

# Systems biology and elephants

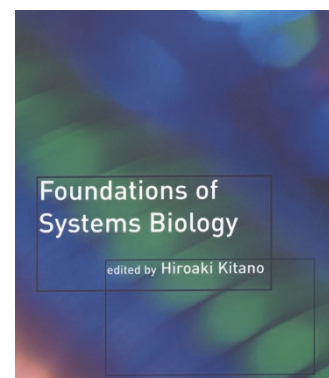
## Foundations of Systems Biology

edited by Hiroaki Kitano

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In an ancient Indian story, a group of blind men attempt to explore an elephant by touching one of its parts. The man who feels the trunk has a very different idea of the beast than does the man who feels his ears and so on, and the elephant as a whole fails to emerge. This allegory captures a shortcoming of the traditional reductionist approach to the biological sciences that today's genome-scale datasets make us painfully aware of: high-level properties of biological systems are frequently not easily discernible from observation of its elements in isolation. Systems biology is an approach to tackle this problem in dynamic and integrated biological systems. In the book *Foundations of Systems Biology*, Hiroaki Kitano provides the reader with a collection of scientific contributions that represent the state-of-the-art in this burgeoning field.

Tremendous technical advances in molecular biology have provided us with an unprecedented amount of data: we know the genetics lists for an increasing number of organisms; DNA microarrays and mass spectrometry allow us to measure concerted cellular responses to defined genetic and environmental perturbations on a global scale; and large scale studies are beginning to identify the potential interactions among cellular components. This virtual treasure trove of data is the biologists dream, but also presents the enormous challenge of understanding how these components function together to endow the organism with its system properties.

Systems biology takes aim at this challenge with an ultimate goal of, as Kitano puts it, "the computer simulation of life". With this lofty goal in mind, the author uses the introduction to describe some of the tremendous opportunities this provides for biology and medicine. In his view, new high-throughput experimental and computational technologies will continue to develop, and the sciences of biology and chemistry will assimilate elements of engineering and system sciences to accomplish this aim. Kitano also proposes a coordinated "sys-

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teome project" on the scale of the human genome project, directed towards the "assembly of systems profiles for all genetic variations and environmental stimuli responses". Kitano argues that a single, problem-independent, albeit large, set of experiments can yield a comprehensive understanding of complex circuit dynamics and ultimately allow precise medical diagnoses and treatments.

The remaining thirteen chapters of the book arose from conference contributions at the First International Conference on Systems Biology in Tokyo, November 2000, and highlight various aspects of systems biology and the current research in the field. What is striking from the book is that computing accurate models of even simple systems is an enormous computational challenge. Pedro Mendes discusses the computational problems in optimizing the parameters of a simple three-enzyme pathway and John Koza *et al.* illustrate how unravelling the topology of a similarly simple biochemical pathway demands massive computational resources. A significant challenge for the future of systems biology is to build on these studies and establish techniques that can also cope with experimental errors, and scale to larger systems of proteins. This aspect is addressed in the article by Jörg Stelling *et al.* By analogy to

how biologists generally deal with the complexity in biological systems, their modeling approach is built on a hierarchical view of the cell, comprised of functional units with specific inputs and outputs that communicate with other modules and can themselves be composed of functional units. In principle, the hierarchy extends from small molecules to entire organisms. Yet another fundamental problem faced by modellers is that many biological processes rely on the interactions of small numbers of molecules. As such stochastic processes are inadequately described by differential equations, Thomas Simon Shimizu and Dennis Bray develop a modeling approach in which molecules are represented as individual entities whose behaviors are governed by probabilities rather than rate laws.

While the book is an exceptional representation of the present challenges and achievements around formal modeling in Systems Biology, it falls short of representing the current state, or future, of the other technical challenges of systems approaches, as outlined in the author's introduction. To make the strongest impact on our understanding of living systems, new and emergent technologies are needed to reliably and quantitatively measure the hierarchical levels of biology in increasingly higher throughput, and ultimately at the level of single cells.

Even the current aspects of systems biology are so diverse that it seems virtually impossible to tie them together in a collection of individual research papers. So, ironically, *Foundations of Systems Biology* also suffers from the elephant problem. Nonetheless, the book will serve as an excellent source book to engineers, mathematicians and biologists who want to grasp the state of the art, or are seeking to acquaint themselves with the mathematical challenges of modeling biological systems. □  
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