The development of the shapes of living organisms and their parts is a field of science in which there are no generally accepted theoretical principles. What form these principles are likely to take, when they emerge, is a subject in which there is a wide gulf of disagreement between physical scientists and experimental biologists.

This book contains both an extensive philosophical commentary on this dichotomy in views and an exposition of the type of theory most favoured by physical scientists. In this theory, living form is a manifestation of the dynamics of chemical change and physical transport or other physics of spatial communication. The reaction-diffusion theory, as initiated by Turing in 1952 and since elaborated by Prigogine and by Gierer and Meinhardt and others, is discussed in detail at a level that requires a good knowledge of a first course in calculus, but no more than that. In some respects this book takes up the theme that "the *things* which we see in the cell are less important than the *actions* which we recognize in the cell," which was a major theme of D'Arcy W. Thompson's classic 1917 work *On Growth and Form*. The rapid growth of the field of molecular biology has tended to overshadow the increase in our understanding of the nature of these kinetic processes. This book seeks to reawaken interest in dynamics in the hope that a better balance between the importance of things and the importance of actions may gradually emerge in the field of biology in the twenty-first century.

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KINETIC THEORY OF LIVING PATTERN

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KINETIC THEORY OF LIVING PATTERN

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To the memory of Joyce and Julian

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Preface

Once upon a time I was a physical chemist working chiefly on the reactivity of sodium chloride with rather simple gases, and never on a complex organism, not even anything with a carbon atom in it. This book is the product of a change of field which started twenty years ago. This Preface must serve both to acknowledge those people who were most important in bringing about that change and to argue the case for the possible utility of a classical physical chemist in biological theory.

In 1971 my colleague Dr. R. E. Pincock gave a seminar on an instance of spontaneous optical resolution which he had discovered: Supercooled liquid 1,1′-binaphthyl in a sealed vial, when induced to crystallize suddenly, usually gave an asymmetric product. In some experiments that product contained more left-handed crystals than right-handed ones; in others, the reverse. He claimed that this was closer to truly spontaneous resolution than was Pasteur's crystallization of sodium ammonium tartrate, in which asymmetry was finally achieved only through the intervention of a biological organism, namely, Pasteur himself sorting the crystals into two piles.

Pincock's report presented two problems: first, the philosophical meaning of "spontaneity." How can asymmetry arise with no apparent antecedent, seeming to defy the precept that asymmetry begets asymmetry? Second, what kind of mechanism can one envisage for this phenomenon? Given this provocation, I published (Harrison, 1973) a speculative kinetic mechanism for the origin of chiral asymmetry in biochemical evolution. This invoked the cooperation of two molecules in autocatalytic formation of the same molecular species, and I proposed a territorial separation of systems of opposite chirality as an intermediate stage.

In 1973, I acted as chairman for the final oral examination of T. C. Lacalli for his Ph.D. degree. His thesis, "Morphogenesis in *Micrasterias*" (Lacalli, 1973), and more particularly his verbal presentation of it, led me to realize that the kind of kinetic equations I had been using in relation to optical resolution might be relevant to this much more extensive biological field. This led me to acquaint myself with the reaction-diffusion theory of pattern formation, as originated by A. M. Turing in 1952. From a pedagogic viewpoint, it led me also to recognize that the basic concept of kinetic generation of pattern can be more clearly understood in relation to optical resolution than in any other way. Therefore, I invite the beginner in kinetic theory to take my discussions of optical resolution not merely as a matter of personal biography, but as one of the best paths for anyone wishing to approach these concepts. It is the essence of symmetry-breaking.

My debt is enormous to both Pincock and Lacalli. If, on an afternoon in 1971, I had decided that I had something to do other than attend Pincock's seminar, or if in the summer of 1973 I had told the Faculty of Graduate Studies of the University of British Columbia that I had something to do other than to take the chair at an oral in a field of science quite unknown to me, then it is almost certain that I would never have worked in this field, nor written this book. Lacalli and I went on to develop a close collaboration which continues today.

Each of the three great divisions of physical chemistry – equilibrium, kinetics, and structure – is founded on a rock which was cemented firmly in place before I was born (1929): the universally accepted thermodynamics of Kelvin, Clausius, and Gibbs; the kinetics and statistics of Arrhenius and Boltzmann; and the quantum mechanics of Schrödinger and Heisenberg. In developmental biology I found something different, and immensely exciting: a field with a Great Unknown, and no firmly established conceptual basis. To pursue it is like trying to account for the rainbow in the fourteenth century, to do celestial mechanics before Newton, or to pursue quantum theory in the 1890s. There are many ideas around. Some of them are elaborately developed, and some will eventually be recognized as the correct concepts, but none has reached that status yet.

More specifically, the unresolved strategic question is whether the formation of pattern can be adequately described in the language of molecular biology and biochemistry (both of which deal with a spatial scale much tinier than that of pattern) or whether it requires description, in mathematical language, of the dynamics of interactions on a much larger scale. This book is concerned with the latter aspect. To me, it is a "scientific belief" (Polanyi, 1946, 1949) or "preconception" (Crombie, 1959) (see also the epigraph to Part III herein) or "paradigm" (Kuhn, 1962) that pattern formation on the scale of the organism cannot be accounted for without consideration of long-range dynamics. The kinetic preconception is that living pattern is generated by movement away from thermodynamic equilibrium, and therefore is explicable only in terms of rates of processes. It has been my experience that most physical scientists, given the problem of living self-organization, and with no prior knowledge of its theories, will instantly adopt the kinetic preconception, because they see nothing else in all our philosophies that seems suitable to this task. It is difficult to convey to them that most biologists are not envisaging explanations along kinetic lines: "But what else could do it?"

My primary purpose in writing this book is thus of an evangelical sort: to encourage adoption of the kinetic preconception, as a very promising working hypothesis on the strategic scale, among experimental developmental biologists. Why should I bother? Often a paradigm is, for a fairly long time, the preserve of a particular group among scientists, and this one has a good circle of adherents in the physical sciences. I was, however, brought up to accept as a credo that statement of the scientific method in which continuous interaction between theory and experiment is of the essence. That process of science cannot occur if the theoreticians and experimentalists are living in different worlds. The theories then become parts of pure mathematics, unrelated to the science of the physical universe. The experimental data become the dead body of science. A list of facts is as devoid of the intellectual life which constitutes science as a pile of assorted molecules, all in the right places, may be devoid of the life which makes a human being. The essence of both biological life and true science lies in processes and interactions.

This metaphor is not intended to deny the validity of the microstructural preconception nor the validity of the impressive living body of modern molecular biology which has grown out of it. The proper evolution of biological science needs more than one kind of body, with more than one conceptual basis. Essentially, the microstructural preconception or paradigm is that deterministic behaviour can stem from a single DNA molecule and extend in continuous deterministic sequence to larger scales of organization. The kinetic (and also thermodynamic) paradigm is that the single molecule behaves randomly (stochastically) and that deterministic behaviour on the macroscopic scale arises only as a statistical property of very many molecules. Work within this paradigm almost always requires the use of mathematical language in discussing and interpreting experimental results.

Both kinds of behaviour, deterministic-to-deterministic and stochastic-to-deterministic, as one goes from the molecular to the macroscopic scale, are well known from their widespread examples in nature. Surely both must be essential components of the complex sequences of events in biological development. But for the latter type, it is the physical scientist, rather than the biologist or biochemist, who is generally more accustomed to the type of discussion needed. In particular, the *experimental* physical chemist is accustomed to using fairly extensive mathematics in the discussion sections of most experimental publications. To my mind, advances in some large areas of developmental biology will be accelerated when many more experimentalists are using this conventional style of the physical chemist. That is why I presume to enter the field. I am not a theoretician – my theoretician friends keep reminding me of it.

Therefore, although I began moving into this field of pattern formation by doing only theoretical work, I was soon led into doing biological experiments myself. The advantages of using very large single-celled algae as systems for study were first brought to my attention by Lacalli's thesis on *Micrasterias*. This organism had been very carefully chosen in discussions between Lacalli and his supervisor, Dr. A. Acton, and I am grateful to both of them for orienting me toward the Chlorophyta. But in the event, my own experimental work has been on *Acetabularia*. This organism was in culture in the 1970s in the laboratory of Dr. B. R. Green, a plant biochemist whose laboratory in the Botany Department was just across the road from mine. For some years we collaborated on culture maintenance, and my first observations on the morphogenesis of whorls were made in her laboratory. Over an extended period the entire operation was gradually transferred to my own laboratory. I am greatly indebted to Dr. Green for enabling me to become, step by step, at least some sort of approximation to an experimental biologist.

An unrelated scientist with the same remarkably appropriate surname for a botanist, Dr. P. B. Green of Stanford University, has for ten years given me very substantial encouragement in two enterprises: pursuing experiment and theory together, and trying to express the theory in language suitable for the experimental biologist. He is entirely to blame for the existence of this book, which was his suggestion.

What manner of book is this, and what is its intended readership? When people ask me whether I am writing a textbook or a monograph, I am unsure how to answer. The intended readership can be found chiefly among research workers in developmental biology. But the purpose of the book, as discussed earlier, is to lend my weight to that of other practitioners of kinetic theory (reaction-diffusion, or mechanochemical, or other types) in seeking to bring about a "paradigm shift." The expositions of the mathematical material needed for those ready to accept the paradigm and go on from there will necessarily have something of the flavour of a textbook. But I have not sought to repeat the mathematical expositions of the books by H. Meinhardt (1982), L. Edelstein-Keshet (1988), and J. D. Murray (1989). A large part of the content of this book is essentially philosophical commentary on the various approaches to explanation of large-scale phenomena and their relationships to molecular phenomena.

Such considerations lie not within the realm of mathematics, but rather that of physical chemistry. This discipline has for more than a century been concerned primarily with the world immediately around us, a world that is at ordinary temperatures and therefore consists of large numbers of molecules organized into solid, liquid, and gaseous phases. This world includes all living material, and that presents a challenge to the phase approximation because of its content of a multitude of structures intermediate in size between the molecule and the macroscopic phase. Certainly the physicochemical concepts appropriate to this material are still at an embryonic stage, and their full development should give rise to one of the exciting fields of science in the twenty-first century.

There should be a place in this development for physical chemists and physicists, and people in those disciplines are also among my intended readership. Many are indeed interested in the theoretical concepts and already accept the kinetic preconception. But few are actually pursuing the interaction between theory and the experimental phenomena of biological development. The reason for this has to do with a different paradigm. For three hundred years, since Robert Boyle defined elements as "the ultimate limits of chemical analysis," a principal driving force in chemistry has been the simplification of systems by separations and purifications. The chemist likes to handle a system with very few substances present in it at any one time. Notwithstanding the well-known witticism that a physical chemist is someone who makes accurate measurements on impure substances, in fact the physical chemist is just as uncomfortable with an impure system as is any other kind of chemist.

The common denigration of living material as being irreproducible with respect to physical measurements is quite at variance with the definition of life in terms of the property of reproduction. Anyone who, like myself, has done experiments on the catalytic activity of inorganic solid surfaces must be well aware that they can be irreproducible beyond the limits of any trouble that one sees in the catalytic processes that support life. The modern surface chemist usually keeps everything except the one desired reactant away from the surface under investigation by the use of ultra-high vacuum. Anything approaching the multitude of substances present in a living being would quite destroy not only such ideally clean experimental systems but also the operation of industrial catalysts, which have to cope with much dirtier systems.

In living systems, unlike inanimate ones, chemical complexity is not synonymous with dirt. This is because the multitudinous substances of life are not a set of ignorant armies clashing by night, but participants in the most highly organized type of system in our universe. We may seek to study the processes of life one at a time because all the other processes interacting with the one of interest have been self-designed not to interfere, but even to provide assistance. That is the basic meaning of self-organization.

Physical chemistry from the 1920s to the 1950s was largely concerned with the properties of condensed phases, or gases at fairly high molecular concentrations. It has subsequently developed in a number of new directions, but many of them have involved either very clean conditions or sophisticated experimental techniques in which the physics of the technique itself occupies much of the time of the physical chemist. By comparison, remarkably little has been done to extend the conceptual basis of macroscopic organization from simple systems to ones which are complex but have acquired the knack of remaining organized, that is, living material.

Faced with the problem of chemical generation of time-order and space-order, physical chemists may tend to study, instead of life, the few simple inanimate systems which produce periodicities and patterns, such as the Belousov–Zhabotinski reaction (cerium-catalyzed oxidation of malonate by bromate). That particular system generates travelling waves which may have some correspondence to neural and cardiac electrochemical phenomena, but it does not generate the stationary wave patterns which are the essence of morphogenesis. Such patterns were, however, first produced in vitro in 1990 from two chemical reaction systems, and they appear to be in the category of Turing structures. Perhaps this new evidence will help to point physical chemists in the direction I would like to see them go: Study life itself! (For further information on all these chemical systems, see Section 10.3.4.)

The tripartite division (structure, equilibrium, kinetics) which I advocate as the first stage in classifying developmental mechanisms is also a classification of preconceptions or paradigms. Different basic attitudes of mind are needed to envisage the formation of shape as, first, small pieces fitting together to make larger ones; second, pieces aggregating so as to minimize the total free energy; or, third, processes acting kinetically to form shape as it is in a waveform of the surface of flowing water. This last is among a number of nonliving analogues of biological pattern formation shown by Meinhardt (1982). Very few biologists have entered into this third way of thinking. Among those who have encouraged me by doing so and who are not mentioned elsewhere in this Preface I must mention F. M. Harold (1990), J. Frankel (1990a,b), and especially Jay E. Mittenthal, with whom I have had substantial interactions on this topic over a number of years, including his comments to me on an early draft of this book.

I do not want this to be known principally as a "reaction-diffusion book." Although that kind of kinetic theory is quite a broad field – the one which has been most extensively elaborated in regard to pattern formation, and the one which I describe in most detail here – nevertheless reaction-diffusion is still but one example of the triumvirate *activation–inhibition–communication* which collectively has the power to generate pattern ab initio. Other examples are mechanochemical theory, self-electrophoresis, and complex intercellular interactions such as mutual reinforcement of synapses in a self-assembling nervous system. It is the fundamental unity of all these kinds of theories which I most want to convey to the reader under the heading "kinetic theory."

In all my advocacy for this I remain essentially a physical chemist. I must express my gratitude to the Chemistry Department of the University of British Columbia and all my colleagues there, especially the Department Head for many years, Charles A. McDowell, for their tolerance toward (and often definite interest in and material assistance with) my chemically unconventional activities. Also, I am grateful to the Natural Sciences and Engineering Research Council (NSERC), Canada, for continuing financial support of my research through all stages of my switch of fields, in the face of an astounding diversity of referees' opinions. (One set of eleven referees assessing a certain grant application gave numerical box scores on my "originality" and "methodology" ranging all the way from 2/10 to 10/10; such is the range of views on the value of pursuing the kinetic paradigm and on how one should go about it.)

The "field" of a scientist may be classified in three different ways: (1) by experimental method, especially for those devoted to a complex time- and money-consuming machine (e.g., "an NMR imaging group"); (2) by the natural materials and phenomena studied ("a solid-state physicist," "a natural

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products chemist," "an invertebrate embryologist"); and (3) by the conceptual basis of one's thinking ("a physical chemist"). I have changed principally in the second of these three respects, from studies of inorganic gas–solid reactions to studies of living organisms. My biological knowledge, such as it is, has been picked up piecemeal, especially at diverse meetings and seminars, and I am indebted to more people than I can list for bits of my information. In addition to the people already acknowledged in this Preface, I would like to thank Dr. N. Auersperg for organizing many graduate seminars at this university and various symposia at scientific meetings elsewhere, from which I have received much factual knowledge and considerable intellectual stimulation.

Of the three bases for classifying one's "field" listed in the preceding paragraph, the most difficult to change is the conceptual basis of one's thinking. I remain a physical chemist, but, paradoxically, I am trying to influence biologists toward changing to that kind of thinking. To be steadfast in one's own mind-set while expecting other people to change theirs is the characteristic affliction of the evangelist, but some of them succeed!

At one point in a course on plant development which I attended, one of my botanical colleagues enquired, "Shouldn't we be talking about rates?" That query was inadequate to give the rest of the course a kinetic bias. In a multiple-author book on positional controls in plant development edited by Barlow and Carr (1984) the first chapter is by Meinhardt. Presumably the editors asked him to write it because they believed his approach to be important. But a conspicuous feature in comparison with the rest of the book is that although Meinhardt is referenced in several chapters, no one is actually *using* his approach. Likewise, in a recent set of papers on mechanisms of segmentation (French et al., 1988), also containing a Meinhardt contribution, both Meinhardt and Turing are referenced only very sparsely, and again the references do not represent extensive *use* of kinetic concepts by other authors. The most striking contrast remains that between Turing's account of "The Chemical Basis of Morphogenesis," which is entirely kinetic, and Lehninger's (1975) chapter "The Molecular Basis of Morphogenesis," which offers a completely structural account.

Let us now discuss the rates of processes and how they can work to form patterns.