BOOK REVIEWS

Final Theory in Biology

The Origins of Order. Self-Organization and Selection in Evolution. STUART A. KAUFFMAN. Oxford University Press, New York, 1993. xviii, 709 pp., illus. $75; paper, $29.95.

If one asks why there is and ought to be a science of biology a proper answer has to be derived from the empirically discernible differences between systems classified as living and those considered nonliving. Granted that historically the line of demarcation between living and nonliving things has shifted (flowing water, for instance, was once considered living), the distinction as drawn in the present era neatly differentiates between self-maintaining and self-reproducing material systems as living and all others as nonliving. The commonly accepted view is that this distinction is not due to some nonphysical forces acting in the living systems, although this is an empirical question. Instead, it seems that living things owe their status to the peculiar spatiotemporal organization of quite ordinary physicochemical processes. Consequently, biology is the science of the organizational principles that make living things living. Kauffman's book is a massive attempt to provide the foundations of a theory of such organization.

The big triumph of late-19th– and early-20th–century biology was the discovery of natural selection, that is, of a mechanism able to explain the origin of order in the living world. This discovery together with cell biology and genetics is the basis for the unity of biological sciences. What is to be learned from further exploration of the origins of order? Kauffman is describing a path that leads beyond the well-known pastures of Neo-Darwinism. But unlike many others who have attempted such a course, he does not start out by downplaying the importance of natural selection to further his own ideas. Instead he begins his argument with an analysis of the selection process and its limitations that leads to a larger framework in which selection finds its proper place. The larger framework Kauffman envisions is one in which selection is embedded in a theory of self-organization that defines both the preconditions under which evolution by natural selection is possible and the limits to its influence.

Kauffman begins by providing an outline of current evolutionary theory and then expounds his theory of adaptation in a general way, setting the stage for integrating self-organization into the theory of evolution. He then applies this framework to the origin of life and to ontogenetic development.

Readers who think they have already read enough about the history of biology to skip Kauffman's first chapter will misjudge. Even if with its 23 pages it can only be a sketch of the history and content of Neo-Darwinism, this chapter is a revealing outline of the intellectual undercurrents that determine the direction of current biological thinking. I will leave the question of historical accuracy for historians to assess. What I like most about Kauffman's outline is that it reconstructs an internal logic that pinpoints the inherited conceptual biases in current evolutionary theory. For instance, the triumph of evolutionary thinking after Darwin not only destroyed the idea of fixed species, it also eliminated the idea that nonhistorical factors may influence organic form, a theme that is central to Kauffman's project. He then goes on to identify the lines of reasoning that reinforced the exclusion of nonhistoric factors from evolutionary thinking. One point is Weismann's idea that offspring resemble their parents because of identical processes of growth and development, dictated by the germ plasm ("genes" in modern terminology). "The organism therefore is not a self-organizing whole but an expression of the commands of the central directing agency of the germ plasm" (p. 8). Tightly linked to this idea is a second central assumption of Neo-Darwinism, that the elementary evolutionary event is the replacement of one gene by another (gene substitution). Population genetics is the study of this elementary event. With these premises in place there is no room left for much else. According to Kauffman this theory became conceptually closed as a result of the logically unnecessary assumption that genetic variation causes unbounded phenotypic variation, which leaves natural selection as the sole source of order. Given this diagnosis of the biases of evolutionary theory Kauffman's next step is to analyze the conditions under which evolution by natural selection can take place and the limitations that follow from them.

The first main part of the book is devoted to the problem of adaptation of complex systems. The availability of computer programs has made all of us aware that not all systems are able to improve by random variation and selection. For instance, in the case of computer programs small changes in the code do not lead to small changes in the behavior of the computer. Hence, gradual improvement of the program by small random changes of the code is impossible. A complete theory of adaptation should tell us under which conditions adaptation by natural selection is possible. The founding fathers of population genetics were not unaware of this problem (see for instance Fisher's *The Genetical Theory of Natural Selection*), but it never occupied center stage in the Neo-Darwinian research program. Kauffman's mathematical tool for devising a theory of adaptation of complex systems is the so-called *NK* model, which formally is equivalent to a spin glass model. It makes it possible to model evolution on complex, "rugged" landscapes and has interesting statistical properties. In analyzing this model Kauffman opens a way for self-organization to enter the otherwise hermetic world of Neo-Darwinism. He notes that the interplay of spontaneous formation of order and selection can be seen in how selection is able to control the movement of the population through the space of possible genotypes or phenotypes. The structure of the phenotype space reflects the influence of spontaneous self-organization on what is possible, because it determines which features are statistically likely and which are unlikely. Selection can in principle move the population to statistically unlikely regions of the phenotype space. It can create order that would not be attained spontaneously. However, if selection is weak relative to stochastic factors like mutation and drift, the population will escape control by it and will be found to occupy statistically likely states; that is, the observed order will be due to self-organization. Another circumstance in which self-organization can become the dominating force in evolution is when selection is strong but the fitness landscape has many local optima. In this case the population will be trapped on one randomly chosen optimum, which in most cases will be representative of a likely state of the system. Kauffman calls these two ways in which evolution can become dominated by self-organization "complexity catastrophes."

The idea of limitations to selection is not in itself alien to classical population genetics theory. In fact the theory of Muller's ratchet in population genetics deals with phenomena analogous to those Kauffman treats, the process by which deleterious mutations accumulate in populations (see for example John Maynard Smith's *The*

Evolution of Sex [Cambridge University Press, 1978] and references cited therein). This whole body of literature is essentially ignored by Kauffman. Admittedly, the relationship between Muller's ratchet and the various models of error catastrophes is not entirely clear and Muller's ratchet was invented to deal with another problem (the maintenance of sex and recombination). The analogy only indicates that both population genetics theory and the theory of self-organization could benefit from intenser communication.

The remainder of the first part of the book is devoted to two major points. One is the concept of the "edge of chaos" and its implication for evolvability. The other is the possibility that evolvability is attained through the action of natural selection. The mathematical tools here are Boolean networks, which are used as paradigms of complex dynamical systems. The edge of chaos is a dynamical state between the range where the system is frozen into largely stable states and the other extreme, where long, complex cycles of activity are observed. Kauffman demonstrates that this state is optimal for problem-solving by an artificial system and that it is attained by selection in simulation experiments. This concept is then exported to the case of coevolution, where Kauffman shows that the model ecosystems evolve toward the edge of chaos. Evolvability is not only the prerequisite for evolution by natural selection, it can also be actively attained and maintained by natural selection.

The next part of the book is devoted to models explaining the origin of life. Kauffman rephrases the question of the origin of life by asking how likely it is that a random collection of catalytic molecules forms a closed autocatalytic set, that is, a set whose members catalyze each other's production. He finds that on combinatorial grounds there is reason to expect that the likelihood of autocatalytic closure increases with the number of molecules in such a collection. Hence there is a complexity threshold beyond which autocatalytically closed sets of reactions are likely to occur.

Whatever the fate of this theory for the origin of life may be, Kauffman's treatment of the problem leads to a new type of model that holds great promise for biology in general and possibly also for the social sciences. Large sets of molecules that produce other molecules by reacting with each other are not easily described by dynamical systems models, in which quantitative variables change over time according to some prespecified rules, usually a set of coupled ordinary differential equations. In chemical kinetics the variables are the concentrations of the different kinds of compounds in the reaction mixture. This means that at the outset the model has to specify explicitly which molecules will appear in the reaction and how they interact. The structure of the reaction network is an assumption of dynamical systems models and cannot be a prediction of any model of this kind. Kauffman describes a modeling framework invented by Walter Fontana at the Santa Fe Institute that overcomes this limitation. The models of this framework are random grammars, in which the objects are syntactical expressions of a grammar (in particular the λ-calculus) and act on each other to produce other syntactical objects. Hence, what the model specifies are the rules of interactions among all combinatorially possible objects, leaving open which objects appear in a particular simulation run. It is thus a natural modeling framework for exploring the central goal of biology, to understand the origin and structure of organizations, whereas traditional approaches only allow one to predict the dynamics of a given organization. Kauffman develops very suggestive metaphors—eggs, jets, mushrooms, and so on—to classify the possible organizations. He is also very convincing in arguing for the potential of this modeling approach for biology and perhaps also for the social sciences.

In the final part of the book Kauffman takes up the basic problems of developmental biology, differentiation and morphogenesis. Again he uses his ensemble approach to explain major patterns, such as the relationship between DNA content and the number of cell types possible. It is in this section that he also reflects explicitly on the philosophical background of this approach and its ontological implications. The argument runs as follows: In order to understand the interplay between self-organization and selection we need to know what could be expected if selection were not acting. Such predictions of course cannot be detailed, because many possibilities exist. However, it is possible to use the information we have about the molecular processes to construct a combinatorial model compatible with the molecular information. For instance, in the case of cell differentiation it is known that all the cells in principle can have the same genes as the fertilized egg cell and that the differences between cells are due to differential gene expression. Further, it is known that differential gene expression is caused by the action of transcription factors, which are also proteins from genes that in turn are regulated by other transcription factors. This leads to a model of possible gene-regulatory networks whose statistical properties can be analyzed. Kauffman's main point is that many known features of gene regulation and development are just what one would expect on the basis of the statistics of the gene-regulatory network ensemble and do not need selection as explanation. But other features are not compatible with such expectations and are likely to be caused by natural selection.

The book is as much an explication of a specific style of scientific thinking as it is a book on adaptation, the origin of life, and ontogeny. The style of thinking can be characterized by the assumption that there are deep and simple conceptual structures that will allow us to understand life and not merely describe it. Further, it seeks meaningful abstractions for building models and replaces details we do not know and are unlikely to know soon with random processes. An example is the *NK* model of molecular evolution or Kauffman's ensemble model of gene-regulatory networks. These ensembles are used to predict what features self-organization might come up with. The predictions are then tested against data. If the observations are compatible with the ensemble distribution, then selection is not a necessary part of the explanation. Finally, organic wholeness is thought to be modeled in terms of closed networks of interactions among abstract objects.

Successful science depends as much on an adequate style of thinking as it does on adequate experimental and observational methods. As attractive as Kauffman's thinking style is to the reviewer, a rational decision about its heuristic value will only be reached in retrospect. In the interim it must be said that the book is certainly not one that is enjoyable to read from the first to the last page. Actually it seems not to be intended for that. It very much invites discontinuous reading by providing an overview at the beginning and a summary at the end of each chapter. It further is highly redundant in many arguments, ensuring that the important message is not missed by selective readers. Finally, another warning is appropriate. The book is to be read as an approximate map of a vast and largely unexplored territory. As such it almost certainly contains errors, simply because nobody has yet covered this vast range of scientific inquiry with the rigorous tools of analytical proof and experimental test. Experts from neighboring disciplines will be able to correct some of the errors immediately, but for other parts of Kauffman's outline we will need much work to attain the rigor necessary for science to continue to advance.

In his first chapter Kauffman notes that "new conceptual systems such as Darwin's theory emerge as intellectual wholes" (p. 6). It might be added that the intellectual power of Darwinism is enhanced by the unitary character of its central idea, natural selection. It is in recognition of that that Kauffman is searching vigorously for concepts of similar intellectual power for the science of self-organization. He has identified several candidates—the edge of chaos, the complexity catastrophe, the topology of combinatorial spaces, and self-maintaining organizations in random grammars. If his project is to be successful this is the way to go. But suggestive as many of his proposals are, it is not clear whether they are just facets of a deeper principle yet to be discovered or what their actual range of legitimate applications and their explanatory potential are. For instance, the dynamical properties of systems at the edge of chaos, as expounded by Christopher Langton, are an important discovery, but how can we ensure that this concept does not degenerate to an empty metaphor for everything that exists somewhere between two extremes? It is not that Kauffman does not see the difference between an empty metaphor and a scientifically valid concept. The question is rather how to recognize it in practice. I hope that Kauffman's book will be a strong stimulus for many scientists to search actively for the principles that govern the organization of living states of matter.

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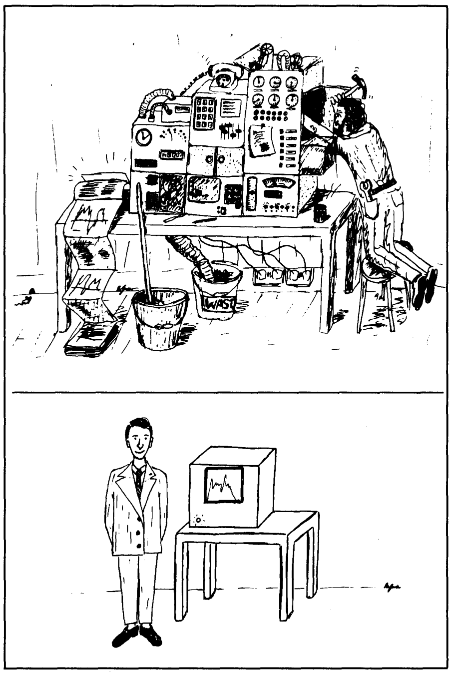
Cell Measurement

Flow Cytometry. First Principles. ALICE LONGOBARDI GIVAN. Wiley-Liss, New York, 1992. xiv, 202 pp., illus. Paper, $34.95.

A flow cytometer measures physical and chemical characteristics of single cells or organelles passing through the apparatus in a fluid stream. On the basis of measurements of light scattering and of the fluorescence of labeled antibodies and other dyes, subpopulations of cells in mixed populations can be identified, counted, subjected to quantitative analysis, and physically separated (sorted) for further study.

Flow cytometers perform the T lymphocyte counts used to monitor the course and treatment of HIV infection and have also been used to isolate human chromosomes for the construction of genetic libraries, to separate X- and Y-chromosome–bearing sperm, to identify the elusive hematopoietic stem cell, to count single virions and large molecules, and to reveal at least one widely distributed but previously unknown genus of marine microorganisms.

The first commercial flow cytometer capable of fluorescence measurements appeared in 1970. The first book on flow cytometry appeared in 1980; a thousand copies were sold. There are now approximately 7000 instruments worldwide, and they help generate seven of every thousand new biomedical publications. The instruments themselves have evolved from temperamental behemoths, now, like the dinosaurs, on view at the Smithsonian, to user-friendly benchtop systems employing personal computers for data acquisition and analysis. The user-friendly instruments, however, demand an increasingly sophisticated diet of cell samples stained with three or four different fluorescent reagents, and their associated computer monitors yield multicolored displays resembling five-dimensional Rorschach tests and only slightly more susceptible to intuitive objective interpretation.



"Two opposing fantasies of what flow cytometry is all about." [From *Flow Cytometry*; drawings by Ben Givan]

Although there are now a dozen or so books on various aspects of flow cytometry, Alice Givan's is the only one written for the beginner; Givan leads the novice into a field in which "computer buffs, electronics experts, mathematicians, laser technologists, and organic chemists rub shoulders with biologists, physicians, and surgeons around the bench." In a chatty, matter-of-fact style, the author introduces the instruments and their history, the physical and chemical principles involved in the optical measurements made in flow cytometers, and the methods of data analysis used in the most common applications—characterization of mixed cell populations using fluorescently labeled monoclonal antibodies and analysis of the cell cycle based on measurements of DNA content. She then takes up the uses of flow cytometry in clinical hematology, immunology, and oncology and discusses chromosome sorting and other applications to molecular biology. The last two chapters treat newer areas of interest, including flow-cytometric methods for kinetic measurement of physiologic characteristics such as cytoplasmic calcium ion concentration and for characterization of bacteria and phytoplankton. Many well-chosen illustrations, most of which are taken from the current literature, supplement the text. The book concludes with a brief list of general references and a longer, thoughtfully written glossary.

No book on a field in flux can provide more than a snapshot; *Flow Cytometry: First Principles* does as good a job as any book could in portraying the sense and the direction of motion of the discipline. In the preface Givan states: "I have tried to describe the theory of flow cytometry in a way that also provides a firm (and accurate) foundation for those few who will want to study the technique in greater depth." Writing clearly, and with obvious wit and enthusiasm, she has succeeded.

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Chemistry of the Cosmos

Elements and the Cosmos. MIKE G. EDMUNDS and ROBERTO TERLEVICH, Eds. Cambridge University Press, New York, 1992. xiv, 332 pp., illus. $59.95. From a conference, Cambridge, U.K., July 1990.

Bernard Pagel, the honoree of these proceedings of the 31st Herstmonceux Conference, is an irrefutable argument against general policies of compulsory retirement. After reaching the statutory maximum age for a British civil servant at Royal Greenwich Observatory, where he was a recognized expert on the abundances of the elements in different kinds of stars, he became professor of astrophysics at the Nordic Institute for Theoretical Physics in Copenhagen and is now considered the foremost authority on the amount of helium left from the Big Bang. Somewhere, a farsighted institution undoubtedly awaits the Danish witching hour and further developments in Pagel's interests.

The subject of the book, nucleosynthesis and galactic chemical evolution, is a many-faceted one, requiring an understanding of nearly all of astronomy and significant chunks of chemistry and physics as well. The goal is to