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Systems biology: In view of engineering perspective

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Abstract
Systems biology is a new biological science applied to biomedical and biological scientific research. This new field of systems biology is changing the way biology has been perceived classically. This field not only needs scientists and mathematicians but also calls for engineers willing to embrace fresh challenges. This review outlines the new opportunities available in this nascent field for significant engineering-related advances. It is anticipated that engineers will be at the forefront to motivate and lead new developments in this field via theoretical systems approaches. The aim of this article is to divert the attraction of engineers towards biological science as they can revolutionize the field of biology.

Keywords: Systems biology, biological networks, stochastic simulation, robustness

INTRODUCTION

Systems biology is a newly emergent field with its origins in the early years of the 21st century. The field was formally inaugurated by the publication of a book [1] and two papers in the leading journals *Science* and *Nature* [2-3]. Further impetus was provided by the prescient perspective of Stokes [4].
The highlight of this new field of systems biology are its multidisciplinary and integrative approaches. While the era of genetic engineering was dominated by a reductionist approach with the focus being on a handful of genes or a handful of proteins, the focus of systems biology is to understand biological processes at the systems level, i.e., to take into consideration the functioning of complex biological system as a whole [5]. What is equally important is that the field combines approaches from diverse areas of science such as biology, chemistry, physics, mathematics, engineering, cybernetics and computer science [6-13]. This review attempts to examine the various opportunities for engineers to contribute to this exciting new field of research.

HISTORY

The pre-1950s traditional biology occupied itself with botany, zoology and ecology. Later came biochemistry and molecular biology and the emphasis was shifted to the structure of proteins, the structure of DNA and RNA, principles of DNA replication as well as transcription and translation, and function of membranes. A massive body of knowledge had been gathered by the biochemists and the molecular biologists. Thus the field was set to make the next step, i.e., a holistic view towards a systematic investigation of cells, organs and organisms and of (mainly) cellular processes such as cellular communication, cell division, homoeostasis and adaptation. This systems-oriented perspective of biological processes is termed *systems biology*.

But this step cannot be taken by biologists alone. While systems biology is deeply rooted in biology, it is also about modeling, network analysis and data integration. These are areas in which engineers excel and can contribute significantly.

A systems-level understanding of biological systems is a recurrent theme in science. The pioneering work of D'Arcy Thompson entitled *On Growth and Form* [14] was one of the first to elucidate general scientific and geometric principles running through the immense variety displayed by nature. Norbert Wiener was a pre-1950 proponent of a systems-level understanding of biological processes and this led to the field of "Cybernetics" [15]. Ludwig von Bertalanffy applied general systems theory to various scientific fields, including biology, but the theory was too abstract for practical applications [1]. Walter Cannon, in 1933, proposed the concept of homoeostasis, with remarkably prescient intuition about the systematic behaviour of the organism as a whole [1].

Turing [16] proposed a pioneering systems-level description of the chemical basis of morphogenesis in biology. The Prigogine school [17-18] has shown that several aspects of life can be explained through the concept of "dissipative structures" which exist in "far from equilibrium" situations.

It must be noted that, in the pre-1950s era, due to limited knowledge of molecular biology, most of the descriptions and analyses of biological systems has been at the physiological level [1]. Systems biology departs from these past attempts in that it seeks a systems level understanding directly at the molecular level such as genes and proteins. Thus genomics and proteomics are the pillars on which the field of systems biology rests [19].

IMPACT OF SYSTEMS BIOLOGY

As emphasized in Klipp et al [7], systems biology though rooted in biology also steps upwards to model development of networks while encompassing the features of modularity and robustness (more on this later) and also towards integration of data delivered by high-

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throughput technologies such as DNA microarrays [20], 2D gels, mass-spectrometry etc.

Engineers can play an important role by effecting the following impacts via systems biology:

1. A systems-level understanding of natural biological systems (animals, plants, microorganisms). This understanding need not only be structural and static, but also possibly about the dynamics. This can also intrude into the domains of metabolic engineering [21-23], proteomic network modeling [24], sensitivity analysis [25] and bifurcation analysis.

2. A systems-level understanding of pathology and malfunction leading to the ability to control the state from the cell to the whole body. This has important implications for toxicogenomics and pharmacogenomics [26-28].

3. The development of a systems-level approach in biotechnology which may, from a futuristic point of view, design biological systems having desired properties not existing in nature [29].

ELEMENTS OF SYSTEMS BIOLOGY

A major component of systems biology is network analysis. This includes network identification. Along with this comes mathematical modeling to understand system behavior (including system identification through linear and nonlinear methods), followed by control of biological processes via robust techniques in the face of model uncertainities. These topics are discussed in more detail below.

Networks

Network analysis is one of the strongholds of engineers. Electrical and electronics engineers frequently deal with complex electrical and electronic circuits. Chemical engineers deal with complex reaction networks regularly [30]. Central to the analysis of biological systems are biological circuits, namely regulatory and metabolic networks [13],[31]. It has been suggested that understanding network connectivity may usher in a new revolution more important than the current "omics" measurement revolution [32].

Especially in biological systems, a form of "nested complexity" emerges when networks of interactions form a complex pyramid [33]. At a lower level, the interactions are between molecular components such as genes, RNA, proteins and metabolites. These interactions are, in turn, integrated into interacting motifs that eventually give rise to an organism's response. Examples are (i) the DNA-mRNA-enzyme-metabolite cascade or (ii) the signal transduction cascades consisting of covalent modification cycles [7],[34]. These networks exhibit additional systemic properties and dynamic characteristics that often cannot be deduced from the individual properties of the elements.

As Doyle and Stelling [35] point out, many components of the networks have direct analogues in system engineering architecture. For instance, the *Escherischia coli* regulatory network shows the following features [36]:

- autoregulation: regulation of a gene by its gene product
- coherent feedforward loop: in this, one transcription factor regulates another factor, and in turn, the two jointly regulate a third transcription factor.
- Single input module (SIM): which contains a single input, multiple output block architecture.
- Densely overlapping regulons: which contains a multiple input, multiple output (MIMO) block architecture.

Similar resemblances have also been seen in *S. cerevisiae* [37]. Indeed, according to Alon [13], the above four motif families appear to account for almost all of the interactions in sensory transcription networks.

Moreover, gene networks have been found to exhibit various classes of behaviour such as positive feedback, integral feedback, negative feedback, time delay and multistate oscillations. These studies indicate that cell functions (both prokaryotic and eukaryotic) are controlled by a sophisticated network of control loops which are interconnected with other control loops [35],[38]. It becomes clear that such systems cannot be studied by the reductionist approaches of biochemistry and molecular biology but must be treated via the integrative perspective of systems biology.

An important problem in systems biology is network identification. Biological networks can, as a first approximation, be described as linear systems. Linear models (state-space models) capture the local dynamics in the vicinity of a steady state.

In contrast to linear approximations mentioned above, mechanistic models are usually nonlinear systems. The identification of such models is extremely challenging and comes at a very high computational cost [35].

Systems behavior

Understanding the behaviour of complex biological networks is an extremely challenging task [1],[13]. Computer simulation is indispensible to provide in-depth knowledge on the mechanisms behind the circuits.

For a successful simulation, the intrinsic *dynamic* features of biophysical networks need to be described mathematically. Models can be of three types: (i) first-principles models, (ii) empirical models, and (iii) a hybrid model combining the above two approaches. Such mathematical models can be constructed using a combination of algebraic equations and ordinary differential equations, concepts familiar to most engineers. However, since biosystems are complex, self-organizing, highly adaptive, operating at several levels of hierarchy and are higly nonlinear, it is highly challenging to apply mathematical modeling tools to living systems [32]. Encouragingly, models at the signal transduction pathway level have been developed yielding ordinary differential equations [35]. Mechanistic models have also been attempted for entire biological systems such as the bacteriophage system [39].

System control

Various control schemes used in complex engineering systems (e.g. feed-forward and feedback control) are found in biological systems. Indeed robustness can be related to the feedback control mechanisms prevalent almost ubiquitously at all levels [38]. An important example is the discovery of integral feedback control in bacterial chemotaxis [40]. Future developments in this area may address the challenging problem of transforming malfunctioning cells into healthy cells and also regulating apoptosis [1].

STOCHASTIC SIMULATION

A deterministic viewpoint is very suitable for analyzing certain events, such as some metabolic reactions, which frequently occur simultaneously [41]. However, there are processes that are not amenable to deterministic simulation, especially in gene regulatory systems where the copy number of some key species (e.g. transcription factors) is very low.

For such systems, stochastic simulation has been proposed as a solution [42-44]. Arkin and co-workers have also demonstrated the application of stochastic models to a class of biochemical reactions (enzymatic futile cycles). Gunawan et al. [45] have developed methods to characterize robustness properties of stochastic systems. Experimental methods have been devised for quantifying the characteristics of biological noise [46-48]. For instance, Raser and O'Shea [48] analyze eukaryotic systems with both cis- and trans-acting mutations to distinguish between the noise effects that are intrinsic to transcription as opposed to upstream processes. Ao [22] has proposed a general systems approach to model metabolic network dynamics in a stochastic manner.

ROBUSTNESS

As in engineering systems, in biology too, robustness refers to the maintenance of functional properties by a system in the presence of uncertainty [1],[35]. Robustness is a very much desired property of biological processes as they are subjected to constant uncertainty in the form of stochastic phenomena [42]. Recent reviews on robustness in cellular functions are by Stelling et al [49-50].

In engineering systems, robustness and stability are achieved by [35]:

- back-up systems (redundancy)
- disturbance attenuation by feedback and feedforward control
- structuring of network systems into semi-autonomous functional units (modular design)
- reliable coordination of network elements through hierarchical ordering

It is hypothesized that such an approach is adapted by complex biological systems too [1].

It is clear that robustness is a fertile ground for further research by engineers. The field of robust control [51] holds many results that may be applicable to describe interactions in biological systems.

CONCLUSION

It is evident from the above discussion that the field of systems biology possesses tremendous potential for the creative engineer. At the same time, the pitfalls of this new field should not be overlooked. A fundamental assumption of systems biology is that the cell is a machine and can be measured in parallel by using high throughput technologies. An additional assumption is that by perturbing the cell and observing its change in state, one can learn about the mechanism of the cell [52]. The assumptions rely heavily on the soundness of the database. But this may not always be the case. Drawbacks in DNA microarray analysis [20], for instance, can lead to misleading results. Even if the database is sound, different labs often give different results [52]. This makes cross-experimental comparison very challenging, requiring advanced statistical techniques. These are issues to be looked into.

Finally, this new field of systems biology requires a new kind of researcher, one who is not only well-versed in biological concepts but also in mathematical, chemical and computer science oriented concepts. This calls for tailor-made courses at the undergraduate and postgraduate levels in all engineering streams. Kumar [53], for instance advocates a co-operative-learning strategy in which students of different backgrounds are arranged in groups so that the students can complement each other's individual weaknesses leading to synergistic results.

According to Dhurjati and Mahadevan [32], one needs to have a whole new generation of students who are equally adept at mathematics and biology just as chemical engineering students are adept in mathematics and chemistry. Until then, one has to manage by taking individuals who are well trained in mathematics and computational sciences and provide them with biology domain knowledge. In short, education of engineers on the elements of systems biology is the need of the day.

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