Unfolding gastrulation

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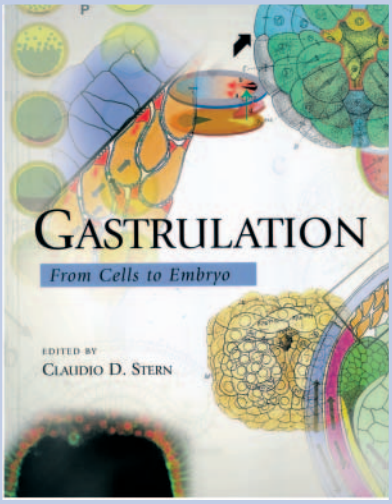
'There is an intangible something about the process of gastrulation that invariably generates enormous awe and curiosity', writes Claudio Stern in the Preface to an excellent and timely book that he has edited, titled *Gastrulation: From Cells to Embryo*, and that has been recently published by Cold Spring Harbor Laboratory Press. Indeed, it is the process of gastrulation that transforms an unimpressive, amorphous heap of cells that makes up each animal at the blastula stage of development, into a gastrula in which three germ layers, the endoderm, mesoderm and ectoderm, are shaped into a body plan that is characteristic of each systematic group. It is also during gastrulation that largely pluripotent embryonic cells become initially biased, then specified and finally committed to form specialized cell types such as muscles, blood and neurons. Thus, a two-dimensional map of tissues and organs in the blastula is translated through dramatic gastrulation movements into a three-dimensional configuration. In this triploblastic structure, the future skin and neural tissues reside in the most superficial ectoderm, the prospective alimentary structures form from the most internal endoderm layer, and sandwiched between these two is the mesodermal layer, which will give rise to the cardiovascular organs, musculature and bones.

Gastrulation is accomplished by the concurrent and concerted actions of four evolutionarily conserved morphogenetic movements. Epibolic movements result in the expansion and thinning of tissues; internalization movements (emboly) bring future mesodermal and endodermal germ layers beneath the ectoderm; and, lastly, the nascent germ layers narrow mediolaterally through convergence movements, while extension movements elongate them from head to tail. This dynamic and complex combination of cell movements, rearrangements and inductive events during gastrulation is so intriguing, almost magical, that many students, upon encountering it, become hooked forever.

The same features of gastrulation that make it an object of fascination also make it a challenging subject of study. Whereas in the past two decades embryologists, geneticists and molecular biologists made large strides in our understanding of the inductive processes that specify embryonic polarity, germ layers and their patterning, the morphogenetic aspects of gastrulation proved to be less tractable. Consequently, only a few books that focus on gastrulation have been published in recent decades (Keller et al., 1991; Stern and Ingham, 1992).



Gastrulation: From Cells to Embryo
Edited by Claudio D. Stern
Cold Spring Harbor Laboratory Press (2004)
731 pages
ISBN 0-87969-707-5
$150.00 (hardback)

In recent years, however, new imaging and cell tracing technologies, fluorescent fusion proteins, as well as new molecular and genetic approaches in many model systems, have begun to unveil the mysteries of gastrulation. Many molecular pathways have been implicated in this process, and in some cases have been linked to individual gastrulation movements, or even to specific cell behaviors. This fast rate of discovery in gastrulation research is likely to continue. Although several reviews have been published that focus on individual model systems, or on the roles of specific pathways in gastrulation, a comprehensive and current view of gastrulation has been missing. For the gastrulation enthusiast, hungry for a good and modern source of information, the new book edited by Claudio Stern is simply a feast. It is the most extensive treatment of gastrulation yet attempted in book form. The editor has collected together an impressive constellation of experts in the field to write for the book, who have contributed 54 chapters discussing individual aspects of gastrulation. It is carefully crafted with the first chapter placing the study of gastrulation into a historical context. A short glossary at the beginning of the book will also help uninitiated readers to appreciate the intricacies of gastrulation. Chapters are written in an accessible style and include effective illustrations.

Gastrulation is a truly organismal phenomenon, whereby the entire embryo changes its architecture and shape through the concerted movements of individual cells, cell populations and cellular sheets. These morphogenetic cell behaviors are precisely regulated in time and space, and are coordinated with cell fate specification events. The specification of both cell movement behavior and fate likely reflect the current position of a cell in the embryo, as well as its developmental history. Therefore, the complete set of instructions on how to construct an

embryo during gastrulation from its cellular constituents must be encoded in the genome. The book takes this reductionistic approach to gastrulation, guiding the reader from the embryonic through cellular level, and finally to the molecular genetic mechanisms of gastrulation. In the first part, 'The Embryology of Gastrulation', we learn about gastrulation movements in different animals, from simple sponges to humans. A real strength of this book is that it is not limited to the most popular model systems; it also features chapters that describe gastrulation movements in less well-studied organisms, such as crustaceans, ctenophores, mollusks, dogfish, reptiles and the rabbit. On the one hand, these chapters illustrate the wonderful diversity of gastrulation movements among metazoans, and on the other, they reveal that the basic types of morphogenetic movements of epiboly, internalization, convergence and extension are universally, albeit somewhat differently, employed by these distinct organisms.

Getting down to the cellular level, Part II considers the morphogenetic cell behaviors that execute gastrulation, including how they are patterned in time and space. The reader will enjoy exploring various mechanisms of mesendoderm internalization, such as invagination, involution and ingression, or their intermediates such as 'synchronized ingression', which is proposed to occur in teleost gastrulae. Gastrulation aficionados will appreciate delving into more complex issues. For example, how local morphogenetic cell behaviors, such as intercalations that are uniform across a cellular field, might result in different rates of movement in distinct regions of the field. A few chapters consider the role of chemotaxis and the extracellular matrix in orchestrating gastrulation cell behaviors. In this part of the book, one can also learn about the inductive and patterning processes through which embryos gear up for the morphogenetic movements of gastrulation. After all, gastrulation movements make embryonic asymmetries morphologically apparent, but these asymmetries are established before the morphogenetic movements are initiated. Several chapters provide overviews of the early symmetry breaking events in distinct embryos, such as frog and mammals. The next series of chapters guide the reader through processes that specify and then pattern the mesodermal, endodermal and ectodermal germ layers. The concepts of morphogens and their specific deployment in patterning the nascent mesodermal and neuroectodermal tissues are discussed. I especially enjoyed reading these chapters, as they do not focus on any particular animal model, but rather take a comparative approach. Of note here are the chapters discussing endoderm development and the specification of the left/right axis, two areas that have experienced particularly fast progress in recent years.

But it is Part III, concerning 'The Molecular Biology of Gastrulation', that makes this book qualitatively different from its predecessors published a decade ago. Whereas only a handful of pathways and molecules were linked to inductive or morphogenetic events of gastrulation at that time, now almost 20 chapters of this book are devoted to either the different signaling pathways (all the usual suspects from Nodal, through FGFs and the canonical and non-canonical WNTs, to BMPs and Notch), the array of transcription factors, or the extracellular matrix components involved in gastrulation. This part of the book illustrates the rapid progress in our understanding of gastrulation, but it also articulates many outstanding questions and future experimental priorities. For example, we learn that among the genes implicated in gastrulation, those that impact primarily on embryonic pattern and cell fates predominate over those regulating only morphogenetic cellular behaviors. Therefore, the question remains as to the relationship between genes regulating cellular fates and those regulating movements during gastrulation. However, few answers can be offered at the moment. Another conclusion emerging from this part of the book is that with increasing knowledge of the molecular players in gastrulation comes somewhat daunting complexity. It becomes clear that a gastrulating cell needs to integrate its positional information, developmental history and a multitude of movement cues from several sources. The chapter 'System-level Properties Revealed by a Gene Regulatory Network Analysis of Pre-gastrular Specification in Sea Urchins' offers a view of how such complex molecular information can be harnessed.

Part IV looks at gastrulation from the evolutionary perspective, exploring fossil embryos, as well as taking a comparative approach to cellular and molecular aspects of gastrulation in modern animals. Chapters in this part of the book illustrate well the symbiotic relationship between the studies of evolution and gastrulation; we learn about the evolution of animals by studying their development and vice versa. The final chapter of the book is contributed by Lewis Wolpert, a long-standing proponent of the importance of gastrulation over the less exciting events in life such as birth, death or even marriage. He considers the progress achieved in the field, as well as the challenges ahead, concluding that many of the mysteries of gastrulation are still to be uncovered.

The limitations of the book are few and largely unavoidable. The rate of progress in the area of gastrulation research is so rapid that, even in a book still hot off the press, important new regulators of gastrulation such as STAT3 and its downstream effector LIV1 are not discussed. Whereas there was an effort to maintain a uniform color scheme for germ layers and specific tissues in the book's illustrations, this could be more consistent. Moreover, some colors must have been misprinted during the printing process, with yellow looking rather greenish in some chapters. These are, however, only minor issues in this otherwise outstanding book.

Gastrulation is a dynamic process and nothing illustrates it so well as movies. The book is associated with a modest but useful web site (www.gastrulation.org) where time-lapse movies of live embryos, or schematic visualizations provide an

excellent addition to the individual chapters. This website will likely grow with new editions of the book, or possibly take on a life of its own, with new materials being added as they become available.

In conclusion, I enthusiastically recommend this book, and expect it will be highly valuable to students, teachers and researchers. The book provides a comprehensive, authoritative and modern view of our knowledge of gastrulation, and captures the excitement in this rapidly developing field. I imagine that many young readers will become intrigued by gastrulation and at least a few will become hooked by it forever after reading this book.

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Beyond Darwin – towards an inclusive evolutionary synthesis

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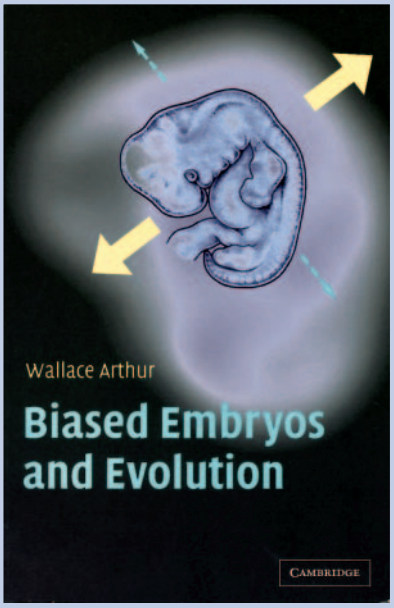
What is the main driving force of evolution? What determines the direction of evolutionary change? What causes novelties to arise? During most of the last century, these questions have been addressed by evolutionary biologists and the answer they have come up with is well known, not only to biologists: it's natural selection. In his latest book, Wallace Arthur forces us to re-think. He claims that besides natural selection, there is embryological development as a second major player determining the direction of evolutionary change.

Biased Embryos and Evolution is a short book, which is easy to read and aimed at both biologists and general readers. Although laid out in 17 chapters, it has a straightforward, if provocative, message: 'natural selection is not the main orienting agent of evolution, as Darwin claimed. Rather, it is one partner in an interacting duo'. Arthur claims that developmental bias, 'the tendency of the developmental system of a creature to produce variant trajectories in some directions more readily than others, is a second major agent of evolution'. He starts his argument by summarizing textbook thinking in developmental biology, evolutionary biology and the history of life. But already in the first part of the book, he sets the stage for his provocative statement by highlighting the limitations of the modern synthesis. Arthur argues that the contributions of Fisher, Haldane, Wright, Dobzhansky, Mayr, Ford and Simpson were all correct and important, but what followed was often an 'arrogance about the synthesis that was entirely absent from Darwin's beautiful book'. The importance of mutations that affect the development and, ultimately, the morphology of an organism has been largely ignored in the modern synthesis. Therefore, it is more than logical that one of the central chapters of Arthur's book is entitled 'The Return of the Organism'. What follows is an excellent account of how development influences evolution and how developmental biology can influence evolutionary theory.

Evolutionary change has three major components: mutation, which acts at the level of the gene; natural selection, which acts at the level of the population; and developmental reprogramming, which acts at the level of the organism. Arthur uses 'developmental reprogramming' as an umbrella term to describe the many ways in which mutations can affect the timing (heterochrony), the spacing (heterotopy), the quantity (heterometry) or the quality (heterotypy) of developmental processes. It is at this point, at the latest, that it becomes clear that when Arthur talks about the 'organism', he mostly means the development of the individual. Molecular changes brought about by mutations affect developmental processes, cause developmental reprogramming, and thereby generate developmental and morphological novelty. Although we are far from having a full account of developmental reprogramming between, and within, any major groups of animals or plants, there are many case studies on their way that will ultimately provide fresh data to support this theoretical assumption. At the same time, the scarce data already available clearly support the



Biased Embryos and Evolution
By Wallace Arthur
Cambridge University Press (2004) 248 pages
ISBN 0-521-54161-1 (paperback)
ISBN 0-521-83382-5 (hardback)
£18.95 (paperback)/£50.00 (hardback)

importance of incorporating developmental thinking into evolutionary theory.

And here it comes: the book is neither unique nor novel in its attempt to postulate a closer interdependence between evolution and development – this theory is already at the heart of evolutionary developmental biology and several books and even more reviews have been written on this topic. What is novel, and what is only superficially discussed in the last paragraphs of original evo-devo research papers, is the way in which development can influence the direction of evolutionary change. This is what Arthur calls 'developmental bias', and what Gould, Lewontin and others have termed 'developmental constraints' in former times. Arthur makes a significant contribution to this debate by claiming that one of the reasons for the limited acceptance of the term 'developmental constraint' is its negative touch. He argues that 'development biases evolutionary directions in both positive (drive) and negative (constraint) ways'. Thus, the internal factors in evolution, the genome and the developmental program on which mutations act, can have a positive or a negative effect. They make some changes more likely than others, and thereby are important components in the evolutionary game. There is no doubt that these considerations and the growing knowledge in the field of evo-devo have to be incorporated in an 'inclusive' evolutionary synthesis.

'So what?', the evo-devo folks will ask. We all agree on this, and many of us express it one way or the other in our papers. However, even if this thinking is common, original research papers never provide the space for developing this idea all the way through. Wallace Arthur has taken the time and energy to write a book to precisely drive home that point. In order to do that, he had to criticize 'neo-Darwinian' thinking, which he did in a balanced way, while still getting across the important point of the 'incompleteness' of the modern synthesis. Even if some people might not like this style, I believe he deserves credit for doing it the way he did. The book is therefore not just another addition to the long list of monographic evo-devo texts. Arthur has a novel and important point. His argument is short and precise. He does his readers, but mostly himself, the favor of driving this point home straight. The style of the book is entertaining and light-hearted, and includes some gossip, which makes it even more rewarding for the non-specialist.

In conclusion, I highly recommend Arthur's book to all fellows of developmental and evolutionary biology. Not that they will learn from it new details in evo-devo, that is not the aim of the book, and Arthur was well-advised in not even trying to persuade the reader with case studies in order to make his argument. Rather, he urges us (in particular the evolutionary biologists) to be open-minded and to accept the concept of 'developmental bias' as a major addition to the evolutionary synthesis. The time was ripe for a distinguished fellow – such as Wallace Arthur – to make the claim that embryological development can make a specific contribution to evolutionary theory, and that without it the 'modern' synthesis cannot be complete. If the book can persuade evolutionary biologists to embrace its central message as whole-heartedly as the evo-devo crowd surely will, it will have served its purpose. Hopefully they'll read and re-think.

Between toyland and the jungle

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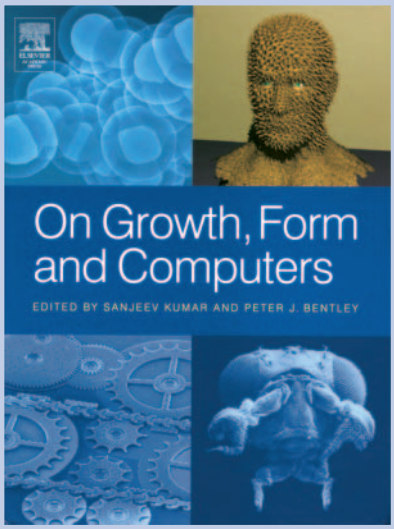
The editors of this compilation declare two goals: to show how computer science can help us to understand biological development, and to show how ideas from developmental biology can stimulate new thinking in computer science. The objectives are neatly symmetrical, but they do not sit comfortably together. Developmental biologists and computer scientists speak different languages and inhabit different worlds. On one side of the cultural divide, the developmental biologists struggle to digest complex experimental findings and make sense of them, tangled in wearisome quantities of data that defy quantitative analysis. On the other side, the computer modellers construct ingenious idealized systems, with a blithe disregard for biological realities and a greater concern for what is possible than for what is actual. A terrible jungle or a ridiculous toyland: in bad moments that seems to be the dichotomy. The question in my mind as I embarked on *On Growth, Form and Computers* was whether it would show us some happy middle ground, where computer modelling casts clear fresh light on the workings of biological systems, and in particular of real developing organisms.

The book begins with an introductory chapter that is mainly addressed to computer scientists and in which, among other things, the editors rashly undertake to summarise developmental, cell and molecular biology in nine pages for the benefit of those who do not know about these things. The rest of the book consists of 21 heterogeneous essays by different authors, including six pieces that are reprinted from other publications. The first few contributions (Wolpert on development and evolution, Hancock on cell signalling, Bolker on the genotype-phenotype relationship, and Brockes and Kumar on amphibian regeneration) discuss aspects of developmental biology but say little or

nothing directly about computer modelling. Developmental biologists will find some things to interest them here, but not much enlightenment on the main theme of the book.

Subsequent chapters get down to brass tacks, and fall roughly into two groups. First come those directed towards biological questions – attempts to use computer modelling to understand specific developmental systems, as well as general essays on the application of mathematics or computer modelling to developmental biology. Second, there are accounts of computer constructs inspired by ideas from biology, but studied by computer scientists for their own sake. A good representative of the first category is Meinhardt's contribution, reviewing the work for which he is famous on the role of short-range activation and long-range inhibition in the creation of spatial patterns of differentiation. Even though it has been difficult in most cases to substantiate Meinhardt's models with detailed quantitative data, and some of Meinhardt's specific applications are highly speculative, his basic ideas about how symmetry is broken and signalling centres are set up are simple and illuminating, and are backed up by serious consideration of specific biological examples. They have become a significant part of the developmental biologist's conceptual toolkit, helping us to think about how real systems work. The breaking of symmetry is certainly fundamental to pattern formation, and this is emphasized in a nice (reprinted) essay on the subject by Ian Stewart, although his final disquisition on the symmetry classification of the gaits of quadrupeds strays rather far from the theme of this book.

The book contains relatively few contributions that focus on one particular developmental system and show how computer modelling can really help us understand it. This is a pity, and perhaps a reflection of the editors' backgound as computer scientists rather than developmental biologists. The book does, however, include an essay on one of the most interesting systems from this point of view, the shoot apical meristem, with its



On Growth, Form and Computers

Edited by Sanjeev Kumar and Peter J. Bentley

Academic Press (2003) 444 pages
ISBN 0-12-428765-4
£69.95 (hardback)

regular sequential emergence of leaf primordia, each one positioned precisely in relation to those already present. Work in the last few years has identified many of the key molecules governing this process, to the point where a close interaction between experimentalists and modellers can be very fruitful. The chapter by Jönsson, Shapiro, Meyerowitz and Mjolsness describes one such collaboration, although it is too brief and condensed to do the subject justice.

A central task for computer modellers, addressed by several contributors (e.g. De Jong, Geiselmann and Thieffry, and Reil), is to describe and analyse the behaviour of gene regulatory networks. The standard approach is through partial differential equations. The difficulty is that in most biological systems we have only an incomplete knowledge of network topology, and, worse still, virtually no information about the quantitative parameters of the regulatory mechanisms: the experiments may tell us that X goes up when Y goes down, but they rarely tell us how steeply, or within what range of concentrations, or with what sort of non-linearity. One response is to is to make models that avoid quantitative description and seek to represent the available qualitative information in terms of logical (yes-no) variables instead of continuous variables. The fallacy is that such idealizations, at least for networks with feedback, sadly fail to capture correctly even the qualitative behaviour of the underlying continuum system. Even if we only want to make qualitative predictions, we have to have quantitative information. The lack of quantitation is, I think, the fundamental reason why developmental biology has yet to find its Newton, or its Hodgkin and Huxley.

These problems become more severe, and the computer models markedly more complex and difficult to construct, when cell movement and cell rearrangements also have to be taken into account. Several chapters (e.g. Miodownik, Fleischer, Eggenberger Hotz) discuss this enterprise and convey a flavour of the problem, though with an emphasis on general principles and idealized systems, rather than on analysis of specific real cases.

A still more ambitious undertaking is to model the evolution of developmental programs. This involves setting up a description of the rules of gene regulation, cell proliferation and cell movement, computing the resultant phenotype, and then allowing the rules to change through successive rounds of mutation and reproduction, with selection applied according to some measure of fitness of the computed phenotype. Hogeweg's studies of her 'critters' are an example. Here, as in most undertakings of this sort, the assumptions needed to construct a tractable model become so artificial that it is hard to identify any correspondence with a specific real biological system. Whether useful insights are gained into general biological principles is a matter of debate.

The chapters in the final section of the book for the most part abandon any claim to answer specific concrete biological problems. They ask not what computer science can do for biology, but what biology can do for computer science. They are addressed primarily to computer scientists, and

make rather hard, though interesting, reading for outsiders. So far, the main achievement of biologically inspired computing has been to cause everyone a lot of trouble, in the form of computer viruses. The book passes over these in silence; the emphasis instead is on more benign forms of 'artificial life' – that is, on non-malignant computer programs that evolve by random mutation and selection according to the output that they produce. Ray and Hart (in a reprinted paper) do, however, explore the evolution of software constructs that can migrate from computer to computer to computer, sense their environment, and compete with one another. 'Artificial life' is a rich and intriguing topic, with practical applications to such things as the development of control systems for robots (discussed by Jakobi). It raises many general questions. Will such computer constructs tend to evolve in the direction of increasing size and complexity? If the selected phenotype is behavioural, reflecting the connectivity of a control network, how will the structure and performance of that network evolve (Rust, Adams, Schilstra and Bolouri; Dellaert and Beer)? What course will evolution take if the programs operate in a variable environment and are capable of 'learning' from 'experiences' (discussed by Cangelosii, Nolfi and Parisi)? Will the programs evolve to outstrip the ingenuity of their human creators? The last few chapters of the book do not give straightforward answers to questions such as these – none, at least, that I as an outsider to the field could easily grasp; but they provide much food for thought.

In short, the book is a mixed bag. Reading it makes one all too well aware of the difficulties of the relationship between developmental biology and computer modelling. There are some nicely written essays that make good points of principle, but few shining examples of models that succeed in adding to our understanding of specific events in the development of real organisms.

Searching for the Devil

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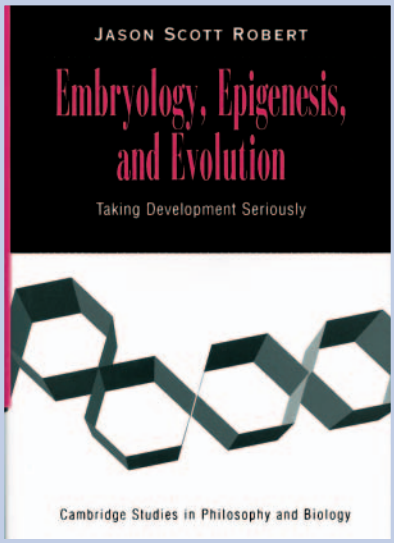
This is a beautifully written philosophical book on the nature of the developmental process, and on both past and current thinking about its relationship with evolution. I would urge all developmental and evolutionary biologists to read it. You will probably find, as I did, that there are some things you agree with and some that you don't. But of course, 'twas ever thus.

I'll start with the things that I liked. Jason Scott Robert is enthusiastic about the new 'evo-devo' approach, and he emphasizes its philosophical significance, rather than its minutiae. In particular, he notes the possibility that development may 'bias' (p. 32) or 'drive' (pp. 101-102) evolution in particular directions – something that I have long felt to be important (Arthur, 2004). However, he also draws attention to 'developmental systems theory' (DST), the existence of which had entirely escaped me, as it seems to have been a story told largely in the philosophical, rather than the biological, literature (not that this is any excuse for my having missed it). In particular, Robert focuses on the work of Oyama [(Oyama, 1985) and subsequent publications]. The main difference between DST and evo-devo, according to Robert, is that the former adopts a holistic stance in which genes are simply some of the players in a very multifactorial process, whereas much evo-devo is centred on comparisons of gene expression patterns between different taxa, and so tends to emphasize the roles of genes above those of the other players in the developmental game. I'm sure there's some truth in this contrast, although my own view of evo-devo is that it is also a holistic endeavour. But in any event, I entirely agree with one of Robert's closing comments – that 'evolutionary developmental biologists and developmental systems theorists would do well to interact with each other in establishing a genuinely synthetic biology' (p. 130).

And so to the location of the Devil. Robert's final chapter is entitled 'The Devil is in the Gestalt'. By this, he means that it is in the flavour of the whole, and not in the detail, where the Devil is proverbially to be found. The particular devil to which Robert is alluding is that of actual, or apparent, disagreement between different camps on the nature of the relationship between development and evolution. And I believe that he's right in his identification of its location. Few if any evo-devo folk would deny the importance of population processes, such as changing gene frequencies, in evolution (though of course they do rebel against the excesses of some neo-Darwinians, such as those who define evolution as changes in gene frequency). Equally, few, if any, of the more enlightened wing of neo-Darwinism (such as quantitative geneticists) would now deny the possibility that development may indeed often 'drive' or 'bias' evolution in certain directions. But the emphases of the two endeavours are still much more different than they should be. I think this is a case of the need to discard historical baggage, and I



Embryology, Epigenesis, and Evolution: Taking Development Seriously
By Jason Scott Robert
Cambridge University Press (2004) 158 pages
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believe that Robert's book will help to achieve this.

Finally (in terms of my likes), the book is not only well written but also well structured, with 'summaries of the argument so far' available at sensible places, just when you feel the need for them. It also has a certain humility of style that is endearing. At one point (p. 90), Robert goes so far as to contemplate the possibility that his book might be considered to be 'verbal gymnastics' that are 'utterly useless to practicing biologists'. Of course, he doesn't really believe this is true, and neither do I. It is entirely sensible, even perhaps necessary, for practising biologists to stand back from the individual trees from time to time, and to reconsider the nature of the wood.

Now for the things I didn't like. There are just two of these, but they're both important, one from a scientific and one from a historical perspective. I'll discuss them in that order.

In his favouring of a holistic stance, Robert sometimes goes too far. In trying to correct what he sees as an overplaying of the role of genes, he sometimes comes across as not being balanced but rather as being equally unbalanced – in the opposite direction – as the folk he criticizes as being too pro-gene. So, he sometimes seems almost anti-gene, and, associated with this, anti-genetic programme For example, he states that 'we don't need genetic programmes or instructions, or even specifically genetic information, in order to understand and explain the developmental effects or evolutionary significance of genes' (p. 31).

Now this is one of the craziest statements in a generally sane book, and I suspect it is one that the author himself, in retrospect, might feel slightly uneasy about. But his dislike for genetic programmes re-surfaces all over the place, usually in less extreme forms. For example, in the context of a reference to the work of Keller [(Keller, 2001) and others], he states (p. 86) that 'the genome does not itself contain or comprise a programme for development'. I have mixed feelings about this. If he simply means that epigenetic and environmental factors also influence the course of development, then I (and probably everyone) would agree. However, I have tended to think of development as an interplay between a genetic programme and an epigenetic programme, with that interplay itself being potentially altered by many environmental variables (Arthur, 2004). So in my view, the idea of a genetic programme, if used broadly, is entirely compatible, rather than at odds, with a holistic view of development. This train of thought leads inexorably to a crucial question: exactly what is meant by a 'programme'? I was hoping that Robert would devote a substantial block of text to this issue (in the same way that he does for the meaning of modularity on pp. 122-124), but I was disappointed to find that he did not.

Now to my historical gripe, which concerns our current interpretation of the work of Haeckel. Robert re-iterates the view of some other recent authors that 'according to Haeckel, the ancestral stages of adults could be identified in the embryos of descendants' (p. 94). He refers to Hall (Hall, 1999) here rather than to any of Haeckel's works. Personally, I don't buy this argument. Although Haeckel may have thought that 'higher' vertebrate embryos pass through, for example, a 'molluscan' stage, did he really think that they resemble adult molluscs? If so, which ones? Perhaps a garden snail or an octopus? Surely not. It is clear from some of Haeckel's later work that he did not think in this way at that stage of his life. I will only be persuaded that he thought in this way at an earlier stage if someone can come up with a specific quotation to that effect. Meanwhile, anyone interested in this issue should consult Sander (Sander, 2002).

In conclusion, I liked more than I disliked Robert's book. And I think its main virtue is to force readers to reflect on where theoretical biology in general, and evo-devo in particular, are going, both philosophically and scientifically. Such reflection is all the more necessary in these pressured times, when many biologists feel forced to concentrate on the latest-emerging details in their own particular neck of the woods, in order to keep sufficiently up to date to get that next grant. Of course, without research funds, few of the details that ultimately accumulate to give us something substantial enough on which to reflect would be discovered. So, like much in life, it is all a question of balance. Despite some ups and downs along the way, on reaching the final page I felt that I had become better balanced than I had been before beginning this interesting book.

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The Matryoshka dolls of plant polarity

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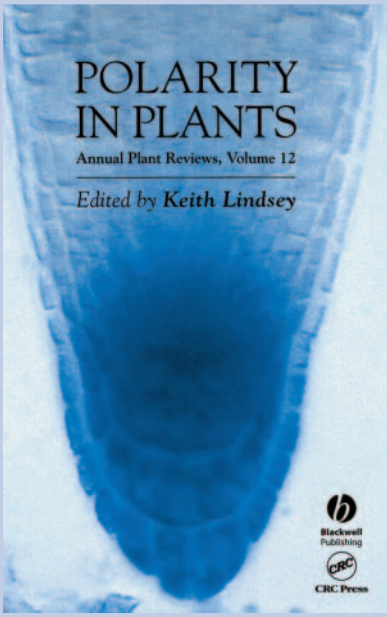
In its broadest sense, polarity can be described as asymmetry. And, if you look at a plant, you will immediately notice a variety of asymmetric features at different levels of complexity. There is a root at the bottom and a shoot at the top. Leaves are attached to the shoot at one end and are free at the other. The upper side of the leaf may have hairs on it, while the underside is smooth. When you take a closer look at a hair, you might see that it is asymmetrically branched. If you happen to have a microscope handy, a cross-section of the plant's stem will reveal that the cells at the core look different from those further out. Even better equipped, you will recognize polarity at the cellular level, which manifests itself in the directions of vesicle movement and in the asymmetric distribution of organelles, cytoskeletal strands, and even of single proteins. Finally, if you are really inquisitive and do not mind leaving the realm of biology, you can go further and look at the polarity of single molecules, atoms and elementary particles, and end up in the dark and vast space of the ultimate microcosmos (but please be back for lunch). You have just discovered different levels of polarity at different orders of magnitude, nested like Russian Matryoshka dolls, and you may speculate that polarities at lower levels in some way underlie the polarity found in bigger structures.

In general, polarity is a very common phenomenon and it is an intrinsic property of matter at every level of complexity. However, for plants, polarity is something more – it is the means by which they maintain developmental continuity, communicate, expand and adapt. For plants, polarity is a real theme of life. In his new book *Polarity in Plants*, Keith Lindsey explores the multiple levels at which polarity arises and the integral role that polarity plays during development. In spite of the obvious presence of polarity in plants and the attention that has been given to this topic for centuries, we are only beginning to unravel the complex mechanisms that underlie cellular polarity and its connection to the polarity of tissues, organs and the whole plant. The plant polarity field is still in its infancy; delimitation of the field is unclear, many concepts are intriguing but largely speculative (such as the analogies drawn between auxin and neurotransmitters), and there is a lack of consensus about basic nomenclature (for example, the issue of whether the tip of the root should be referred to as an apical or a basal structure). Above all, polarity exists at many different structural levels, and these issues make plant polarity a very difficult topic to discuss in a comprehensive synopsis, as it does not break down easily into small, separate entities that can be presented in an intuitive sequence.

Keith Lindsey has arranged the eleven reviews about various facets of polarity in plants that make up this book in a logical way, along the axes of both space and time. The first few chapters, which have been written by various contributors, cover polarity at the single-cell level, with special consideration given to the cytoskeleton and cell walls. The rest of the book follows the course of plant development. It starts with polarity in the zygote and during embryogenesis, and then considers the different organs and tissue structures as they develop in time, which eventually leads us to the 'abominable mystery' of polarity in flowers. This structure provides for a book that is relatively well rounded, in spite of the variable scope and style of the single reviews.

By and large, the chapters are 'stand alone' reviews, and this sometimes leads to a somewhat redundant treatment of certain subjects. However, this arrangement facilitates the selective reading of single topics, which is probably the way this book will be used most often. Much of the data reviewed here, of course, come from the major model plant *Arabidopsis*, but where appropriate, work from other plants, such as *Fucus* or *Antirrhinum*, is also discussed.

The first chapter, about cell growth and the plant cytoskeleton, comes closest to an introduction to the whole book, as it is very comprehensive and introduces some of the key molecules and mechanisms that are involved in polarity at the cellular level. To some extent, this chapter even serves as a glossary. Comparisons with polarity in animal cells make this a good overview, and also a starting point for those interested in more than one kingdom. Here, the reader encounters root hairs and their growth for the first time, and since root hairs are a great



Polarity in Plants: Annual Plant Reviews, Volume 12
Edited by Keith Lindsey
Blackwell Publishing (2004) 360 pages
ISBN 1-405-11432-0
£99.50 (hardback)

model system for growing cells, they also appear in several other chapters, although with varying success. Chapter 2 attempts to connect the role of ROPs (RhoGTPases of Plants) with polar cell-to-cell auxin transport, and contains broad information about both topics. Chapter 3 is the last of the general chapters, and thoroughly covers plant cell walls as major determinants of the cell's growth and shape, and their role in polarity. In particular, the roles of targeted vesicle trafficking and auxin transport are highlighted; these and the connection to the cytoskeleton seem to be the recurring themes of the first part of the book. Cell walls are a discriminating feature of plant cells and, with the inherent philosophical tendencies of Chapter 3, they can indeed be seen at the 'transition zone between uni- and multicellularity'. With the little knowledge that we currently have about the molecular mechanisms of polar auxin transport, you can also follow the speculative notion that the smaller, non-elongating transversal walls of root cells resemble animal synapses. This otherwise stimulating analogy is brought to its extreme in Chapter 7, which is on root polarity, where these cell walls are almost exclusively referred to as 'plant synapses'.

All subsequent chapters focus on special structures or processes involving polarity. The reader will learn about trichomes (the little hairs on leaves that are actually single, branched cells), and early events in the development of fucoid algae, and will find an excellent chapter on polarity in *Arabidopsis* embryogenesis, which does not only review the literature thoroughly but expands on it in a truly inspiring way. As mentioned above, the chapter on roots is maybe a bit too inspired by the idea of auxin behaving like a neurotransmitter, but otherwise you will find a thorough review about root and lateral root development, which also considers comparisons between different plant species.

There are no surprises about polarity in the chapter on the shoot apical meristem, but it does give comprehensive information on the meristem's amazing self-regulatory capacities. The next chapter on vascular development is maybe a bit more substantial with regards to polarity, and is also easier to read. The last two chapters cover lateral organ and flower development. It becomes especially clear in the latter that polarity is a phenomenon closely linked to development. During flower development, a multitude of polar growth axes emerge, along which floral development takes place. Actually, most forms of development do require or lead to polarity, and so it is not surprising that this book also serves as quite a comprehensive review of plant development. As such, this book might also prove useful in higher-level graduate classes, although it is aimed at the professional in the field and is certainly not a textbook. Moreover, the price of about £100 will definitely limit the accessibility of this book to students.

Now, what does the reader learn from this book? Overall, it provides a mixed bag of information (a big bag of quality information, that is) that unfortunately lacks synergy. A useful addition might have been a more general introduction or synopsis of the known mechanisms of polarity in a special chapter. This would have helped the reader to see the context more clearly and would have improved some redundant parts; for example, those on the role of the phytohormone auxin. But let us not be greedy but content with what we get: a comprehensive and, for the most part, well-written collection of reviews that deal with polarity in plants, which, to our best knowledge, can also claim the prize of being the first book on this topic.

From the concluding remarks of most of the chapters, one can infer that still little is known about the molecular mechanisms underlying polarity. However, there seems to have been a recent boom in identifying molecular players involved in cell polarity, and, consequently, any attempt to review plant polarity is inevitably condemned to be slightly out of date, even before appearing. A recent major topic in the field is the polar flow of auxin, which on the one hand depends on polar, actin-dependent vesicle trafficking of PIN proteins and on the other determines polarity at higher levels. This model was lately reinforced when PIN-dependent auxin flow was identified as a common player in both embryonic and de novo organ axes formation. However, despite the recent fast pace of findings in this field, there is still a long way to go before we have a clear idea about how polarity is established in plants, and we look forward to a second edition of this book in, maybe, five years from now.

Many scattered bones do not a skeleton make

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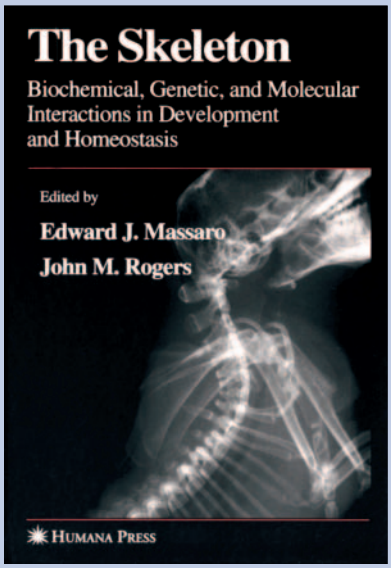
The vertebrate skeleton is an amazing organ system. It pleases one by its exquisite architectural and engineering beauty. It impresses by its strength and remarkable adaptability. It is a veritable beehive of cellular activities: it is constantly being remodeled by the concerted action of bone-resorbing and bone-making cells, and its marrow compartment serves as a factory for several lines of blood cells and adult stem cells. It is a storage facility for Ca^{2+} and plays an essential role in maintaining Ca^{2+} homeostasis in our bodies. It can fascinate and delight: a trip to any natural history museum with a group of preschoolers or kindergarten children to examine dinosaur skeletons almost never fails to generate excitement. Yet, it can also generate fear as a reminder of our 'return to dust', and can elicit deep concerns as we age and its internal structure slowly becomes osteoporotic and more fragile.

The understanding of how this organ system develops, grows and is maintained in the adult has come a long way during the past 25-30 years, as a result of numerous genetic, biochemical, pharmacological, cell biological, biomechanical and clinical studies. This exciting advance is documented in multiple textbooks and review articles, and, of course, in thousands of original research papers. However, for the student, postdoctoral fellow or young scientist who considers entering the field of bone biology, navigating through this mass of published information is a formidable challenge. No single text exists that helps the novice to separate 'signals' from 'noise' so that the most interesting unsolved problems (the 'hot' topics) and the most promising emerging technologies can be identified. It is therefore with considerable interest one opens a book that in around 400 pages promises to represent precisely that type of text, appropriately titled *The Skeleton: Biochemical, Genetic, and Molecular Interactions in Development and Homeostasis*. Edward J. Massaro and John M. Rogers, the editors of the multi-authored volume, state that their goal was 'to provide researchers and students with an overview of selected topics of current interest in bone biology and to stimulate their interest in this fascinating and diverse field'. Have they succeeded? Unfortunately, after spending some time with the book I must sadly report that the editors have not been entirely successful in this endeavor.

The book is divided into six sections, with each section split into several chapters written by different authors. The section titles broadly reflect the sequence of events that characterize the process by which most of the skeleton develops in the vertebrate embryo. In this process, which is known as endochondral bone development (applicable to the formation of all bones, except for parts of the craniofacial skeleton and part of the clavicle), mesenchyme forms condensed regions in which cells differentiate into cartilage-producing chondrocytes. The chondrocytes form cartilage models of the future bones, and these models are then replaced by bone and bone marrow in a process that couples osteoblastic differentiation, angiogenesis and osteoclastic migration with cartilage



The Skeleton: Biochemical, Genetic, and Molecular Interactions in Development and Homeostasis

Edited by Edward J. Massaro and John M. Rogers

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removal and bone marrow establishment. Reflecting this developmental sequence, the editors have grouped the chapters into sections as follows: Chondrogenesis, Chondrocytes and Cartilage; Control of Skeletal Development; Osteoblastic Cell Differentiation; Bone Induction, Growth and Remodeling; Bone Mineralization; and Skeletal Dysmorphology. These are logical subdivisions of the subject matter, but unfortunately it looks as though the editors stopped their work at this point. It is hard to avoid drawing the conclusion that they did not define a detailed framework for the chapters in each section nor provide the authors with clear guidelines for organizing the chapters. I suspect that they also did not work with the authors on revising their work to achieve a product that would be as close as possible to their planned book. Instead, the editors appear to have decided to write a long preface, almost like a mini-review of bone biology, in a late attempt to provide some sort of cohesive structure to the book. This is not effective. As a result, the book, in my mind, is more like a collection of scattered bones than the kind of treatise on the skeletal organ system I was hoping for when I first opened it.

Among the many problems that I can only blame on the lack of strong editorial hands, is the unexplained variation in the structure of different chapters. Some are written as concise reviews or a series of mini-reviews (such as chapters 1, 5, 8, 10, 14, 18 and 23) – excellent for students as an introduction to specific topics in extracellular matrix and bone biology. Other chapters (e.g. chapters 4, 12, 19, 22 and 24) are organized in the format of original research papers, with Introduction, Materials and Methods, Results and Discussion. I suspect that most of the data in these chapters have been or will be published in more appropriate peer-reviewed journals in a slightly (or extensively, as the case may be) modified form. In a third category are chapters (such as chapters 6, 11, 13, 15-17 and 20) that provide a mixture of review with a discussion of recent data (with a description of methods and results) from the authors' own laboratories. I suspect that many of these chapters have their origins in the Background and Significance sections of recent grant applications.

The quality of the different chapters is also very variable. This is perhaps to be expected as they are written by different authors, but some editorial intervention would have helped to make the quality more uniform. For example, removing excess and irrelevant material could have helped in Chapter 2 ('Chondrocyte Cell Fate Determination in Response to Bone Morphogenetic Protein Signaling'). This chapter contains, appropriately, a discussion of the bone morphogenetic proteins (BMPs), their receptors and downstream signaling pathways, but it also contains a table, several pages in length, of gene mutations that are responsible for human genetic skeletal disorders and relevant animal models. Such a table is of course useful, but I cannot understand the rationale for incorporating it in this chapter, and not in, for example, a chapter in the section on Skeletal Dysmorphology!

Another example of the lack of editorial intervention is the repetition of the same basic information throughout many chapters. Thus, after reading about BMPs, their receptors and the downstream Smad proteins, in Chapter 2, the reader is treated to another description in Chapter 3.

Repeating important facts is based on sound pedagogical principles, but in the case of BMPs this principle is taken to the extreme in this book: a basic description of BMPs and their receptors is repeated in chapters 8, 13, 15 and 16. Editorial intervention would have been very helpful here. It may also have helped to improve Chapter 3, which deals with chondrocyte differentiation. Given what we now know about the essential roles of the transcription factors Sox9, Sox5 and Sox6 in chondrocyte differentiation, it is remarkable that the discussion in this chapter is almost entirely focused on the regulation of chondrocyte activities in the epiphyseal/growth plate regions of developing long bones. A detailed description of the transcriptional machinery required for chondrocyte differentiation is entirely omitted! Finally, one has to ask, 'editors, where were you?' when reading the sentence 'collagen I consists of a triple-helix formation' finds α1(I) and α2(I) collagen chains are described as Iα1 and Iα2 chains (Chapter 21) in a book that contains an accurate and up-to-date chapter on 'Molecular Biology and Biosynthesis of Collagens' (Chapter 5).

By now it should have dawned on the reader that I cannot give this book two thumbs up. This is the bad news. The good news is that although it has too many sharp 'bones' to be enjoyed as a full meal, some of the individual 'bones' are very good. The chapters written as concise reviews make excellent reading for students and may be useful as reading assignments in introductory courses. Some of the chapters that describe methods and hypotheses will be useful for postdoctoral fellows and researchers in the field who would like to achieve better insights into the experimental strategy and thinking behind the published work from specific laboratories. For example, Chapter 7, which describes the use of the *loxP*/Cre system in targeted mutagenesis of the mouse *Hoxd* complex, can be read as a supplement to the Materials and Methods section of recent papers from Duboule's group. Chapter 26, which deals with risk assessment issues, will be useful for corporate scientists working on animal studies as part of their companies' submissions to the US Food and Drug Administration and US Environmental Protection Agency.

The really good news is that the opportunity to write a truly outstanding modern treatise on the vertebrate skeleton is still open. Until that happens, one will have to select and use parts of this book.

Elements of developmental biology

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Developmental biology has differentiated into a rich, complex field that continues to progress at breathtaking speed. This presents a conundrum for textbook authors: present students with a comprehensive survey of the entire field or distill it down to the essence that provides students with a framework on which to hang the details and complexities. Fred H. Wilt and Sarah C. Hake have chosen the latter approach. Their target audience is students with a basic background in organismal, molecular and cellular biology who do not intend to make developmental biology their careers.

Is there a need for such a book? How well does it work? Does the book tell a compelling story that is as dynamic as the field itself? Would it be capable of corrupting students who never considered a career in development, tempting them to join the 'dark side'?

The writing style is very accessible, verging on the vernacular, as opposed to a more scholarly style that is standard in most textbooks. Considering the intended audience, the style works quite well. In fact, it is fun to read. Consider this example from Chapter 3, which distills development down to its essence: 'The general "recipe" for animal development was set forth in Chapter 1: make an egg, cut it up into many diploid cells, move cell groups from place to place to produce a three layered embryo, and selectively activate gene expression in different forming tissues and organs'. The rest of the book builds upon this simple statement. The authors have elected to feature a limited number of model organisms, rather than taking a more comprehensive approach that would use the full palette of organisms that developmental biologists study. The marginalization of *C. elegans* and the zebrafish is unfortunate, but choices were necessary to keep the book reasonably short. All chapters begin with a Chapter Preview, which gives readers the context and alerts them to the major concepts to be covered, and end with a summary of Key Concepts, Study Questions and Selected References. Suggested answers to the Study Questions can be found at the end of the book. This provides the book with an interactive aspect, assuming that students take advantage of the opportunity. An additional interactive tool will be the website, which is mentioned on the back cover of the book, but which was not yet 'live' when I prepared this review.

The book begins by presenting the basic conundrum of development: how can a single cell, the fertilized egg, give rise to a complex and ordered assemblage of distinct cell types that function together in the adult, which produces another generation of gametes that contribute to yet another embryonic generation. The authors then outline the concept of differential gene expression, using classical examples and introducing experimental approaches that have been used to study this process. The second chapter is a brief introduction to gametogenesis and fertilization, with an even more succinct overview of cleavage as an introduction to fate mapping through lineage tracing. Given the intended readership, I am surprised that the authors did not take advantage of the

opportunity to discuss reproductive biology in more detail. I cannot imagine a topic of more interest to university students! Next comes a series of overviews of oogenesis and early development in *Drosophila*, frogs, birds and mammals. In each case, the unique role that the organism has played in revealing developmental mechanisms is described, as well as the distinctive developmental processes employed by each group of organisms. In the mammalian section, the emphasis is on the mouse, which is the most extensively studied mammalian embryo. However, I think another opportunity was missed to 'grab' students' interest by featuring human development more prominently.

The next section of the book features vertebrate organogenesis, culminating in metamorphosis. They precede the discussion of amphibian metamorphosis with a discussion of insect metamorphosis. I suspect that students will find this placement a bit confusing. The animal organogenesis section is followed by a section on plant development. It is up to the marketplace to confirm that there are sufficient non-specialist development courses that include plant development to justify its inclusion in the book. I hope that this is the case, because plant development is fascinating and highly relevant.

Principles of Developmental Biology
By Fred H. Wilt and Sarah C. Hake
W. W. Norton & Company (2004) 430 pages
ISBN 0-393-97430-8
$90.00 (paperback)

The remainder of the book is devoted to revisiting topics that are been introduced in earlier chapters and discussing them in depth from a cellular and molecular perspective. Some plant topics are interspersed among mostly animal topics. The first two of these chapters deals with the cellular basis of morphogenesis: how do cells organize themselves into a complex, functional organism? Once again, the authors have missed an opportunity here. In this case, the discussion of cell motility is not complemented by a discussion of metastasis. I think it is instructive to relate academic topics to topics that are relevant to our daily lives – particularly in a book targeted to non-specialists. The final section of the book deals with the regulation of gene expression, returning to the conundrum presented at the outset: how do cells with identical genomes become so very different from one another during development? The book culminates in a fascinating chapter on 'evo-devo'.

In summary, this is a noble effort that is well written. There is a need for a slimmed-down overview of development that is accessible to students who do not intend to specialize in the field. However, I would have preferred a book that did more to emphasize the relevance of developmental biology to them. Reproductive biology, cancer, tissue engineering, and reproductive and therapeutic cloning are topics that fascinate us all. We owe it to our students to inform them about them. It is easier to do that if their course textbook provides a foundation for the understanding of such topics.

From developmental genes to dysmorphology: human development at its best

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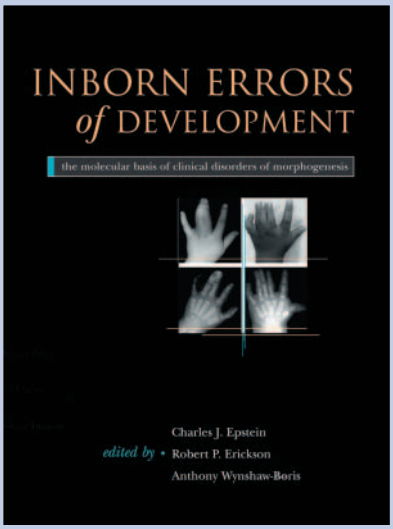
To give you the bottom line first: this book is a masterpiece written by numerous masters who are able to 'speak different languages' and who bridge disciplines from developmental biology, normal and abnormal morphogenesis, and molecular biology, to clinical genetics and dysmorphology. Understanding developmental biology is a crucial requirement for those working in clinical genetics; and the two fields are now coming together through advances in the Human Genome Project and in elucidating the genetic basis of various genetic disorders. I myself feel privileged both to work with families who have a child with a severe birth defect and at the same time to direct a laboratory whose research focuses on identifying the underlying basis of normal and abnormal embryonic development in humans.

Our knowledge of developmental pathways is still in its infancy compared with what is known about biochemical pathways. The editors have accomplished a monumental task by putting together chapters on the large number of human multiple malformation syndromes that are known about and organizing them within developmental pathways. This is the first time human developmental disorders have been covered in this way in a textbook. As mentioned in the preface, the idea for *Inborn Errors of Development* was influenced by Garrod's concept of inborn errors of metabolism, which has been expanded on here to

inborn errors of development. If the goal of this book is to integrate clinical genetic disorders with molecular findings to place these in the context of development, it is a goal that has been clearly accomplished. This does not come as a surprise, as all of three editors, and many of the contributing authors, are clinicians as well as bench scientists.

The book begins with an overview of some general concepts, with introductory chapters on approaches to understanding congenital malformations, general principles of differentiation and morphogenesis, and the role of model organisms in understanding development. The chapters that follow detail patterns of development of various organ systems. Most of the chapters of this book are devoted to over 100 clinical genetic disorders for which the underlying causes have been identified. These include disorders caused by anomalies in genes such as sonic hedgehog (*SHH*), *WNT*, transforming growth factor β, tumour necrosis factor, fibroblast growth factor receptor and Notch. Disorders that are caused by mutations in genes or gene families that have uncertain or unknown positions in a developmental pathway include members of the HOX, PAX, Forkhead and the T-box gene families. The book concludes with chapters on numerous genetic disorders that are caused by changes in genes that encode proteins involved in the regulation of chromatin structure and gene expression, and in transcription, post-translational control and ubiquination, and in those that encode guanine nucleotide-binding proteins, kinases and phosphatases. Many of the disorders resulting from mutations in the latter are tantalizing, as they affect multiple organ systems in common and rare dysmorphic syndromes. Only now that their underlying molecular basis is known, does the combination of clinical findings make sense.



Inborn Errors of Development

Edited by Charles J. Epstein, Robert P. Erickson and Anthony Wynshaw-Boris

Oxford University Press (2004) 1082 pages
ISBN 0-19-514502-X
£150.00 (hardback)

An area close to my own research interest is cholesterol biosynthesis and SHH signaling, which is very well covered in this book. SHH signaling is a prime example of a well-defined pathway that is critically important during early embryogenesis and is specifically required in limb and brain development. As the book discusses, abnormal SHH signaling can lead to disorders that affect different organ systems, such as Smith-Lemli-Opitz syndrome, a birth defect that is caused by abnormal cholesterol biosynthesis. Loss of function of SHH can cause the most common forebrain anomaly in humans, holoprosencephaly. Loss of function of PATCHED1, the receptor for SHH, leads to basal cell nevuscarcinoma or Gorlin syndrome. And distinct disorders with anomaliesof the hands and feet, such as Pallister-Hall and Greig Cephalopolysyndactyly syndromes, are caused by mutations in *GLI3*, another gene in the SHH signaling pathway.

This book is written for health professional and basic scientists alike. I learned that it is already used as a textbook in developmental biology classes. As the director of medical genetics training at NIH, I will recommend this book to clinical and PhD fellows in my program. At the same time, I also recommend it to the connoisseurs of dysmorphology – my colleagues from the David W. Smith Workshop on Malformations and Morphogenesis. I have no doubts that this book will become one of the standard textbooks, comparable with (yet uniquely different from) other classics by Jones, Scriver et al. and Gilbert (Jones, 1997; Scriver et al., 2001; Gilbert, 2000).

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'Remember Irena: flies are not freedom'*

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The first edition of Ralph Greenspan's fly-pusher's hand-book appeared in 1997 and was an immediate hit because it filled a gap. At that time the *Drosophila* field was booming as never before, and new people were taking up the way of the fly. There were of course existing books on *Drosophila* methodologies but these were either dated (e.g. Demerec, 1950; Roberts, 1986), or comprehensive and beyond the digestive capacity of the larval fly-pusher (Ashburner, 1989b; Ashburner, 1989a). The Greenspan book grew from his teaching (at Cold Spring Harbor and on various university courses), and was beautifully written and accessible to beginners. We ourselves have used it as a first resort: telling any new student or

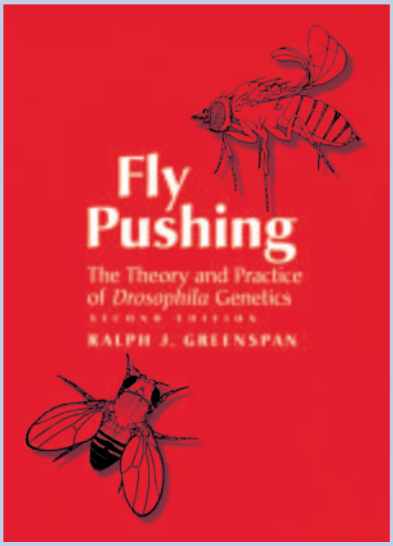
*Misquote from Martin Cruz Smith's *Gorky Park*.

visitor to the lab to go away and read it before asking a lot of questions. We can attest to its popularity: it is the most stolen book from the office and we must have bought six copies by now. In fact, when we went to the shelf for the 1997 edition to prepare this review, it was gone, and we had to borrow one from a post-doc who happened not to be at his bench. He will get his copy back tomorrow, promise!

The 1997 edition dealt with the basics of fruit-fly technology in seven chapters and 126 pages of text. The new edition still has only seven chapters, but it has gained weight (22 more pages). Many new fly people are also new geneticists, and this book starts at the beginning with basic explanations of the major phenomena of classical genetics (it is very light on molecular biology). Even for people coming in from other genetic systems, there is still the barrier of nomenclature and the sheer sophistication of fly genetic tools, many of which have no equivalent in other organisms. Greenspan does an outstanding job of making things plain.

The first chapter explains how to do crosses, even telling the reader how to collect flies. Mutant and gene names are explained, as are the chief glory of fly genetics: the balancers (chromosomes with markers and multiple inversions that allow us to manipulate genotypes with relative ease by preserving haplotypes). Greenspan adds a new explanation of why genes and mutations that have been re-identifed should retain the name first given to them in the literature. Sometimes large egos rename genes, and this leads only to confusion.

The second chapter discusses techniques for isolating new mutations in new or known genes. Good descriptions of chemical, radiation and transposon mutagenesis are preserved from the first edition, as are the crossing schemes that can be employed. Also included are descriptions of 'enhancer trapping', which allows one to detect genes by their expression patterns (a technique now in vogue in mice and fish). New material includes two new techniques for 'reverse' genetics in the fly: obtaining genetic mutations in genes known from molecular data (now



Fly Pushing: The Theory and Practice of *Drosophila* Genetics, 2nd Edition

By Ralph J. Greenspan

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usually the genomic DNA sequence). These are homologous recombination (long developed in yeast and mice), which has been done a few times in the fly and is quite clever but also arduous, and RNA interference, which is well established in worms. The latter has some drawbacks (it's hard to get a complete null) but has become very popular. Clearly, reverse genetic tools are required to exploit the genome data and these are important additions to the book.

The third chapter is on mapping mutations and retains good descriptions from the first edition on classic techniques, as well as details of newer tricks. One item has gone: polytene chromosome in situ hybridization. This was a beautiful technique and a challenge to master. It is sad for us to admit that something that we learned how to do is now really obsolete (along with running sequencing gels and chromosome walking), but Greenspan is right: nobody does this anymore. Nowadays, new P-element insertions, for example, are mapped instead by sequencing flanking DNA and finding the short sequence in the genome computationally. Although forward genetic screens are a strength of the fly system, assigning the recovered mutations to specific genes known in the genomic sequence remains slow. The 'new-tech' approaches to mapping described in the new edition of the book have made a significant difference. The issue is one of getting phenotype-based mapping down to a very fine scale. Greenspan describes how to do this in four ways, three of which depend on the increasingly dense forest of known and characterized P-element transposon insertions. The simplest is by fine-scale meiotic recombination using transgenic markers (usually a wild-type white gene), which, in the case of lethals, comes down to looking for the rare white-eyed flies in a pile of red (or orange) ones and counting both piles – a trivial task. This is great until you get very close to the mutant, when the pile of red-eyed flies may become huge. The second way is to use site-specific recombination, in which the position of the cross-over is pre-determined (usually at the chromosomal locus of a specific transgenic P-element). Because the position of the cross-over is now fixed, the frequency of the cross-over is independent of the distance between the transgene and the mutation, and thus the technique only gives the direction from the cross-over point to the mutation (using an outside marker). This works for just fine for very small distances, and so becomes very useful as you get close to the mutant. Thirdly, when P-elements are excised from the chromosome during transposition, they often tear off some additional DNA, and Greenspan describes how to derive small deletions by inducing this imprecise excision from a P-element that resides close to the mutation. The fourth approach does not depend on P-elements, but uses sequence polymorphisms as markers. This last seems onerous (you have to sequence), but is likely to become more popular as tricks for detecting polymorphisms improve.

Chapter 4 is almost unchanged from the previous edition and deals with the construction of genotypes (chromosome juggling). The fifth chapter is also little changed, but is really crucial – we wish it were first! This is a consideration of the different types of mutation as first

defined by Herman Muller (Muller, 1932). The idea of a null mutation, versus partial loss of function, versus several kinds of gain of function are discussed, as well as how to tell the difference between them. This is really important because the interpretation of the function of a gene in the biology of the fly often relies on what sort of mutation you have. For example, a mutation that is recessive and confers extra wings (such as some combinations of *bithorax* mutations) might lead you to conclude that the normal and sole function of the wild-type gene is to suppress the growth of extra wings. However, in this case, later study of complete nulls (mutations of the same gene, with no protein expression at all, called *Ultrabithorax*) upset the theory and revealed that the gene has a much broader and more basic role in determining the identity of segments.

The fifth chapter also explains conditional alleles (usually temperature sensitives), and how they can arise. These are of increasing importance as they are one of the few ways we can study the (often many) late functions of genes required early for cell viability or proliferation. The clearest case that Greenspan discusses is that of Notch, which is involved in an enormous number of developmental decisions; without the Notch temperature-sensitive mutation we would only know about a few of these.

The sixth chapter considers another leading fly tool: the construction of genetic mosaics so that only a part of the animal is mutant, or overexpresses a gene, or even both! There are techniques for inducing such mosaics at random positions, or in specific places, and for marking them positively or negatively (so that the mutant cells either loose or gain some marker, such as the Green Fluorescent Protein). Again, this is an area in which the fly is far ahead of other systems. The book ends with a brief chapter encouraging the new '*Drosophilist*' to go forth and prosper. The initial effect of this avalanche of technology is bound to be daunting for the new fly-person, but if they take Greenspan's advice and get started with something easy, expertise will follow.

Although the book is really excellent, it's not perfect and three important topics are left out, so we will continue to have to explain them to new lab members. While Greenspan does a good job of explaining what null and conditional mutations are, he doesn't explain how to get them. Given the importance of nulls, the common P-excision technique should have been explained in this context. The second omission is how we can really nail down in which gene a mutation really lies: i.e. going from genetic mutant to molecular locus. This used to be called 'cloning' the gene, but it is really the end-point of mapping. We agree with Greenspan in thinking that fly screens are really our great gift to other systems – but we are not finished until we can identify our mutations as being in a specific gene. This can be done in a few different ways – usually the best is by transgenic rescue – but for some reason Greenspan does not discuss the topic conceptually, or describe how fly transgenics are made. The third topic that we really would liked to have seen is a description of the resources available to fly workers: the stock center and the databases. *Drosophila* benefits hugely from a wealth of free (or almost free) material and information, but the ground-rules for getting it are not obvious (FlyBase searches are sometimes quite tricky), and some basic and clear explanations of the conventions and places to start would have been really useful.

Overall, the first edition of this book was a hit and we are confident that the second will be also. New techniques have been added while retaining the accessibility of the previous version. We're sure we'll have many copies of the second edition stolen off our shelves in the future. We had better order six.

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