

An introduction to mathematical biology

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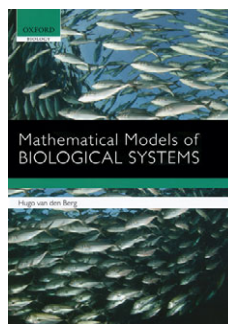
Mathematical Models of Biological Systems

By Hugo van den Berg

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One of the key goals of modern cell and developmental biology is to expose the underlying principles that drive cell differentiation and to elucidate how organisms construct functional multicellular structures. Thanks to advances in sequencing, high throughput screens and sophisticated imaging technologies, these fields are now awash with quantitative descriptions of gene transcription, cell signaling and cell mechanics. However, extracting key principles from the flood of new data is a major challenge for researchers and a central obstacle to fundamental progress in cell and developmental biology. The tools required to interpret this vast amount of biological data and to test hypotheses based on these studies can be found in quantitative analysis and mathematical modeling. With the book *Mathematical Models of Biological Systems*, Hugo van den Berg aims to contribute to the training of a new generation of biologists and mathematicians and to provide them with an introduction to the methods that are now available to quantitatively analyze biological data.

Like many quantitative biologists, my first exposure to mathematical modeling was not in the context of cell biology or developmental biology, but came through examples from physical chemistry, physiology and population ecology. In these fields, simple problems can be formulated using ordinary differential equations (ODEs) with complete statements of the state variables, such as initial conditions. As students, we learned to write ‘word-models’ and to translate these into sets of ODEs. Word models are narrative passages intended to translate the details of a biological problem such that biologists and mathematicians alike can understand the



problem in a way that allows equations to be written which capture those details. For instance, we can distil the interactions between predators and prey by stating the rules that govern their populations. Rules that govern the population of prey might include sources of population growth, such as birth or migration, and losses to the population due to predation or disease. The precise statement of these rules should be complete enough to govern the mathematical formulation of the model. Given a well-defined word model, the mathematical biologist can then write a series of ODEs; for example, with variables that represent the number of predators and prey and equations to describe how populations of predators and prey change. As students, we sometimes discovered that there were closed form solutions of these ODEs, in which changes in variables can be predicted explicitly by equations. But more often we found that we could only evaluate the general dynamic behavior of the variables; for instance, whether populations of predators and prey are stable or not. The insights and training that these model-building exercises gave us were instrumental in becoming fluent in the basic skills of mathematical modeling. The processes of formulating a model and relating fundamental principles to the mathematics and experimental outcomes were often more informative than the solution itself. However, after marveling at the awesome power of ODEs, we soon realized that the solution of some, or indeed most sets of, ODEs was intractable, that there was no way to capture relevant details of complex biology with continuous variables, or that model predictions could not be tested experimentally. As such, the tool kit of ODEs used to learn the skills of mathematical modeling is less useful for developing the quantitative models that are needed to describe problems in cell and developmental biology.

Unlike physics or chemistry, biology has very few universal theories. In classical physics, theoretical frameworks can connect

multiple experimental fields. By contrast, most models in mathematical biology are developed ad hoc to describe a single series of experiments. To think that a slim textbook could capture the entirety of mathematical biology, with all its ad hoc models, would be absurd, but this book provides a good introduction to it by presenting classical applications of ODEs. The first half of the book introduces the reader to the mathematical tool kit needed to formulate models and to solve or characterize their behavior. Most of the second half focuses on specific applications of modeling, with chapters on population growth (ecology), dynamics of disease in populations (epidemiology) and within the individual (immunology), and physiology. Many of the examples are similar to those found in classical texts, such as James Murray’s series on *Mathematical Biology* (Murray, 2007), Leah Edelstein-Keshet’s *Mathematical Models in Biology* (Edelstein-Keshet, 2005) or Lee Segel’s excellent *Modeling Dynamic Phenomena in Molecular and Cellular Biology* (Segel, 1984). Despite some organizational flaws, such as the placement of a chapter on the philosophy of mathematical modeling in the middle of the book, and the introduction of stochastic processes at the end of the book, developmental biologists may be interested in using van den Berg’s book to explore the basic principles of mathematical modeling;

A glaring omission from this book is any discussion of pattern formation or ... diffusion-reaction equations

for example, for developing word models and methods for solving and analyzing systems of ODEs. From the perspective of a developmental biologist, a glaring omission from this book is any discussion of pattern formation or examples of diffusion-reaction equations. Early work on partial differential equations and pattern formation by Alan Turing in the 1950s (Turing, 1952) and Hans Meinhardt in the 1970s (Gierer and Meinhardt, 1972; Meinhardt, 1977) provided the stimulus for many theorists to enter the field of developmental biology and attracted quantitative biologists to challenge those models. Given the lack of textbooks focused on mathematical models in developmental biology, students interested in modeling the complex problems of modern cell and

developmental biology would be well advised to augment this text with other books on modeling specific biophysical systems and with more targeted reading of extensive supplemental materials that accompany the primary literature of gene regulatory networks, cell signaling and morphogenesis.

Current state-of-the-art modeling efforts in developmental biology range from Bayesian models to finite element models to agent-based models, but the model-building exercises and focus on ODEs presented in van den Berg's text are still essential to form an understanding of the field of mathematical modeling in biology. The tutorial forms presented by van den Berg provide a concise introduction to the principles of modeling and dynamical systems and are suitable for an introductory course in mathematical

biology. However, more advanced students and quantitatively inclined developmental biologists will have to wait for textbooks that provide a more complete introduction to computational tools that have seen extensive application in recent years.

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We hold these principles to be self-evident

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Principles of Development By Lewis Wolpert and Cheryll Tickle

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£36.99 (paperback)

What is to be taught in an undergraduate course on developmental biology? As in all branches of biology, there is far too much known to be able to teach it all, and any introductory course would sacrifice depth. Inevitably, choices must be made, and one choice is to emphasize important principles and concepts of development across all organisms. Lewis Wolpert and Cheryll Tickle, with a cast of impressive supporting authors, have made excellent selections in *Principles of Development*. This is the fourth edition of the book and the thoughtful choice of topics that went into the first edition is still evident, although there have also been many useful updates.

The book begins with some history and a summary of general concepts. The concepts are important ones, especially when framed by the title of the book, but they may be a little dry out of the context of real organisms. However, one has to start somewhere, and the general concepts are

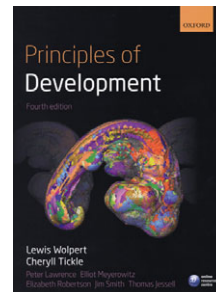
illustrated in later chapters with examples from real animals and plants. The principles and concepts could be re-stated more forcefully throughout the book, though, as they may be missed by the inattentive reader. Along the way, boxes explain the important experimental techniques that provide approaches to questions. The figures are drawn in a consistent style, which helps to give a coherent presentation and lets the student focus on content. Although the images are variants of the kinds of drawings we have seen in original journal articles and other textbooks, they are rendered here with style and clarity. The photographs are usually well chosen, though in some cases they don't seem to be as clear or as relevant as they should be. For example, it isn't clear why a well-camouflaged California false hellebore, the source of the teratogen cyclopamine, is shown, rather than the (admittedly grisly) cyclopic consequences of its action.

Once the concepts are dealt with, the book goes justifiably into detail on different organisms. It is difficult to grasp general concepts without knowing the descriptive background; although the plethora of terms and structures may be daunting to the student,

there seems to be no other way to understand the mechanisms underlying developmental processes than to know, at the descriptive level, how an organism undergoes normal development. Chapter 2 focuses on *Drosophila* development, appropriately because, as the authors point out, we have more in-depth developmental knowledge about the fly than about any other animal. The treatment is systematic and clearly presented, with beautiful illustrations. Most of the important concepts are presented here; although, not surprisingly in a text of limited size, much of the crucial evidence is not. It is a justifiable way to present material to the student, presumably providing reinforcement for lecture material, but leaving the lecturer something of substance to talk about. Some might argue that the descriptions of concepts don't matter a whit, and what is more important is that the students can reason and can design or interpret experiments to establish for themselves how a concept is established. The ideal probably lies in between. Perhaps in a book about principles, the authors could have put more emphasis on some of the general principles of developmental biology experiments, such as the inferences that can be drawn from gain- and loss-of-function experiments, approaches which enjoy so many variations. The boxes that include the methods are generally excellent, though they are not necessarily presented in a consistent manner: The Cre-lox system in the mouse and mutagenesis in the fish receive nice pink boxes, but homologous recombination in embryonic stem cells is in line with the text.

The latter techniques are described in the chapters on vertebrate development. An introductory chapter to this section describes vertebrate development and common methods, and is followed by a chapter on setting up the body axes. This represents a change from the previous edition, in which these topics were covered in a single chapter, and is one of the good updates. The chapters on vertebrate development, just like the others, are clear and beautifully written and illustrated. Chapters covering the more complex topics, such as somite and nervous system development, follow as epigenesis proceeds. At this juncture, the early embryology of other prominent model animals, the nematode, sea urchin and ascidian, take center stage, and a chapter on plant development rounds out the coverage of organisms.

The book then circles back to various developmental processes. Admirable examples from various phyla are used to



illustrate the process of morphogenesis, in which underlying cellular processes can be seen to give rise to changes in the shape of the organism or tissue. The selection of examples from diverse organisms is made possible by the earlier descriptive coverage, which no longer need get in the way of the discussion of concepts. Germ cells and sex determination are followed by gene expression, cell differentiation and plasticity, including another excellent update in the current edition – inevitably, on stem cells and the plasticity of gene expression.

Lewis Wolpert and Cheryll Tickle ... have made excellent selections in *Principles of Development*

A book by Wolpert and Tickle would be incomplete without extended treatment of the limb, and a chapter on organogenesis includes vertebrate and insect limbs, eyes and various internal organs. The authors' expertise in limb development is reflected in the greater citation of experiments in this area, though this may challenge the undergraduate who wants a clear-cut story. One has to admire Wolpert for giving prominent treatment to his progress zone model, which most people might present as a great idea that is no longer tenable. But, perhaps if a book is to emphasize principles, it only matters if they are good possibilities, not whether they are currently supported.

The book closes with an excellent summary of developmental neurobiology, a chapter on post-embryonic growth and development, an expanded treatment of regeneration and a good evo-devo summary.

If the book is to remain manageable in size, it is inevitable that some favorite topics of the reader might be glossed over. However, despite the admirable emphasis on principles and concepts, I occasionally felt short-changed. With these authors, I might have expected a deeper treatment of what surely must be one of the most important principles: the existence of threshold responses to morphogens – molecules that diffuse from a source and set up a graded concentration. Instead, when it gets to the nitty gritty of boundaries, the activating and repressing activities of one gradient (such as hunchback or dorsal) are mentioned, but how one protein both activates and represses is not explained. Indeed, the text gets pretty dense and lacks

figures that would clarify the molecular mechanisms at play in threshold activation. Later in the book, one might have expected a deeper treatment of hedgehog signaling and threshold responses, as that might be the clearest case of a morphogen gradient at work in vertebrates. And what is the best evidence that these molecules really act as morphogens? It certainly isn't simple, but many students can deal with the evidence. Similarly, an important developmental principle is that internal organs achieve a high surface area by branching morphogenesis. The treatment is again a bit glib; genes and proteins that promote or inhibit branching are enumerated, but I don't think the authors can have stood up in front of a class and tried to argue that this really explains branching, unless their students are more passive than ours. One hopes that the undergraduates will test the lecturer's understanding at points like this and demand a deeper explanation, or an admission that the emperor indeed has no clothes.

Finally, although the opening chapter addresses what may be some important principles and concepts, these should be more explicitly re-stated throughout the book. I don't think that students find these concepts obvious, particularly when the details, terms and descriptions come thick and fast. Indeed, one might ask why there

should be principles of development – after all, evolution selects whatever process happens to work and developmental biology is full of ad hoc solutions to problems. Nevertheless, there are some core principles that recur in development, suggesting that these must be either ancient and inherited, or arrived at by convergence. Anterior-posterior patterning by deployment of Hox genes might be an example of the former, whereas branching morphogenesis might be an example of the latter, for which it is arguable that each organ might employ a different morphogenetic program.

It is inevitable that a reviewer will raise some criticisms; nevertheless, as it stands this is an outstanding text with a well-digested and comprehensive presentation of current views in developmental biology. It is a text I can enthusiastically recommend for adoption in developmental biology courses.

For those courses that have previously used this text, is the fourth edition worth the upgrade? The hardback edition is expensive and it would be hard to justify the burden of an expensive new edition on a fresh set of undergraduates when the cheaper previous editions of *Principles of Development* might be available. The paperback is a better deal and my review copy hasn't fallen apart yet. Still, as Oliver Wendell Holmes said, "A man is usually more careful of his money than of his principles."

Fast-forward: the fourth dimension in development

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Imaging in Developmental Biology: A Laboratory Manual

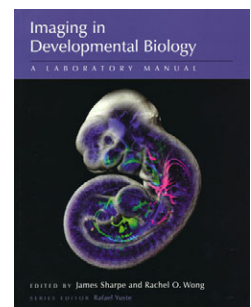
Edited by James Sharp and Rachel O. Wong

Series Editor, Rafael Yuste

Cold Spring Harbor Laboratory Press (2011) 883 Pages
ISBN 978-0-879699-40-6 (paperback), 978-0-879699-39-0 (hardback)
\$165 (paperback), \$246 (hardback)

Development is a bit like Star Trek, the long-running television series in which 'space' is the final frontier. For development, the final frontier is the fourth dimension, 'time'. Time travel through the

embryo, from the zygote to gastrulation, to organogenesis, and birth, has been a subject of fascination and science (fiction?) for centuries. This fascination is reflected in the many historical drawings of developing embryos and by advances in the field of embryology that came with the invention of the microscope. With the aid of microscopy, the field advanced from drawings of embryos to static images of fixed sections, which could be rendered, with some mental effort, into three-dimensional (3D) structures. However, comparisons of embryos at different formative stages could



only hint at the patterns of dynamic cell growth and morphological change that occur during development, which recent molecular and genetic analyses have begun to uncover. Importantly, the current advances being made in innovative, real-time imaging technologies and in the computational processing of images have now fast-forwarded the field boldly into the dynamic fourth dimension. These advances are now summarized and explained in a newly published book on imaging, *Imaging in Developmental Biology*, edited by James Sharp and Rachel O. Wong, both experts in this field.

It is a valuable guide ... although serious training might be required to perform the more complex experiments

Imaging in Developmental Biology is an excellent resource from which both novices and experienced researchers can obtain current state-of-the-art embryo-imaging protocols for studying key developmental events, such as cell-fate determination, morphogen gradient formation, cell-cell interactions, cell migration and morphogenesis. The eye-catching cover immediately attracted passing lab members, encouraging them to browse the book, which they did with increasing interest. The first comment often expressed was: "I did not know that we could do so much!" Upon first perusal, this comprehensive book seems almost overwhelming with an impressive 57 chapters and seven appendices. But it does contain just about everything known about imaging embryos. This is not surprising as the volume is based, in part, on the popular and excellent Cold Spring Harbor imaging course. The editors have organized the book into four large sections, which contain chapters that are frequently and conveniently cross-referenced. A particularly helpful table is provided in Chapter 1 that guides the reader to specific protocols of interest in different animal models.

Section 1 (Chapters 1-7) provides a general entry into the imaging of common model organisms. This section's emphasis on the advantages and disadvantages of each model organism allows researchers to evaluate quickly which animal model and procedures might be most useful for their specific investigations. Information is

provided on embryo accessibility and size, tissue transparency, different cell-marking techniques, phototoxicity, mounting methods and compatibility with imaging resolution, and image analysis. Chapters are written by experts in the field, and each starts with a brief introduction into the mechanisms of development being addressed and with a description of the specific imaging method used, followed by one or more protocols. Concise troubleshooting, discussion, recipes, web resources and reference sections provided at the end of each chapter are of added benefit in ensuring the success of the approach.

Live imaging of cells is the focus of Section 2. Cell-labeling protocols in Chapters 8-13 provide an extensive coverage of dye injection and electroporation techniques for groups of, and for single, cells in chick, mouse, *Xenopus* and zebrafish embryos. The protocols provide important technical details about, for example, injection pipette production, electrode placement, voltage strength, pulse duration and intervals. Other labeling techniques covered include the difficult MARCM (mosaic analysis with repressible cell marker) in *Drosophila* and MADM (mosaic analysis with double marker) in mice. Commonly used direct transgenesis and knock-in strategies with fluorescent marker genes, as well as Cre-Lox recombination and fluorescence-photoactivation methods, are presented in the context of specific developmental questions concerning cell-lineage tracing. The relative merits of the different strategies are clearly described in Chapter 13. Chapters 14-23 cover live cell imaging of cell migration, mostly of the neuronal system. Particularly useful here are the descriptions of the use of the photoconvertible fluorescence marker Kaede to study neuron birth dating in zebrafish embryos, and the explanation of DNA injection methods, embryo embedding, image acquisition and software usage in the context of studies of zebrafish retina and lateral line development. As mouse developmental biologists, we found the zebrafish protocols and figures (in Chapters 16-18) easy to understand. Of special interest to us were Chapters 20 and 21, as the details of pre- and post-gastrulation mouse embryo dissections with excellent accompanying figures are an important resource for our students. These chapters contain detailed protocols for tagging cells with dyes, grafting cells into embryos and for electroporating DNA into

groups of cells. The excellent figures and descriptions that detail how to culture embryos, hold them in place and manipulate them will be of great use for studying cell-fate determination and migration in early mouse development. Chapters 19 and 23 describe the imaging of embryo slice cultures in various species and tissues. As an important aspect of neural development, the imaging of circuit formation is the focus of Chapters 24-35, which are aimed at specialists studying neuron excitation, axon pathfinding or synapse formation. However, these approaches are also of broader relevance to research in other developmental systems.

Imaging multicellular tissues and organs as a whole dynamic entity is covered in Section 3. The first two chapters (Chapters 36 and 37) explain how to quantify morphogen gradients over time in *Drosophila* embryos. We found these chapters harder to understand and aimed more at the specialist reader. By contrast, Chapters 38-43 on cell movement describe more commonly used methods to acquire high-resolution dynamic movies of cells or subcellular proteins during morphogenesis in *Xenopus*, zebrafish, chick, quail and mouse embryos. Protocols provided in this section include how to generate *Xenopus* and zebrafish embryos with mosaic fluorescent reporter expression and how to prepare and mount tissue explants or whole embryos for long-term imaging, together with useful troubleshooting tips. This section also contains a well-illustrated protocol to perform high-resolution multiphoton time-lapse imaging of a developing chick embryo and protocols for 3D time-lapse imaging of epithelial morphogenesis and of the mouse metanephric kidney. Two relatively new imaging technologies are presented in Chapters 44-46 that allow live imaging of developing whole embryonic organs – optical coherence tomography (OCT, an optical version of ultrasound used to image high-speed events) and a non-invasive ultrasound technology used to image 3D organ geometry (which allows developmental events to be imaged over time).

After single cells and organs, Section 4 focuses on imaging the whole embryo in 3D and 4D. These chapters provide detailed protocols for the collection of spatial and temporal patterns of gene expression, for embryo phenotyping and for generating static or dynamic 3D atlases of model systems. Of particular interest is Chapter 48, which provides a didactic description of the intellectual and technical efforts of

the Berkeley *Drosophila* transcription network project, which has produced a computationally analyzable, gene expression and morphological 3D atlas of a blastoderm embryo. The use of hardware and software is also well explained and illustrated in detail, including chapters on optical projection tomography (OPT), X-ray micro-computed tomography (μ CT), episcopic fluorescence image capturing (EFIC), high-resolution episcopic microscopy (HREM) and macroscopic magnetic resonance imaging (μ MRI), with detailed information again provided for troubleshooting as well as additional web resources. Descriptions of the advantages, disadvantages, limitations and future prospects of each technique will definitely assist readers in choosing the appropriate method for their own application. The fourth dimension, time, is finally reached in the last chapters (56 and 57). Protocols are provided here for high-volume 3D time-lapse imaging of live adult *Caenorhabditis elegans* and of zebrafish and *Drosophila* embryos. Digital representations of these embryos permit cell tracking in time, revealing their origin and fate, which is of

particular interest to developmental biologists.

Altogether, *Imaging in Developmental Biology* is a book for those *Development* readers who are curious to know more about new technical developments and possibilities within the exciting field of imaging. It is a valuable guide and a very helpful laboratory manual for students, although serious training might be required to perform the more complex experiments. Seven appendices at the end of the book are particularly helpful for new people entering the field and include a must-have list of fluorescent filters and excitation/emission spectra, lens cleaning tips, a list of cautions and potential disasters, and an all-important glossary of terms. The book is pleasant to read, with its clever use of illustrations, photos and online protocol videos. Thus, we highly recommend this book and hope that multidisciplinary collaborative expertise in biology, imaging, image analysis, computer science, visualization and database construction will continue to fast-forward 4D imaging techniques and, consequently, our knowledge of development.

ways in which gene expression is regulated post-transcriptionally, have meant that the field of RNA has undergone rapid growth in the past few decades. This rapid growth has recently increased even further because of the discovery of RNA interference (RNAi), as well as the discovery that small RNAs, distinct from tRNA and snRNA, undergo processing to fulfil a range of cellular functions. These include the regulation of transposable element transposition by piRNAs, regulation of translation by microRNAs and still poorly explored large non-coding RNAs (ncRNA). Many of these ncRNAs have turned out to have important roles in development and during disease processes, such as cancer. Therefore, it is clear that all aspects of RNA molecular biology have now become central to our understanding of cell and developmental biology.

Despite the rapid growth and exciting discoveries made recently in the field of RNA, to my knowledge there has not been a comprehensive textbook for undergraduates and postgraduate students that focuses on the molecular biology of the cell from the perspective of RNA. *Molecular Biology of RNA*, by David Elliot and Michael Ladomery, now plugs this gap. This comprehensive textbook is pitched at just the right level and explains the concepts in sufficient detail to make them come to life without swamping the uninitiated with confusing information and jargon. The authors have to be congratulated on the comprehensive nature of the textbook, which means that even RNA aficionados will find useful information within its pages. At the same time, it is a relatively short tome (400 or so pages) and reasonably priced.

After introducing some important general principles of RNA structure, catalysis and RNA-binding proteins, the chapters of the book are structured according to the life cycle of an mRNA, starting with its birth in the nucleus, its splicing and processing and exit from the nucleus, and moving onto its subsequent cytoplasmic localisation, translation and degradation. These broad themes are broken down into more detailed concepts; for example, RNA processing is covered by chapters on co-transcriptional processing, splicing, alternative splicing, and splicing defects in development and disease. Nuclear exit is broken down into the processes of mRNA nucleocytoplasmic trafficking and ncRNA nucleocytoplasmic trafficking. It is clear that the authors have placed greater

A molecular view of the life and time of RNA

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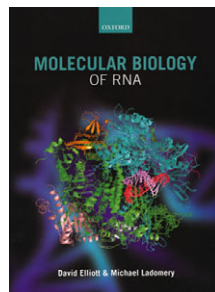
Molecular Biology of RNA

By David Elliot and Michael Ladomery

Oxford University Press (2010) 460 pages
ISBN 978-0-19-928837-3
£34.99/\$55 (paperback)

Following the discovery of the structure of DNA and during the early days of molecular biology, RNA was considered to be a less interesting cellular component to study than DNA. This was primarily because RNA was thought to be simply a molecular photocopy of the genetic blue print stored in DNA. But how things have changed! Since those early days, our understanding of the cellular roles of RNA has changed radically. RNA is now considered to be of central importance to both molecular biology and cellular function. Far from only containing genetic information, RNA is

now regarded to have credible catalytic properties through the availability of its 2'-OH, a reactive group that replaces a non-reactive 'O' atom in DNA. Moreover, its catalytic roles include key functions in the most important molecular machines of the cell, such as the spliceosome and ribosome. In hindsight, it would perhaps not be so surprising if the RNA world hypothesis turned out to be correct. This hypothesis states that the first life forms on our planet were RNA-based simple cells in the pre-biotic soup. RNA is certainly a better candidate than either DNA or proteins for a self-replicating molecule that acts both as a template for, and that has the necessary catalytic machinery to perform, its own replication. Moreover, the discovery that most mRNAs are spliced, and the gradual uncovering of a breathtaking number of



emphasis on nuclear events than on those in the cytoplasm. Although this makes the textbook a little unbalanced, it does mean that for anyone interested in nuclear events related to RNA, there is considerable detail. By contrast, for topics like mRNA localisation, the book offers a simplified overview to less experienced scientists, but lacks necessary details.

This comprehensive textbook is pitched at just the right level and explains the concepts in sufficient detail to make them come to life

The book is well written, easy to follow and, on the whole, strikes a good balance between providing sufficient detail and providing a simplified description of complex concepts. The authors have succeeded in producing a volume that is very useful for both undergraduate and graduate students starting a research career in an RNA-related topic, as it includes a comprehensive glossary at the end of the book. The textbook will still be of value to more experienced researchers from other fields that wish to get a quick comprehensive introduction to RNA research or to get started with a particular subtopic, such as splicing or mRNA localisation, as each section has a well chosen set of references as an entry point to a field. When deciding whether to purchase the book, readers may wish to consider what else is available covering the topic of RNA. There are a number of other excellent textbooks that focus on methods used in the RNA field; for example, *RNA Worlds: From Life's Origins to Diversity in Gene Regulation*. In general, these textbooks are more specialised, more expensive and appeal to more experienced researchers. This year has also seen the publication of *RNA: Life's Indispensable Molecule* by James Darnell, which, like the textbook by Elliot and Ladomery, is also being sold at an affordable price and is also meant for young researchers at the beginning of their research careers. However, Darnell uses a very personal and subjective style to describe the history of RNA research – a very different approach from the systematic textbook description employed by Elliot and Ladomery in *Molecular Biology of RNA*.

Although *Molecular Biology of RNA* offers a good systematic introduction to RNA research, it is also important to consider the limitations of the book. The diagrams are perhaps a little too simplistic and would certainly have benefited from a more stylised approach and perhaps from being in colour. However, this may have pushed up the cost of the textbook. As mentioned earlier, perhaps most importantly, there is an over-representation of events in the nucleus, particularly splicing, at the expense of equivalent levels of detail on topics in the

cytoplasm, such as mRNA localisation, translation and degradation. I am already looking forward to the next edition, in which these deficiencies can be addressed, perhaps at the expense of making the textbook a little longer and increasing its cost slightly.

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Epigenetics in all its glory

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Epigenetics

Linking Genotype and Phenotype in Development and Evolution

Edited by Benedikt Hallgrímsson and Brian K. Hall

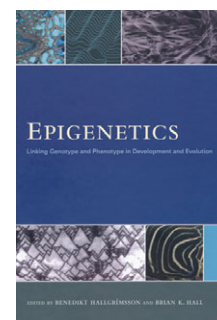
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Ask ten scientists their definition of epigenetics and you may get ten answers. In its simplest form, epigenetics can be defined as above (epi) the level of genes (genetics), and in the book entitled *Epigenetics: Linking Genotype and Phenotype in Development and Evolution*, the editors, Benedikt Hallgrímsson and Brian K. Hall, have assembled 23 chapters that collectively embody epigenetics as described by this broad definition. Although the book is organized into four parts, it can be distilled into three themes that each discusses a more detailed interpretation of the field: molecular epigenetics, classical epigenetics/epigenetic interactions, and epigenetic interactions and evolution.

In its modern molecular reiteration, epigenetics is defined as a change in gene activity without a change in DNA sequence. Most molecular definitions of epigenetics also include the idea of heritability, or memory of gene activity, through cell division. Here, epigenetic modifications modulate gene expression through DNA

methylation, histone modifications, changes in chromatin structure, and effects of non-coding RNAs. This book includes five chapters on molecular epigenetics, covering various organisms and topics from asexual organisms in the study of epigenetic variation to epigenetics and human disease. One chapter highlights neural development in which cell-fate switches are intimately linked with epigenetic changes. For example, transition from a neural stem cell to a progenitor cell involves a switch in co-factor associations. In response to Notch effector molecules, the HES1 repressor complex is transformed into a HES1 activator complex, thereby inducing a progenitor cell fate. A different mechanism may be utilized in neuronal fate specification in the neocortex. Changes in DNA looping and nuclear matrix binding may specify an upper layer neocortical fate. This chapter describes the current understanding of various epigenetic mechanisms involved in neural cell fate decisions.

The second theme of the book is classical epigenetics or epigenetic interactions. It is referred to as classical because the term 'epigenetics' was first coined by Conrad Waddington in 1942. Waddington's definition of epigenetics was 'the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into



being' (Waddington, 1942). In Chapter 7, Ellen Larsen and Joel Atallah introduce epigenesis as the gradual unfolding of structure and function during development and present the analogy of a fertilized hen's egg that develops into a downy chick: scrambling the egg retains all the genetic material and yet there is no development. This exemplifies the point of epigenetic interactions that occur above the gene level. Here, epigenetic interaction is the umbrella term for cell migration, physical interaction among cells and tissues, mechanical forces, embryonic induction (including cell signalling and hormones), and interactions between cells and their intrinsic or extrinsic environment. All these interactions may play a role in generating the 'epigenetic landscape' through which a cell must transverse to reach its final differentiated state within a tissue or organ. These epigenetic interactions are discussed in nine chapters, each of which focuses on the development of a specific cell type, tissue or organ. One chapter describes the mechanical force of muscle activity on bone as an epigenetic stimulus for developmental change. Using the mammalian jaw as the model system, the effects of mechanical force (muscle force, bite force and compression load) on lower mandible condylar cartilage growth are explored. Evidence is presented for increasing force leading to shorter, wider condylar cartilage growth and decreasing force for longer, thinner condylar cartilage growth. This chapter illustrates mechanical forces on development as an epigenetic mechanism.

Ask ten scientists their definition of epigenetics and you may get ten answers

The third theme, covered by six chapters in this book, is epigenetic interactions as a framework for evolution. For example, one chapter focuses on the epigenetic integration of various head modules (brain, bone/cartilage, muscle, eyes, tongue, teeth, muscles, sinuses/cavities) in development and its variations during human craniofacial evolution. Another chapter discusses the concept of adaptive plasticity and genetic assimilation in evolutionary change, as exemplified by the phenotypic and behavioural changes in threespine sticklebacks in different ecotypes. In deep, nutrient-poor lakes, threespine sticklebacks

have evolved long snouts with upturned mouths suitable for planktonic prey, have lost group cannibalistic behaviour and display conspicuous courtship displays. In shallow, nutrient-rich lakes, threespine sticklebacks have short snouts and wide mouths for feeding on benthic invertebrates, display group cannibalistic foraging and have inconspicuous courtship, consisting of dorsal pricking. This chapter explores the phenotypic plasticity of an ancestral population in response to novel environments and its role in influencing subsequent evolutionary change.

In all languages, including the language of biology, words and terms can evolve and, thus, their meaning can change. Over time, the modern molecular definition of 'epigenetics' has supplanted other definitions. In *Epigenetics: Linking Genotype and Phenotype in Development and Evolution*, Hallgrímsson and Hall provide a comprehensive selection of epigenetics in its many forms and appeal to the reader to accept a broader definition of epigenetics – one that includes all things epigenetic: not just molecular epigenetics, but also classical epigenetics and epigenetic interactions related to evolution. Importantly, the context inherently linked in

these definitions of epigenetics is the complex and finely tuned choreography of development. In the not too distant future, we will probably find that these definitions are intimately linked. As stated by Root Gorelick, Manfred Laubichler and Rachel Massicotte in Chapter 6 'the molecular epigenetic signals [can be considered] the nuts and bolts underlying the classical epigenesis *sensu* Waddington'.

This book celebrates epigenetics in all its glory. As a first of its kind, I recommend this book to researchers and graduate students who want to widen their perspective of epigenetics and its role in development and evolution. Because of the division in meaning, this book does require the reader to switch gear depending on whether the chapter is on molecular or classical epigenetics. Furthermore, it is steeped in epigenetic, development and evolution terminology. This makes it less than suitable for the undergraduate student. However, this book would be an excellent resource for a graduate course in classical epigenetics, or epigenetic interactions and evolution.

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A wake-up call to delve deeper into the cell

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The Nucleus

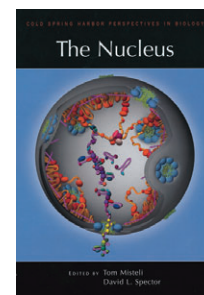
Edited by Tom Misteli and David L. Spector

Cold Spring Harbor Laboratory Press (2011) 517 pages
ISBN 978-0-879698-94-2
\$135 (hardback)

Why should a developmental biologist be interested in a book about the nucleus? Almost 80 years ago, Conrad Waddington put forward ideas about how gene products could regulate development. In modern parlance, much of development is the result of the differential use of the same genome in different cell types and at different developmental stages within the same organism. This originates in the nucleus, where the processes that act upon the genome

– transcription, replication, repair – occur. In developmental biology papers it is not uncommon to find a final summary figure in which a signaling pathway ends up pointing into an oval-shaped nucleus, devoid of any structure or organization, save for a linear depiction of a target gene locus. However, the nucleus is not a homogenous space and neither is the genome in its natural nuclear environment arranged in a linear fashion.

The contributions in this book, from international leaders in the field of nuclear organization and function, are based upon the premise that we cannot really understand how genomes function without an appreciation and understanding of their natural cellular environment – the nucleus.



The 28 chapters are organized to provide a comprehensive overview of nuclear compartments and their components (e.g. nuclear membrane, nuclear pore complex, chromosome territories, Cajal body, nucleolus), to discuss how this organization relates to function (transcription, DNA replication and repair, RNA processing) and to describe the defects in nuclear organization in human disease. The focus is primarily on the nucleus in mammalian cells, but there are also discussions on other simpler model organisms – budding yeast, *Caenorhabditis elegans* and *Drosophila*. Each chapter is relatively short and accessible, making this a great resource to dip into. Illustrations are used sparingly but are well chosen.

The main target audience for this book is likely to be teachers and students of cell biology. The most interest for developmental biologists will lie in those chapters that deal with the organization of the genome and the transcriptional machinery within the nucleus. Spatial and temporal changes in genome organization are increasingly recognized as important aspects of gene regulation, especially in stem cells and differentiation. Thus, from a developmental biologist's perspective, it is disappointing that no specific chapter is dedicated to the nucleus in development, but there are nuggets of relevant information within most chapters. The chapter on dosage compensation (written by Jennifer Chow and Edith Heard) is of direct relevance to events that occur in early embryogenesis, and a chapter on Lamin-binding proteins (written by Katherine Wilson and Roland Foisner) emphasizes the fact that proteins of the nuclear periphery that link the nucleus to the cytoskeleton are particularly important in regulating the position of the nucleus in specific cell-types or tissues (e.g. retina and neurons) and in relaying signals from the cytoplasm to the nucleus.

No specific chapter is dedicated to the nucleus in development, but there are nuggets of relevant information within most chapters

Developmental biologists often ask where and when a gene or protein is expressed in the developing organism. However, rarely do they ask precisely where within the cell a particular protein is located.

There are several examples of proteins that are expressed within a particular cell type, but are sequestered into a nuclear compartment that renders them functionally inactive. Thoru Pederson gives a fascinating example of this (sequestration of the Hand1 transcription factor into the nucleolus of trophoblasts) in his chapter on the nucleolus. This should be a wake-up call for developmental biologists to delve deeper into subcellular organization. Conversely, most cell biology of the nucleus is still studied in cell lines rather than in real biological organisms or embryos. There is clearly scope to bridge these two disciplines. Indeed, in their chapter on Chromosome Territories, Thomas and Marion Cremer provide a superb example of the benefits that can come from considering nuclear organization in a developmental setting.

They describe the amazing nuclear reorganization of the genome that occurs, after birth, in the rod cells of nocturnal mammals and they emphasize how such a fundamental aspect of nuclear organization can be turned on its head in the face of selection pressure – in this case, to facilitate the passage of photons to photoreceptors in low light levels.

There are other equally fascinating examples to be found in this book where nuclear organization impinges directly on developmental processes. Nuclear condensation in terminally differentiated cells and aberrant nuclear organization in cancer are just two examples that come immediately to mind. So, although not targeted at developmental biologists, if your interest in the nucleus is piqued, then this book is a good place to start.

A practical guide to human stem cell biology

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Human Stem Cell Technology and Biology: A Research Guide and Laboratory Manual

Edited by Gary S. Stein, Maria Borowski, Mai X. Luong, Meng-Jiao Shi, Kelly P. Smith and Priscilla Vasquez

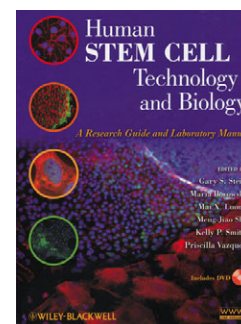
Wiley-Blackwell (2011) 419 pages
ISBN 978-0-470-59545-9
£93.50/€112.20 (hardback)

Do we need another book on human stem cell biology? The field is fairly long in the tooth now, thirteen years after Thomson first derived human embryonic stem (ES) cells (Thomson et al., 1998). There are many books that cover the theoretical aspects of the discipline (Oderico et al., 2004) and others that attempt to collate protocols useful to human stem cell biologists (Sullivan et al., 2007). Nevertheless, the new book *Human Stem Cell Technology and Biology* succeeds in combining both of these characteristics, providing not only a clear account of the scientific discoveries underpinning human stem cell biology, but also a useful range of laboratory protocols. The end product may be less comprehensive than Lanza's classic text (Lanza et al., 2009), but it is perhaps more

manageable and appropriate for a newcomer to the field or for an early career scientist working with human pluripotent cell lines for the first time.

The editors are all based at the Center for Stem Cell Biology & Regenerative Medicine at the University of Massachusetts Medical School. The individual chapters are written predominantly by scientists from institutes on the East coast of the United States, although some contributors are based in Australia, Canada and China. The book is divided broadly into five sections: an introduction; two sections on the culture and characterisation of human pluripotent stem cells; and two sections covering more recent technologies and applications relevant to human ES cells.

In the introduction, the authors have managed to distil over 50 years of stem cell advances in just a few pages of text. Although this may be too short for experienced scientists hoping for a colourful narrative history of each breakthrough, we think it does well to bring even novice readers up to speed with current thinking in stem cell biology, from the bottom up.



The sections containing protocols are excellent and provide the perfect framework for experimental work on human stem cells. Each chapter is devoted to a separate technique and begins with an extremely helpful overview that underlines the basic steps, and importance, of each protocol. The layout has been well thought out, supplementing the customary 'equipment' and 'procedure' sections with helpful tables, log sheets with blanks to be filled in and space for the reader to make their own notes in the margin. These protocols have been used as part of practical courses in stem cell biology at the University of Massachusetts Medical School for several years, and this is evident by the careful explanation of each technique in the book and the thoughtful addition of pros and cons of each technique.

Later sections of the book will appeal to established stem cell investigators as they summarise the latest in bioinformatic, genomic, epigenetic and proteomic analyses of human stem cells. These chapters provide a brief account of the logic and application of these various techniques, and feature tables and pictorial representations of the scientific basis of the techniques. This is most notable in the chapter on epigenetics.

Four years after Yamanaka's group first successfully reprogrammed differentiated adult human dermal fibroblasts into pluripotent cells (Takahashi et al., 2007), much attention should be paid to the chapter devoted to reprogramming and induced pluripotent stem cells. It outlines the differences between reprogramming during fertilisation and during somatic cell nuclear transfer. The chapter describes the major developments in reprogramming, such as the use both of cell extracts and of transcription factors, most notably the Yamanaka factors: Oct4, Sox2, c-myc and Klf4. The chapter does well to highlight the limitations of the current protocols, as well as recent attempts to improve the efficiency and safety of classical directed reprogramming using the Yamanaka factors.

Much has been made of the potential applications of human stem cell biology. The final section deals with these applications. These include the use of stem cells in drug screening (testing various types and doses of medications to streamline the drug development process); stem cells as in vitro models of disease (to further understanding of aetiology and pathogenesis); and stem cells in cell therapy

(using stem cells or insights into growth conditions to help repopulate and regenerate degenerative and diseased organs). Although brief, the final chapter manages to encapsulate the major recent breakthroughs and future prospects for cell replacement therapies in ectodermal, mesodermal and endodermal tissues.

One of the book's major strengths is the accompanying DVD. It provides printable copies of the protocols from the book, and even has a helpful search tool, which we found extremely useful. The DVD also contains six videos, which demonstrate good laboratory practice, aseptic technique and how to harvest, passage and thaw cells. We would strongly recommend that laboratories use these videos as part of the induction of new members to stem cell labs, as few laboratory members have the time or training to offer such a clear and standardised tutelage on the basics of laboratory practice and stem cell culture. The lead editor, Professor Gary Stein, provides much of the training in these videos himself. The book also boasts a student companion website (<http://www.wiley.com/go/stein/human>) which is supposed to collate updates, amendments and additional resources. However, we were disappointed to discover that at the time of writing there were no additional resources available.

To the beginner, the field of stem cell biology ... can seem impossible to navigate. This book will act as an excellent guide.

We would recommend this readable and well-organised book to all laboratories dealing with human ES cells. We envisage that a laboratory copy will prove to be invaluable as a reference text for all new members of your laboratory, and the later sections will be of benefit to more senior investigators. Although not the most energetic nor the most exhaustive book of this type on the market, this volume succeeds by summarising the historic and recent research breakthroughs in human ES cell science and combining this with excellent and reliable laboratory protocols. To the beginner, the field of stem cell biology – with a burgeoning number of principles, terms and techniques to master – can seem impossible to navigate. This book will act as an excellent guide.

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