's state space can be considered a projection of the full biomarker space onto a three-dimensional subspace. This projection of course loses resolution, because many other physiological features are ignored. As a consequence, the most accurate predictions possible from this reduction are still inferred from averages, although over a more pertinent subgroup. In the full health simplex, the personal stratification becomes much more detailed and accounts for the patient's history, which takes the form of a personal trajectory, as we will discuss next.

*Footnote: Strictly speaking, the health simplex has to be subtracted from the transient disease simplex, thereby resulting in an irregularly thick “simplex shell”; the analogous happens with the larger more permanent disease simplexes. For simplicity of discussion, we refer to a disease simplex rather than a shell. Furthermore, one may argue whether the health simplex is truly compact, because some variables exhibit bistable behavior. For instance, a gene may be turned on or off. It seems that this issue is mainly a matter of semantics, because the unstable state in between might still be considered healthy, even though it is never truly realized. What is more important is the implication that the health simplex is not populated with equal density. Some regions are prevalent, others are not.

Personal Health and Disease Trajectories

The onset and development of each case of disease are defined by a personal trajectory. The initial point of this trajectory is the person's health state at birth (or conception). Many biomarker dimensions of this state are fixed at individual-specific values because they represent the person's unalienable genetic makeup and predisposition. Outside gene therapy, the person's trajectory retains a constant set of values with respect to these coordinates. Expressed differently, every person is confined by heredity to a high-dimensional “slice” through the health and disease simplexes. Other dimensions within the biomarker space are driven by environmental exposures and life style choices. These may affect the dependent variables (consumption of sweets) or have an impact on some of the independent variables (blood sugar regulatory system), which secondarily lead to alterations in the profile of dependent variables (diabetes). Modest and infrequent changes in dependent variables are usually not critical, because physiological systems are robust and tolerate variations in dependent variables by returning them to their normal value. Changes in independent variables are more consequential, because they may affect the settings of the organism's regulatory systems.

Each change in values of the dependent and independent variables moves a person's health state to another point in biomarker space, thereby creating a life-long trajectory which may temporarily or permanently leave the health simplex and migrate through the disease simplexes of various severities. In cases of acute disease, the trajectory progresses quickly, but may eventually return to the health state. By contrast, chronic diseases are characterized by slow trajectories that are driven by slow changes in independent variables. For instance, the decrease in the lumen of arteries during atherosclerosis is a well-characterized process that progresses over a time period of decades.

While most disease trajectories are rather smooth, the speed along the trajectory can vary quite a bit. The trajectory may even exhibit “jumps” in a quasi-discontinuous fashion, for instance, in the case of acute trauma. Similarly, in situations of natural bistability, where a process is either turned on or off, an independent variable Z_i may vary a lot without much consequence, as long as it stays below some threshold. However, as soon as Z_i crosses this threshold, dependent variables that are affected by Z_i jump to distinctly different values.

An interesting aspect of these personal trajectories is that their characteristics are typically not known until a patient presents with a disease. In an ideal situation, a full diagnosis at this time positions the patient at particular coordinates in disease space, and this point serves as the beginning of the known, future trajectory. Follow-up examinations augment the coordinates with a direction that may provide hints regarding the patient's prognosis. It seems difficult to say whether the patient's history truly matters at this point or whether his or her future trajectory is independent of the path that led to the measured point in disease space. On one hand it has been argued convincingly [16;27;28] that preconditioning critically determines disease outcome. On the other hand, one might assume that different preconditioning scenarios would be distinguishable by a comprehensive biomarker analysis. Throughout the history of “annual check-ups,” primary care physicians have been engaged in recording baseline parameters for their patients, and interpreted subsequent recordings as possible trends. These recordings are thus projections of the patient's trajectory. Novel efforts of true predictive medicine address this issue by establishing incomparably more comprehensive biomarker profiles long before disease strikes, at a time of apparently perfect health [29]. These efforts will eventually characterize sets of pre-morbid conditions that help distinguish healthy from problematic trajectories before they enter the disease simplex.

It is interesting to note that the concept of a health trajectory is directly compatible with the proposition of a separatrix that divides the health outcome space such that patients on one side

have a positive outcome and those on the other side will face problems. In the case of inflammation, such a separatrix was found to be related to endotoxin levels [23] and to separate healthy responses from sepsis and multi-organ failure [22]. On which side of a separatrix an individual is located depends on a variety of physiological factors. Especially influential in inflammation is a possible desensitization in earlier life, for instance, through exposure to Gram-negative bacterial lipopolysaccharide, which is known to be an acute inflammatory stimulus [27;28]. This desensitization, or preconditioning, in combination with many other factors, can thus cause an individual's early trajectory to move to the favorable side of the separatrix within the health simplex [16]. The separatrix is not unique. For instance, it seems that desensitization may also result from the shedding of TNF receptors [13;30], which could thereby create a different separatrix. Furthermore, the immunological responses, which modulate the cytokine cascades and affect the interactions of the involved biochemical mediators, depend on the nature of the stimulus and seem to differ if they result from trauma, surgery, and infectious disease, or cancer [15;31]. Thus, it is to be expected that the health simplex is dissected by a large number of separatrices, most of which we presently do not know. In some cases it may be possible through intervention to cross a separatrix, but this may not always be the case.

Health Prediction, Risk Profiles, and Disease Prevention

A disease should not exclusively be studied in its ultimate state or with a single trajectory, but through investigations of *all* trajectories in biomarker space that eventually lead to this state. At present, such trajectories are ill defined, based on case histories or on averages from retrospective studies, but it will certainly be beneficial in the future to study them individually. Pursuing this goal, nascent efforts of “predictive health” are under way to address the trajectories in a prospective manner by measuring large numbers of biomarkers in initially healthy subjects over many years and in regular time intervals [29].

It is evident that each person follows a single lifetime trajectory and that sufficiently many biomarker measurements identify the person's trajectory as sequential points in biomarker space. Each of these points indicates how far the person is from the boundary of the health simplex. This distance is a generalization from similar considerations in the state space representation of inflammatory responses proposed by Rixen *et al.* [15;25], where disease severity is measured as the distance between a patient's coordinates and those of one of the disease states.

With sufficient experience in retrospective and predictive health, it will one day be possible to gauge how quickly an individual is likely to cross the boundary from a near-by point. Such an assessment will be based first on population studies and later complemented with insights into the fundamental principles of physiology and pathology. The particular boundary in closest vicinity of the trajectory, and the associated typical speed of progress, are direct manifestations of the person's health risk profile. They also suggest the need and expected efficacy of countermeasures. Today's physicians are trained to make such suggestions based on their intuitive perception of the biomarker space and their experience from prior, similar cases. Given the trajectories of many individuals, it will eventually be possible to gauge an individual's disease risk or health outcome with high accuracy.

Finally, once the biomarker space for a given disease is better understood, it will be possible to predict the efficacy of different medical treatments, which aim to push the trajectory away from the disease boundary, and the risks associated with combined drug regimens that move the trajectory in several directions at the same time.

Mathematical Treatment

The construction of health and disease simplexes may proceed in distinctly different ways. The most natural progression will be a continuation of current biomedical research and target the discovery of novel biomarkers, along with their normal ranges and interactions. As described earlier, these ranges and interactions will gradually lead to larger and more refined simplexes. A second component of the construction is the increasing, world-wide collation of biomarker networks, which will help identify significant interaction patterns of causative and symptomatic biomarkers. Ultimately, the results should be merged into large dynamic models, for reasons discussed in the introduction.

The concepts of simplexes and trajectories described before are independent of a particular mathematical modeling framework and of specific types of equations. Their mathematical formulation becomes especially straightforward if we use the so-called S-system form within the modeling framework of Biochemical Systems Theory [3;4;5;6].

In the S-system format, the dynamics of each dependent variable is driven by a first set of processes that increase or augment the variable and by a second set of processes that degrade or diminish the variable. Each set is collectively represented by a product of power-law functions that contain all variables that directly affect this set. For instance, in the simple case of an enzyme catalyzed reaction, the power-law function contains the substrate, the enzyme, cofactors, inhibitors, and other modulators that are modeled as either dependent or independent variables.

Each S-system, independent of size, has the format

$$\dot{X}_i = \alpha_i \prod_{j=1}^{n+m} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{n+m} X_j^{h_{ij}} \quad (i=1, \dots, n). \quad (1)$$

Here, the first n variables are traditionally dependent and the remaining m variables are independent. Dependent variables are affected by the dynamics of the system, while independent variables are constant or outside the control of the system. For instance, independent variables may include external factors such as food input and environmental exposures, but also internal components such as enzyme affinities or gene alleles that do not change, at least over short time periods. The real-valued exponents g and h are called kinetic orders; they quantify the direct effect of their base variable on the process in which the variable is involved. The non-negative parameters α and β are called rate constants. For most specific analyses, both sets of parameters are considered constant. Even if two systems have the same parameter values, variability between them is possible due to different manifestations of the independent variables $X_{n+1}, \dots, X_{n+m}$.

Three features make this approach appealing for the purposes of this discussion. First, while the S-system format may seem very restricted with respect to the range of responses it can model, it has been shown that S-systems can accurately represent any type of nonlinearities that can be formulated as ordinary differential equations, including different types of oscillations and chaos [32;33]. Second, the format scales up directly to any number of dependent and independent variables. Third, while the S-system equations are highly nonlinear, the steady state of an S-system is characterized by a system of linear equations, in which variables are formulated as logarithms of the original variables [34]. This linearity is important here, because it streamlines the following discussion enormously.

The steady state of an S-system model is given as a system of linear equations of the form [6;34;35;36]

$$\mathbf{A}_D \cdot \mathbf{Y}_D + \mathbf{A}_I \cdot \mathbf{Y}_I = \mathbf{b} \quad (2)$$

Here, $\mathbf{Y}_D$ and $\mathbf{Y}_I$ are the vectors of dependent and independent variables in logarithmic coordinates, respectively, $\mathbf{A}_D$ and $\mathbf{A}_I$ are matrices containing combinations of kinetic orders and $\mathbf{b}$ is a vector containing logs of ratios of rate constants. Note that this formulation holds for arbitrarily high-dimensional systems. Typically, the system is solved for $\mathbf{Y}_D$ as a function of $\mathbf{Y}_I$ and the system parameters. In other words, the question is asked: Given all fixed settings (parameter values) and the specific values of all independent variables, what is the steady state of the system, in which none of the dependent variables changes in amount or concentration?

This solution is mathematically given as

$$\mathbf{Y}_D = \mathbf{S} \cdot \mathbf{b} + \mathbf{L} \cdot \mathbf{Y}_I \quad (3)$$

[36], where $\mathbf{S} = \mathbf{A}_D^{-1}$ and $\mathbf{L} = -\mathbf{A}_D^{-1} \mathbf{A}_I$ are the so-called sensitivity and the logarithmic gain matrices, respectively. With respect to health and disease systems, the parameter values and steady-state values of the variables are expected to vary from person to person, thereby forming sets of parameters and values associated with health or disease.

A realistic system contains more processes than dependent variables, and because most processes contain an independent variable, a system typically contains many more independent than dependent variables. For each given profile of independent variables $\mathbf{Y}_I$ there is a unique solution $\mathbf{Y}_D$, *i.e.*, a vector of dependent variables, according to Eq. 3. In the context of health and disease processes, each component within $\mathbf{Y}_I$ is taken from a “normal” range, so that the solution to Eq. 3 is no longer a point, but a linearly bounded set. Furthermore, the independent and dependent variables within the healthy ranges may lead to combinations of extreme values that are no longer healthy, as indicated in Figure 2. Under the reasonable default assumption that these combinations are linear combinations in log space as well, they create linear dependencies that, together with the ranges in hyperspace lead to a health simplex in a high-dimensional (logarithmic) biomarker space. The same arguments hold for simplexes that correspond to transient, reversible, or premorbid disease.

In mathematical terms, the health simplex solution may be written as

$$\begin{aligned} \mathbf{Y}_D - \mathbf{S} \cdot \mathbf{b} - \mathbf{L} \cdot \mathbf{Y}_I &\leq \mathbf{C}_1 \\ \sum \gamma \mathbf{Y}_D &\leq \mathbf{C}_2 \end{aligned} \quad (4)$$

where $\mathbf{C}_1$ and $\mathbf{C}_2$ are constraint vectors containing collections of the health-admissible variations in all parameters and independent variables. The parameters γ are weights characterizing admissible constraint combinations, as it is typical in linear programming (see also Figure 2). Selecting wider constraints leads to a larger simplex, which corresponds to a temporary disease simplex, from which the health simplex is to be subtracted. The persistent disease simplex (shell) is defined in an analogous manner. The formulation in Eq. (4) is reminiscent of a linear programming approach proposed by Vera *et al.* [10] for forcing a

metabolic disease state to return to the neighborhood of the health state by manipulation of some of the enzyme activities.

Suppose it is possible (by means of physiology and medicine, rather than mathematics) to classify each possible state $\mathbf{Y}_D$ as healthy or diseased (possibly with a measure of severity). It is not difficult to imagine that one could execute a mega-simulation with the dynamic system (Eq. 1), testing different combinations of independent variables and flagging those that lead to points within or outside the health simplex. The linearity of Eq. 2 permits a more elegant solution. Namely, if Eq. 2 can be inverted, either directly or through a pseudoinverse $\mathbf{A}^+$, it is possible to characterize the set of *all* combinations of independent variables (genetic predisposition, life style, ...) that lead to the disease. Specifically, each given health or disease state $\mathbf{Y}_D$ corresponds to solutions of the form

$$\mathbf{Y}_I = \mathbf{A}_I^+ \cdot \mathbf{b} - \mathbf{A}_I^+ \cdot \mathbf{A}_D \cdot \mathbf{Y}_D. \quad (5)$$

Collectively, these solutions describe the space of all combinations of independent variables that correspond to health or a disease state. As a variation of this strategy, it is possible to fix some of the independent variables (such as unalienable genetic markers) and explore the role of other independent variables (such as life style choices) and their potential of leading to a steady state point within a disease simplex.

So far all considerations have focused on steady-state solutions.* Indeed, using the argument of separation of time scales it seems reasonable to consider many disease patterns at least as quasi-steady states where all fast changing variables are essentially always in steady state and some variables may be changing very slowly, so that their derivatives are almost zero. However, it might be of interest to investigate the dynamics of the health system as well. This investigation falls into two distinct classes. First, if the independent variables are fixed, it is possible to use Eq. 1 to run simulations that flag if the system crosses the boundaries of health during its transient dynamics toward a steady state. Second, over long periods of time, such as aging, some independent variables may slowly change, thereby eventually leading to greater risk of disease. An example is the slowly decreasing lumen of arteries in atherosclerotic disease. In these cases, even if life style and other factors with fast dynamics don't change, the individual's trajectory slowly shifts and may move closer to a boundary between the health and disease simplexes.

The health and disease simplexes (shells) defined above are defined based on the principles of physiology, and should theoretically be the same for all individuals. Within the simplexes, every type of personalization corresponds to a unique trajectory. Supposing health at birth, the initial value of the trajectory is located somewhere in the health simplex, and its vicinity to or distance from the simplex boundaries is a characteristic of the individual in question. Throughout life, the person moves along this trajectory through the biomarker space, and under the idealistic assumption of a valid model, each point in time can be assessed with regard to present health, future disease risks or disease severity. These risks can be defined rigorously through metrics that quantify the distance from each of the simplex boundaries and the speed that is typically seen at the given point of the trajectory. For this point it is easy to simulate scenarios of unchecked future trajectories and the efficacy of targeted control measures.

*Footnote: It is known that some variables do not operate in steady state but, for instance, exhibit the dynamics of a limit cycle. Conceptually, one may imagine the reformulation of this limit cycle with an angular velocity and a constant radius r , and consider the steady state as characterized by $\dot{r} = 0$.

Conclusions

Health and disease are multivariate phenomena that we currently monitor with occasional, low-dimensional snapshots. As a consequence, disease biomarkers are plentiful, but each taken separately is afflicted with substantial uncertainty. This uncertainty can only be overcome with deeper insights into the regulatory systems that govern healthy physiology and an understanding of how local perturbations can eventually lead to system malfunctioning. Given the complexity of health and disease processes, the task of connecting local insights with clinical performance will almost certainly require a computational model, because only such a model is capable of keeping track of the thousands of processes that interact within an organism.

At this point, our modeling abilities are not yet at a level where we can capture the rich dynamics of complex disease processes. However, extrapolating recent trends in data generation, parameter estimation, high-performance computation and simulation, it is reasonable to assume that models of specific diseases will reach a level of accuracy and reliability permitting diagnostic and clinical decisions. Once such models are available, the methods proposed here will aid our assessments of health and disease states and allow us to engage in personalized health predictions and disease treatments. At the core of these considerations is the set of nested simplexes that classify health and various degrees of disease severity. These simplexes are bounded by physiological constraints and therefore the same for all people. At conception, every person is positioned within a personal subspace that is determined by his or her genetic and otherwise unalienable make-up. Confined to this high-dimensional “slice” through the biomarker space, every person migrates along a trajectory that may occasionally traverse the simplex shell of temporary disease or enter the domain of permanent, chronic disease. The closeness of each point along the trajectory to one of the disease boundaries is a measure of health risk, which changes over time and identifies, at each time point, the most likely adverse outcome for the immediate future.

The proposed mathematical formulation in terms of simplexes presents a conceptual framework for the consideration and quantification of health and disease in general, as well as the assessment of unchecked or managed disease trajectories, the utility of specific biomarkers, the development of rational prevention and treatment strategies, and the comparison of treatment options. This framework could eventually become a means of qualitatively or quantitatively characterizing risk profiles and suggest personalized, preemptive measures of disease avoidance. It would also permit treatment decisions to be based on personal biomarkers, rather than average numerical scores developed for the general population [1].

The case of inflammation, seen as a complex dynamic system, seems to be a particularly interesting application for the proposed methods, because some crucial biomarkers have already been characterized and a large body of knowledge about diverse inflammatory responses is available.

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Fig. 1.
Normal “biomarker” values are replaced by ranges, possibly in logarithmic coordinates.

Fig. 2.
Constrained normal biomarker ranges become health simplexes in two or more dimensions.

Fig. 3. Constrained normal biomarker ranges become nested health and disease simplexes in a high-dimensional space; illustrations are given here in two and three dimensions, respectively.

Fig. 4. Two individuals P_1 and P_2 have exactly the same score ($x_1 = x_2 > \vartheta$) with respect to biomarker x , which exceeds the alleged disease threshold ϑ . Nonetheless, P_1 resides (with coordinates $x_1 > \vartheta, y_1, z_1$) within the health simplex, while P_2 is diseased, because P_2 's coordinates ($x_2 > \vartheta, y_2, z_2$) fall outside the health simplex.