

Theme and variations on biology and civilisation

Alfonso Martinez Arias

Department of Genetics, University of Cambridge, Cambridge CB2 3EH, UK.

ama11@hermes.cam.ac.uk

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Cells to Civilizations: The Principles of Change that Shape Life

By Enrico Coen

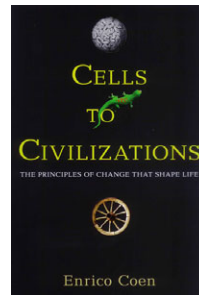
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In 1953, Alan Turing, a mathematician who had enabled the allies to break the Nazi communication codes – thereby making a significant contribution to ending the war in Europe – turned his attention to biology. Acknowledging the chemical make-up of living systems, he wondered what kind of reactions could generate the spatial patterns that are so pervasive in the outer layers of plants and animals. He noted that carefully coordinated interactions between an activator and an inhibitor, coupled to their diffusion, would, under certain conditions, be able to generate stable patterns of spots and stripes that resemble some of those found in nature. This simple chemical circuit had the potential to explain many phenotypes and as such has received attention over the last 50 years, although Turing himself only studied it as a proof of principle.

Biology is not just about the spots of the leopard. The field encompasses an apparently bewildering array of remarkable facts, from the ability to sense our environment to the workings of the cell cycle or the amazing periods of the cicadas. As our understanding of the elementary composition of biological systems increases, the question emerges whether there are any unifying principles to the variety that is their hallmark. Biology is not rich in laws or principles in the way that the physical sciences are. Thus, if a common thread, a principle of some sort, could be found, running from DNA to the behaviour of a population of ants, or even further to our ability to conceive and execute a painting or a symphony, this would be a remarkable observation with the power to transform our understanding of nature. In *Cells to Civilizations*, Enrico Coen, who stimulated us with *The Art of Genes*, shares his insights and solution to this puzzle. What he calls



“life’s creative recipe” is claimed to be a collection of simple principles that, when applied to diverse biological systems, reveal a surprising number of similarities and relationships that can be cast into an understandable, explanatory diagram. If true, it is tantalisingly close to a unified theory for biology. Furthermore, Coen dares to extend it further and explores the possibility that his recipe applies to culture, thus claiming to establish a seamless connection from genes to the paragon of human nature – its creativity.

Understanding heredity, development, evolution and the mind are the big challenges of biology. Coen sets out in search of a general explanation that encompasses the structure and function of each challenge and brings them together. He recounts that similar principles have been dreamt of before, but hastens to add that nobody has managed to produce something lasting. However, we are told that here we might find this elusive idea. Do not be daunted by the scope of the book, which is written for a wide audience, although it contains enough science for biologists and anthropologists to ponder and argue with Coen. For the rest, it is an easy read, particularly as the biology it contains is peppered with vignettes drawn from painting and art history, which act as a guide for the more dry science that forms the meat of the argument.

Having outlined the problem, and taking evolutionary biology as a reference, Coen rephrases some of the notions associated with Darwinism to put forward seven principles that can be seen at work at many levels in biology and which are the fabric of “life’s creative recipe”: population variation, persistence, reinforcement, competition, cooperation, combinatorial richness and recurrence. These principles are then applied to several biological questions, to bring together different phenomena under a unifying umbrella. “Life’s creative recipe”, at least qualitatively, provides a common mechanism underlying diverse processes at different scales of time and space. It is a deceptively simple double-feedback loop,

resembling an abstraction of Turing’s chemical machine but looking more like a Moebius strip. At the heart of the loop is a positive catalytic system (the principle of reinforcement), which is restrained by the negative effect: the principle of competition. The book unfolds as a sequential application of these principles to the major problems of biology, and shows that when these opposing forces are applied to a specific process they reveal related behaviours. The recipe is brought to bear on evolutionary theory and developmental biology in four chapters of about 50 pages each. From here the pace slows down and Coen launches into neurobiology, which is less familiar territory for him. He carries us slowly through his view of sensory neurobiology, learning and memory: a remarkable tour de force. The promise of a general recipe appears to work. As simplified examples, if the recipe has ‘reproductive success’ at the centre of the engine, ‘genes’ as activator and ‘environmental limitations’ as inhibitor, it models evolution. Plug in ‘firing’ and ‘neural inhibition’ onto ‘synaptic strength’ in the same recipe and you have learning. The patterns that shape life at different levels emerge from a regulated dialogue between opposites. Simple and effective. Interesting references to art history will retain your interest through the more challenging parts of the book. I particularly enjoyed the reference to the biologist and medieval armour expert Bashford Dean on the evolution of the helmet as a paradigm of biological evolution.

How can we know whether Coen’s [book] really tells us something about nature?

Having dealt with biology, Coen becomes ambitious and in Chapter 11 tackles culture. He acknowledges that this is a serious challenge and tells us that “we should be careful not to push (...) resemblances too far” and that “it is important to stand back to view the relationship between culture and the other processes at an appropriate level of abstraction”. I agree on both accounts, and the reader should bear Coen’s warning in mind when reading the book. At such a high level of abstraction, relationships can emerge that might not be real. To use one of the analogies in the book: there is a portrait of Ambroise Vollard by Cézanne, which was reinterpreted by Picasso. However, if

we looked at the Picasso alone, without knowing about this relationship, we would very likely make different interpretations as to what the canvas represents. Sometimes we see what we want to see. In the end, the problem with abstractions in science, particularly with qualitative ones, is that they turn into metaphors of limited value. Science is about the ability of a thought to explain detail rather than to describe a loosely defined reality. Herein lies an important consideration for the still young biological sciences. When the physicists strive to find unified theories, they have numbers to aim for and experiments that they can do – experiments that have drowned more than one sublime theory. In physics, knowing whether we understand something is well defined: either you get the number or your predictions – which often consist of numbers – are wrong. At first sight, biology is not like this and determining whether or not a certain theory, principle or even idea is right or wrong requires a precise definition of what is being implied or said, as well as

considerable time to investigate it. So, how can we know whether Coen's proposed "life's creative recipe" really tells us something about nature, or whether his book provides just another pleasant read?

Caveat lector. In physics, unifying theories have a strong quantitative basis and outlook. The theories live or die by how much of the detail, in particular of the quantitative world, they can explain and how much they can predict. Art, on the other hand, is content with the view it creates of a reality, which it captures without constraints. Enrico Coen is aware of this difference and only time will tell what exactly his effort has achieved, how much it explains and how much it predicts. It is likely that recent developments in the quantitative analysis of biological processes will lead to a rewriting of biology over the next few years. This in turn should provide some precise elements to the general argument developed in *Cells to Civilizations*, which is still very much grounded on the qualitative analysis of biological phenomena.

comprehensive introduction to genomics that covers a diversity of topics, from genome sequencing to systems biology approaches used for understanding the metabolome, transcriptome and proteome. This new edition strives to highlight the progress made in genomics due to the increased application of high-throughput sequencing techniques. The text is accessible to undergraduate students; it does a thorough job of providing the basic principles before moving on to more in-depth concepts. The author presents an important discussion of the ethical issues surrounding genome sequencing, including the efforts taken to protect individuals who contribute samples to the large-scale human genome sequencing projects that are currently underway. These issues are presented in a well-balanced and unbiased manner. Importantly, the text is a pleasure to read; detailed colour illustrations are provided throughout, as well as helpful analogies that allow the reader to get to grips with difficult concepts. For example, biological networks are compared to the London Underground map, where the stations are the nodes and the edges the tracks that connect them.

This new edition highlights recent advances in sequencing techniques while still presenting the historical context for the discovery of genomes. Early in the text, the history of the discovery of DNA structure, the need to understand the 'language of the genome', and early progress in sequencing techniques are discussed in a narrative manner. Lesk writes, "*the sequence of the bases was like a text everyone wanted to read, not only was the text in an unknown language, but there were not even any examples of the language, because the sequences were unknown*", thus framing the importance of early DNA sequencing efforts in ultimately decoding the human genome. This leads into the development of Sanger sequencing, a method developed by Frederick Sanger, and the sequencing of the 5386 bp Φ X174 bacteriophage genome, the first completed DNA genome sequence. Following on from this is the adaptation of Sanger sequencing to automated DNA sequencing using fluorescent tags and next-generation high-throughput sequencing techniques. As in the rest of the book, colour illustrations are used to great effect to explain the techniques and to provide examples of data output. These examples of data output are increasingly important, as so few students today will ever perform a Sanger sequencing reaction and see how the individual base-terminated chains resolved

An introduction to decoding genomes

Jennifer A. Mitchell

Department of Cell and Systems Biology, University of Toronto, 25 Harbord Street, Toronto, ON M5S 3G5, Canada.

ja.mitchell@utoronto.ca

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Introduction to Genomics

By Arthur M. Lesk

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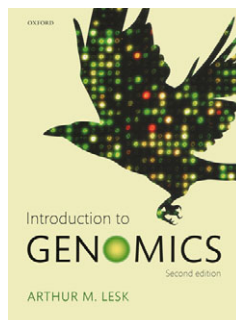
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The past 20 years has seen a revolution in genomics. From the completion of the human genome in 2003, which took 13 years, we are well on our way to achieving the next benchmark goal of having 1000 human genomes sequenced (The 1000 Genomes Project). This endeavour will provide a deep catalogue of human genetic variation. In addition, and as part of The Genome 10K Project (which aims to sequence the genomes of 10,000 vertebrate species), 2012 saw the initial assembly of the medium ground finch (*Geospiza fortis*) genome, one of the iconic Galapagos finches described by Charles Darwin. The

results of these genome sequencing projects are available through freely accessible public databases, thus accelerating discoveries in diverse fields of biology. With the advent of next-generation sequencing platforms, the time and cost of sequencing have dropped dramatically, making the ability to sequence the human genome in a day for less than \$1000 no longer science fiction but rather an event that will happen in the immediate future. The effects of this genomics revolution are widespread, and no field of biology or medicine remains untouched by the changes in sequencing throughput. Furthermore, genomic studies are so commonly highlighted by the media that a working understanding of genomics is increasingly important in undergraduate biology education.

The second edition of *Introduction to Genomics* by Arthur M. Lesk is a



on the gel are composed into a sequence. So, although this technique has been replaced with higher throughput variations, the visual understanding of the sequencing process provided by inspecting a Sanger sequencing gel remains unmatched.

Biological networks are compared to the London Underground map, where the stations are the nodes and the edges the tracks that connect them

At the end of each chapter, selected additional reading is provided with problems that test the concepts discussed. The problems posed range from testing the basic understanding of the material to more thought-provoking questions that will allow students to test and deepen their understanding of the material. Of special note are the ‘weblem’ problems, which require the use of online genomics resources. These encourage students to develop a proficiency in the use of these resources, many of which are linked to the text through the publisher’s website. A ‘guided tour’ of genomics websites provides a list of websites with short descriptions and links to instructions or tutorials where available; however, this is merely a teaser that will hopefully push young scientists to explore more thoroughly the information that is available online to the scientific community.

Although the second edition is updated with expanded content, the information on data gathered from next-generation sequencing projects is rather limited. However, as the author points out, this is a moving target with advances made weekly, and it is therefore difficult to ensure that the material is up to date in a text of this type. Even with this in mind, I found that the section on deep sequencing of transcriptomes and functional genomics could have been expanded upon; there is a huge wealth of genome-wide functional genomics data for human, mouse, fly and worm genomes generated by the ENCODE and modENCODE projects, which are only briefly mentioned (Gerstein et al., 2010; modENCODE Consortium, 2010; ENCODE Project Consortium, 2011). These data are easily accessible through online browsers (UCSC Genome Browser, modENCODE GBrowse), massively accelerating the discovery of new genes,

non-coding RNAs and regulatory elements such as enhancers and insulators. With the focus on students exploring genomics data on the web, these resources could have been better highlighted.

Given the widespread impact that sequenced genomes have on research, medicine and the general public, an introductory text such as this is an important resource. *Introduction to Genomics* is beautifully illustrated, supported by end of chapter and additional online resources, and written in an eloquent and readable style. Beyond focusing on genome sequencing and comparative genomics, a good deal of the text is concerned with transcripts, proteins and proteomics. However, there is minimal mention of transcriptional regulatory regions of the genome. I would have liked to see more emphasis given to transcription factor binding in the genome, epigenetic modifications and chromatin features, which are proving invaluable in identifying intergenic regulatory regions. Given the observation that disease-linked single-nucleotide polymorphisms are more often found in non-coding than in coding

regions (Manolio, 2010), understanding how regulatory regions function is crucial in decoding the human genome and understanding predisposition to disease. Nonetheless, *Introduction to Genomics* is a comprehensive textbook that provides a solid introduction to the study of genomes and will be a great resource to undergraduate students with a background in molecular biology. The text also provides a useful resource for graduate students in other fields who want to make use of the growing number of online genomics resources.

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Everything you always wanted to know about auxin but were afraid to ask

Sabrina Sabatini

Dipartimento di Biologia e Biotecnologie ‘Charles Darwin’, Sapienza Università di Roma, Via dei Sardi 70, Rome 00185, Italy.

sabrina.sabatini@uniroma1.it

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Auxin Signaling: From Synthesis to Systems Biology

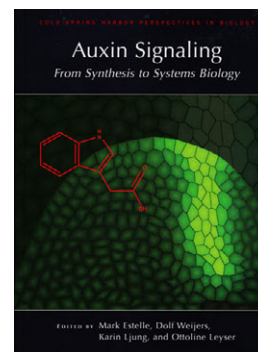
Edited by Mark Estelle, Dolf Weijers, Karin Ljung and Ottoline Leyser

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Whether you like it or not, if you work in plant science it is of utmost importance that you know what auxin is and does, since your research will, at some point, most certainly cross the auxin path. The plant hormone auxin regulates a plethora of developmental and physiological processes in plants. At the organismal level, the

differential accumulation of auxin forms gradients, which, through interactions with other hormones, regulate processes as diverse as responses to external stimuli and embryonic and postembryonic development. All of these macroscopic processes are a reflection of the changes in gene expression triggered by auxin. The book *Auxin Signaling* tries to provide a broad coverage of each aspect of auxin signaling, from synthesis to transport and signal transduction, along with an in-depth description of auxin’s role in various events in plant development.

The book opens with a chapter by Abel and Theologis on the historical context of



auxin research, which provides an evocative description of the scientific journey that brought us to the present level of knowledge of auxin signaling. This section thrills the reader with the ups and downs of auxin research, and spurs them to read the rest of the book to discover where the frontline of auxin research is now. The book then divides into four sections: auxin synthesis and transport, auxin perception and cellular responses, auxin in development, and signal integration.

The second and the third sections work together to illustrate the conceptually sequential mechanisms by which auxin is synthesized, metabolized, transported and perceived by the cell, followed by the basic cellular response. The first chapter of these describes the state of our knowledge of the auxin homeostasis pathway, despite the difficulties in the quantification of auxin and its intermediates. Apart from giving an in-depth description of the pathway, the authors have included many references to the experiments behind the facts, enticing the reader to critically assess the source of information. The next two chapters provide a unique perspective on classical topics such as auxin transport and perception. In 'Auxin transporters – why so many?', the authors illustrate the complexity and redundancy of the auxin transport machinery in the light of evolution, offering a refreshing (and for once non-PIN-centric) point of view. The authors of the next chapter provide a very interesting structural insight into auxin perception, cleverly describing how auxin acts differently from other hormones, the application of this mechanism as a model in drug development, and, notably, a controversial idea of what truly constitutes an auxin receptor. Perrot-Rechenmann nicely concludes this section by bringing the reader from the purely molecular to the cellular level of the auxin response, as she skillfully describes all the intricate networks that regulate the two major destinies of a non-dying cell: division or differentiation.

After explaining all the main features of auxin cellular signaling, the fourth section of the book, which might interest the readers of *Development* most, focuses on the role of auxin in plant development. The seven chapters that constitute this section cover the classical developmental events in which auxin has been known to play a major role: embryogenesis, shoot and root meristem activity, lateral root and vascular formation, and the differentiation of reproductive organs. The added bonus of this section is an opening chapter on mathematical modeling and a closing chapter on auxin in

monocotyledon (monocot) development, which nicely broaden the horizon of the reader from the classical topics of auxin-regulated plant development.

The chapter on mathematical modeling describes recent efforts made to assist research on the role of auxin in plant development. Modeling is an invaluable tool for the study of convoluted signaling pathways, such as auxin's, in the context of complex events, such as those that occur in development. In addition to its descriptive function, mathematical modeling is, most importantly, an invaluable instrument for the generation of new hypotheses, and any researcher working in development nowadays cannot ignore it. This chapter, by explaining each model in terms that are not overly technical, gives a good basic overview of modeling in auxin biology while also representing a good starting point for those who, after reading it, want to know more.

The role of auxin in plant development is complex, but the chapters that constitute the core of this section do an excellent job at summarizing the vast literature on the topic. Moreover, each piece covers the most advanced data and theories of their topic, making this section a very good read, even, if not especially, for those that already work in the auxin field. Despite the clarity and the brief introductory remarks in all chapters, it will be better for the novice reader to have grasped the notions illustrated in the previous sections in order to get the most from these chapters.

The concluding chapter of this section not only describes the role of auxin in monocot development, but also gives a detailed overview on monocot development itself. Some plant researchers tend to focus their attention, for practical reasons, on dicots. This chapter, although explicative and comprehensive, reminds us that the comparative study of auxin function can, in the light of evolution, tell us more about auxin signaling than independent study in a single phylum.

The last section of the book deals with signal integration. The introductory chapter offers an unusual view of auxin as the currency of the plant cell. Beyond this singular metaphor, the chapter gives a broad overview of auxin pathway interaction with the light response, the circadian clock, other hormones and pathogens. The chapter that follows neatly describes all the molecular principles underlying the complexity that can be generated within the auxin pathway. In my opinion, this piece should be read before the chapters on development, as it lays fundamental concepts that would help

the reader to better interpret the events covered in the previous section. This is actually easy to do, since, as can be said for the whole book, each chapter is quite autonomous and can be read independently. The remaining chapters in this section cover the interplay between the auxin pathway and the response to light, and the importance of auxin in the plant-microbe interaction. Despite the high quality of this section, I believe that it lacks chapters on the role of auxin in the response to nutrient abundance, drought and the effects of other hormones on the auxin pathway. Although hints on these topics are given throughout, dedicated chapters would have made this book truly comprehensive.

Overall, this volume suffers slightly from being a subject collection, rather than a book. In particular, even though there is a preface from the editors and an excellent opening chapter, there is no concluding chapter, which leaves the reader slightly baffled at the end of the book. This is a common problem in scientific texts, but in a volume on a topic as complex as auxin signaling, a concluding chapter would have made the work feel more like a book and less like a well-edited collection of reviews.

The book is not only descriptive, but also provides the personal perspectives of the authors

However, each chapter in *Auxin Signaling* is truly remarkable: well written and easy to follow, providing sufficiently detailed yet understandable descriptions of complex concepts, and allowing a glimpse at the experimental procedures behind them. The authors have succeeded in producing a volume that could be extremely useful for a graduate student pursuing a research career in plant biology and, most certainly, for more experienced scientists who wish to gain comprehensive knowledge of the current state of auxin research. Indeed, the book is not only descriptive, but also provides the personal perspectives of the authors and thought-provoking discussions, making it of great interest for those who work in the auxin field. Although *Auxin Signaling* might be too specific for an undergraduate reader, its clarity makes it a good tool for lecturers and for those curious students who could still extract important notions and concepts from it.

Updated interpretation of the principles of neural development

Tatsumi Hirata

Division of Brain Function, National Institute of Genetics, Graduate University for Advanced Studies (SOKENDAI), Yata 1111, Mishima 411-8540, Japan.

tathirat@lab.nig.ac.jp

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Neuronal Guidance: The Biology of Brain Wiring

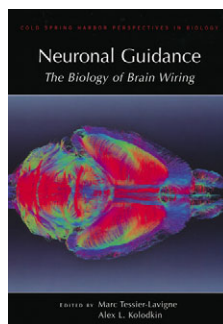
Edited by Marc Tessier-Lavigne and Alex L. Kolodkin

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As a graduate student, I learned developmental neurobiology from the *Principles of Neural Development* (Purves and Lichtman, 1985). This masterpiece textbook taught me the fundamental concepts of how neurons are interconnected, vividly described the historical experimental basis, and introduced me to the exciting field of developmental biology. However, this book is obviously out of date today, particularly since a great number of guidance molecules and pathways have been identified in the meantime, so I have had to look for a good alternative for graduate students and postdocs interested in this field. *Neuronal Guidance: The Biology of Brain Wiring* completely fulfilled my expectations.

As this book specifically focuses on neural guidance, it might not be an appropriate textbook for undergraduate students with a broad interest in developmental biology, but it will provide a very good read for postgraduates who have some experience in neurobiology or who are keen to have a research career in this or related fields. It will also be very useful for senior investigators wanting to catch up with the latest data in the field.

Following a brief primer written by the editors, Marc Tessier-Lavigne and Alex L. Kolodkin, the book is organized into 19 chapters, each contributed by experts on the topic. Initially, I was somewhat afraid that this style might make the book a selective collection of highly specialized reviews, but, thanks to the thoughtful choice of topics and contributors, the book is, in fact, much more comprehensive than I anticipated.



The chapters are grouped into three sections, each on a different aspect of neural guidance. The first chapter, by Jonathan Raper and Carol Mason, is entitled 'Cellular strategies of axon pathfinding', and provides a good basic overview of the history of axon guidance research and the general concepts obtained therefrom. The following eight chapters in this first section describe comprehensive guidance strategies in traditional and new models of nervous systems. These include chapters on such as visual map development by David A. Feldheim and Dennis D. M. O'Leary, nervous system midline crossing by Barry J. Dickson and Yimin Zou, and dendrite and axon tiling by Wesley B. Grueber and Alvaro Sagasti. A little unexpected is the inclusion of the chapter entitled 'Human genetic disorders of axon guidance' by Elizabeth C. Engle, which effectively provides a fresh perspective on this topic.

The second section of the book includes five chapters dealing with intercellular signaling in neural guidance. This section is more detailed than the first part of the book, and is devoted to the introduction of many molecules and their signaling pathways, reflecting the rapid expansion of this field in recent years. Among the chapters here, 'Signaling from axon guidance receptors' is a clear overview presented by Greg J. Bashaw and Rüdiger Klein, and 'Trafficking guidance receptors' by Bettina Winckler and Ira Mellman describes a topic that is not always covered in axon guidance books and is informative to read.

The final section introduces other cellular processes that use common guidance signals. Several of these topics are already familiar to developmental neurobiologists, such as those described in the chapters on neural cell migration by Oscar Marín and colleagues, axon pruning by Pierre Vanderhaeghen and Hwai-Jong Cheng, and axon regeneration by Roman J. Giger and colleagues. These authors very successfully

provide a good, broad perspective to the reader.

Overall, the selection of topics is well balanced, and the chapters are arranged to accurately represent the current scenario in research on neural guidance. Although a few chapters seem a little too specific for people with interests outside of that particular subdiscipline, most are written in a coherent holistic manner to provide a broad overview of our current understanding of neural guidance.

Some topics are repeatedly discussed in several sections of the book. This is the case with guidance molecules such as netrin, semaphorins, slits and ephrins, which function in various systems. Nevertheless, the overlap in the content between chapters is kept to a minimum. I prefer this approach, as it helps the reader to understand, in a step-by-step manner, how the nervous system is systematically constructed by multiple guidance signals. This makes the book more suitable to providing an understanding of the underlying biology, rather than comprising a thick directory of guidance molecules listed with location and time of action.

One feature that really impressed me is that most chapters devote a lot of attention to historical background

One feature that really impressed me is that most chapters devote a lot of attention to historical background and the description of general concepts that have led to the current state of research in the field. As mentioned above, several major principles of neural development were already established by 1985, when the classic text *Principles of Neural Development* was published, even though support in the form of molecular data was lacking at that time. Surprisingly, the subsequent identification of many guidance molecules and their signaling pathways has barely challenged these classic principles. Rather, new findings have confirmed established models, and, in fact, identification of most guidance molecules was based on general deductions from these principles. For example, the identification of ephrins was inspired by the historic transplantation experiments conducted on the retinectal system by Roger Sperry and others: researchers looked for the magic

chemoaffinity label that, according to theory, would form a 'gradient' over the tectum, and identified ephrins, which possessed exactly the predicted properties (Cheng et al., 1995; Drescher et al., 1995). *Neuronal Guidance: The Biology of Brain Wiring* pleasantly reminded me of such links between historic concepts and the latest data on molecular mechanisms. Realization of such connections will clarify, especially to newcomers in this field, the real significance of ongoing studies.

In summary, *Neuronal Guidance: The Biology of Brain Wiring* achieves a good balance between basic principles and leading cutting-edge research and will prove to be an excellent introductory text for

students and postgraduates who are curious about this branch of developmental biology. The book is also refreshing for old hands: after reading it, I felt full of new ideas.

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enables a first-pass checkpoint for growth and developmental signals, it is the vehicle for morphogenetic gradients in development, and it is the spatial rheostat for intracellular signalling pathways. ECM receptors thus convert both chemical and physical extracellular inputs to determine cell survival, proliferation, migration and tissue-specific gene expression.

A book on such a profoundly important topic requires a clear vision of the breadth of the ECM and its roles in development, cell and tissue function and disease. *Extracellular Matrix Biology* has been organised by two of the most eminent scientists in the ECM research field, Richard Hynes and Kenneth Yamada, and, predictably, the book hits the mark. This volume, one in a series from Cold Spring Harbor Laboratory Press, contains a superb collection of review articles. Well-known opinion-makers in the field have written the chapters, which are detailed, authoritative and up to date. The organisation of the book is sensible, beginning with an overview of the matrisome and its evolution, and then working through the key ECM components, basement membranes, collagens, proteoglycans, tenascins, thrombospondins and fibronectin. This is followed by chapters on integrin activation, genetics, and links with TGF β , as well as adhesion complexes, mechanotransduction, and matrix remodelling. Towards the end, links between ECM and tissues are considered, with chapters on cell migration, embryonic development, angiogenesis, skin, and the nervous and haemostatic systems. I am slightly disappointed that mucins have been omitted, as they are crucial components of the pericellular matrix, but nevertheless the coverage in the book is excellent overall.

Looking through my (rather dusty) volume of Betty Hay's *Cell Biology of Extracellular Matrix* (2nd edition, 1991), which was one of the last comprehensive books on ECM, it is startling to see how many advances have been made since then. Prior to our era of genomics, knockouts and dynamic imaging, much of the knowledge about ECM was based on biochemistry and cytology. Disease associations with altered ECM were known, but many of the molecules involved had not been identified and mechanisms were largely unexplored. Little was understood about the structures of matrix molecules or their receptors, and there was only an indication that integrins could transmit signals from the ECM to the cell interior. It is also interesting that the focus of illustrations has largely switched from electron microscopy images and some

Life and the matrix

Charles H. Streuli

Wellcome Trust Centre for Cell-Matrix Research, Faculty of Life Sciences, University of Manchester, Manchester M13 9PT, UK.

cstreuli@manchester.ac.uk

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Extracellular Matrix Biology

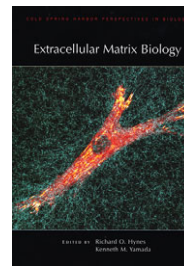
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To be metazoan is to have an extracellular matrix (ECM). ECM components evolved simultaneously with animals and provided the architectural scaffold onto which multicellularity could emerge several hundred million years ago. From a primitive basement membrane toolkit and the primordial fibrillin and thrombospondin genes that allowed the evolution of multilayered animals, successive gene duplications and crises permitted the appearance of protostomes and deuterostomes, leading to vertebrates and eventually to us. Along the way, the evolutionary shuffling of pre-existing and novel protein domains to form tenascins, fibronectin and other matrix proteins coincided with the emergence of neural crest, vasculature and the nervous systems that characterise chordates and advanced vertebrates. Coinciding with this, metazoans evolved complex plasma membrane machines containing adhesome proteins that link the ECM to the cytoskeleton and intracellular signalling pathways.

Core ECM proteins make up ~1.5% of the mammalian proteome. This enormous parts-list of around 300 matrix proteins, newly christened the 'matrisome', highlights the diverse and extraordinary roles of the matrix in metazoan biology. ECMs range from pericellular matrices, such as basement membranes, to the grander structures of connective tissue that give organs their shape, and the tendons, cartilage and bones that bestow humans and animals with their form. It is therefore not surprising that the ECM pervades every aspect of metazoan life. The matrix is essential for early embryonic development and it regulates nearly every facet of cell behaviour. Moreover, altered ECM and ECM-cell interactions lie at the root of many diseases, including cancer, diabetes, inflammatory disorders and osteoarthritis.

The ancient history of the association between the ECM and cells effectively means that the two are inseparable. Although the prosaic view of cells is that they end at the plasma membrane, the cell and its pericellular matrix are actually a continuum in all complex animals. A cell's ECM coat provides the architectural hardware for cell positioning and migration, which is meshed together with intracellular cytoskeletal networks by myriad components of the adhesome. The matrix



relatively sketchy diagrams to detailed lists of ECM components, domain organisations, interaction networks, disease associations, and mouse and human mutations. This new book is therefore a timely addition, and many of the chapters also consider where the field is going now and what unknowns might be unravelled in the cell-matrix field over the next 20 years. Overwhelmingly, the shift in focus from the organisation of the ECM in tissues, to cataloguing its vast array of constituents and interactions with cells, indicates that a central challenge is to understand how all the matrix and adhesion components fit together and how they control cell fate and function.

Although crystal ball gazing is inevitably difficult, there are certainly some exciting opportunities that are alluded to in the book. The emerging awareness that biology occurs in four dimensions and is completely dependent on the ECM (incidentally, this was well understood by Hay) will undoubtedly be a major focus for cell-matrix research at least for the next few years. For example, knowledge of how matrices are assembled in 3D and remodelled in 4D is beginning to appear. Most cells function within communities, often of different cell types, and we are just beginning to understand how the matrix influences cell function and dynamics in 4D and how different cell types use the ECM to communicate, e.g. via stromal-epithelial interactions. The notion that the physics of the ECM profoundly influences cell and tissue function is fuelling new research on how forces are built into ECMs, how they are sensed by cells, and how they are converted to chemical signals that control transcription and cell fate. The structures of ECM proteins and some adhesion signalling proteins have been solved (some only at low resolution), leading to a new focus on

atomic interactions at the protein-protein interface. ECM and adhesion receptors are crucial regulators of the immune system, and the dawn of immunomatrix biology is changing the thinking about immunological control. And, most profoundly, the basic discoveries of cell-matrix research are yielding novel small-molecule, bioengineered and genetic therapies for the vast array of diseases caused by altered ECM and interactions between the cell and the matrix. For example, there are no effective cures for osteoarthritis beyond surgery; advances in this (and other) areas using genetic analysis based on genome-wide association studies and systems biology are needed to dissect all of the component parts that cause debilitating diseases of injury and old age, and thereby to develop new treatments.

I would recommend those entering the field of cell-matrix biology, as well as those already in it, to read the book from cover to cover

One of the challenges posed by reviewing this book was to ask who it is for. The original chapters appeared over several months in the online publication *Cold Spring Harbor Perspectives in Biology*, and they have now been collated for the book. Although some of the articles are available online (depending on your library's subscription), by combining them in a single volume the editors have created a very nice resource that will provide a valuable reference work for several years to come. I

would recommend those entering the field of cell-matrix biology, as well as those already in it, to read the book from cover to cover. The ECM is now understood as being so much more than a tissue scaffold and a precursor for building bones, and this new book definitively indicates where the field is now and where it is going. The intimate connections between the ECM and most cellular processes in animal development are gradually being recognised by mainstream biologists, and this could be accelerated when the key advances in this book are used to update current undergraduate texts on cell biology. At a broader level, once some of these concepts are incorporated within school biology education, then we'll know that ECM biology has truly come of age.

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