

now have the more modest goal of understanding high-energy physics by means of some interesting dualities that enable easy calculations to give results for very hard ones. But this aim has not received the same publicity as that of finding a unified 'theory of everything'.

So, a theory that is unable to produce any testable new predictions has dominated theoretical physics for 30 years. Given the difficulty of the task, there is nothing wrong with this: we can hope it will eventually work out, and it is reasonable to expect such a fundamentally important enterprise to take a long time. More problematic is the attitude of some string theorists that it is not worth investigating alternatives. There is an unquestioning assumption that string theory's claims must be true, even though there is no solid evidence for them, and this is often expressed with considerable arrogance and an attitude that nothing else is worthwhile physics. String theory has dominated appointments to academic positions in theoretical physics for decades, effectively impeding a broader investigation of quantum gravity and the fundamental nature of space-time. It is claimed to be the only game in town, but insofar as the aim is to quantize gravity, there are alternatives, and Smolin briefly outlines some of the more promising ones.

Some of the sociological issues that come into play here are the subject of interesting chapters, based on Smolin's own experiences. A sad aspect is the *ad hominem* attacks made on those who question the theory, including serious thinkers being labelled by the derogatory term 'popperazzi'. This term makes clear how some string theorists regard their views as so overwhelmingly convincing that it is no longer necessary to retain experimental testing as the core of the scientific approach. Smolin crystallizes what many in the physics community feel about these extravagances of string theory.

Those advocating a focus on 'beauty' and 'miracles' when evaluating their theories don't seem to have thought through the implications. The weakening of criteria proposed by some string theorists will, if accepted, open the doors to many other faith-based enterprises that would be only too glad to be viewed as science. In particular, scientific opposition to 'intelligent design' centres on an insistence that for a theory to be scientific it must be testable, observationally or experimentally. Proponents of intelligent design must surely welcome the freedom from evidential constraints that some string theorists are proposing.

What is crucially needed in developing string theory is a serious attempt to engage with the philosophy of science, developing an approach to theory validation that is adequate where insubstantial evidential support has to be supplemented by other principles of inference. So far, this has not been done. ■

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Developing diversity

The Regulatory Genome: Gene Regulatory Networks in Development and Evolution
by Eric H. Davidson

Elsevier: 2006. 304 pp. \$69.95, £43.99

Michael Karin

All living organisms deploy similar evolutionarily conserved mechanisms to generate energy, replicate their genomes, use genetic information and synthesize basic building-blocks for their cells. Yet the myriad shapes and forms of both plants and animals are overwhelming in their variety and extremes. What is even more amazing is that most plants and animals start their life as a single diploid cell (a zygote) created by the union of a sperm and an egg. How these simple cells give rise to such complex creatures with diverse body shapes is a major preoccupation of developmental biologists.

Developmental biology mainly deals with the processes and regulatory mechanisms that guide the conversion of a unicellular zygote into a multicellular organism. The progression of body shapes and forms over evolutionary time is another fascinating topic that occupies students of development and evolution alike. As Eric Davidson convincingly argues in his book *The Regulatory Genome*, animal (and plant) development is driven by a "dynamic progression of regulatory states, defined by the presence and state of activity in the cell nuclei of particular sets of DNA recognizing regulatory proteins (transcription factors), which determine gene expression". An equally important contributor to development is the "genomic apparatus that encodes the interpretation of these regulatory states". Over evolutionary time, "the alteration of body plans is caused by changes in the organization of this core genomic code for developmental gene

regulation". The genomic code that dictates animal development and the genetic apparatus that implements it are the main topics of the book.

Initially a descriptive science, developmental biology has benefited hugely from the revolution in molecular biology of the past 30 years. Indeed, *The Regulatory Genome* is entirely different from Davidson's first book, *Gene Activity in Early Development* (Academic Press, 1968), which preceded molecular cloning and rapid DNA sequencing. However, even in the earlier book, which I remember reading as a graduate student, Davidson championed a quantitative, biochemical and mechanistic approach to the study of developmental biology. His latest book goes many steps beyond that, explaining the basic processes of development and evolution in terms of information processing and computational logic. *The Regulatory Genome* incorporates and integrates many recent advances in understanding gene regulation and genomic organization in a quest for a unified model to explain animal development and the evolution of body shapes and forms.

As a scientist interested in gene regulation and signal transduction, I think the most important and valuable message conveyed by the book is the central role of the DNA elements, the *cis*-regulatory elements and control units, in both development and evolution. Most molecular biologists are occupied as I am with the study of regulatory proteins, either transcription factors or signal transducers that eventually modulate transcription-factor activity. So it is a refreshing and sobering realization that the *cis*-regulatory elements — the genomic DNA units recognized by sequence-specific transcription factors — occupy a more central role in the design of the genetic circuits and networks that control developmental



Variety show: how did animals develop diverse body shapes like this nudibranch and these tunicates?

T. LAMAN/GETTY

processes and mediate evolutionary diversification than the transcription factors themselves. This makes sense because, in most cases, sequence-specific transcription factors or the signalling proteins that modulate their activity are highly conserved among organisms with very different shapes and forms. Yet the constellations of *cis*-regulatory elements, which together make up the *cis*-regulatory control units that dictate the time, place and magnitude of gene expression, are more diverse and seem to evolve more rapidly than the transcription factors that recognize them. Furthermore, such control units also dictate the expression patterns of transcription factors and signalling proteins in time and space, and thereby

determine the exact patterns and repertoires of developmental gene expression.

In general, Davidson does an excellent job of reducing the complexity of different developmental pathways and modes of embryonic development in diverse animal phyla to a set of simplified and logical concepts and principles. He provides excellent illustrations and experimental examples derived from several model organisms: nematode worms, fruitflies, sea urchins, tunicates and vertebrates of different sorts. What is especially attractive about the book are the regulatory networks drawn as simple wiring and computational diagrams. These go a long way towards explaining the basic regulatory logic and engineering principles of

some of the most complex biological phenomena: animal development and the evolution of body forms.

This book should be read by all biologists who want to understand how development and evolution take place and what governs the workings of genomes. I also recommend it to computer scientists and engineers who are interested in the budding field of computational biology, as reading it does not require an extensive background in developmental biology. ■

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Putting DNA on the map

Reconceiving the Gene: Seymour Benzer's Adventures in Phage Genetics

by Frederic Lawrence Holmes

Yale University Press: 2006. 320 pp. \$50

Denis Thieffry

In the 1950s, Seymour Benzer set out on a daunting research programme aimed at resolving the fine structure of the gene. Using bacteriophages and various strains of bacteria, his genetic-mapping enterprise ultimately united genetics and structural chemistry. How did Benzer conceive and achieve this goal? And what were the critical components and influences that led to the success of his enterprise?

In *Reconceiving the Gene*, Larry Holmes addresses these questions in a scrupulous and captivating historical analysis. Making extensive use of Benzer's laboratory notebooks, scientific correspondence, reports and grant proposals, and complementing these with interviews, Holmes carefully retraces Benzer's sinuous investigative path and offers us a well-documented day-to-day analysis of the development of his work. Although Benzer had previously published his own biographical recollection of this period as a chapter in the edited volume *Phage and the Origins of Molecular Biology* (Cold Spring Harbor Laboratory Press, 1966), Holmes' extensive analysis shows how Benzer sometimes condensed events in his relatively sketchy autobiographical reconstruction.

Trained as a solid-state physicist, Benzer was well prepared for quantitative analyses and genetic abstraction. In two years of training at the California Institute of Technology and a year at the Pasteur Institute in Paris, Benzer progressively penetrated the informal international phage network. Initially, he was deeply influenced by key players of the phage group, including Max Delbrück, Salvador Luria, André Lwoff, François Jacob, Alfred Hershey and Sidney Brenner. However, he progressively altered his pathway in the light of



Fine work: Seymour Benzer created a map of the gene with a resolution of just a few nucleotides.

his own results, as well as those of others — notably an experiment by Hershey and Martha Chase demonstrating the hereditary role of phage DNA, and James Watson and Francis Crick's work to develop the double-helix model of DNA.

Holmes ends his book with extensive accounts of the main public presentations by Benzer of his mapping results. About Benzer's landmark publication (*Proc. Natl Acad. Sci. USA* **41**, 344–354; 1955), Holmes states: "Like most modern scientific papers, Benzer's 'Fine Structure of a Genetic Region in Bacteriophage' is a logical reconstruction of the experiments, observations, and arguments supporting his conclusions. It has little narrative structure and does not purport to follow the investigative pathway from which it came."

Holmes patiently reconstructs the investigative path that led Benzer to draw the first high-resolution genetic map (down to a few nucleotides). The map supports the contention

that hereditary units are ordered linearly on the chromosome, and that genetic mutations and crossing-over experiments could be traced back to the underlying linear arrangement of DNA. Holmes says that Benzer isolated, characterized and crossed about a thousand T4 phage mutants, most of them in the limited rII region. This was possible thanks to the fantastic resolving power of Benzer's experimental system, which he progressively improved by using different types of mutants (extended deletions) to speed the mapping of novel mutants.

Benzer's results reached a wide audience through his contributions to two major conferences: the Brookhaven Symposium on Biology in 1955 and the McCollum-Pratt Institute Symposium on the Chemical Basis of Heredity at Johns Hopkins University in 1956. On the latter occasion, Benzer proposed three new terms — cistron, recon and muton — to solve the ambiguities associated with the term 'gene', which is considered altogether as a unit of function, recombination (crossing-over) and mutation. Although these terms (perhaps with the exception of 'cistron') did not become really popular among the emerging molecular-biology community, these distinctions helped to clarify the relationships between the different gene definitions. For a broader historical analysis, see *The Concept of the Gene in Development and Evolution*, edited by Peter Beurton, Raphael Falk and Hans-Jörg Rheinberger (Cambridge University Press, 2000).

Although technical in places, *Reconceiving the Gene* should nevertheless be accessible to a wide scientifically literate audience as it further introduces the broader context of classical and phage genetics. Holmes initially planned to go beyond Benzer's fine rII mapping and also cover his contributions towards solving the genetic code. This plan was impeded by illness, however, and Holmes died on 27 March 2003. Hopefully, his captivating book will stimulate other historians of biology to complete his project. ■

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