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A new vision for BioMedicine: a Systems Approach

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***Index Terms*—systems biology, category theory, robustness, stability, adaptation**

***Abstract*—While it is widely recognised that, on the one hand, reductionistic approaches are inadequate to deal with the multifactorial and complex nature of health and disease, and on the other hand, a system level understanding of the normal and pathological functioning of biological systems is sorely needed; no clear procedure have been put forth about the actual implementation of such a program. In this paper we review the tools and the mode of thinking that systems biology has set forward in the last twenty years, pinpointing its key methodological and epistemic aspects, together with the technical obstacles and conceptual limitations that it is faced with. A new approach conducive to a system level understanding of biomedical systems is thus, proposed.**

I. Introduction

Systems biology is a relatively new scientific discipline that aims at a system-level understanding of complex biological systems, ranging from metabolic and signaling networks inside the cell, to organelles, tissues, organs and the whole body [1], [2]. The quest for a system-level understanding is far from new, physiology or the study of living systems in an integrative way, dates from Ancient Greece. The increasing interest in systems biology must be found in its capacity to use a variety of mathematical models and computational tools directed to the understanding of biological processes, normal and pathological, anchored in molecular data[3],[4].

Systems biology emerged in the last stages of genome sequencing projects, as an alternative to the reductionistic approach in molecular biology, able to deal with the large amount of data of complex genetic interactions produced by, for example, the Human Genome Project[5]. It ought to be remarked that Systems Biology entails more than the application of engineering tools i.e. mathematical models and simulation, to cellular and molecular biology problems. System biology is an attempt to put forward the engineering perspective in the understanding of cellular behavior, by describing cellular structure and function in the language of systems theory[6].

A mechanistic understanding described in quantitative terms of how function emerges out of the interplay of different biological information, from genes to whole organisms, is arguably the most important challenge in biomedical science. A truly personalised health care will benefit from this systemic effort, in which vast amounts of data of particular individuals are translated into actual knowledge, that may help in putting forward individualised therapeutics [7], [8].

II. Systems Biology

Kitano [3] establishes the methodological agenda of systems biology in four sequential steps:

1) System Structure Identification
2) System Behavioral Analysis
3) System Control
4) System Design

Structure identification aims to define the basic organization of the system, that is, relevant interaction networks such as gene regulation, metabolic and signal transduction networks. The next step is to analyze the system's behavior. The approach is mainly engineering-based, external stimulus or perturbations triggers a response or trajectory in the phase space, and relevant features and qualitative changes in systems's dynamics are analyzed using mathematical methods like steady state, flux balance or bifurcation analysis. The rationale of this step is to set the basis for steps 3 *Control* and 4 *Design*, by investigating system-level properties like robustness. Step 3, *Control*, addresses the control of the state of the biological system, for example, adjust or rectify malfunctioning processes. Finally in Step 4, *System Design*, the goal is to synthesize biological systems, maybe not found in nature, with the potential to cure diseases.

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III. Why we need a systems approach in Medicine

In this section we outline several issues relevant for clinical medicine that are in need to be addressed with a different outlook, that of systems science.

A. Conceptualization of disease and health

Disease is a condition of living systems characterised by malfunctioning or impairment of the normal operation of the organism. In this definition it is assumed that the organism normally operates within an admissible range of states, therefore, disease occurs when system's dynamics moves to a state not included in the healthy set of states.

From a systems science perspective, disease and health are emergent or systemic properties of the organ or the organism under study.

B. Misapplication of Homeostasis

The concept of homeostasis is a widely used concept in medical practice since the original work of Cannon [9]. Precursors to the concept of homeostasis and its potential to physiology, can be found also in the work of Claude Bertrand and the early physiologists[10]. Homeostasis was the pivotal concept in Cybernetics and it is the predominant modeling technique, in the form of feedback loop in Engineering Control.

In clinical medicine, disease may be conceptualised as a failure in the homeostatic mechanism. Thus, the organism by means of homeostasis, must be able to maintain its key parameters within a "healthy" range. In this vein, treatment can be seen as a supplementary regulatory loop, aiming at bringing back system's dynamics to a previous healthy state.

However, as Ahn has pointed out [11], while the corrective treatment that homeostasis epitomizes is appropriate in treating diseases such as hypothyroidism or hypokalemia, more complex disorders like asthma or cancer are in need of a different approach. Moreover, the idea of homeostasis as an universal principle is unjustified. This view as purported by for example, Friston, "the physiology of biological systems can be reduced almost entirely to their homeostasis"[12], disregards other forms to achieve dynamic stability different to homeostasis. For example, the synchronous dynamics found in circadian rhythms, or the chaotic dynamics found in heart rate and epileptic seizures are ill suited for homeostatic modeling[13].

C. Obesity: a study case for a new approach to homeostasis

Both the metabolic and the immune systems are crucial for survival, which mainly relies upon the organism's capacity to sense nutrients and pathogens. The organism needs both to resist starvation by sensing nutrients in its environment, and to respond to harmful pathogens that bring about infectious diseases. While in simple biological systems e.g. the drosophila fly, the integration between pathogen and metabolic systems have advantageous effects, in higher animals with abundant availability of nutrients e.g. humans in developed countries, the existing closed loop among inflammatory and metabolic responses may be detrimental [14]. The metabolic and immune pathways that mediate in the sensing of either energy/nutrients and pathogens are not clearly decomposable, rather they are coupled, a characteristic feature of complex systems [15].

In [16], Hotamisligil suggests that the actual environmental conditions in terms of excess of nutrients, may be at the core in the epidemic of obesity. The chronic excess of nutrients triggers metabolic signals, that at its turn trigger inflammatory responses which disrupt metabolic function, eliciting more stress and inflammatory responses. This positive feedback loop of pathogen-metabolic responses is inherently unstable. A correct understanding of the interplay of metabolic and inflammatory mechanisms will help to understand obesity, which is a chronic metabolic disorder that is acquiring alarming dimensions[17]. Prevention and treatment of obesity will likely require new ways to understand regulatory mechanisms in the body, for example designing new homeostatic-like methods that target metabolic and pathogenic pathways that may result in the enhancement of the system's stability and long-term adaptation. Thus, we need to integrate the pathogen and the nutrient/energetic sensing systems in a solid theoretical basis. Moreover, the models produced must incorporate factors not usually considered in the traditional analysis, like alimentary habits, stress or sleeping habits.

We are now beginning to understand that the coupling between regulatory pathways in metabolic and immune functions, which was an advantageous trait in evolutionary terms, in our today's society of abundant and cheap calorie supply, is "establishing the groundwork for chronic metabolic diseases"[16]. A systems approach for treatment and prevention that rather than focus on single molecules, target the interface of clusters of immune (pathogen) and metabolic (nutrient) activity, may provide novel insights to the etiology and prognosis of complex diseases such as obesity.

We may need to formulate additional control mechanisms able to compensate for the positive feedback loops that may be intrinsically related with obesity. A different approach to control in complex biological systems, that focus on computing integrated outcomes, rather incrementing or decrementing single signal values is still missing.

D. Disease as a multifactorial complex system

The relationship between factor risk and disease is not necessarily 1:1. While diseases like appendicitis are monofactorial, in the sense that one single pathology is responsible for the disorder and its prognosis, complex diseases such as atherosclerosis, cancer, diabetes, asthma etc. are multifactorial, that is, the disease is driven by multiple pathologies and etiologies. Thus, when delivering a treatment for a

complex disease we must expect different prognosis and responsiveness. Although in clinical medicine this fact is widely reckoned, the tools and concepts that may allow us to clearly understand the multiple and nonlinear relationships between pathology, disease and treatment are not in place.

E. Defining Stability, Adaptation and Robustness

Terms like stability, adaptation and robustness are profusely used in clinical medicine. Nevertheless, due to the lack of a sound theoretical framework, they are used in a rather vague way, even conflating them. It goes without saying that these concepts are manifold and may have different meanings depending on the context therein.

1) Stability: Stability is the most important property in a control system, is an attribute of the equilibria, that is, of the solutions of the differential equations, and not of the system that is governed by those equations. A general definition of stability is the ability of systems to go on working at a given regime, or close to it, on a sufficiently long time span. The conventional interpretation of stability in medicine as the maintenance of a set of states in the face of perturbations, assumes that the persistence of system states, that is, macroscopic variables, is achieved trough homeostasis.

2) Adaptation: Adaptability applies to features of the systems, that is, adaptation is a phenotypic aspect of the organism. Adaptation is always referred to the system's environment, so we must talk of adaptation always in relative terms, with regard to the actual organism's milieu. In this view, to state that an organism, for example the Escherichia coli, is adaptive is inexact, rather we must indicate which particular feature of the Escherichia coli is adaptive. For example, the chemotactic behavior of the bacterium is adaptive and it is possible to quantify its adaptiveness. Exact adaptation gives the degree of efectiveness of adaptation in the bacterium's chemotaxis [18].

3) Robustness: Robustness is a property of the whole system e.g. organ, organism, that refers to the ability of the system to cope with the environment. Accordingly, robustness is an organic property that relies on the adaptiveness of a number of features of the organism. For example, we say that the E .coli is robust in a particular environment or experimental setting, when is able to pursue normal functions like cell division, reproduction and ultimately survival. Thus, robustness is achieved on account of adaptiveness of certain features, for example chemotactic behavior, in which the organism moves away from repellents and towards nutrients by measuring the concentration gradient.

IV. Complex Systems Biology

In the precedent section we outlined some of the major conceptual obstacles that medicine is facing, and we provided working definitions of key concepts like stability, robustness and adaptation. Here we suggest new avenues for clinical medicine, having as premise the need for a shift towards a systemic approach grounded on the molecular level, and conducive to an integrative understanding of biological function.

The scientific problem that Complex Systems Biology tries to solve can be stated as: How do the components of a cell interact in order to bring about its structure and realise its function? This same question is recurrent in nature, so we can ask How do cells interact in order to higher levels of organization and function arise? or How organs interact inside the body or how organisms mediate in the maintenance of ecosystems?**.** It does not matter which organizational level we are interested in, the complexity is always mind numbing due to the high dimensionality and non-linearity found in biological systems.

In order to acquire a system-wide understanding we need to be able to build models and theories that address the emergent properties that are conducive to its complex behavior. Robustness is a crucial feature of biological systems, the mechanisms that may be at the basis of the organism's ability to persevere against perturbation are among others, modularity, feedback or redundancy. It is only through the investigation of global properties like robustness that the system-wide understanding of organisms, as avowed in systems biology, may be attained.

The central tenet of systems biology is that system's dynamics lead to the functioning of the cell. Dynamic motifs are recurrent patterns responsible for characteristic behavior such as hysteresis and oscillations. The detection of meaningful patterns from the big collections of data available, is an ongoing process that will likely open new views in the diagnose and therapeutics of diseases. It is important to remark a paradoxical situation that exists in biomedical science with regard to the variability of experimental data, there is too much but also not enough data [19]. For example, we are lacking of quality and cost-effective data in dynamic pathway modeling. Simulation models may help to advance in this direction, by generating quantitative data suitable to be read and exchanged in a computer-based format [20].

V. Building a new theoretical framework

One of the most important challenges that Complex Systems Medicine faces is the formalization of the concepts of health and disease.

A. Simplexes

In [21] Voit suggests a novel approach in which health and disease are conceptualized as simplexes rather than as states. A simplex is the generalization of triangle to a n-dimensional geometrical figure.

While the idea of disease (or health) state is based on statistical averaging, in which individual variability of biomakers is subsumed in population diseases scores, a disease simplex generalizes the disease state. Biomarkers are objectively measured variables that are relevant for health and

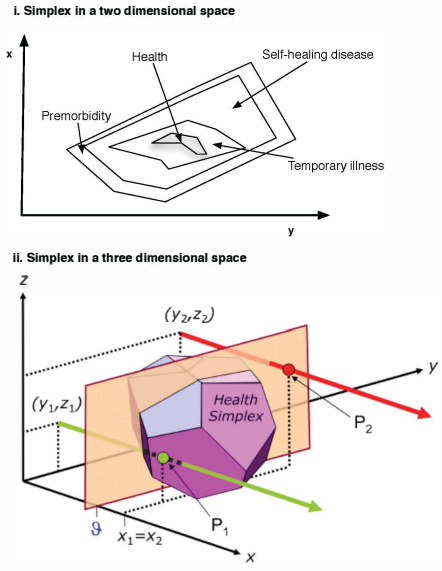

Fig. 1. The upper figure represents two biomarkers, x and y, that give rise to nested health and disease simplexes. The health simplex is sorrounded by larger simplexes that represent unhealthy states. Thus, healthy and disease states can be represented as simplexes which embody regions in the biomarkers space. The bottom figure, from [21], shows two individuals $P1$ and $P2$, with the same value for biomarker x that exceeds the threshold θ ($x1 = x2 > \theta$). Nonetheless, $P1$ resides within the health simplex, while $P2$ is in disease state, because its coordinates fall outside the health simplex.

disease, that is, they are indicators of normal or pathogenic response. The multifactorial nature of health and disease is modeled here, with a mathematical formalism that aims at the quantification of health and disease, together with the study of trajectories of health and disease for specific individuals, expressed in their own biomarker space. The biomarker space is a n-dimensional space composed of variables that collect information relevant of the individual's health, including environmental exposures and life habits.

Importantly, this formalism challenges the idea that when the biomarker value fall outside a static range it is causative of diseases, and offers a new outlook to distinguish between causative and symptomatic behavior, Figure (1).

B. Category theory

The structural identification of components and their relationships inside a cell is mainly described using graph based representation of networks. At higher level of biological organization, the graph theoretic approach is also predominant. For example, brain connectivity is explored using network theory which is a field of graph theory. However the graph theoretic approach imposes important limitations, for example, is ill suited to represent different types of relations between elements, or the change of relationships over time. Moreover, interactions may be spatially dependant and therefore a three-dimensional account may be necessary

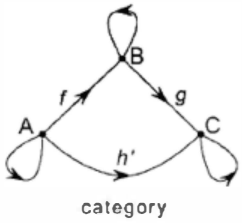

Fig. 2. Example of a graph induced in the smallest category. Note that the composition law holds Dom(g) = Cod(f), $h' = g \circ f$.

[22]. Explore new topological representations of biological networks is much needed.

Category Theory is strongly related to graph theory [23]. A category is a composite item consisting of a graph and an internal law which associates an arrow of the graph to each path of the graph2. Category theory has been utilized to tackle the Binding problem i.e. how do simple objects bind together to form a complex object forming [24], which is a critical issue, for example, in visual perception.

Category theory opens new perspectives in graph analysis in BOLD fMRI data, the richer structure of categories compared to graphs, due to the internal law of the former, may be used to test network global properties like robustness [25]. Small-world networks are characterized by short paths and high clustering, which enables fast communication between distant nodes, facilitating synchronization. In this kind of networks, transitivity is likely found, so the composition law of Category Theory holds and may underlie a category.

A straight forward application of category theory in brain connectivity networks, may be found in studies that indicate the existence of small-world networks in brain connectivity. For example in [26] it is shown a loss of small-world networks in Alzheimer's disease.

C. Including time in biomedical models

The diagnoses of complex diseases e.g. diabetes are based on the measurement of the concentration of a biomarker e.g. glucose in a given instant. This procedure pays no attention to the rate of change, that is, the gradient of glucose concentration, by assuming that all the relevant information is captured in a single arbitrary instant.

It may be illuminating to relate this procedure with the responses of the E .coli to chemical stimuli. This bacterium, is one of the simplest and best understood organisms, its motility is characterized by chemotaxis. The E. coli swims toward substances such as amino acids (serine and aspartic acid), sugars (maltose, ribose, galactose, glucose), and away from potentially noxious chemicals, such as alcohols and fatty acids [27]. The chemotactic ability of the E. coli relies in its capacity to sense the rate of change of concentration of certain chemicals in its vicinity.

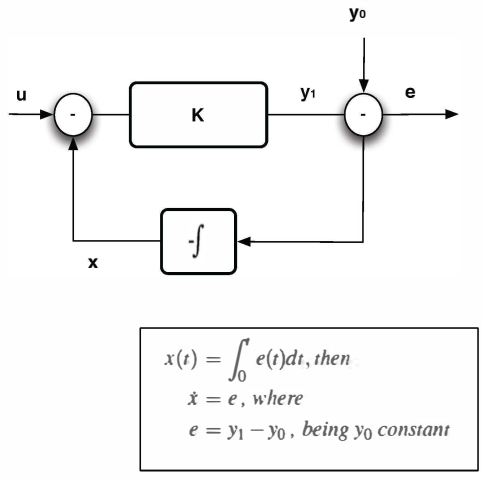

Fig. 3. At steady state $\dot{x} = e = 0$ for all input u. In the *E. coli* case this means that the tumbling frequency of the bacterium is independent of the sensed attractants in its surroundings. In habituation learning in sensory neurons, the membrane potential is independent of the concentration of glutamate. For the *E coli*, the control signal u is the concentration of attractants in the bacterium's surrounding, y_1 is the tumbling frequency, y_0 is the tumbling frequency previous pre-stimulus and e is the difference between the actual tumbling frequency and the desired one. In habituation learning, u is concentration of glutamate in the synaptic cleft prompted to be binded in the membrane's receptors, y_1 is the membrane potential V_m, y_0 is the membrane potential pre-stimulus and e is the difference between the actual membrane potential and the desired one, y_0.

The point that deserves emphasis here is that chemotaxis in the E. coli is a process of adaptation, that strives to maintain certain physiological conditions within acceptable limits, by sensing the rate of change of concentration (not the concentration itself) of external stimuli. The first author in [28] has shown that perfect adaptation in bacterial chemotaxis may serve as a simplified system model to understand stability in neural plasticity and related cognitive processes like habituation learning3.

VI. Conclusion

Arguing the need for a new systemic approach for clinical medicine is difficult, not least because much of the practical consequences that the view presented here will depend on technological advances. Nevertheless, complex diseases such as cancer, diabetes or Alzheimer's disease are in much need to be addressed with a systemic perspective, on the basis of a new theoretical framework in which the interplay between etiologies, pathologies and disease treatment, may be understood in a coherent way. By incorporating systems science into medicine we shorten the distance to the final objective, a predictive, preventive and personalized medicine.

Systems biology will necessarily evolve in the future towards a Complex Systems Biology, with more sophisticated model systems, but also systems biology will be including diet and nutrition in the development of diseases, will need to be addressed using a systemic perspective.

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