Cambridge University Press
0521306914 - Kinetic Theory of Living Pattern
Lionel G. Harrison
Excerpt
More information

PART I

Macroscopics without mathematics

> Pour demeurer symétrique et beau, un corps doit se modifier tout entier à la fois. . . .
> [To remain symmetrical and elegant, a body must modify itself all together at the same time. . . .]
>
> —Pierre Teilhard de Chardin, *Le Phénomène Humain* (1955)

For Part I, this quotation is the first axiom of macroscopics. But it could also have been used as epigraph to Chapter 5, which seeks to suggest that the statement may not be an axiom. The existence of overall control may be observable if the smoothed symmetry of the whole is superior to statistical expectation based on the disorder of the parts.

1

Introduction

1.1 Philosophy: lumping, splitting, abstraction, and reality

D'Arcy Thompson (1917) wrote that "the *things* which we see in the cell are less important than the *actions* which we recognize in the cell." He expected that in the following few decades biology would advance in the direction of mathematical description of actions or processes. He, and most others at the time, believed that microscopy had reached the limits of its capacity to reveal microstructure, and few people believed that determination of the structure of genes was foreseeable. In the event, as everyone knows, developments that were not foreseen have made up a great part of the most spectacular advances in science over the past forty years. Meanwhile, those advances which Thompson anticipated have not occurred – to such an extent that Bonner (1961) omitted from his abridgement of Thompson's *On Growth and Form* the entire chapter containing the foregoing quotation. Was Thompson wrong?

My thesis is that Thompson erred only in regard to his expectation of the timing of an advance which would unite mathematical-physical science to biology in the same way that physics and chemistry had become united in the late nineteenth and early twentieth centuries. That unfulfilled union must take place, to my mind, in the twenty-first century if many of the problems of developmental biology, which today remain as mysterious to us as they were a hundred years ago, are ever to be solved. I cannot conceive of solutions excluding the extensive use of mathematical-physical science, and I see such approaches as being entirely complementary to the existing molecular biology and in no way antagonistic to it.

This thesis has two parts: first, that developmental biology is now at a different stage of the scientific method than are most other branches of science and needs different attitudes; second, that to establish the nature of a process can be as solid a scientific objective as to discover the nature of a concrete object, such as a molecule. Sections 1.1.1 and 1.1.2 respectively address these topics.

Neither of these statements finds ready acceptance among the generality of experimental developmental biologists today. Quite often, physical scientists attribute this to a reluctance among biologists to adopt mathematical language; and, over many decades, some biologists have from time to time vehemently rejected mathematical explanations. But this is not, I believe, the main problem. Scientists (like most other people) will do what they find necessary to reach a highly desired objective, even if this involves activities which are difficult, time-consuming, and not what they had expected to be doing. They must be convinced, however, that an unexpected line of approach is necessary.

Mathematics is not essentially different from verbal explanation. Mathematical reasoning is simply the continuation of verbal logic by other means, when the complexity of the logic makes its expression in words cumbersome and obscure. (For instance, puzzles of the following kind are designed to exploit the equivalence between trivially simple algebra and quite obscure verbiage: “Bill is twice as old as Joe was when Bill was ten years older than Joe is now; and Bill was thirteen years old when Joe was born. How old is Bill?”) Occasionally, a view is put forward that mathematical reasoning is qualitatively different from verbal explanation and probably irrelevant to biology. I cannot argue against that viewpoint, because I have never even begun to understand it. The essential equivalence of mathematical logic and verbal logic is to me an axiom, a credo. My book can cater to readers who are not fluent in mathematical languages, but it can do nothing for definite unbelievers in this credo. All the words lead toward the equations, and the words are really useful only to people who are going to follow them that far.

If, then, the philosophical chasm between experimentalist and theoretician is not just a question of words versus equations as explanations, what is it?

1.1.1 Lumping and splitting

As a physical scientist, I was brought up to believe that the ultimate objective of science is unifying – that science is a climb toward some minute and distant shining summit which might turn out to be the one equation that describes everything. That objective may be far off, but those who have that basic attitude tend to feel that they have made a step upward whenever they find some common principle definitely or possibly present in two sets of phenomena which up to that point had appeared quite different. Thus, on my first encounter with the problem of morphogenesis, I became quite excited at the idea that something fundamental to it might be the same as something equally fundamental to the problem of optical resolution. In my writing on the latter problem, I pointed out that at the very earliest stages of biochemical evolution, an autocatalysis requiring the assistance of two product molecules was hardly distinguishable from sexual reproduction, and I indicated a number of other correspondences between processes which become quite different at later, more complex stages of organization.

Closer interaction with biologists over the next few years impressed upon me that many of them do not recite this unifying credo of the physicist’s

Cambridge University Press
0521306914 - Kinetic Theory of Living Pattern
Lionel G. Harrison
Excerpt
More information

beliefs. Indeed, a referee commenting on one of my manuscripts wrote that several mechanisms might be mathematically similar, but that biologists would consider them different. The clear implication was that I had better do the latter if I wanted to publish in biological journals. Much more recently, a referee of another manuscript wrote that "I don't think the weaknesses of the paper lie in the mathematical aspects, but rather in the failure of the authors to appreciate how divorced their abstract entities are from the real entities which govern early body patterning." (This comment at least makes it clear that the use of mathematics is not the matter at issue.)

There are, of course, excellent reasons for this tendency of biologists to concentrate upon the analytical aspect of science as against the synthetic. One of the most striking features of life is its diversity, and the precise description of that is a sine qua non of biological science, a task great enough to command the total attention of large numbers of people. Yet it would be an insult to biology to suggest that it does not get beyond the first step of the scientific methods, the gathering of facts. Science has as its essential attribute the continual reworking of facts through all the steps of the scientific methods. And in that method, fact and theory are by no means as clearly separable as they are represented in elementary statements of the scientific method. Today's experimental results are commonly set down in the language of yesterday's theories, which would have been unintelligible a few years or decades earlier.

Within all the rigour of a definition of science as intellectual process, modern molecularly based biology is fully a science, and a rapidly advancing one. But the bias of its practitioners is analytical, and strongly so. They are splitters, not lumpers. (These succinct equivalents for analytically and synthetically minded scientists are well known in the conversation of physicists.) Surely, however, any complete scientist needs to give some attention to both lumping and splitting? The balance here is a matter of historical timing. In a field which seems just now to have all the unifying concepts it needs, there is room for the work of a multitude of splitters who want to give very little of their attention to lumping. For molecularly based biology, the general concepts of the structures of nucleic acids and proteins, as well as the nature of the genetic code and its transcription and translation, are thoroughly established and universally accepted. Secure in these generalities, the modern biochemical biologist can devote a lifetime to ferreting out what particular proteins or genes are responsible for a few particular phenomena within a single species of organism.

By contrast, developmental biology, concerned with the macroscopic organization of the organism, stands across a gulf from molecular biology, a gulf which structural concepts have been unable to bridge. Apparently the unifying concepts have not yet been found; if they are already in the literature, they have not yet achieved that consensus of recognition which is the foundation on which many splitters base their work. The lumping is needed first.

Cambridge University Press
0521306914 - Kinetic Theory of Living Pattern
Lionel G. Harrison
Excerpt
More information

That noted champion of unpopular theories, the astronomer F. Hoyle, has remarked that when a problem remains unsolved, general opinion must be wrong. This, to my mind, expresses an important philosophic truth very relevant to the present state of developmental biology. Yet the neatly epigrammatic form of Hoyle's statement runs some risk of showing that brevity is the soul of unmannerliness. It is not my objective to suggest that the philosophic approaches of molecular biology are wrong. They are obviously right for the field, and have led to great triumphs of scientific discovery. I wish to assert merely that development is a different field and needs some *additional* approaches, which are likely to be radically different from (but in the end complementary to) the current microstructural emphasis.

The only opinion which I would call *wrong* would be one which denies that there is, in biological development, a Great Unknown, and therefore a new concept or set of concepts to be established. Surely it is evident that in living pattern and form, nature has provocatively concealed some essential underlying simplicity in an excess of ornament. There is no lack of diverse and fascinating experimental data. Yet phenomena which were meticulously described by embryologists of the 1880s remain, a century later, without generally accepted theoretical explanation – which cannot be said of atomic spectroscopy, Mendelian genetics, or a host of other century-old experimental topics.

1.1.2 Abstraction **is** *reality*

A few years ago, on giving a seminar in a series entitled "Simulation and Modelling in Science," I remarked to the organizer that the title was wrong. It should have been "simulation and modelling *is* science." The comment delighted him, but many scientists would not, I think, be equally pleased. The words "simulation" and "modelling" can be interpreted as having something of a pejorative cast, throwing doubt on their relation to reality. But when I first heard of the scientific method, neither of these words was being used at all in relation to it. Surely both are to be seen as parts of theory, the means by which science seeks to express a vision of the truth or of reality, whichever word one happens to prefer?

By the same token, the scientific enterprise could also be defined as an effort to take experimental facts and extract from them increasingly close approximations to truth by a process of abstraction. This implies, of course, that I deny totally the distinction between "abstract entities" and "real entities" in the quotation in Section 1.1.1.

The problem here is, I think, that sometimes a group of scientists will become preoccupied with the virtues of one particular kind of model, which they have found to be powerful, to such an extent that they come to regard this model as more "real" than the models used in branches of science less familiar to them. In more than one branch of science today the molecule has acquired such an exalted status. To be sure, the molecule is one of our best models, but it is in no sense an ultimate truth. For the purposes of the biologist and biochemist, a molecule often may be viewed in very concrete terms, as a geometrical object of definite size and shape. But to the chemical physicist, the reality of a molecule is that it is a solution of the Schrödinger equation. Many of its properties cannot be understood at all in classical terms, and the quantum-mechanical equations describing the molecule compose an altogether higher and more powerful model of reality than the concrete geometry.

One of my colleagues in chemical physics gave a seminar in which he was most adamant that he was a pure experimentalist; he sounded as though he might not even like theoreticians. He then proceeded to present some data in the form of drawings of molecular orbitals, not in ordinary space but in momentum space. To most experimental biologists, such a presentation would seem to belong to one of the most distant reaches of theoretical abstraction. What one sees as an abstract model, and what one selects as the concise language for immediate presentation and discussion of one's experimental data, will depend upon one's preconceptions or paradigms.

What, then, is the kind of "abstract explanation" which I am advocating that we adopt and regard as a down-to-earth description of the "real entities" of developmental pattern formation? When I described to a biochemist some results showing quantitative control of a morphogenetic feature of *Acetabularia* by some unknown bound state of calcium, he remarked that "it's going to be difficult to find out what is doing it." This is a problem which confronts most biologists most of the time: to find out what is doing it. I invite my readers to take a moment to formulate a conception of the kind of solution each is usually expecting; I anticipate that most modern biologists, for a very wide variety of problems, will most commonly be expecting that the nature and structure of a particular protein will turn out to be "what is doing it." For my part, I would usually be looking for a *process,* and I would be happy if I could measure kinetic rate constants, or diffusivities, or elastic constants, or conductivities, and show that they were attributes of that process, without necessarily knowing what molecules might be involved. I would hope that these things would eventually give some pointers to the biochemists as to where some kinds of molecules may be found, but only over a long time scale.

More recently I have found spatial patterns of bound calcium which correspond to my concept of a two-stage hierarchical process. I consider that to be a scientific step forward toward establishing the nature of the process. But I am not one step nearer to identifying the molecular species to which the calcium is bound, and the molecularly devoted scientist might say that I have made no advance at all.

1.1.3 Macroscopics and the structure of processes

A hundred years ago, the disputes between the positivist philosophers led by Ernst Mach and the advocates of molecular reality led by Ludwig Boltzmann were approaching a climax. Basically, the positivists believed that the supremacy in science of observation of macroscopic phenomena was incompatible with a concept of molecules as real entities – they had to be abstractions. The supporters of Boltzmann believed that macroscopic objects and molecular objects were both real and that the connection between them could be readily made provided that one recognized that connection as being statistical and therefore requiring primarily mathematical discussion. The ultimate victory of this viewpoint was achieved early in the twentieth century, and that provided the philosophical foundation on which twentieth-century science has been built.

Today in biology there is something of a dichotomy between the molecular biologists and those who believe that the whole organism (or large parts of it) should be the principal object of study. This division has something of the flavour of a repetition of that debate of a century ago. What is it going to lead to as a foundation for the biology of the twenty-first century? The hope, of course, must be that macroscopic and microscopic studies will advance so as to complement each other. But, in my opinion, that is very unlikely to happen by simple extension of the structural approaches which have proved so powerful on the molecular scale. In the tripartite division of physicochemical concepts into structure, equilibrium, and kinetics, it is the second and third which I tend to think of as comprising "macroscopics." I define this term (suggested to me by my colleague Dr. R. F. Snider) as "the nature of change, and the organization of matter in states above the molecular." I envisage that the study of macroscopics for the present purpose is going to need, just as it did in Boltzmann's day, statistical and mathematical treatment.

In a preliminary outline for this book I mentioned the word "macroscopics" to Paul Green, the instigator for the writing of the book. His immediate reaction, in slightly edited version, was as follows:

> The issue of "macroscopics" is one I deal with a lot. The puzzle of development can be likened to a multi-span bridge. One terminus is DNA and the other is a developmental progression. The first few islands joined are clear enough: RNA, protein, etc.; and the spans are conversion processes, like transcription and translation. The problem we both address is, "What's between the last island reached (self-assembly) and developmental progression? Most biologists subconsciously think that some "silver bullet" or single protein will clear up everything in one stroke. A hard look at developmental processes, however, shows that one has to account for a myriad of changes over large distances (many cells). The idea of coupling one developmental change to one section of the genome is inadequate because there are far too many developmental events. The solution to this information paradox is that an organism inherits rules that spell out the progression. The rules are, or are like, time-based differential equations which have

the ability to encode complex sequences with high efficiency. Thus one has to regard development as an integration through space and time, the genome providing the equivalent of the differential equations. Thus there is no escaping the calculus when studying development.

The difference here is that the molecular scientist, in seeking the explanation of some large-scale phenomenon, goes ever downward in spatial scale, and usually in time scale also, ending up in nanometres and picoseconds. The macroscopist, if I may so designate a devotee of macroscopics, goes through different levels of explanation, including many different concepts, such as differential equations, force fields, and so forth, but never changes the spatial scale or time scale, considering always the whole extent of the development. An analogy by Lacalli (1973), following J. Needham, concerns the study of a Swiss watch to discover how it functions. One may take the watch apart and examine, list, and diagram the springs, gears, shafts, and so forth, and how they fit together. Yet one does not have a full explanation without the application of equations of motion to the whole. These involve concepts of momentum, moments of inertia, and simple harmonic motion arising from a restoring force proportional to displacement.

If in the light of such a study of one oscillating system one were to set up a team to examine some other oscillating system of unknown contents, one might designate some people to take it apart and describe its parts in ever greater detail, and others to tackle other questions: What is the displacement that produces a restoring force, and what is the origin of that force? To be sure, these two parts of the team should exchange information, and the whole team is needed to produce the whole story. Also, a question of applied science versus pure science arises here. If one wishes to know *how to make* a Swiss watch, the information from the first part of the team will suffice; but if one wants to know *how it works*, the second part of the team is vital, with only a limited amount of the structural information being necessary. This analogy would seem to give the edge to the molecular biologist for practical utility, in conformity with current developments and expected advances in so-called genetic engineering. Yet consider: Suppose that one wishes to *design* an oscillatory system other than those already studied. To which part of the team should one have paid attention?

The relation of the Swiss-watch analogy to Green's comments on biological development cited earlier is that in a biological system we know that the genome decrees the manufacture of a number of enzymes, and thereby specifies the kinetic rate constants for a number of chemical reactions; but one cannot therefrom predict how much of each reaction product is going to be produced at various places in the system until one has written down, and solved, the differential equations containing those rate constants. In the Swiss-watch analogy, the "genome" would specify the force constant of the balance spring and the moment of inertia of the balance wheel. From these, we could get the frequency of oscillation simply by solving equations of motion.

In Part I of this book I have tried to use as few equations as possible. Therefore, the full comparison between the activities of molecular biologists and those of kinetic-theory practitioners will not emerge until Part II, which will get closer to the daily work of the latter group. There it should become apparent that these people can be as much splitters as are the molecule hunters. Equations also have complex details. The theorist will often refer to the "structure" of a dynamical mechanism and will think of the terms in the equations as components of that structure, just as the molecular scientist will think of a carboxyl group as a component of the structure of a molecule. This, of course, obscures my distinction among structure, equilibrium, and kinetics. But I hope it tends to make clear that two groups of scientists may be engaged in essentially parallel enterprises which appear different because the two groups have different perceptions of the "ultimate realities" they are seeking: molecule versus process, matter versus motion.

The structure of processes is taken up again in Section 6.4.3, particularly with regard to the concept of the "structural stability" of equations of motion. For instance, an equation for oscillations which will continue undiminished forever may be converted into one for oscillations which, more realistically for most observed processes, will die away as time goes on. This requires one additional term in the equation, and the immortal oscillations are destroyed by that term; the equation is structurally unstable with respect to that addition, which effectively is a poison for the oscillations. It is, of course, a velocity-dependent term representing viscous resistance (or friction) in the case of mechanical oscillations; in more general terms it would be called a relaxation process, a term well known in magnetic resonance.

Molecularly minded scientists at once want to know the nature of the viscous substance, or the promoter of relaxation. The kineticist would like to know that, but not necessarily now. For complex systems, such as biological material, a magnetic-resonance experiment can establish thoroughly, scientifically, that there are, say, five different relaxation processes for water protons, with a quantitatively measurable relaxation time for each, and clearly characterized changes if one takes the system to pieces or makes other disturbances. All this can constitute years of good publishable science, throughout which the chemical nature of the relaxing species remains a puzzle, probably to be solved much later by someone else.

1.2 Strategies of research

1.2.1 On starting to build a bridge from both ends

In a referee's report on a recent reaction-diffusion paper by T. C. Lacalli, the following comment appeared: ". . . the paper could be published as a demonstration of a strategy for modelling these phenomena. However, at the present pace of inquiry, such models will soon be supplanted by models that relate in

Cambridge University Press
0521306914 - Kinetic Theory of Living Pattern
Lionel G. Harrison
Excerpt
More information

detail to molecular processes." This was a favourable report, but nonetheless this quotation provides another illustration of the conceptual gap in the field. If I may continue Paul Green's metaphor, one cannot supplant one end of a bridge by building the other. They are planted in different ground, and neither will ever occupy the place of the other. But ultimately, one has a bridge when they meet in the middle. The phenomena referred to in this example were those of *Drosophila* segmentation. To be sure, molecular information is being accumulated at a quite astonishing rate. But how the molecules participate in *processes* is an inquiry which is hardly advancing at all. The discoverers of molecules often postulate some processes, but usually with insufficiently rigorous descriptions of their dynamics to permit the essential tests, in the computer, of whether or not the models actually work. Meanwhile, as the referee quoted earlier pointed out, the modellers who are studying dynamics with some scientific rigour usually do not have precise and detailed ideas of which molecules are participating in the processes. There is still a big gap in the middle of the bridge.

Figure 1.1 is my strategic overview, a surveyor's map of the islands to be joined by the bridge. The arrowed lines at top and bottom are the engineering supervisor's notes regarding who is currently doing what in the construction work. They illustrate the contrasting approaches of physicists and biologists. They show also a limitation in the analogy. The two groups building from opposite ends are using quite different materials and ways of joining them together. There is no resolution for this which can completely save the analogy. But it is partly resolved by my discussion in Chapter 4 of developmental control of the shapes of crystals. There I indicate that one should enquire in regard to any shape-generating phenomenon what *aspects* of it fall into each of the three divisions – structure, equilibrium, and kinetics – rather than trying to classify the whole complex phenomenon into one of these categories exclusively. This means that at island 2 (second from left) in Figure 1.1 the builders may discover that though their materials are different, there are ways of fitting them together which make sound engineering to complete the bridge.

1.2.2 Making the join: bridges versus brains

In the language of the bridge-building analogy, there are two problems to be addressed: First, how shall the workers from opposite sides go about making the join in the middle? Second, and not so obvious from the analogy, will they recognize the join when it has been made? On the latter, my experience has been (especially in relation to *Drosophila* segmentation stripes) that when I have become excited about what has seemed to me to be the first girder in place linking the two sides, the value, relevance, and methodology of what I have seen as the linking step have been vehemently denounced by some prominent experimentalists in the field.