more to come. As the author concludes: "Looking forward, it seems likely that lateral DNA transfer will be increasingly in the news. The effects of gene transfer on our daily lives are only starting to be appreciated."

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BOOKS: CELL BIOLOGY

Bridging the Genotype-Phenotype Gap

Stig W. Omholt

Biology is finally in position to start revealing the causal links between genotype and phenotype in the wide sense. In this century, biological research will become almost synonymous with the efforts to understand the functional expression of genes within the context of integrated biological systems. The task is among the most complex scientific endeavors ever, and it will force substantial numbers of biologists to become much more theoretically oriented and interdisciplinary. We have now reached the beginning of the end of a 400-year period in which most biologists could understand their subject matter without formal analytical skills.

The need for system-level thinking has become increasingly appreciated over the last 25 years. But the experimental means for making real progress have not been available before now. *Foundations of Systems Biology* reflects the excitement of this emerging field and demonstrates that it has caught the attention of people who approach systems thinking with a strong background in technology. The volume is based on papers that were presented at the First International Conference on Systems Biology in Tokyo in November 2000. Most of the contributors are researchers from Japan or the United States. The editor is Hiroaki Kitano, a senior researcher at Sony Computer Science Laboratories and the director of the Systems Biology Institute in Tokyo, who has been a driving force behind the efforts to establish this systems approach. As he explains in the preface, one of the book's principal missions is "to define the scope and provide the vision and perspectives of this new born field."

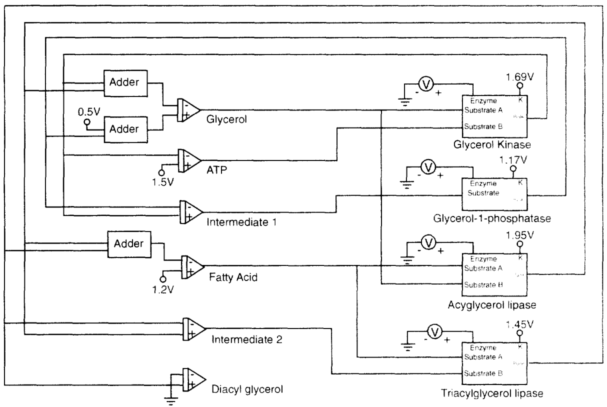
Foundations of Systems Biology
Hiroaki Kitano, Ed.
MIT Press, Cambridge, MA, 2001. 313 pp., illus. $45, £30.95. ISBN 0-262-11266-3.

Kitano describes an ultimate goal of being able to ground systems-level descriptions and understanding of cells, organisms, and humans "on a consistent framework of knowledge that is underpinned by the basic principles of physics." The task facing systems biology is thus to establish principles and methodologies by which system characteristics and functions can be derived from the behaviors of molecules. Though the volume is by no means an exhaustive overview of current research in systems biology, it is intended to cover the field's central themes including automated measurements, reverse engineering of gene and metabolic networks, simulation, and systems-level analysis. Books of this nature are bound to be uneven, but the important perspectives on and approaches to these topics that *Foundations* contains deserve attention.

I share the view that control theory and a general engineering approach will provide fruitful concepts and mathematical methods for understanding complex regulatory systems. Engineers construct systems from the bottom up, and by this approach they can develop a thorough mathematical understanding of the behavior of complex regulatory systems from first principles. Biologists are far from being in such a position. Nevertheless, biology may become a place to seek inspiration for the advancement of control theory itself. Biological systems actively use positive feedback to build structures and patterns, and regulatory biology really concerns the interplay between negative and positive feedback loops. Current control theory does not. Biological systems are also partly constrained adaptive structures with an evolutionary history driven by biotic and abiotic forces that work solely on what is currently available; engineering systems are not. A true understanding of organisms cannot be achieved until these aspects are taken into account.

The book may leave the impression that its subject matter is a new field that has no conceptual and methodological history worth serious consideration. But there already exists a substantial body of relevant theory and data concerning aspects such as frameworks for mathematical modeling, generic regulatory principles, the necessity of regulatory modules or standard parts, and methods for making a conceptual bridge between regulatory biology and classical genetics. For the next couple of decades, I think we will be more than busy with a data-driven, gradual evolution of existing theoretical structures, one in which the statisticians will play a more prominent role as providers of patterns than is suggested by this book.

The search for principles and methodologies that link the behaviors of molecules (genes) to system characteristics and functions (phenotypes) has been the prime occupation of the field called genetics for the last 100 years. This is the primary reason I prefer using the term integrative genetics to describe the efforts toward constructing a coherent explanatory bridge between genotype and phenotype, where nonlinear system dynamics glues the pieces together. The naming of the research program that Kitano and his colleagues advocate is more than a semantic issue. Calling the enterprise systems biology not only renames the field of genetics, but it also neglects the well-established systems-focused fields of population dynamics and systems ecology.



Simulation circuitry. This electrical circuit corresponds to the chemical reaction network of the phospholipid cycle.

CREDIT: J. R. KOZA ET AL. IN *FOUNDATIONS OF SYSTEMS BIOLOGY*

It is fascinating to be a biologist at this time of transition, when we are beginning to obtain the means to construct a sophisticated formalism for detecting, describing, analyzing, and understanding, at various levels, the complex genetic systems that underlie phenotypic characters and their responses to changing environments. Among the fields that stand to gain from this formalism are evolutionary biology, microbial biotechnology, biomedicine, and the breeding and production of livestock, poultry, fish, and plants. A whole series of discoveries important to these fields will emerge long before the vision outlined in *Foundations of Systems Biology* has become reality. But visions are still important, as long as we also remember the details. The dream of understanding the causal basis of biological forms has been with us since Aristotle. As the late Peter Sellers, in the role of Inspector Clouseau, observed: "Ahhh, now we are getting somewhere."

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