BOOKS & ARTS

All systems go

Three authors present very different views of the developing field of systems biology.

Life: An Introduction to Complex Systems Biology
by Kunihiko Kaneko
Springer: 2006. 383 pp. £61.50, $99
An Introduction to Systems Biology: Design Principles of Biological Circuits
by Uri Alon
Chapman & Hall: 2006. 320 pp. £28.99
Systems Biology: Properties of Reconstructed Networks
by Bernhard Palsson
Cambridge University Press: 2006. 334 pp. £35, $75

Eric Werner

The authors of three books profess to give an introduction to systems biology, but each takes a very different approach. Such divergence might be expected from a field that is still emerging and broad in scope. Yet systems biology is not as new as many of its practitioners like to claim. It is a mutated soup of artificial life, computational biology and computational chemistry, with a bit of mathematics, physics and computer science thrown in. Because it is so broad and has few recognized boundaries and plenty of funding, it is attractive to anyone who has ever thought about life and has some relevant technical expertise.

The discovery that dynamic systems can exhibit complex, chaotic and self-organizing behaviour made many scientists see analogies with living systems. In *Life*, Kunihiko Kaneko attempts to describe living organisms as complex systems akin to those seen in chemistry and physics. The problem is that the theory of dynamic complex systems used in physics and chemistry may have little to do with biological organisms and the way they grow and function.

For instance, Kaneko views differentiation from a group of uniform cells as resulting from slight stochastic perturbations that are gradually amplified by intracellular and intercellular interactions. After a while, these become fixed, resulting in a pattern of different cell types. One problem with this theory is that it gives no account of how differentiation repeats itself so consistently in the development of organisms. It fails to explain why identical twins remain identical, and why horse embryos develop into horses, not chimpanzees.

Kaneko also claims that stem cells are fundamentally unstable and that this leads to different cell types. But stem cells are not unstable.
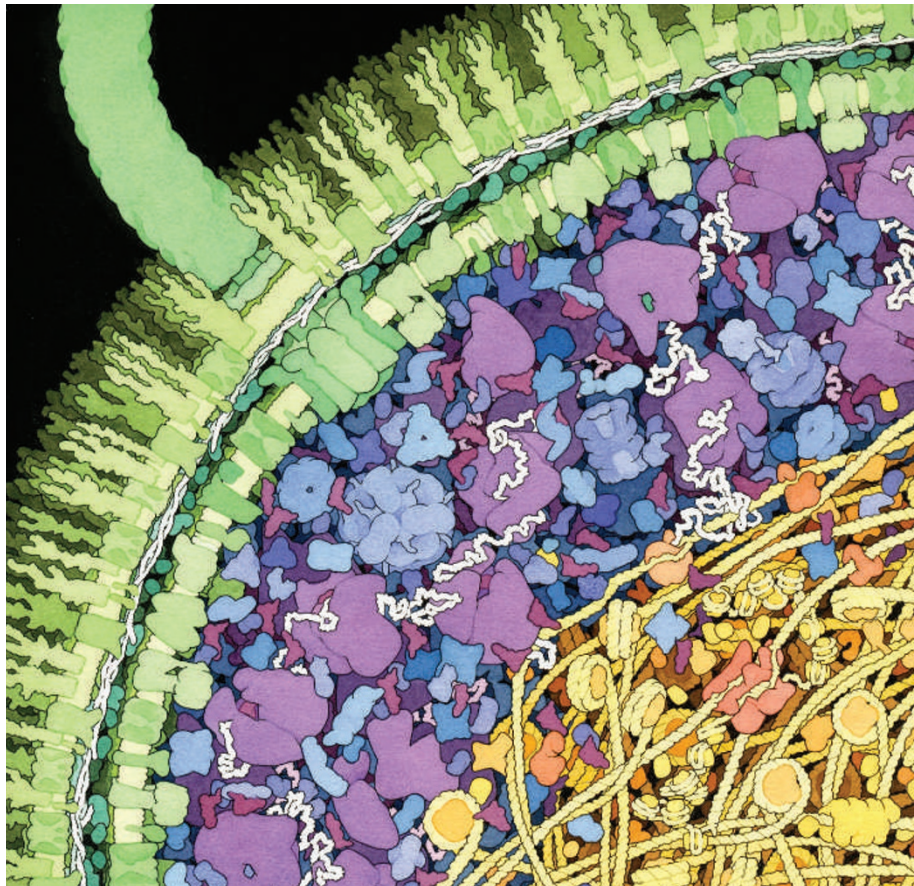
The activity of cells is determined by complex interactions governed by a range of control signals.

Rather, when stimulated by signals or by their own genetic clock, they start a very precise process of differentiation that is dependent on internal and external control signals.

There is one big player missing from the dynamic-systems account: the genome. For this reason, it seems to me that dynamic-systems theory fails to give sufficient insight into biological processes. Cells are highly complex agents containing a vast amount of control information that cannot be reduced to a few simple rules (or even sophisticated mathematical functions) that attempt to describe cell dynamics and cell interactions externally without recourse to the information contained in the genome. A similar problem lies at the heart of the failure of Turing-like models to describe embryonic development. Kaneko provides a good summary of the standard weaknesses of Turing's theory of development, but fails to see that some of the same

weaknesses apply to his own ideas as well.

Kaneko assumes that because complex patterns can form from simple interacting physical elements, such interactions can also generate arbitrary complexity. Even a simple counting algorithm that sequentially generates every integer will generate every complex state (binary sequences), but no algorithm can generate any particular number or state and stop without having the information contained in that number or state. Moreover, any process that generates a complex structure and stops must contain the information required to generate that structure. This is why cells need the vast amount of information encoded in their genome. Kaneko and many others who have fallen for the myth of interactionism, complex-systems theory or Turing-like models are in fundamental conflict with the complexity conservation principle, which states that a space-time event generated by a set of agents

cannot be more complex than the information available to the agents.

Evolution gets round this principle by the stochastic generation of new states. Stochastic processes can be random so they can generate arbitrary complexity, within physical chemical constraints, because random strings or structures are maximally complex.

Uri Alon's *An Introduction to Systems Biology* is a superb, beautifully written and organized work that takes an engineering approach to systems biology (see also Connections, page 497). Alon provides nicely written appendices to explain the basic mathematical and biological concepts clearly and succinctly without interfering with the main text. He starts with a mathematical description of transcriptional activation and then describes some basic transcription-network motifs (patterns) that can then be combined to form larger networks.

The elegance and simplicity of Alon's book might lead the reader to believe that all the basics of the control of living systems have been worked out. It only remains, it seems, to combine the network motifs to get a total understanding of networks in the dynamics and development of living systems.

All is fine except that in the very first page of the book, Alon defines networks as functions that map inputs to protein production. In other words, the meaning of genomic transcription networks is restricted to the production of proteins or cell parts. Granted, some of these proteins are transcription factors that in turn activate other genes and, thereby, are a key part of the network itself. But this prejudices the enterprise by presupposing that protein states are all there is to understanding life. Such a view is bottom-up in the extreme.

What's missing is a relation between higher-level organizational, functional states and networks. This is indicative of a more fundamental problem. Because Alon focuses on very basic low-level circuits, the global organization and its effects are largely ignored.

In some ways, Bernhard Palsson's *Systems Biology* is a more practical book for those wishing to understand and analyse actual biological data and systems. It directly relates chemistry to networks, processes and functions in living systems. The book's main focus is on metabolic networks of single cells such as bacteria. Palsson argues that classical modelling using differential equations requires complete information about the state of the system. Such data, however, are not available for complex biological systems. Palsson's response is to accept biological uncertainty. The approach is to describe a space of all the possible states of a system or network (relative to a set of dimensions of interest) and then use biological and chemical data to constrain this space. This is similar to the process of entropy reduction described in statistical thermodynamics.

Specifically, Palsson espouses a mathematically ingenious method of formalizing metabolic reactions, pathways and networks, and

uses this to formalize uncertainty about biological chemical states. This space of possibilities can then be systematically constrained by high- and low-level information. In this way, he manages to formalize states of uncertainty in a biological system so he can extract useful predictive information about it, despite the fact that many of its parameters and values of variables are unknown.

Unfortunately, Palsson's book is a difficult read. It is not well organized and refers the reader to later chapters to explain concepts needed in earlier ones, and vice versa. Often no explanation of basic concepts is provided; additional appendices would have been helpful. Palsson admits that he had help writing some of the chapters, and the book does feel like the work of a committee. However, it brings together many of Palsson's contributions to metabolic network formalization and analysis and, for this reason, deserves to be part of a systems-biology curriculum. I look forward to

improvements in the promised future editions.

Of the three books, Palsson's is the most practical and immediately relevant to modelling low-level metabolic networks. Alon investigates networks at a higher level, including genomic regulatory networks. He does an excellent job of explaining and motivating a useful toolbox of engineering models and methods using network-based controls. Kaneko's book is conceptually deep but further removed from Palsson's chemical networks and even from Alon's more abstract regulatory networks. Even though I am critical of his approach, the book is filled with insights and useful criticisms of some of the standard models and theories used in systems biology, and in biology generally. All three books will be valuable and non-overlapping additions to a systems-biology curriculum. ∎

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A little movement

Middle World: The Restless Heart of Matter and Life
by Mark Haw
Macmillan Science: 2006. 256 pp. £16.99, $24.95

Tom McLeish

The fascinating tale of brownian motion has been looking for a story-teller for a long time. The tangled threads knot together, rather than begin, in the nineteenth century with botanist Robert Brown's original observations of the random, ceaseless motion of particles in pollen grains of *Clarkia pulchella*. The threads lead back in time to medieval theories of matter that tangled physics with theology — a pattern that ran deep through the work of Galileo and Newton — and further back still to the Epicureans. Going forwards from Brown, they twist through the nineteenth century's ambivalence towards molecular theory and the thermodynamics of Sadi Carnot and Lord Kelvin. Weaving through the kinetic theory of James Clerk Maxwell and the statistical mechanics of Ludwig Boltzmann that finally grasped the physics of randomness, they lead to the complementary beauties of Einstein's theory of brownian motion and Jean Baptiste Perrin's experiments that led to modern soft-matter physics and a new understanding of the role of brownian dynamics in molecular biology. This is a remarkable story of science and scientists that leaves no major science untouched and summons onto the stage a colourful and eminent cast from centuries of endeavour.

In *Middle World*, Mark Haw provides an accessible and racy account that succeeds in opening up technical ideas without losing momentum. Haw is not insensitive to dramatic

Jean Baptiste Perrin (above) provided a new understanding of Robert Brown's notion of random motion.

irony, and makes a satisfying conclusion out of the return of brownian motion to illuminate dynamical processes in biology, where it originated, after spending a century wandering the worlds of physics and physical chemistry. We fleetingly visit the role of brownian motion in polymer physics, oxygen capture by myoglobin, the protein-folding problem and the question of how molecular motors (the cell's cargo transporters) can possibly execute controlled and directed motion in a turbulent brownian world. It's not quite T. S. Eliot, but we are almost back where we began, yet knowing for the first time.

Although it is a fitting window onto a selection of hot topics in current science, the final 'contemporary' section drops the connected storyline of the preceding historical material.