# Introduction

## Modeling Neural Development

The focus of most modeling studies in neuroscience is on information processing in the mature nervous system, at the level of ion channels, neurons, or neuronal networks. Relatively few modeling studies are directed at understanding how the nervous system develops—for example, how neurons attain their characteristic morphology, or how they are assembled into functional networks. Just as models are needed to help to understand the functioning of the nervous system, they are also needed in order to obtain a better understanding of its development. The development of the nervous system is an extremely complex dynamical process, spanning many levels of organization, from the molecular and cellular to the system level, and involving an overwhelming number of interactions and feedback loops within and between each level. To obtain insight into such a complex process, human intuition and commonsense arguments are not sufficient, and we need the guidance of appropriate mathematical and simulation models.

The present volume brings together examples from different levels of organization (from molecule to system) and from different phases of development (from neurulation to cognition) that demonstrate the power of modeling for investigating the development of the nervous system. In most cases, each chapter contains an overview of the biology of the topic in question, a brief review of the modeling efforts in the field, a discussion in more detail of some of the models, and some perspectives on future theoretical and experimental work.

This book is intended primarily for computational and experimental neuroscientists, but it will also be of interest to anyone interested in developmental biology. We hope that it will stimulate further research in developmental neurobiology, both theoretical and experimental. Not only is development fascinating in its own right, but its study may lead to new insights into the functioning of the mature nervous system (e.g., learning and memory), since many mechanisms that operate during development remain operative in later life.

In the following section, I summarize why modeling is an integral part of neuroscience. Before describing the structure of the book in the last section, I present a brief overview of the development of the nervous system in order for the reader to be able to see where each chapter fits into the overall scheme of neural development, and thus to be better able to appreciate the choice of topics.

## Modeling

All neuroscientists, not only theoretical and computational neuroscientists, make models. An experimentalist's verbal description of how a system works already constitutes a model. Such a verbal model, however, works satisfactorily only when the system under consideration is simple. When several interacting elements and feedback loops are involved, the

system rapidly becomes too complex to be understood without the help of mathematical or simulation models.

Given that the nervous system is one of the most complex systems that exists, formal models are an essential research tool in neuroscience (see, e.g., Jennings and Aamodt, 2000; McCollum, 2000):

**1.** Formal models—in terms of mathematical equations or computer programs—provide precise and exact ways of expression. Without formal models, complex systems and their dynamics cannot be precisely described and analyzed. Constructing formal models (e.g., by translating a verbal model into a mathematical or simulation model) therefore often identifies inconsistencies, hidden assumptions, and missing pieces of empirical data. In addition, translating hypotheses and theories into formal representations makes it possible to communicate them to other researchers in an unambiguous way.

**2.** Models can lead to the generation of new hypotheses and give structure and meaning to empirical data. Underlying links between data can become clear, and seemingly unrelated observations or phenomena may be shown to be aspects of the same process (integration and unification). Similarly, models can highlight the overlaps among disparate fields of research or among alternative hypotheses. Finally, models may show that our intuition about the system under investigation is wrong; counterintuitive or unexpected dynamics and patterns can easily arise as the result of even simple interactions.

**3.** Models enable us to study how phenomena at higher levels of organization arise from processes at lower levels of organization. Even for biological systems in which the components are completely known, it is seldom understood precisely how they interact to make the system work. Using only the traditional intuitive approach, a system's collective behavior (the dynamics and the patterns it can generate, or in other words, the working of the system) is very difficult to deduce from knowledge of its constituent parts. Models can provide unique insights because they allow us to explore the consequences of postulated interactions among a system's components and to test the plausibility of hypothetical mechanisms.

**4.** Model studies can help guide experimental research. The insights and predictions obtained by modeling can alter our outlook and suggest new experiments, which in turn may lead to new models. A comparison between model and experiment will sometimes be qualitative and sometimes quantitative. It is important to realize that often the aim of modeling is not just to build a quantitative replica and to do "mere" computation, which would assume that the principles of how the system works are already fully known. In addition to quantification, mathematical and simulation models provide precise aids to conceptualization and to deepening structural and biological insights.

## Neural Development

In order for the reader to see where each chapter fits into the overall scheme of neural development, this section briefly summarizes the development of the vertebrate nervous system. More detailed accounts can be found in, for example, Slack (1991), Cowan et al. (1997), Zigmond et al. (1999), Sanes et al. (2000), and Price and Willshaw (2000).

During the first rounds of cell division, the fertilized egg generates a ball of cells with an internal cavity (the blastula stage). Through invagination of tissues the embryo is converted into a three-layered structure with ectoderm on the outside, mesoderm in the middle, and endoderm on the inside (the gastrula stage). In response to molecules secreted by a region of the

mesoderm called the organizer, a portion of the ectoderm on the dorsal surface of the embryo becomes specified as neural tissue (neural induction) rather than as epidermis. From this flat, one cell-thick sheet of neuroectoderm cells (called the neural plate) the nervous system develops.

During the next phase of embryogenesis (called neurulation), the lateral edges of the neural plate elevate, appose each other, and later fuse at the dorsal midline to form a hollow cylinder (the neural tube) inside the embryo. Neural tube formation involves cell movements, changes in cell shape, and differential cell adhesion. As the tube forms, some cells along the edges of the neural plate (called neural crest cells) are pinched off. Guided by attractive and repulsive cues in the extracellular matrix, neural crest cells migrate away from the closing tube and eventually give rise to the peripheral nervous system. The central nervous system derives from the neural tube. Molecules emanating from the underlying mesoderm (and, earlier in development, from the organizer) create gradients, enabling cells in the neural tube to sense their position and express their genes differentially. As a result, the neural tube becomes specified along the rostrocaudal and dorsoventral axes into distinct domains (neural patterning), which later become the various areas of the differentiated nervous system. The neural tube develops three rostrocaudally arranged vesicles: the forebrain, midbrain, and hindbrain vesicles. The area of the tube caudal to the hindbrain is the prospective spinal cord. Later, the forebrain vesicle divides into two telencephalic vesicles and a diencephalic vesicle. At the level of the diencephalon, a bilateral evagination forms the optic vesicles, which subsequently transform into cups, whose inner walls eventually give rise to the retina of each eye.

During the next stage of development, the wall of the neural tube begins to thicken as newly generated neurons migrate away from the zone of proliferation (near the inside surface of the tube) toward the outer surface of the tube, to form new zones. Neurons migrate radially through the wall, but also tangentially (i.e., parallel to the surface of the tube). In some regions, the movements of neurons away from the proliferation zone lead to layered structures—for example, in the cerebral cortex, which emerges from the telencephalon. In the developing retina, tangential movements of cells within their destination layer help to create regular distributions of cells (retinal mosaics).

During migration and at the site of their final destination, neurons gradually become specified into many different cellular types. The determination of type involves differential gene expression and is controlled by both intrinsic and extrinsic factors. Intrinsic factors include proteins that are inherited from the neuron's precursors. Extrinsic factors are provided by other cells in the form of diffusible molecules, membrane-bound molecules, and molecules bound on the extracellular matrix (ECM); upon binding to receptors on the recipient cell, these molecules influence the proteins that regulate the expression of genes.

During or after migration, neurons begin to grow out by projecting many broad, sheetlike extensions, which subsequently condense into a number of small, undifferentiated neurites. Eventually one of the neurites increases its length and differentiates into an axon, while the remaining neurites later differentiate into dendrites. By way of the dynamic behavior of growth cones—specialized structures at the terminal ends of outgrowing neurites that mediate neurite elongation and branching—dendrites branch extensively and gradually form their characteristic morphologies. Axons continue growing out and migrate to their targets. One of the mechanisms by which they are guided is the diffusion of chemoattractant molecules from the target. This creates a gradient of increasing concentration, which the growth cone at the tip of a migrating axon can sense and follow. The

actions of the growth cone (axon guidance, neurite elongation and branching) are influenced by the concentration of calcium within the growth cone; as a consequence, all the factors that can change this concentration, such as neuronal electrical activity, can modulate neurite outgrowth. Intracellular calcium constitutes an important signal for many aspects of neuronal development, not only for neuronal morphogenesis but also, for example, for the activity-dependent development of intrinsic and synaptic conductances.

Once arrived in their target region, axons may branch considerably before terminating to form initial synaptic connections with permanent and transient target structures. In many parts of the nervous system, large numbers of neurons die at the time that their synaptic connections are being formed, but they also die at earlier phases of development, during proliferation and migration. During the period when initial connections are being formed, the survival of individual neurons depends on anterograde signals received through their input connections as well as on retrograde, target-derived signals received through their output connections. Both types of signals involve neurotrophic factors (growth- and survival-promoting substances) and both include a component that depends on electrical activity.

Once the initial connections are well established, neuronal cell death becomes rare. Further refinement of connections occurs by retraction of axonal branches that project to the wrong targets and elaboration of branches that project to the correct targets, and thus involves both synapse elimination and continued synapse formation. In some cases, such as in the innervation of skeletal muscle fibers, retraction of connections continues until the target remains innervated by just a single axon. Remodeling of axonal arborizations, as well as axon guidance cues, also underlies the formation of topographic maps (e.g., the retinotopic map; neighboring ganglion cells in the retina project to neighboring neurons in the visual cortex) and ocular dominance stripes (i.e., alternating stripes of visual cortical cells that respond prefererentially to input from either the left or the right eye). Refinement of connectivity is influenced by patterns of neuronal electrical activity and involves competition among innervating axons for target-derived neurotrophic factors, which affect axonal arborization. In adulthood, further fine tuning of connectivity, in the form of activity-dependent changes in the signal strength of synapses, participates in learning and memory.

## Structure of the Book

The order of the chapters follows loosely the chronology of development as described in the preceding section. Chapters 1 and 2 discuss the very early development of the nervous system. Chapter 1 first shows how, as a result of smooth gradients of transcription factors, sharp boundaries in gene expression can become established between cellular regions—a first step in the way in which areas become specified into distinct regions. It then shows how interactions among transcription factors, cell adhesion, cell division, and cell movement can account for neural tube formation (in vertebrates) and neural cord formation (in insects). Chapter 2 introduces a general framework for modeling molecular-level interactions—for example, gene expression—coupled to cell-cell interactions and changes in the number and properties of cells. The framework is used to examine how, in *Drosophila*, cells become specified as neural cells.

Chapters 3 through 5 cover neuronal morphogenesis and neurite outgrowth. Chapter 3 describes early morphogenesis and shows how positive feedback loops—involving calcium and active axonal

transport—may underlie the formation of neuritic structures from intitally spherical cells, and the differentiation of one of the neurites into the axon. Chapter 4 then further discusses dendritic outgrowth and describes how the actions of the growth cone and the underlying cellular and molecular mechanisms give rise to characteristic branching patterns. Chapter 5 looks further at axonal outgrowth, exploring quantitative constraints on axon guidance by target-derived diffusible factors.

Chapters 6 through 8 focus on different aspects of the self-organization of neurons into networks. Chapter 6 explores the consequences for neuronal morphology and network development when neurons self-assemble into networks by means of activity-dependent neurite outgrowth. Chapter 7 examines several mechanisms by which cells in the retina can organize themselves into regular spatial patterns, or mosaics. Chapter 8 explores how single neurons and networks can self-assemble by means of activity-dependent modification of conductances to produce desired activity patterns.

Chapters 9 through 12 discuss the refinement of connectivity and the development of specific connectivity patterns, involving neuronal death (chapter 9) and remodeling of axonal arborizations and changes in synaptic strength (chapters 10 through 12). Chapter 9 describes models that show how the many neuron-to-neuron signals controlling neuronal death combine to affect development at the network level. Chapter 10 describes models of the competitive phenomena involved in the refinement of connectivity (e.g., in the visual and neuromuscular systems). Chapter 11 examines the various models that have been put forward for the generation of topographically ordered connections, or maps, between two discrete neural structures (e.g., between the retina and the visual cortex). Chapter 12 describes models for the generation of the connectivity patterns that underlie ocular dominance and orientation selectivity in the visual cortex.

While chapters 1 through 12 are concerned with how neuronal morphology and networks develop, the last two chapters of this book concentrate more on the functional implications of morphology and development. Chapter 13 focuses on the hypothesis that the development of connections and learning in the mature brain depend critically on structural plasticity at the axodendritic interface, assuming an important role for individual dendrites in computation. Chapter 14 discusses the link between developmental processes at the cellular level and those at the systems level and explores how structural brain development relates to cognitive development.

## Acknowledgments

I wish to thank all who were involved in producing this book, in particular its many authors. I wish to thank Michael Rutter at MIT Press for inviting me to create this book and for help in planning it; Sara Meirowitz and Katherine Almeida assisted in all the further stages of preparing the manuscript. I am also grateful to Jaap van Pelt, Michael Corner, Geoffrey Goodhill, Stephen Eglen, David Price, and Harry Uylings for refereeing chapters and comments on the text and to Narcisa Cuceanu for assistance in proofreading.

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