The Shaping of Life

Biological development, how organisms acquire their form, is one of the great frontiers in science. While a vast knowledge of the molecules involved in development has been gained in recent decades, big questions remain on the molecular organization and physics that shape cells, tissues and organisms. Physical scientists and biologists traditionally have very different backgrounds and perspectives, yet some of the fundamental questions in developmental biology will only be answered by combining expertise from a range of disciplines. This book is a personal account of an interdisciplinary approach to studying biological pattern formation. It articulates the power of studying dynamics in development: that, to understand how an organism is made, we must know not only the structure of its molecules; we must also understand how they interact and how fast they do so.

LIONEL G. HARRISON (1929–2008) was Professor Emeritus in the Department of Chemistry, University of British Columbia, where he was a Faculty member for 50 years. A physical chemist by training, he was inspired to study biological form and 'in developmental biology . . . found something different and immensely exciting: a field with a Great Unknown' as he wrote in his 1993 book, *Kinetic Theory of Living Pattern*. 'To pursue it is like trying to account for the rainbow in the 14th century, to do celestial mechanics before Newton, or to pursue quantum theory in the 1890s.'

The Shaping of Life

The Generation of Biological Pattern

LIONEL G. HARRISON
University of British Columbia
(1929–2008)

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Foreword

The Shaping of Life is Lionel's second book, completed shortly before his death in March 2008. It is in part an update of his earlier volume, *Kinetic Theory of Living Pattern* (Cambridge University Press, 1993), following developments in the field and in his own research. Lionel was always an energetic individual, both physically and intellectually, climbing mountains and arguing points of scientific theory with equal determination. Those interested will find a tribute covering salient aspects of his personal and professional life in *The Globe & Mail* for 26 April 2008. He experienced a great loss in the early 1980s with the deaths, within the space of a few weeks, of both his wife and only son. His life afterward was increasingly centred on scientific activities, and he continued with research to retirement and after. This book is a chronicle of his observations and insights during that time, and of the people who influenced him and helped along the way. His proximate goal was to discover how patterns of living things are formed or, to use the title from an earlier draft of this book, 'how life devises its shapes and sizes'. Though it contains considerable experimental detail, the book is addressed to a non-specialist audience, and especially to those interested in how science is done in a field still in embryo, whose mature form is as yet unknown.

Working in an emerging area of science is a challenge and an adventure, and can be terribly exciting. There are, however, definite risks to reputation and career, as the methods may be unconventional or untried, and there is often no clear criterion for what constitutes progress. Cautious academics will avoid such fields until the ground rules are better worked out, and until it is clear that a predictable and, hence, grant-worthy rate of progress can be sustained. Coming from the relatively mature discipline of surface chemistry, Lionel, by contrast, was immensely excited by the prospect of doing research on aspects of biology still at a very early stage of their development. It was, to him, like doing ‘celestial mechanics before Newton’. All things were possible, and even very simple observations might lead to far-reaching insights. Like others in the physical sciences, he was particularly struck by the elephant in the room, one that working biologists are usually loath to acknowledge: that biology today, excepting the great insight of Darwin, is essentially a descriptive science devoid of a set of fully developed principles. Most physical scientists assume this situation is simply temporary, and that biology will proceed along the path already taken by physics and chemistry, from the specific and descriptive to the synthetic and analytical, using, eventually, a mathematical formulation.

What will this ‘new biology’ look like? First, it will need to improve on the vague way we currently deal with the concepts that, so far as we can tell, must lie at the core of biology. ‘Organization’ is one example. ‘Order’ is another, including spatial pattern, but also the ordering of genomic and metabolic networks in living cells, as is ‘differentiation’, the process by which such things change over time. None of these is as yet more than a name attached to a notion, and none are properly defined and measurable. What, for example, are the dimensions (units of measure) of organization, and what precisely is its role in a subsidiary process like pattern formation? To answer this, one needs to be quantitative, so that the amount of the former (organization) that is required for, involved in or used up by the production of the latter (pattern) can be calculated. Only then do the words take on concrete meaning, and only then can the analysis be fruitfully carried forward. Consider, for example, the production of the five-digit human hand from its flattened, paddle-like beginnings: this is generally accepted as a form of differentiation, and the end product does look more ordered, or at least anatomically more complicated, than the beginning. But the cells involved, of cartilage, connective tissue and skin, are still doing pretty much the same jobs, only the locations have changed. So how much ordering has actually occurred, and if this is truly differentiation, is it a trivial amount in quantitative terms, or something worth accounting for in relation to the cost paid in disorder by the rest of the universe? Thermodynamics is the way to deal with such questions, but we as yet have only the most rudimentary beginnings of a thermodynamics applicable to the complexities of living systems. Lacking this, Lionel’s approach, best exemplified in his *Acetabularia* experiments (Chapter 3), was necessarily empirical, and as such, entirely characteristic for a physical chemist: measure patterns and pattern change directly, vary the conditions over which you have control, and analyse the outcome.

Here he came closest to putting meaningful numbers on an otherwise mysterious process, deducing such exotic thermodynamic beasties as ΔH and ΔS from measurements requiring only a dissecting microscope, thermometer and micrometer measuring scale. A complete thermodynamics of living systems is clearly some distance in the future, but of various routes to that future, this is certainly one. Lionel's book is, in this respect, as much an object lesson in scientific methodology as an exploration of pattern in nature.

Lionel's wide-ranging interests within and outside science are evident in his writing, which is liberally supplied with references to literature, historical anecdote and, especially, music. The operas of Wagner were a particular interest, especially where these touched on issues of creativity and intellectual challenge. Two of his favourites: first, Act I of *Die Meistersinger*, which beautifully captures the unavoidable and sometimes comic conflict inherent in any human endeavour, but especially academic ones. On the one side is accepted convention and governance by rules, here represented in the character of Beckmesser. On the other, the need for periodic inspiration and renewal through the intervention of a more gifted practitioner – the headstrong young knight Walther von Stolzing in this case. No prize is offered for guessing how Lionel saw himself in this context. A second favourite was Act I of *Siegfried*, which offers a different sort of confrontation, between Mime, a dwarf, and Wotan, King of the Gods, here in the guise of the one-eyed Wanderer. Mime is obsessed with the task of re-forging the magical sword *Notung*, which, despite his mastery of dwarvish technology, he is unable to do. Wotan knows precisely what is needed, but given the chance to question Wotan, Mime instead wastes the opportunity on set questions for which he already knows the answers. For scientists confronting Nature, and especially those outside the confines of an established discipline, one needs bold questions indeed. Lionel's questions were always as bold as he could make them, and he clearly hoped by example to encourage others to do the same.

Thurston Lacalli
Victoria, May 2009

Acknowledgements

Lionel inspired a great many of us over the years with his energy and brilliance. It is with great pleasure that we are able to present the fruits of his last decade of labour, and hopefully inspire many more with his ideas and questions.

It took the efforts of many friends and colleagues to bring this book to completion. Thurston Lacalli (in addition to writing the Foreword), Michael Lyons and Harold Kasinsky made careful readings and many comments on the text, as Lionel left it in February 2008. Axel Hunding supplied some of the updated references in Chapters 8 and 9. Members of the UBC Chemistry Department have been extremely helpful and supportive – to single out a few, but not exclude the many others: Elliott Burnell, Ed Grant, Elena Polishchuk, Nick Burlinson, Gren Patey, David Walker, Yoshi Koga and Elizabeth Varty, who helped on many of the figures. Thanks go to the Belkin Gallery at UBC and the Shadbolt estate for the cover image.

I have coordinated this job, finalized the text and figures and written the Epilogue to provide a current context. I have done minimal editing within the text; rather opting to insert comments and bring references up to date in footnotes throughout the book. The aim is to let Lionel's ideas shine through, and give pointers to further reading in the current literature. I am very grateful for the support and guidance of the Cambridge University Press production team, in particular Katrina Halliday and Lynette Talbot. My institution, the BC Institute of Technology, has supported my time on this work. The outpouring of support and remembrances by Lionel's friends and colleagues is a testament to his life; and it has made finishing this book much easier. To Lionel.

David Holloway
Burnaby, April 2010

Having used 'once upon a time' to start the preface of my previous Cambridge University Press book, *Kinetic Theory of Living Pattern* (1993), what else could I do but use a Lewis Carroll quotation as the epigraph to the preface of its sequel,[1] especially since my interest in mechanisms of biological development began from the looking-glass problem of optical resolution? As a physical chemist, hitherto concerned only with inorganic materials, I was certainly wandering into unknown territory, demanding of me a grand survey that I was certainly not about to make when, through 1972–3, a couple of chance occurrences redirected me into this field of enquiry. These, as mentioned in my 1993 preface, were attending a talk by my colleague R. E. Pincock on an instance of 'spontaneous optical resolution' that he had observed in careful experiments, and my first introduction to studies of biological morphogenesis by taking the chair at the PhD defence of Thurston Lacalli, who received a degree in zoology by working on development of an alga. Those two afternoons led me to get excited about the concept of 'non-linear dynamics' as probably being a major part of the explanation of both classes of phenomena. I might quite easily have decided that I could attend neither of these events; and in that case, I might never have undertaken any work in this field. My first enthusiastic thanks must therefore be to both of these gentlemen, and to whosoever among the gods *does* play dice in arranging human encounters. (For further commentary on optical resolution, non-linear dynamics and gods playing dice, see the introductory paragraphs to Part II.)

From the later 1970s, I was greatly encouraged by the late Paul Green, a botanist who insisted that 'there is no escaping the calculus when studying development'. He proposed the writing of my previous book, and is hence responsible (at one remove) for the existence of this sequel. His death from a rapidly fatal cancer in 1998 was the loss to biology of an important scientist whose work had not yet reached its proper fulfilment, and to me also of a very congenial friend.

In the projects from my own work that I describe here, much was collaborative and I have many thanks to give to: Beverley R. Green, University of British Columbia, a biochemically trained botanist whose work on the alga *Acetabularia* gave me a highroad into experimental biology; John B. Armstrong, University of Ottawa, who studied

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[1] These acknowledgements of Dr Harrison's are a year older than his final version of the text; the final preface did not have the Carroll quote. Taken from *Through the Looking Glass*, it is: 'Of course the first thing to do was to make a grand survey of the country she was going to travel through.'

embryonic development of the axolotl (a salamander) and got sufficiently interested in the possibilities of reaction–diffusion theory in this topic that the exploration of that possibility made most of the PhD thesis of my student, David M. Holloway, who remains a close collaborator; Patrick von Aderkas, University of Victoria, BC, who worked experimentally on somatic embryos of conifers, giving me the chance to do some measurements myself and find the Bessel functions in the seed leaves; Harold E. Kasinsky, University of British Columbia, who kept bothering me about patterns of condensing DNA in sperm until I got to believe that even these could have a dynamic explanation, and collaborated with him and his collaborators Manel Chiva and Enric Ribes at the University of Barcelona; Jacques Dumais, now at Harvard, whose Master's thesis work with me led on to a PhD with Paul B. Green at Stanford University and continuing interaction on mechanical forces in plant surfaces; and once again but fully deserving a second mention, Thurston C. Lacalli, successively of the Universities of British Columbia, Saskatchewan and Victoria, whose intensive collaboration with me for several years in the 1970s, which has continued less intensively ever since, was the way we both developed our understandings in some depth of Turing's 'chemical basis of morphogenesis'.

Lionel Harrison
Vancouver, November 2006

Preface

This book is intended for anyone who is interested in contemplating the question posed in the title,[1] and who has a modicum of general scientific education. It is not directed specifically to people working in the sciences; and of those who are, it is not specifically for physical or biological scientists. It is mainly for people who would like to think about unsolved questions rather than to receive answers. Thus, it is not a review of any specific specialized field, and particularly not of those aspects of biology that have recently been producing answers most rapidly – the aspects to do with genes and genomes and the daily increasing number of words ending in the sacred syllable –ome. My subtitle, 'the kinetic aspect',[2] implies that I am interested much more in how rapidly things happen to various objects than in what the objects are. Further, I believe that the study of rates of change can often be pursued as a primary objective, independent of knowing in advance the material composition of the objects that are changing. (Perhaps not only the primary objective, but also the ultimate – philosophers have long pondered whether the deepest understanding of the universe must be in terms of matter or motion.) This implies that if I consider a biological phenomenon and have the urge to find out 'what is doing it', I am not usually trying to find the name or formula of a substance or molecule, but rather the forms of some expressions showing how the amounts or concentrations of a few substances must be changing in space and time.

This attitude can, however, seem old-fashioned, and I am vulnerable, like all emeritus professors, to the sneer that I have passed the

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[1] The question in an earlier draft was 'How does life devise its shapes and sizes?'

[2] This was an earlier subtitle, referring back to Dr Harrison's 1993 book, *Kinetic Theory of Living Pattern*.

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'philosopause' (a word I learned as current from Natalie Angier's *The Canon*, 2007). Indeed, my attitude can be seen as representing the way D'Arcy Thompson expected biology to advance when he first wrote *On Growth and Form* in 1917 (the frequently referenced version of 1942 was the second edition). Neither he nor anyone else at that time anticipated that in the twentieth century, via electron microscopy and molecular chemistry, anatomy would advance to its ultimate limit of minuscule size, the very sequences of molecules and hence of atoms in living beings. I think also that many scientists intensely concerned with continuing the elaboration of such detailed descriptions, and therefore immersed in the work of the past few years or even months, may find something apparently philosopausal in the habit of theoreticians to reach back to treatments of kinetics or diffusion or vibrations of discs or whatever was published between the 1920s and 1950s. But this is a necessary feature of such work; to be sure, we do not regularly reference Newton's original writings of three and a half centuries ago whenever we relate forces to accelerations, but 60 years or so ago is yesterday. When theory has been founded upon rocks, we have to keep on digging back all the way to the rocks as the foundations on which to build.

It has been opined to me by a reviewer of the penultimate draft of this book that biologists reading it 'are going to be hostile because of the fact that genomes and bioinformatics etc do not get much of a treatment'. I can see that many people absorbed in those popular branches of biology might be uninterested in my topic, and might therefore decide not to read this book beyond this sentence. But I do not understand hostility to it, because my topic is entirely complementary to the molecular aspects, and in no way inimical to them. (Nevertheless, I have indeed encountered negative attitudes, as indicated at places in my account.) Still less do I comprehend the attitude well described by the same reviewer in the words, 'the biological world, almost hysterically, embraces "systems biology" with a zeal and faith that can only be described as "religious"'. The attitude thus defined disturbs me in two ways: first, in my home discipline of chemistry, people working in manners ranging from almost a mathematician's to almost a biologist's and everything in between are not only tolerated but welcomed into the community of the discipline. I appreciate the chasms across which different people gaze at each others' viewpoints, often without finding the means to cross over, but not why this should lead to hostility. The source of enmity is more usually covetousness for land that is easy for both opponents to grab because there is no chasm

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to cross. But second, even in regard to the analogue of religion, I hold pantheistic views that, when two religions are such that it seems necessary for the adherents of one to regard the other as necessarily untrue, I am inclined to think that both have equal quanta of the truth, but neither has the monopoly on it that its adherents think.

Let's get back to the chasm. There is one, between dynamical theorists and molecular biologists, and it is desirable that it should soon be spanned by one or more bridges in other than ramshackle shape, so that equations of motion and structural details of genes and proteins can become parts of the same territory in which everyone is free to wander. Living organisms have for centuries (or even millennia) provided much inspiration for research in all of the sciences (even astronomy, when its practitioners go looking for distant planets likely to have life-supporting conditions or little shreds of organic stuff littering the solar system).

Many of these sub-disciplines need no mutual interaction. But for finding out how organisms organize their development, a junction between molecular detail and the vastly larger macroscopic scale of spatial patterning does need to be built. It has been suggested to me that I should write a chapter describing that bridge. I both appreciated the suggestion and found it quite alarming, because it amounted to describing in some detail the middle of something of which only the extreme end sections have yet been built by anybody. But one should never refuse the challenge to write an essay about nothing. And while bridges are being built, there are structures in place at crucial stages called the falsework. They are made of wood, and show where the bridge is going to be, but give very little idea of what it is eventually going to look like, and no idea at all of what it will be made of. I can describe the existing falsework adequately in this prefatory account; and quite recently, at the time of writing, it has acquired at least one thin line that seems to span the entire chasm.

To begin at my end: dynamics can be studied for instances involving known substances, sometimes even for reactions with known values of rate constants. In the general realm of cell biology, it is becoming fairly popular for applied mathematicians to tackle such systems. A contrasting approach is to characterize the properties of particular kinds of dynamics without regard for the particular matter that may display them. The simplest well-known example is what is variously known as an exponential decay, first-order decay or relaxation process. It has mathematical properties, such as the constant time for a concentration to halve, that are the same whether one is thinking of

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radioactive decay, degradation of a protein or free induction decay of a set of nuclear spins in an NMR experiment. It is important to many types of scientist to know the properties of such dynamics.

I contend that, for the phenomena of developmental biology, the scope of pattern-forming dynamics should likewise be common knowledge, at least in fairly general terms. The route towards this knowledge has been well indicated by Hans Meinhardt, especially in his book on sea-shell pigmentation patterns (1995, 1998, 2003 editions), which makes some characteristics of solutions of partial differential equations accessible at the level of coffee-table presentation. I have seen Meinhardt's approach described (by an anonymous reviewer) as 'toy models', a term used by some trendy physicists to downgrade what I think of as a proper route into theory by setting out hypotheses.

That approach stems from four essential preconceptions (or paradigms, for any who prefer that much-misused word):

(1) a pattern, as formed by an event in biological development, frequently starts as a single entity on the macroscopic scale, often tens of micrometres between repeating parts in examples as diverse as whorls in single-celled algae (Chapter 3) and somites in vertebrate embryos, including human (Chapter 9). The pattern often starts out as a harmonic spatial waveform (Sections 3.2 and 4.4), and needs to be studied as an entity.

(2) These events are capable of setting up quantitative scales of distance, and therefore, wherever possible, it is useful to characterize the events by spatially quantitative measurements. This is good for a physical chemist blundering into biology and wanting to do experiments, because much can be done by high-school methods at low magnifications. One graduate student I converted from a chemist to a developmental biologist remarked that I had taught him that research can be done with a dissecting microscope.

(3) The mechanisms that control such pattern formation are likely to be matters that it is the proper business of physics and physical chemistry to address, with, therefore, a modicum of mathematical language used in even the first tentative interpretation of the experimental results.

(4) Many patterns may be kinetically generated and kinetically maintained, and theories of their formation must deal in depth with rates of reaction and transport of substances

in mechanisms belonging to non-linear dynamics (and mechanical forces may also be involved in ways that demand mathematically expressed theory).

The obvious basis for the start (in 1973) of my own work in this field was the well-known (but still to my mind lamentably under-used in developmental biology) theory of pattern generation by activator–inhibitor interactions initiated by Alan Turing (1952) and elaborated by Prigogine, Meinhardt and others so that 'reaction–diffusion' is now a familiar and extensively studied branch of applied mathematics. Should this type of theory, in which no more than a handful of substances do the whole job of making complex repeated patterns out of uniformity, be thought of as out-of-date when enormous networks of genetic interactions now loom over the discipline and it is repeatedly said that no-one has positively identified a Turing morphogen pair? The latter point brings me back to my example of a thin line that now seems to span the chasm: a group in Freiburg (Sick *et al.* 2006) have made the definite statement that 'WNT and DKK determine hair follicle spacing by a reaction–diffusion mechanism'. That paper identifies these two proteins as activator and inhibitor in a Turing mechanism (see Section 6.3.5).[3]

As to the question of a few substances versus a vast network, I believe that knowledge of what a few substances can do dynamically with a particular pattern of interactions between them is akin to having a divining rod that, on a wander through the tangles of the network, will twitch when one reaches the small region that has what it takes to make spatial pattern. Here, perhaps, is some reason for the 'hostility' that I have mentioned as puzzling me. The twitch may delight the theorist anxious for a source of equations that quench the thirst for unification and understanding, but cast into despondency the careful cartographers of a broad landscape of genes and proteins, who are being told that most of their country has only dry wells for the particular pattern-forming phenomenon being considered. Fear not, cartographer, nor cast out the theorist into the unmapped desert. The gene you have discovered will turn out to be nectar in another pattern-forming event that neither of you has yet ever thought of.

But what do I think is necessary to make a divining rod that twitches at the right places? Does it have to have a phoenix feather

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[3] See also Digiuni *et al.* (2008), identifying GLABRA and TRIPTYCHON as acting through Turing dynamics to control the spacing of trichome structures on leaf surfaces.

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embedded in it, or anything that the experimental biologist will believe equally mythical and unlikely to be findable? In other words, what different kinds of experiments need to be done? To approach this kind of question, I was effectively forced into making large parts of this book effectively a memoir of large parts of the work of me and my group since about 1973 (most of Part I, and Section 9.1). I have already stated (as my 'essential preoccupation (2)' above) that much of this involves spatially quantitative work on a large enough spatial scale that it requires only low magnifications and may seem to be a reversion to high-school biology. The essence of this kind of work is that it is like classical chemical kinetics (yes, of the 1930s). One does not leave a system to make something and come back later to see what it has made. One keeps on observing and measuring as a function of time, and particularly in the hope of catching the system at exactly the point at which it seems to be making the rudiment of the pattern. Geneticists tend to avoid any encouragement I give them to look for mutants in pattern formation, because what I want to see is no spectacular change in development, but, for instance, a quantitative change in the spacing between repeated parts in a pattern; and that is in no way easy to spot, except by multitudinous painstaking measurements, most of which may turn out to be wasted effort.

From the first encouragement I received from Cambridge University Press editors to write this book, it was intended to be in a more 'popular' style than my 1993 book – 'popular' meaning readily readable by anyone with fairly substantial education in *any* of the sciences. In the earlier book, I tried to hit a level of mathematical presentation accessible to anyone with a good first course in calculus, which wasn't difficult since I have never taken a university course in mathematics and have always been coasting along on a knowledge of calculus from sixth-form high school in England in 1944–6. But even that level of presentation led me to put 143 numbered equations in Chapters 6, 7 and 9 of that book. (One does not need a high level of sophistication to be unconscionably verbose, or should I say 'equationose'.)

The present book contains only a handful of equations. (Despite having heard that Stephen Hawking was told, when he was writing *A Brief History of Time*, that putting in even one equation halves the sales of the book, I couldn't get rid of them all.)

This account is, above all, interdisciplinary; I advocate attempts to bring together some aspects of the physical and biological sciences for the common aim of finding out by what means biological organisms go about developing the myriad complexities of their shapes. And one only brings together aspects by bringing together people. What difficulties does this involve? First, there is language. Science, as a whole, has become enormous, and therefore divided into numerous almost completely separated specialties, each with its own little language unknown to any of the others. Twenty-first-century science has far surpassed the Tower of Babel in this property. Science is becoming a multicellular organism with practitioners like molecules that can't cross membranes. I am disturbed at the number of seminars I attend at which the speakers know they are addressing general audiences but have made no attempt to adjust their use of specialized terminology to that situation. A lot of time has to be devoted to this if the Tower of Babel is to become syncytial, with passages like gap junctions or plasmodesmata between all its rooms. (Now, how many readers have I lost with the terminology in that sentence? I'm just talking about routes by which substances manage to pass from cell to cell.)

Never let it be said that the chasm between the sciences is just that biologists can't do mathematics. The barrier is both ways across every interdisciplinary boundary. But I still believe that many more developmental biologists must make the effort to understand somewhat more mathematics if some essential aspects of their discipline are to advance at all. As I understand the meaning of 'science', the essence of it lies in putting experiment and theory together. Far fewer people can achieve real science than can do reliable experiments or manipulate mathematical formalisms well; the greater part of science lies in putting these two together. In physics and chemistry, that union can commonly be made at a social level, with any particular individual identified as an experimentalist or a theoretician. Not so, I believe, in developmental biology at the present time. The connection between theory and experiment is still at a rudimentary level at which totipotency in the scientific enterprise needs to be present at the level of the small research group. While I advocate more knowledge by everyone of what's on the other side of the fence, I don't generally anticipate that plant-breeding in culture vessels and model-breeding in computers will be done most usually by the same person. The interdisciplinary perspective needs only to be enough that both people can talk to each other to the extent of designing research projects together, and be trained enough in each others' disciplines to understand their relative preconceptions and expectations and be interested in talking!

With the above list, serving as acknowledgement and as advocacy of small-group but broad-perspective collaborations, I may unwittingly have provided evidence to condemn me as an incurable dilettante, who

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never stays long with work on one organism. I prefer to say that I thoroughly deplore the concept of basing biology chiefly on the study of a few 'model organisms'; that one cannot establish the unifying nature of concepts in biology other than by looking for them in a wide range of biological diversity; and that the value of the comparative approach was best put a long time ago by William Harvey (1578–1657), who established the concept that blood circulates, and wrote:

> The common practice of anatomists in dogmatizing on the general make-up of the animal body, from the dissection of dead human subjects alone, is objectionable. It is like devising a general system of politics, from the study of a single state, or pretending to know all agriculture from an examination of a single field. It is fallacious to attempt to draw general conclusions from one particular proposition . . . . Had anatomists only been as conversant with the dissection of the lower animals as they are with that of the human body, the matters that have hitherto kept them in a perplexity of doubt would, in my opinion, have met them freed from every kind of difficulty. (copied as quoted by Crombie 1953, from Chapter 6 of Harvey's *De Motu Cordis, On the Movement of the Heart*).

Following Harvey's attitude perhaps even more broadly, I am quite happy to present an account of developmental concepts, the greater part of which is about plants when the greater part of biology today is about animals. Where would our knowledge of genetic diseases have got to without Mendel's groundwork on peas? In regard to the concepts of developmental theory that I like to pursue, a big advantage of plants is that, because of the rigidity of their cell walls, they are more amenable than animals to quantitative spatial measurements on patterns as they form. Paradoxically, this implies that organisms that display the least cellular motion within tissues during development may be the best for studies seeking to explore the roles of dynamics in pattern formation.

Since I wrote my 1993 book, there have been some substantial advances in the recognition that there are places for mathematical work in biology. University departments are establishing mathematical biology groups and making faculty appointments in them. The complete determination of genome composition in a number of species has led, on the one hand, to another version of stamp-collecting in the matter of proteomes, but also to the recognition that when one has all the structures, the next focus of attention should be on the functions of all these molecules. And that means looking at changes, and hence rates of change, and hence using differential equations. Or am I over-interpreting the trends with a bit of wishful thinking? I tend to get interested when

I hear (increasingly often) the terms ‘genetic networks’ and ‘systems biology’, and then to be rather disappointed when I find that what is being presented is not approaching my interests at all directly.

But surely, schematics of networks of interactions between genes via, for instance, a protein product of one gene activity being a transcriptional regulator for the activity of another gene, are likely to contain many of the processes having non-linear dynamics capable of pattern formation. (I write ‘many’, not ‘all’ of the processes because I believe that pattern formation may often involve biochemistry very distant from such relatively direct interactions of genes; see my opinions on identities of Turing morphogens in Section 7.3.3.) Between thousands of genes there are potentially millions of pairwise interactions. The kinds of dynamics my work is devoted to can produce complex spatial patterning out of the four self and mutual interactions of two substances. To find these in a network can be the needle-in-a-haystack problem; but this needle must be found because a prick from it can change the shape of the whole haystack.

To clarify this point, in Section 1.5, especially Fig. 1.1, I compare two diagrams: one is of my devising (Harrison 1993, Fig. 1.1). It has four columns; the second column from the left contains a partial differential equation. The other figure is from Bornholdt (2005), in an article entitled ‘Less is more in modeling large genetic networks’. It has four columns; the second from the left contains two ordinary differential equations. There is at some level a similarity between the approaches symbolized in these two schematics, and at other levels strong contrasts. I present this, and everything else in the following pages, to let readers make up their own minds what approaches are going to lead to bridge-building between people from diverse academic disciplines all fascinated by the shaping of life. One of the commonest and simplest-looking events around us is the branching of one plant stalk into two; and the fact is, we don’t yet know the spatial controls that decide when this is going to happen. Perhaps there is a clue to this and many problems of development somewhere through the looking-glass: how can my body have grown both a left hand and a right hand when all the aminoacid molecules in its proteins are left-handed? Geometrical self-assembly should fit together parts of either left or right handedness to give a whole of one handedness, and the term self-assembly is conventionally used, both in developmental biology and increasingly in chemistry to mean that kind of geometrical fitting. When the macroscopic patterns of development defy the inevitable consequences of self-assembly, the mechanisms of their formation must belong to some broader class of ways in which symmetry-breaking can arise. It is in that wider sense that I use the term ‘self-organization’. The most obvious way for a system to escape from the dictates of geometry is to use mechanisms dependent directly on dynamics, such as the rates of reaction provided by the catalytic activities of enzymes, and thus only quite indirectly on the structural features that give those enzymes their activity. That this type of mechanism can account for the loss of one handedness on the molecular scale has been known since 1932 (see the introduction to Part II). By the same token, it can take particles of a single handedness and generate both right and left hands. This book is about how that kind of self-organization may work, and what evidence there is that it does in diverse instances of biological development.

My interest in working on development was triggered by the doctoral research of Thurston Lacalli on the alga *Micrasterias* (see Chapter 5). In his thesis (1973a), he gave an analogy (following an idea of J. Needham) for the two contrasting ways to go about investigating development, which I further elaborated in my 1993 book. It concerned 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.
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> If in the light of such a study . . . 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 contents 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.

In this analogy, the Swiss watch does not stand for a fully formed living organism. All its parts symbolize the genome and its products that are in active use during development to make patterns. And the oscillations of the watch movement correspond to the *spatial* periodicities of those patterns. But to appreciate what is in ‘the whole story’ one needs to consider what one is going to do with that story. What parts of it must one give most attention to if one wants to know: how to make a Swiss watch; how it works; or how to design some quite different oscillatory system. For pattern-forming systems, this book is about how they work, and how one tries to find out how they work.