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Book Reviews

Edited by Robert E. O'Malley, Jr.

Featured Review: Two Books on Neuroscience.

Mathematical Foundations of Neuroscience. *By G. Bard Ermentrout and David Terman.* Springer, New York, 2010. $74.95. xvi+422 pp., hardcover. ISBN 978-0-387-87707-5.

Mathematics for Neuroscientists. *By Fabrizio Gabbiani and Steven Cox.* Academic Press, San Diego, CA, 2010. $99.95. 498 pp., hardcover. ISBN 978-0-12-374882-9.

Like many other fields of biology, neuroscience is at a crossroads. Spectacular new technologies are generating unprecedented observations. Multielectrode neural recordings, voltage-sensitive dyes, and optogenetic techniques now allow us to observe and even dynamically manipulate the activity of hundreds of individual cells within large neural networks. Meanwhile, functional magnetic resonance imaging (fMRI) and electrocorticography (eCOG)—together with EEG and MEG—are revealing large-scale brain activity. These measurements of population-wide *dynamics* are joined by "connectomics," new high-resolution anatomical techniques which seek to map the *architecture* of the underlying neuronal networks.

However, interpreting the resulting multivariate, multiscale, and highly interdependent data to extract principles of neural dynamics and computation is a formidable challenge. Fortunately, mathematics has a strong track record of success in neuroscience. Many of the key contributions are tied most closely to either dynamics or statistical inference: Nonlinear PDEs were famously used by Hodgkin and Huxley to describe the mechanisms of the spike, the fundamental unit of neural computation. The propagation of allied signals in dendritic trees began yielding, with surprising grace, to mathematical theories in the decades that followed. Dynamical systems theory has been fundamental in the analysis and reduction of models of cell behavior. This has lead to critical insights into the behavior of single cells, as well as the dynamics produced by random and structured cell networks. Stochastic dynamical systems have also played an important role, as the activity of neurons and networks is irregular and varies considerably between different presentations of the same stimulus. Continuous-time Markov chains coupled to nonlinear PDEs and ODEs can describe single cells, while "population density" continuum equations have been used to model asynchronous collections of neurons [11].

Neuroscience has also been driven forward by key insights and techniques from statistics. Estimation and information theory have been used to analyze how close biological circuits come to theoretically optimal computation and to quantify decision making and signal detection by the nervous system as a whole [15, 7]. Methods of Bayesian inference explain how information from multiple sources, including prior expectations, are best combined—leading to successful predictions of complex behaviors [4]. Moreover, allied system identification methods extract optimal statistical

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models of single neurons and circuits, identifying spatiotemporal filtering and nonlinear stages that have become the lingua franca of neural signal processing.

While open problems remain within the fields of neural dynamics and statistical inference, many exciting opportunities lie at their interface. What combinations of single-neuron dynamics, coupling kinetics, and network architecture enable efficient information transfer and flexible computation? Profound results on the power of abstract computing networks sparked an explosion of work in the 1980s (reviewed in [8]), and rich mathematical findings continue to emerge. For example, coupled point-process systems appear to capture and predict a wide range of neural dynamics and can be directly linked to underlying stochastic differential equations. At the same time, such models allow for efficient fitting, inference, and "decoding" of neuronal activity [14, 13]. New results suggest that the dynamics of interconnected, spiking networks might directly perform Bayesian inference under certain coupling schemes [12].

Still, we believe the majority of connections between neural dynamics and neural statistics awaits discovery. What is the role of network-driven synchrony (see, e.g., [10]) in the encoding of information about sensory inputs? When do dynamical instabilities and apparent chaos impede such encoding (see, e.g., [17])? What dynamics allow adaptation of networks to changing statistics of sensory scenes (see, e.g., [6])? Is the architecture of biological networks optimized for information flow and computation? When does random-seeming "synaptic bombardment" [3] actually serve to usefully modulate neural dynamics? In sum—faced with nonlinear dynamics on an incredible range of spatial and temporal scales, how can we determine (in the words of [1]) which processes matter for neural computation, and which do not?

Regardless of the future of dynamical and statistical methods in neuroscience, mathematical scientists will delight in their elegance, depth, and power. Two new books put this in sharp relief, while offering an excellent introduction to the mathematics that is at the heart of present-day neuroscience, as well as many techniques that are driving emerging research.

Mathematics for Neuroscientists by Fabrizio Gabbiani and Steven Cox (GC) was developed over 8 years of teaching courses on the topic. This experience, as well as the wide-ranging research contributions of the authors, clearly shines through—the text is a landmark for the field in its scope, rigor, and accessibility.

The book opens with dynamical models of single neurons. The strategy is to begin with the simplest possible descriptions of cells and then build the requisite mathematics in tandem with increasing model complexity. The narrative progresses rapidly to describe numerical ODE methods by p. 27 (including in-context overviews of stability and accuracy) and on to numerics and analytics for multivariable, nonlinear branched cable equations by Chapters 8 and 9. Along the way, a clear treatment of Fourier transforms translates into interesting analyses of the filtering properties of spatially extended, "quasi-active" cells. Chapter 10 gives a brief overview of the types of reduced dynamical models that are a mainstay of the book by Ermentrout and Terman reviewed next.

Chapters 11–18 give an introduction to probability theory and stochastic processes. Also discussed is a mathematical description of variability in neural dynamics, such as stochastic synaptic transmission and trial-to-trial differences in spike trains elicited by identical sensory stimuli. An excellent chapter on the singular value decomposition includes a beautiful demonstration of model reduction via "balanced truncation" ideas with links to control theory. The reader sees these techniques in action, readily participating in the reduction of a very complex and highdimensional model of a dendritic tree to a handful of relevant dynamical variables (see below).

The following chapters cover important statistical models, starting with influential signal processing models in the visual system. The authors explain how the ubiquitous method of reverse correlation, in which white noise stimuli are used for system identification, leads to "cascade" point-process models of the form

$$\nu(t) = g(K * I(\mathbf{x}, t)).$$

Here the cell's spiking is described as an inhomogeneous Poisson process with rate $\nu(t)$. This rate is determined by a convolution with kernel K of the spatiotemporal stimulus I, passed through a static nonlinearity g. After they are fit to neural data—or, as in emerging studies mentioned above, a dynamical systems model—such statistical representations are often used with great success for signal estimation and detection. The latter is often referred to as *decoding*, as it involves transformations of spike patterns into optimized approximations of the signals most likely to have elicited them. The multivariate version of this problem, in which many cells represent the same stimulus, is tackled in a fascinating chapter on population coding. This chapter is notable for clearly illustrating topics of major current interest and debate, such as the role of cooperative (or correlated) activity among multiple cells.

The final chapter, on neural network dynamics, is remarkable for its range of deeply interesting and diverse topics that are covered in a comprehensible fashion in only 20 pages or so. These range from abstract models of associative memory to spiking networks with plastic synapses.

This is a hallmark of the book: elegance, completeness, and economy that leave the reader with much more mathematics and science than one might expect even in a work of this size. The book further benefits from the availability of MATLAB code provided to regenerate almost every figure. The narrative also invites readers to run short MATLAB scripts as they progress. For instance, an introductory code illustrates instability in elementary numerical schemes, then incrementally adds to both the algorithm and the model, leading to interesting "hybrid" methods for the Hodgkin–Huxley equations. Later, the reader can download code that will reconstruct a highly complex branched model of a pyramidal neuron and simulate it with widely dispersed, synaptic inputs. After a few exercises the reader is then invited to investigate the role of loss of myelination (segmented insulation) in signal propagation, motivated by diseases such as multiple sclerosis. The final stage appears to be a challenging but doable endeavor for keen students. This integration of code and text is by far the best we've seen. It brings alive the science, the mathematical tools, the models, and their implementation.

The text *Mathematical Foundations of Neuroscience* by G. Bard Ermentrout and David Terman (ET) gives an engaging, detailed, and truly authoritative treatment of neural dynamics; the authors were at the heart of the development of many important topics inside. As in GC, the book starts with the theory that describes changes in the membrane voltage of single cells, leading to the Hodgkin–Huxley equations. Together with the second chapter that focuses on the modeling of dendrites using the cable equation, this provides a concise overview of many classical models used in neuroscience.

Chapters 3 through 6 are some of the strongest in the book. They build on an extremely influential chapter by Bard Ermentrout and John Rinzel that introduced many of us to the applications of bifurcation and singular perturbation theory to neural dynamics [16]. In ET this winning approach is developed further. Along with the theory of normal forms, these ideas have been fundamental in understanding and categorizing neuronal dynamics at the single cell and network level and thus frequently recur in the remainder of the book. They are also explored in the beautifully illustrated book by Eugene Izhikevich [9] which may serve to complement Chapter 3 of ET, especially for those wishing for an extensive introduction to bifurcation theory and single neuron dynamics.

A newcomer to the field will likely be bewildered by the zoo of ion channels that drive the electrical activity in single cells. Chapters 4 and 7 make it clear that we are dealing with biological systems. While an overarching framework for modeling channel dynamics is provided, the differences between channel types are clearly explained. Some of these differences may be inconsequential, while others may profoundly affect neuron dynamics. ET provides an excellent demonstration of the importance of mathematical modeling in deciding their role. The reader is also invited to explore their effect with the XPP code that accompanies the book.

Both authors have contributed significantly to our understanding of bursting (the firing of short sequences of action potentials) in single cells, and Chapter 5 presents a thorough overview of the subject. Bursting systems can exhibit complex dynamics, and ET does an admirable job of introducing the rich mathematical theory used in the analysis of such systems.

The careful review of the analysis of action potential propagation in Chapter 6 is a real highlight, and is the most complete we know. The mathematical ideas introduced here—like the Evans function— are sophisticated, but are explained clearly and accessibly. This pattern of concise introductions to the main ideas of rich and useful mathematical constructs repeats throughout the book and, when taken together with the references provided, will offer great value to many readers.

Following an informative discussion of synaptic (coupling) dynamics that is central to the sections that follow, Chapter 8 gives a comprehensive treatment of the dynamics of neural oscillators. The topics here include phase locking, circle maps, weak coupling, and averaging. Starting with limit cycle oscillators, we are led to the famous Kuramoto model

$$\dot{\theta}_i = \omega_i + \sum_j h_{ij}(\theta_i - \theta_j).$$

Here, each oscillator has intrinsic frequency ω_i and the dynamics of its phase, θ_i, is modulated by the coupling functions $h_{ij}(\cdot)$. The core question is: What combination of internal and coupling dynamics determines whether the network will synchronize or desynchronize? ET describe how averaging, together with normal form models for the underlying oscillators, provides surprisingly strong and general results that remain highly influential in mathematical neuroscience.

While weakly coupled oscillators can be studied using averaging methods, an alternative approach is available for networks of cells that can individually be modeled as fast–slow systems:

$$\begin{aligned}\dot{v}_i &= f(v_i, w_i) + \sum_j h_{ij}(v_i, v_j),\\ \dot{w}_i &= \epsilon\, g(v_i, w_i).\end{aligned}$$

Here, geometric singular perturbation yields strong results with interesting, constructive proofs. A beautiful example is provided on p. 260, where network activity is described using discrete dynamics on a graph. Overall, it is an interesting challenge to connect the insights from singular perturbation theory and neural oscillator approaches to network dynamics into a unified view—at least at the places in "model space" where the underlying sets of assumptions (almost) meet.

The following Chapter 10 gives a concise and intuitive introduction to stochastic differential equations and classical results on their application to neural systems, as well as a brief treatment of stochastic, discrete-state systems. We note that this is also a topic of a recent book [11]. ET closes with a discussion of reduced models of averaged neural activity. Lyapunov functions for such reduced models, extremely influential in literature on artificial neural nets, are presented in a very readable manner. The book concludes with a discussion of spatially structured dynamics in application to working memory, bringing it to an exciting and interesting close.

As mentioned, ET includes a host of models that are available at the first author's website, ranging from single-cell to model networks. Similarly, XPP code accompanies many of the central examples and analyses in the text. While XPP is less widely used than MATLAB, it provides an intuitive graphical interface which allows for efficient yet sophisticated exploration of dynamical models [5]. The excellent interface between XPP and AUTO continuation software is a major asset which significantly simplifies bifurcation analysis.

So what is the best audience for these two books? Many pedagogical aspects of GC are exemplary on multiple levels, making it very suitable for an advanced undergraduate or beginning graduate course for any student with a mathematical inclination and drive. Nevertheless, some prior exposure to linear algebra, ordinary differential equations, and probability will make for a smoother journey. Likewise, those new to some aspects of the material will probably find it difficult to appreciate certain sections without outside reading or significant time spent on the well-structured exercises. While a few results (e.g., on Gramians) are stated without extensive development, the reader is rapidly shown how these concepts enable powerful progress in the analysis of neural systems (e.g., rather spectacular reductions in the dimension of large "compartmental" neuronal models). Moreover, these sections are duly marked and can be easily saved for a second read. Overall, the level of detail and completeness with which calculations are carried out in the text, and the beauty and utility with which they are explained, are exemplary. Thus, the title *Mathematics for Neuroscientists* is well deserved.

Does GC also offer "neuroscience for mathematicians"? We think the answer is a resounding yes. A more mathematically advanced reader will want to flip past some—but, we'd expect, not all—sections where mathematical concepts are introduced (though we found ourselves learning from the elegant presentations in many places). Rich mathematics abounds. Moreover, the discussions of key mathematical and biological results, even down to careful discussion of units, make this not only a great book to teach from but also a key learning and reference text for new and practicing theoretical neuroscientists and applied mathematicians.

ET is ideally suited for mathematicians at the advanced undergraduate and beginning graduate level, and beyond, who wish to enter the field. The book provides expert perspective on many fundamental areas in mathematical neuroscience, and will be a valuable and often-consulted text for researchers. It is also an excellent resource for instructors of intermediate to advanced courses: we are both looking forward to using a number of sections in our upcoming graduate classes! This role is strengthened by the varied levels at which material is presented. A direct and intuitive approach is frequently provided, together with detailed pointers to the literature where proofs are developed more fully. As a result, the text is very readable, even with its impressively wide scope. In addition, many subsections give short, independent reviews of mathematical topics that will be very useful in the classroom.

The exercises in the two books also highlight the difference in the audience for whom they were intended. In GC, many exercises cover mathematical topics in depth (for example, the introduction and derivation of matched filters in Chapter 14). The problems in ET are excellent, and many are closer to the form of small projects (this is intentional, and the exercises are marked as such). These are clearly conceived from deep experience with the underlying material, and they frequently ask the student to go well beyond what has been discussed in a given chapter. While all readers will appreciate the challenges and insights that these exercises offer, many new students would benefit from guidance as they tackle them.

With these two books in hand, few readers will be able to resist engaging with the numerous open, but increasingly tractable, questions that connect neural dynamics, statistics, and computation; the list we offer above is just a short segment of an expanding frontier. Throughout, these books also attest to a dialogue between experimental and theoretical neuroscientists that is ever increasing in vibrancy and scope—a sign that theoretical neuroscience is maturing to a position held by theoretical work in fields such as physics [1].

It has been suggested that a mechanistic understanding of biological processes based on experimentally inspired models is becoming obsolete, and that the process of discovery can be automated [2]. We feel that the opposite is the case. Rather than a shift to data mining alone, creative and mathematically sound theoretical principles will be even more important in the future than they have been heretofore. The two books we have reviewed are both first-class introductions and companions for those who will show the way.

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Krešimir Josić
University of Houston

Eric Shea-Brown
University of Washington