

Towards a Theoretical Biology

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Two symposia on theoretical biology were held in 1966 and 1967 at the instigation of the International Union of Biological Sciences. The meetings were organized by Professor Waddington, and in this article he outlines some of the points discussed at the meetings. The essays arising from the first symposium have recently been published under the title *Towards a Theoretical Biology*.

THEORETICAL physics is a well recognized discipline, and there are departments and professorships devoted to the subject in many universities. Moreover, it is widely accepted that theories of the nature of the physical universe have profound consequences for problems of general philosophy. In contrast to this situation, theoretical biology can hardly be said to exist as an academic discipline. There is even little agreement as to what topics it should deal with, or in what manner it should proceed.

The International Union of Biological Sciences has felt that it is its duty, as the central focus of international organizations of all the branches of biology, to explore the possibility of formulating some skeleton of concepts and methods around which theoretical biology can grow. It was clear that the task would not be easy; and it was therefore arranged that a series of three symposia should be held at yearly intervals. The intention was that the discussions would be concerned, not with the theory of particular biological processes, such as membrane permeability, genetics, neural activity, and so on, but rather with an attempt to discover and formulate general concepts and logical relations characteristic of living as contrasted with inorganic systems; and further, with a consideration of any implications these might have for general philosophy. I was asked to invite suitable speakers and to organize the meetings.

Two symposia have so far been held, in 1966 and 1967, both at the Villa Serbelloni, Bellagio, Lake Como, at the kind invitation of the Rockefeller Foundation. Essays arising from the first meeting have been published under the title *Towards a Theoretical Biology—I. Prologomena* (Edinburgh University Press and the Aldine Press, Chicago). The volume arising from the second meeting will appear during the summer.

In an introductory precirculated paper I pointed out that at the beginning of this century it was usually considered that the most characteristic feature of life is its metabolism. "The constant synthesis, then, of specific material from simple compounds of a non-specific character is the chief feature by which living matter differs from non-living matter", was the way it was expressed by Jacques Loeb in 1916. At that time, there was a good deal of discussion about whether living systems presented us with real or only apparent and local exceptions to the Second Law of Thermodynamics.

About 40 years ago, however, it began to be realized that such views gave insufficient attention to the overwhelmingly important phenomenon of evolution and the increase in complexity of living things. The view gradually gained ground, particularly under the urging of H. J. Muller, that the essential feature of life resides in its possession of a hereditary system capable of mutation, and thus of being affected by the process of natural selection. The orthodox view became, and in many quarters perhaps still remains, that the basic elements of life are the genes as units of information. I argued that the older view should not be completely abandoned. One can find examples of mutable hereditary information in extremely simple systems that no one would consider alive. Two examples were fairly thoroughly discussed; irregularities in the crystal lattices of complex materials such as clays

by Cairns Smith, and tactic copolymers by Pattee. The reason why one is not tempted to apply the word living to the product of such processes is, I claimed, that they are not even potentially interesting enough; they do not, that is to say, suffice to provide any way in which one can hope to comprehend the complexity and elaboration which living systems are so obviously capable of producing. The reduction of the biological system to mutable hereditary information therefore leaves out a feature which is essential for any theory which is to be applicable to biology as a whole. We need a hereditary system which does not merely contain information, but which acts as algorithms or programmes and thus leads to the production of a phenotype which takes its place between the genotype and the environment. It is the phenotype which acts on the environment (for example, in metabolism) and it is on phenotypes that the environment exerts its natural selective forces.

The fact that phenotypes are essential features of biological systems, which cannot be omitted from any general theory, and the consequential implication that information theory is inadequate for biology and needs to be replaced by a theory of algorithms or programmes, was emphasized by several other speakers approaching the matter from different, and in many cases more formally mathematical or physical, points of view. Thus Michie and Longuet-Higgins, discussing biological replication in terms of computer programming, emphasized the practical necessity of segregating the programme and the operating machinery of the computer, which corresponds in biological terms to the separation of genome and phenotype. As Pattee remarked, the logic of this necessity has been discussed by von Neumann in *Theory of Self Reproducing Automata* (University of Illinois Press, 1966). Pattee put the same point in another way when he emphasized that an effective hereditary system requires both a memory store, which must be constructed of rather inactive materials if it is to be stable enough and a mechanism not only for being replicated but also for affecting its surroundings. Whether it is theoretically possible to conceive of a substance which is sufficiently unreactive to be an efficient store and also sufficiently reactive to affect the environment is perhaps debatable. In practice, however, it is clear that living things on this Earth have not discovered such a material. They have in general settled on the rather unreactive DNA as the memory store and on RNA and proteins to decode this into enzymes which participate both in the replication of the store and in interactions with the environment.

Following this line of thought, Pattee raised a question from the point of view of quantum mechanics, which seemed perhaps rather recondite to many of the biologists present. The stability of the algorithms stored in DNA is ensured by quantum mechanical processes which define the configuration of single DNA molecules. Their replication and decoding depend on the actions of enzymes, such as the polymerases, which ensure that the bases in a single strand of DNA are paired up correctly with the complementary bases to form the second strand or the corresponding RNA. The existence of such enzymes cannot, he claims, be deduced from the fundamental laws of physics. They are acting as "non-holonomic"

constraints to limit the degrees of freedom of the whole system. Their origin at some very early stage of evolution is one of the major problems. Moreover, the stability of the algorithms stored in DNA is ensured by quantum mechanical processes, but the polymerases decode this into quantities of proteins and other cell constituents sufficiently large to operate according to the laws of classical physics. We are confronted therefore with an example of a "quantum measurement", a matter which seems to cause theoretical physicists many headaches.

The essential dependence of a hereditary system on the existence of non-holonomic constraints on the degrees of freedom is one example of a class of problems which appeared in several different guises during the discussions. A non-holonomic constraint may be regarded as a part of a physical system which has a very long relaxation time in comparison with the remainder of the system (as the polymerase molecules persist for a much longer time than it takes them to perform one base pairing). Bastin, considering the nature of the concept of a hierarchy of levels of organization, which plays such an important part in biology, argued that the only logical way in which it is possible to discriminate a number of activities into a hierarchy is by considering their reaction times, a higher level in the hierarchy always having a much longer reaction time than a level classified as lower. Again, Bohm discussed the concept of order as basic both to quantum mechanics and to fundamental biology, and argued that a hierarchical order or orders must eventually imply the existence of a "timeless order", thus emphasizing the importance of gross differences in reaction time.

On a more down to earth biological level I have often emphasized that no conceptualization of a living system is adequate unless it includes at least four importantly different time scales, those of metabolism, development, heredity and evolution. In those parts of the discussion more concerned with biology than the deeper philosophical questions of quantum theory and the like, all these four levels came in for some consideration. The processes of metabolism were considered mainly in their more fundamental aspects, that is to say, in connexion with the synthesis of new compounds, particularly proteins. The discussions started from the two basic points; that even the simplest living systems are exceedingly complex, so that many synthetic processes are proceeding simultaneously; and that each of these processes is subject to control mechanisms, often of the type loosely referred to as negative feedback. One of the major methods used in the physical sciences for the handling of complex systems is statistical mechanics. At the second symposium in particular, there was an extended discussion of the applications of statistical mechanics to a variety of biological problems, not all at the level of metabolism. Kerner was one of the first to discover a way of handling the non-linear Volterra equations, which were originally formulated in connexion with competition between species in ecology, in such a way as to make them amenable to statistical mechanical techniques. Goodwin showed that the same equations can be applied to metabolic synthetic systems involving feed-back, and discussed at length the oscillatory behaviour to be expected in cells on this basis (see his book, *Temporal Organisation in Cells*, Academic Press, 1964). This is one of the fields in which mathematical theory has led to a considerable amount of experimentation, which has on the whole confirmed the theoretical predictions. Cowan has applied a similar mathematical treatment to complex neural networks, while Ibbert has studied a whole spectrum of oscillatory physiological phenomena, with periods varying from a few seconds to several days, presumably arising from control systems with a similar mathematical structure.

In the field of development or epigenesis the last two decades have again seen great changes in the general tenor of biological theory. Up till about the mid-thirties the emphasis was on the differentiation of the cells of

higher organisms. There was little realization among embryologists of the enormous complexities of such objects, as revealed by genetics. The focus of attention was on the cell as a unified entity, and its differentiation was considered in terms of such vaguely formulated concepts as "potentiality", "organizers", and the like. In recent times attention has shifted to the other end of the spectrum of possible types of theory. Any writer of today about the general principles of differentiation will almost inevitably begin (and very often end) with the Jacob-Monod repressor-operon story of the control of the action of a single gene (or small group of genes) in prokaryotic organisms in the chromosomes of which the DNA is not usually complexed with protein. This is, of course, to trace the alphabet of possible control mechanisms in cell differentiation no further than from *A* to perhaps *C*; but it does certainly provide a line of approach to the much more sophisticated mechanisms which we must expect to find in more highly evolved organisms in which the DNA is normally combined with protein, and in which, the evidence suggests, at least at a crude level, the control is exerted on quite large batteries of genes rather than on single ones.

On the other hand, there is a real intellectual task to be carried out by theoretical biologists in formulating a scheme of thought adequate for discussion of the global epigenetic properties of entities as complex as higher organism cells. The distinctions between a nerve cell, a muscle cell and a liver cell must involve differences in the activities of a large number of genes (at least several hundred, possibly an order of magnitude more). The facts that in normal development only a limited number of different cell types put in an appearance, and that each of them shows some power of "regulation" or resistance to disturbing effects of the environment, indicate that we are dealing with a number of domains of phase space, each containing a vector field dominated by a particular attractor. In the context of development we have to think of these attractors as extended in the time dimension. The fact that the vector fields converge on to the attractors gives rise to a process of "homeorhesis", which can be contrasted with the more conventional idea of homeostasis in which the vector fields converge on to a static point which is not time-extended. I have proposed the name "chreod" for such a multidimensional domain which contains a vector field converging on to a time-extended attractor.

This notion was developed in a way which was both more generalized and more precisely formulated by the French topologist, Rene Thom. He pointed out that the concept can be used over a much wider field than that of embryonic development; for example, the field of the shades of meaning of a word can be regarded as a chreod dominated by the attractor which is its "concise dictionary" meaning. Again, at the second meeting Richard Gregory discussed a theory of perception under the provocative title "How so little information controls so much behaviour". His answer was, roughly, that a small amount of information arriving through the sense organs activates "pre-existing" models in the brain—which can be otherwise expressed by saying that the incoming information falls within the domain of a certain chreod and thus converges on to its attractor.

The main feature of the discussions in this area, however, was an analysis by Thom of the "catastrophes" at which the organization controlling one domain breaks down and the system becomes switched into one or more alternatives. Physical examples are a shock wave, a liquid jet breaking up into drops, a wave breaking. He claims to have shown that in real four dimensional space there are only seven possible types of elementary catastrophe.

Evolution was perhaps the most central theme throughout the whole discussions. Many physicists seem ready to concede that the principle of natural selection imparts to the biological world a type of logical structure, which

they scarcely meet in their own field of interest. Biologists, however, while gratified to be told that physicists admit that biology offers problems which actually need thinking about, still remain doubtful whether physicists have realized just how challenging these problems really are. The most precisely formulated statements of evolutionary theory are enshrined in the mathematical theories of Haldane, Fisher and Wright. The equations which these authors put down in the years around 1930 have, of course, been greatly expanded and developed since then. The basic abstractions or simplifications of reality, however, which they used to enable them to cast the problem into a particular set of differential equations still underlie and limit all the more recent developments. Very few physicists and not many more biologists realize just how limiting these simplifications are. For reasons which it would be invidious to go into in any historical detail, Neo-Darwinism has become an established orthodoxy, any criticism of which is regarded as little less than *lèse-majesté*.

I made the point, however, that mathematical Neo-Darwinism attaches coefficients of selection to genotypes, whereas actually natural selection impinges in the first place on phenotypes. For theoretical Neo-Darwinism, evolutionary effectiveness is reduced to a one dimensional array of fitnesses, fitness being defined as the probability of leaving offspring in the next generation. I argued that in order to get back from this array of fitnesses to genotypes you have to take the following logical steps: (1) accept that there is some validity in averaging, or otherwise compounding, the fitnesses of various phenotypes over the whole range of environments which the population may encounter; (2) from each fitness value you have to make a one-to-many mapping into a space of phenotypes; (3) from each phenotype you have to map back to a genotype, passing through a space of "epigenetic operators" which is not wholly constituted by the active genes, but in which environmental influences may act as programme modifiers (thus again the mapping is not essentially one-to-one). One has, then, the converse of Gregory's situation "How does so little information control so much behaviour?", namely, "What effect does so much behaviour have on so little information?"

The Neo-Darwinist mathematical formulations were acceptable a third of a century ago when the chief point at issue was whether Mendelism could rescue Darwinian natural selection from the doldrums into which it had fallen. They are patently inadequate, however, in connexion with the much deeper ecological and population genetical knowledge which we possess today.

To define fitness as the ability to leave offspring in the next generation, in an environment treated as static if

not uniform, is both unrealistic and so limiting as to be intellectually boring. What if year $n+1$ or even $n+X$ brings a new predator, a new parasite, a new virus or a new ice age? Evolution is really about the ability to cope with futures which cannot be entirely known but may not be wholly unforecastable. Evolutionary theory has to be bold enough to face up to the intellectually challenging problems of "the strategy of the genes" (I wrote a book of the same name, Allen and Unwin, 1957). In what circumstances does it pay off in long term survival of the species to operate like the mouse, which concedes to the difference between living in a tropical environment or in a cold storage depot no more than a fractional increase in the length of its tail in the former and in thickness of its coat in the latter? And, anyhow, how does a species fix it that natural selection brings this situation to reality? Or, alternatively, when is it a "good thing" to be as developmentally flexible as *Artemia* and other Crustacea, which allow their development to be modified by the immediate environment to the extent that the population of almost every ephemeral pond can be recognized as distinct? When, and how, does an evolving species develop a blunderbuss defence mechanism against a whole category of threats that cannot be specified in advance—as the higher vertebrates have done in evolving an antibody producing mechanism? When, again, is it the best line to evolve a mechanism which allows you to avoid a nasty selective threat by either moving elsewhere (as some fish must have done when they colonized the extremely uninviting environment of the oceanic abysses) or by changing your behaviour and food habits (as London sparrows must have done when the streets were taken over by pollution-producing automobiles, instead of horses with all those delicious seeds in their dung).

The discussion of questions like these brings one face to face with problems which offer as much intellectual challenge as quantum indeterminacy or Bohr's complementarity. Theorists in general science have staked out claims for a variety of fields in this area—games theory, decision theory, systems theory, and the like. It is not clear to the biologists wrestling with actual situations that many of these "disciplines" amount to anything more than the formulation of a lot of problems for which no solutions can be provided; there seems to be a singular dearth of actually proved theorems which the biologists can take over and employ. Possibly the people who are trying to discover how to set up a computer to learn to play good chess, or bridge, are among those most likely to make a major contribution to the fundamental theory of evolution.

Upper Miocene Primates from Kenya

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Specimens of *Kenyapithecus wickeri* representing the family Hominidae have already been described from the Upper Miocene site at Fort Ternan, Kenya. The site has also yielded fossil remains of a member of the Hylobatidae resembling *Limnopithecus*; teeth of a primate closely resembling *Oreopithecus*; teeth of a species of *Proconsul*; part of a jaw which suggests the genus *Dryopithecus* and some teeth of the family Cercopithecoidea.

THE importance of the discovery of *Kenyapithecus wickeri* at Fort Ternan^{1,2} attracted much attention, but so far, only passing reference has been made to the fact that the same site has yielded evidence of a number of other contemporary primates^{3,4}. I wish to rectify this position and

record information about the presence of other primate material from this site.

Hylobatidae c.f. *Limnopithecus*

Parts of two mandibles, as well as a number of isolated