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Book review

Modeling Neural Development
Arjen van Ooyen (Ed.), MIT Press, Cambridge, 2003

Modern neuroscience has revolutionized our view of the brain, revealing the elements and functional processes of what some have called the most complex object in the known universe in ever greater detail. The growth of knowledge about all aspects of brain development has been immense, ranging across mechanisms of gene expression, the origins of neuronal morphogenesis, the formation of maps and columns and the emergence of networks capable of generating complex cognitive states. Increasingly, the experimental investigation of brain function is accompanied and informed by the design of computational models that allow the synthesis of large amounts of empirical facts and provide an explanatory and predictive theoretical framework. The volume entitled "Modeling Neural Development", edited by Arjen van Ooyen, an Associate Member of the Institute for Adaptive and Neural Computation at the University of Edinburgh, combines these two lines of research. The book represents an important step in the search for general computational principles of how neurons and brain structures develop and how they shape and refine their structural and functional properties as they interact with each other and with their environment.

The book contains fourteen chapters written by leading developmental neurobiologists and computational neuroscientists. The chapters have been arranged roughly corresponding to the time course of neural development, starting with basic processes of morphogenesis at the molecular and cellular level, and ending in a theory of the neural basis of cognitive development. Overall, the chapters provide a logically connected and comprehensive overview of neural development, progressing from molecular and cellular aspects of neuronal morphogenesis to neurite outgrowth and differentiation, and then on to the formation of networks and the activity-dependent refinement of neuronal connectivity. The volume pays particularly close attention to developmental processes at the level of neurons and small networks. Some of the more integrative aspects of neural development are somewhat under-represented, including topics like the development of large-scale brain structures, of inter-regional connectivity patterns, and the role of neural development in shaping the function of sensory or motor systems in perception and behavior. However, the emphasis on cellular processes accurately reflects the current state of developmental models. Models that bridge multiple levels of organization or span across longer developmental time periods are mostly found in the area of connectionist approaches to cognitive modeling, and area that is not as strongly committed to the neural bases of development and is consequently not represented in the present volume.

The first two chapters are about early stages of neural development, in particular a molecular model for the formation of the neural tube (in vertebrates) and the neural cord (in insects), and a model of gene regulatory interactions during early neurogenesis in Drosophila. These chapters play an important role in connecting models of neural development to the emerging and rapidly growing field of systems biology, with its emphasis on the gathering and analysis of genomics and proteomics data, and on regulatory networks. At the same time, these chapters also provide a link to some of the early and by now classical work on "morphogens" and reaction-diffusion models of Alan Turing and of Meinhardt and Gierer.

Three chapters focus on the crucial issues of how neurons get their characteristic shape, how they form neurites, and how these neurites then differentiate into an axon and dendrites. Ever since Ramon y Cajal's neuroanatomical studies, it is known that neurons exhibit a striking variety of characteristic morphologies, and there is now strong evidence that their morphology is a key determinant of their eventual functional and computational role. How does this morphology arise

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during development? Hentschel and Fine discuss neurobiological evidence and a computational model of early stages in the formation of neuronal morphology, driven by dynamic instabilities in the concentration of diffusive intracellular morphogens such as calcium and leading to the spontaneous formation of lamellipodia and neurites. Computer simulations of growing cells reproduce much of the phenomenology of real neurons, including process extension and retraction, and the formation of enlargements at the tips of processes (growth cones). Axonal differentiation is modeled as "winner-take-all" competitive process among all candidate neurites. Most of the important factors in neuronal morphogenesis captured by these models are intrinsic to the cell, while external factors, signaling events, synaptic activity, or surface interactions with other cells are not yet taken into account. Another open question is what intrinsic or extrinsic factors shape the structural pattern of axonal and dendritic processes, resulting in the characteristic morphologies of different neuronal cell types. The subsequent chapters by van Pelt and colleagues and Goodhill and Urbach extend the modeling of neuronal morphogenesis to the genesis of dendritic branching patterns and the guidance of axonal processes by external signals. Special attention is given to the detection of gradients of target-derived diffusible factors by growth cones, a very active area in experimental studies conducted in in vitro systems. A topic that is missing in this section of the book is the formation (and later, the elimination) of synapses and the early stages in the establishment of functional neuronal connections. Quantitative computational models are still lacking in this area, but its central role in neural development and the intensity of empirical research on synaptogenesis clearly call for future efforts in generating and testing such models.

The next series of chapters begins to address issues related to network formation and activity-dependent processes. A chapter by van Ooyen and colleagues presents a computational model of neurite outgrowth, which incorporates the influence of neural activity on the spatial extent of the outgrowth and on the degree of interconnectivity. Interestingly, the model is capable of producing several key empirical phenomena such as a transient developmental phase of high connectivity levels. Another chapter investigates the origin of regular spatial patterns of neurons in the retina, which is important in ensuring appropriate coverage of the visual inputs space. Abbot and colleagues discuss how neurons generate and maintain their specific and characteristic electrophysiological properties, by expressing channels and receptors that give rise to voltage-dependent and synaptic conductances. These molecules have short lifetimes, far shorter than the cells that express them, and therefore some dynamic regulation is needed for the cell to maintain its physiological "identity". As it turns out, the tuning of neuronal and circuit properties is itself activity-dependent, and Abbott and colleagues present computational models that illustrate how neurons may developmentally converge onto a set of "desired" physiological and dynamical properties.

Several chapters deal with the formation of specific patterns of connectivity, including models that address the role of neuronal cell death, the role of competitive interactions in the developmental refinement of neural connectivity, and the formation of topographic maps as well as ocular dominance columns in visual cortex. This section of the book has perhaps the deepest historical roots and the chapters provide excellent overviews over the "classical" literature as well as represent state-of-the-art empirical and computational studies. In their chapter on competitive refinement, van Ooyen and Ribchester provide a scholarly overview of classical models in this area, which has a long and illustrative history in developmental neurobiology. A new model is proposed which links competitive interactions with biochemical effects of neurotrophins, a class of extracellular molecules that are instrumental in controlling the shape and density of neuronal pathways. A rather ubiquitous feature in the pattern of interconnections linking two neural areas is the presence of a mapping of one set of cells onto the other, quite often by way of a topographic relationship. Willshaw and Price address the question of how such maps might form during development, an issue that has attracted much attention and numerous modeling efforts over past decades. A concise and comprehensive overview of various hypotheses for map formation is provided in their chapter, followed by a discussion of recent models incorporating a variety of cellular and molecular data. Swindale's chapter on the development of ocular dominance columns, orientation selectivity and orientation columns continues where the previous chapter leaves off, with a discussion of principles of mapping in the visual cortex. More so than other chapters, this topic intersects with models of the organization of visual cortex and visual cortical plasticity in the adult.

The remaining chapters explicitly link neuronal morphology and connectivity to the computational roles of neurons in networks and in the development of behavior and cognition. Mel reviews evidence and computational models suggesting that the detailed axo-dendritic morphology of individual neurons actually matters in determining their computational function. The compartmentalization of small dendritic branches or spines may be essential for the generation of cellular output. Structural plasticity and remodeling of spines occurs throughout development and into adulthood, opening the possibility that differential changes in small regions of a cell's axo-dendritic interface may have an impact on its overall function. Clearly, this view is incompatible with the widespread use of idealized "point neurons". The capstone of the book is a chapter by Steven Quartz on a theory of how neural developmental processes may give rise to the development of cognitive function. Systems level model of neural development are still rather elusive (as mentioned above), but Quartz's chapter points the way towards their construction on the basis of a constructivist account of both neural and cognitive development. This chapter also highlights the continuity of developmental processes with processes underlying structural and functional plasticity in the adult organism—in a sense, development never stops and computational models begin to illuminate this continuity between development and adult function.

The editor has done an admirable job of putting together a book that is more than just a collection of chapters. The book accomplishes a remarkable level of synthesis of up-to-date empirical and computational work spanning all relevant levels in development, from genetic regulatory networks to the networks of cognition. The book captures the excitement of finally seeing developmental models that are rigorously based in real neurobiological mechanisms and that will be of tremendous help in unraveling the developmental origins of brain and mind. Everyone interested in neural development and in the design of neurobiologically realistic computational models should be very pleased with this excellent volume.

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