

BOOKS: GENOME EVOLUTION

Keeping Pace with Opportunistic DNA

Margaret G. Kidwell

The metaphorical tree of life that Charles Darwin proposed to represent the relationships among all organisms since the dawn of life has been widely accepted for more than a century. More recently, the serial endosymbiotic theory of the origin of eukaryotic mitochondrial and chloroplast organelles (1) provided exceptions to the strictly branching conformation of a universal tree. Now, a rising flood of evidence for high frequencies of lateral (or horizontal) DNA transfer, particularly in prokaryotes, has made the equation of individual gene phylogenies with organismal phylogenies problematic (2). By reconnecting lineages that had previously diverged, lateral transfer introduces net-like reticulations into molecular phylogenies based on individual DNA sequences.

Lateral DNA transfer is the delivery of DNA from one organism to another where it is stably integrated into the genome of the recipient. The process is distinguished from the more common vertical transfer, which proceeds from parent to offspring. In addition to its effects on evolutionary phylogenetics, lateral transfer has important implications for topics in basic and applied biology as diverse as the threats posed by bacterial resistance to antibiotics, the understanding of the origin of our own genome, and the implications of genetic engineering.

So what is the nature of this emerging field? In *Lateral DNA Transfer: Mechanisms and Consequences*, Frederic Bushman provides an answer that makes informative and fascinating reading. The book, aimed at an audience with some background in biology, delivers much that is new for specialists and general readers alike. It is superbly organized, and its modular design offers easy accessibility to a diversity of readers.

The immense scope of the topic encompasses all living organisms on Earth and touches on all levels of biological organization. Therefore, the subject cannot be accurately pigeonholed into disciplines such as molecular biology or biochemistry. As Bushman points out, "the fields of biology on which lateral transfer impinges are stud-

ied by separate communities of scientists each with their own jargon and objectives." The assembly and synthesis of such a huge body of information was a monumental task for a single author. His success at effectively addressing a broad audience required a grasp of modern biology that is rarely encountered in this era of specialization.

True to its subtitle, the book provides a comprehensive review of both the mechanisms and consequences of lateral DNA transfer. It is only possible here to touch on a small fraction of the range of topics Bushman covers. Early chapters survey mecha-

nisms of lateral DNA transfer in prokaryotes. The author discusses the three broad mechanisms that mediate movement of DNA between cells: transduction, conjugation, and transformation. He also describes transposition, by which mobile elements move from one chromosomal location to another in the same cell, often replicating themselves. Although not itself a mechanism of lateral transfer, transposition is sometimes directly associated with such transfer. And, more frequently, transposition links cellular sequences to vehicles such as viruses that enable lateral transfer between cells, which provides some justification for the book's extensive coverage of mobile elements. Highlighting the relevance of prokaryotic DNA transfer mechanisms to human health are the alarming rates at which antibiotic resistance genes move between different species and the implications of transduction of blocks of genes (pathogenicity islands) that convert bacteria from benign to pathogenic.

Coverage of lateral transfer in eukaryotes includes chapters on retroviruses, the AIDS epidemic, retrotransposons, DNA transposons, and the vertebrate immune system. Although plants and fungi are by no means excluded, the major emphasis is clearly on animals. Bushman reviews evidence for lateral transfer from recently sequenced eukaryotic genomes. These provide informa-

tion that emphasizes the unexpected changeability of genomes and the interconnectedness of all life. For example, gene-coding sequences make up less than 2% of our human genome. In contrast, 8% consists of the decaying remnants of endogenous retroviruses and at least 50% represents mobile elements. The genomes of other eukaryotes contain a highly variable fraction of transposable elements, which the author discusses in considerable detail using examples from a range of simple and complex organisms. Although transposable elements are still commonly dismissed as junk DNA, Bushman describes how they are increasingly viewed as potential sources of genetic variation that may be co-opted for the benefit of the host species.

In discussing lateral transfer between the three domains of life (Bacteria, Archaea, and Eukarya), Bushman includes examples of the transfer of DNA from species of *Agrobacterium* to various plants and the implications of this process for genetic engineering. He also provides a brief review of the endosymbiotic theory of the bacterial

origin of mitochondria and chloroplasts. Two concluding chapters summarize how mechanisms have evolved to regulate the flow of genetic information between species and discuss some of the general evolutionary implications of DNA transfer such as the relation between mobile elements and sexual reproduction. These sections are thought provoking but somewhat limited in scope.

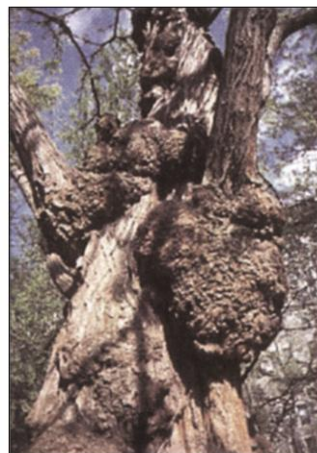
The book emphasizes natural mechanisms of DNA transfer. Applications to biotechnology are covered only briefly, with references to more applied aspects. Nonetheless, a few

implications for artificial gene transfer by genetic engineering do emerge. Our increasing awareness of the myriad of ways that natural transfer can occur emphasizes the need for caution in the release of genetically engineered organisms into the natural environment. In contrast, the more gene transfer is documented in nature, the less the process is likely to be judged as "unnatural." Bushman's valuable survey of our current understanding of natural transfer will help readers make more informed judgments about the broader implications of genetic engineering.

One comes away from *Lateral DNA Transfer* fully persuaded that genomes are far more fluid and unconstrained than previously believed. But there is surely much

**Lateral
DNA Transfer
Mechanisms
and Consequences**
by Frederic Bushman

Cold Spring Harbor
Laboratory Press, Cold
Spring Harbor, NY,
2002. 464 pp. \$59, £43.
ISBN 0-87969-603-6.
Paper, \$39, £28. ISBN
0-87969-621-4.



Inter-domain activity. Crown galls develop through the transfer of DNA from *Agrobacterium tumefaciens* to the host plant's nuclear genome.

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."

References

1. L. Margulis, D. Bermudes, *Symbiosis* 1, 101 (1985).
2. W. F. Doolittle, *Science* 284, 2124 (1999).

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

Foundations of Systems Biology

Hiroaki Kitano, Ed.

MIT Press, Cambridge, MA, 2001. 313 pp., illus. \$45, £30.95. ISBN 0-262-11266-3.

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 de-

fine the scope and provide the vision and perspectives of this new born field."

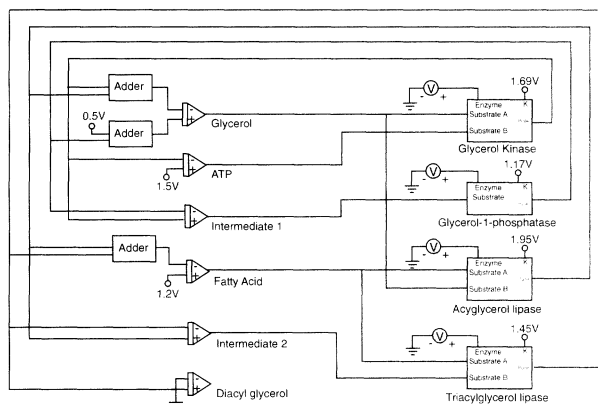
Kitano describes an ultimate goal of being able to ground systems-level descriptions and understanding of cells, organisms, and humans "on a consistent framework of knowledge that is underpinned by the basic principles of physics." The task facing systems biology is thus to establish principles and methodologies 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 genet-

ics. 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



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

biology not only renames the field of genetics, but it also neglects the well-established systems-focused fields of population dynamics and systems ecology.

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."

The author is in the Department of Animal Science, Agricultural University of Norway, Post Office Box 5025, 1432 AAS, Norway. E-mail: stig.omholt@ihf.nln.no