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神经科学研究与进展

Mathematics for Neuroscientists

神经科学中的数学

Fabrizio Gabbiani and Steven James Cox

科学出版社

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原版引进

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北京

图字：01-2011-4373 号

This is an annotated version of

Mathematics for Neuroscientists

By Fabrizio Gabbiani and Steven James Cox.

ISBN：978-0-12-374882-9

图书在版编目(CIP)数据

神经科学中的数学 = Mathematics for Neuroscientists：英文/（美）伽比阿尼（Gabbiani，F.）等编著. —北京：科学出版社，2012

（神经科学研究与进展）

ISBN 978-7-03-033114-4

Ⅰ.①神… Ⅱ.①伽… Ⅲ.①数学方法—应用—神经科学—研究—英文 Ⅳ.①O1②Q189

中国版本图书馆 CIP 数据核字（2011）第 270598 号

责任编辑：李小汀 / 责任印制：钱玉芬

封面设计：耕者设计工作室

科学出版社 出版

北京东黄城根北街 16 号

邮政编码：100717

http://www.sciencep.com

双青印刷厂 印刷

科学出版社发行 各地新华书店经销

*

2012 年 1 月第 一 版 开本：787×1092 1/16

2012 年 1 月第一次印刷 印张：31 1/4

字数：741 000

定价：135.00 元

如有印装质量问题，我社负责调换

导　读

二十世纪中叶以来，关于神经系统的研究从以往生物与心理学研究的边缘地位跃升为神经科学这一交叉学科。这一新学科将生物化学、细胞生物学、解剖学、生理学、心理学、神经病学、精神病学等具有不同背景的科学家与临床医生们联系起来，研究令人激动的脑的秘密。他们探索神经元的功能机制，澄清行为与认知的神经基础，了解神经系统疾病。1969 年神经科学学会的创建大大促进了该学科的发展，如今该学会已经拥有近 37000 名会员。第一个针对神经科学的学术培训项目建立在医学院（1965 年加州大学圣迭戈分校建立神经科学系，1966 年哈佛大学建立神经生物学系）。第一个本科生培训项目于 1972 年建立在 Amherst 学院和 Oberlin 学院，后者培养了诺贝尔奖获得者 Roger Sperry 和三位神经科学学会会长。时至今日，全世界已经有超过 300 个神经科学系或相应的培养项目。

同时，脑又是我们所知的宇宙中最复杂的系统。人脑中的神经元数在 10^{11} 以上，而每个神经元又可能和其他神经元之间建立多达一万个以上的突触联系，由此向下向上，脑是一个具有许多层次的多级系统，在其每个层次上都可以表现出其下一个层次的元件所没有的突现性质。单纯进行实验和观察，已经远远不够，如何找出隐藏在这些海量数据背后的定量规律，已经成为对当代科学的最具挑战的问题之一。

计算神经科学正是为了这个目的应运而生。作为一门跨领域的交叉学科，它把实验神经科学和理论研究密切地联系在一起，从实验数据出发，运用物理、数学及计算机科学的概念和分析工具，对大脑的功能进行概念上的深入阐明，据此提出各种科学假说，并通过与实验的互动进行检验。为工程技术的智能化提供全新的思路。数理方法在物理学、生物学、化学、脑科学、计算机科学、电子工程学、数学和其他学科研究中已经获得了成功的应用，它必将促进脑科学研究产生质的飞跃。各学科已有证据表明，脑不是一个没有系统规律的复杂体，这些系统规律正在被逐渐发现，并且是以计算形式表达的。

计算神经科学（Computational Neuroscience）作为一个新学科领域开始形成，大约是在 1988 年左右。在过去 20 年里，这个领域飞速发展。其中一个标志就是每年在美国、欧洲和日本等地都要举办计算神经科学方面的年会。2006 年 Science 杂志特地为计算神经科学开辟了一个专栏，宣告它的快速成长（Stern and Travis，2006）。但是，需要强调的是这个领域仍然很年轻。在美国，哥伦比亚（2005 年）、耶鲁（2006 年）、普林斯顿（2006 年）、哈佛（2007 年）都是在近年间才建立起计算神经科学中心。（美国）神经科学学会在 2008 年第一次颁发理论神经科学领域的 Swartz 奖。

《神经科学中的数学》（*Mathematics for Neuroscientists*，2010）一书正是在这个大背景下编写出版的，作者 Fabrizio Gabbiani 与 Steven J. Cox 是 Baylor 医学院和 Rice 大学的教授，在过去 8 年来，一直在 Rice 大学教授计算神经生物学的内容。本书涵盖内容广泛，从离子通道这一微观水平出发，多层次有系统地介绍了突触、树突、单个神经元、神经网络到心理物理的相关理论，从而以计算的角度将神经系统的大致轮廓勾勒出来。应该说，

在笔者所接触过的国内外大学的神经生物学教学实践中，这样系统地将计算融入到以往偏重于描述性的课程中，尚属少见。可贵的是，本书的章节组织模式，除了一些重要分析手段的必要交代，与经典的神经生物学章节很好地平行对应，哪怕是为了宽泛地了解神经生物学，本书也不失为一个重要的补充。以兴奋一抑制机制为例，它突破了简单的语言描述，而是在特定的时间以定量的方式进行数学描述，从而直接演绎不同的作用方式。换言之，同样的兴奋和抑制这两个“原料”，在不同的系统中可以采用不同的配方，调制出截然相反的“菜肴”，妙处就在一个“定量”。

本书的另外一个特点是，应用性强，它与配套的 Matlab 程序给读者提供了直接进行计算和模拟的平台，从这一框架出发，可以体会参数设置的微妙，进而体会到依据实验结果搭建模型框架的“良苦用心”，甚至指导科研工作者去遴选各种实验论文，进而提出一些尖锐的实验验证方案，这一切都源于定量计算假设。这样的科研实践过程，远远胜过在茫茫大海中目标不明确地去碰、去试。这样的尝试，对于神经生物学研究的工作者来说，能够带来一种提纲挈领式的启发。

虽然本书作者立足于为数学和神经生物学的入门读者提供介绍，笔者建议将本书与普通神经生物学、统计、Matlab 的相关书籍配合阅读，再搭配本书提供的 Matlab 程序，以达到更好的学习效果。

俞洪波
复旦大学生命科学学院、脑科学研究中心
2011.11.14

前　言

这本书源自于8年多来我们为Rice大学和Baylor医学院的学生在Rice大学共同教授的课程。这门课程和这本书是为了将数学方法引入到神经生物学中，从而加深学生对神经生物学和数学的知识。

就数学知识而言，它将一步步可靠地加强学生们的能力，从而得以解析和拓展本课程提供的232个计算模型与练习相关的Matlab程序。就神经生物学知识而言，它将致力于在学生们了解精细的系统相互作用和整合机制之前，建立起有关刺激和分子、细胞、回路现象之间的基本模型。这些目标能实现到什么地步，很大程度上取决于学生的洞察领悟能力。

我们受益于休斯顿浓厚的神经生物学研究氛围，尤其感谢Jack Byrne，Mike Friedlander，Marty Golubitsky和Kathy Mattews在促进数学与神经生物学对话中的领导作用。在我们与环墨西哥湾理论与计算神经生物学联合会的同事们的紧密合作中，这一对话得以延续。我们特别感谢Mark Embree，Kreso Josic，Weiji Ma，Peter Saggau和Harel Shouval，他们在本书的很多章节中提出了具体的反馈意见。我们也收到了Maurice Chacron，Stephen Coombes，Greg DeAngelis，Brent Doiron，Hans van Hateren，Leonard Maler，Victor Matveev和Ralf Wessel及其研究组的评论意见，在此一并感谢。

我们深深地感谢我们的妻子，Sibylle和Laura，感谢她们在我们工作早期提供的帮助，感谢她们容忍我们在最后阶段不管不顾、一心一意于写作。

我们也要感谢Colin Cox，他的早期激励促成了我们课程中相当大一部分内容的形成，感谢Simon Cox，他将许多数量繁多难以预计的程序和图例组织在了一起。

（俞洪波 译）

Preface

This text sprung from a course we have taught jointly over the last 8 years at Rice University to students from Rice and Baylor College of Medicine. The goal of our course, and this text, is to develop mathematical methods that are most relevant to neuroscience, in a fashion that deepens the student's knowledge of each.

Regarding the mathematics, this means working in concrete incremental steps that enable the student to parse and extend the MATLAB code provided for each of the 232 computational examples and exercises. Regarding the neuroscience, this means establishing basic models of stimuli and molecular, cellular, and circuit level phenomena prior to their systematic elaboration and integration. The degree to which we have succeeded in this goal is, in large measure, due to the perspicacity of our many devoted students.

We have also benefited from Houston's rich neuroscience climate and happily acknowledge the leadership of Jack Byrne, Mike Friedlander, Marty Golubitsky, and Kathy Matthews in promoting dialog between mathematics and neuroscience. This dialog has been sustained by our close collaboration with fellow members of the Gulf Coast Consortium for Theoretical and Computational Neuroscience. In particular, we thank Mark Embree, Kreso Josic, Weiji Ma, Peter Saggau, and Harel Shouval for detailed feedback on a number of our chapters. It is also a pleasure to acknowledge comments received from Maurice Chacron, Stephen Coombes, Greg DeAngelis, Brent Doiron, Hans van Hateren, Leonard Maler, Victor Matveev, and Ralf Wessel and his group.

Our deepest thanks go to our wives, Sibylle and Laura, for nurturing the early stages of our work and for accepting our near single mindedness during our final year of writing.

We also thank Colin Cox for an early animation that catalyzed a good fraction of our course and Simon Cox for coordinating our code and figures at a time when they appeared to be taking on a life of their own.

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(俞洪波 译)

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CHAPTER

1

Introduction

OUTLINE

Faced with the seemingly limitless qualities of the brain, Neuroscience has eschewed provincialism and instead pursued a broad tack that openly draws on insights from biology, physics, chemistry, psychology, and mathematics in its construction of technologies and theories with which to probe and understand the brain. These technologies and theories, in turn, continue to attract scientists and mathematicians to questions of Neuroscience. As a result, we may trace over one hundred years of fruitful interplay between Neuroscience and mathematics. This text aims to prepare the advanced undergraduate or beginning graduate student to take an active part in this dialogue via the application of existing, or the creation of new, mathematics in the interest of a deeper understanding of the brain. Requiring no more than one year of Calculus, and no prior exposure to Neuroscience, we prepare the student by

1. introducing mathematical and computational tools in precisely the contexts that first established their importance for Neuroscience and
2. developing these tools in concrete incremental steps within a common computational environment.

As such, the text may also serve to introduce Neuroscience to readers with a mathematical and/or computational background.

Regarding (1), we introduce ordinary differential equations via the work of Hodgkin and Huxley (1952) on action potentials in the squid giant axon, partial differential equations through the work of Rall on cable theory (see Segev et al. (1994)), probability theory following the analysis of Fatt and Katz (1952) on synaptic transmission, dynamical systems theory in the context of Fitzhugh's (1955) investigation of action potential threshold, and linear algebra in the context of the work of Hodgkin and Huxley (1952) on subthreshold oscillations and the compartmental modeling of Hines (1984) on dendritic trees. In addition, we apply Fourier transforms to describe neuronal receptive fields following Enroth-Cugell and Robson's (1966) work on retinal ganglion cells and its subsequent extension to Hubel and Wiesel's (1962) characterization of cat cortical neurons. We also introduce and motivate statistical decision methods starting with the historical photon detection experiments of Hecht et al. (1942).

Regarding (2), we develop, test, and integrate models of channels, receptors, membranes, cells, circuits and sensory stimuli by working from the simple to the complex within the MATLAB computing environment. Assuming no prior exposure to MATLAB, we develop and implement numerical methods for solving algebraic and differential equations, for computing Fourier transforms, and for generating and analyzing random signals. Through an associated web site we provide the student with MATLAB code for 144 computational figures in the text and we provide the instructor with MATLAB code for 98 computational exercises. The exercises range from routine reinforcement of concepts developed

Mathematics for Neuroscientists. DOI: 10.1016/B978-0-12-374882-9.00001-0

in the text to significant extensions that guide the reader to the research literature. Our reference to exercises both in the text and across the exercises serve to establish them as an integral component of this book.

Concerning the mathematical models considered in the text, we cite the realization of Schrödinger (1961) that "we cannot ask for more than just adequate pictures capable of synthesizing in a comprehensible way all observed facts and giving a reasonable expectation on new ones we are out for." Furthermore, lest "adequate" serve as an invitation to loose or vague modeling, Schrödinger warns that "without an absolutely precise model, thinking itself becomes imprecise, and the consequences derived from the model become ambiguous."

As we enter the 21st century, one of the biggest challenges facing Neuroscience is to integrate knowledge and to craft theories that span multiple scales, both in space from the nanometer neighborhood of an ion channel to the meter that action potentials must travel down the sciatic nerve, and in time from the fraction of a millisecond it takes to release neurotransmitter to the hours it takes to prune or grow synaptic contacts between cells. We hope that this text, by providing an integrated treatment of experimental and mathematical tools within a single computational framework, will prepare our readers to meet this challenge.

1.1 HOW TO USE THIS BOOK

The book is largely self-contained and as such is suited for both self-study and reference use. The chapters need not be read in numerical order. To facilitate a selection for reading, we have sketched in Figure 1.1 the main dependencies between the chapters. The four core chapters that underlie much of the book are Chapters 2–4 and 11. For the reader with limited prior training in mathematics it is in these chapters that we develop, by hand calculation, MATLAB simulation and a thorough suite of exercises, the mathematical maturity required to appreciate the chapters to come. Many of the basic chapters also contain more advanced subsections, indicated by an asterisk, *, which can be skipped on a first reading. Detailed solutions are provided for most exercises, either at the end of the book or through the associated web site. We mark with a dagger, †, each exercise whose solution is not included in this text.

Over the past eight years, we have used a subset of the book's material for a one semester introductory course on Mathematical Neuroscience to an audience comprised of Science and Engineering undergraduate and graduate students from Rice University and Neuroscience graduate students from Baylor College of Medicine. We first cover Chapters 2–5, which set and solve the Hodgkin–Huxley equations for isopotential cells and, via the eigenvector expansion of the cell's subthreshold response, introduce the key concepts of linear algebra needed to tackle the multicompartment cell in Chapters 6 and 8–9. We then open Chapter 11, introduce probabilistic methods and apply them to synaptic transmission, in Chapter 12, and spike train variability, in Chapter 15. We conclude this overview of single neuron properties by covering Chapter 10 on reduced single neuron models. We transition to Systems Neuroscience via the Fourier transform of Chapter 7 and its application to visual neurons in Chapters 20 and 21. Finally, we connect neural response to behavior via the material of Chapters 24 and 25. An alternative possibility is to conclude with Chapters 22 and 23, after an informal introduction to stochastic processes, and power and cross spectra in Chapters 16 and 18.

We have also used the following chapters for advanced courses: 13, 14, 16–19, and 26. Chapter 13 provides a comprehensive coverage of calcium dynamics within single neurons at an advanced level. Similarly, Chapter 14 introduces the singular value decomposition, a mathematical tool that has important applications both in spike sorting and in model reduction. Chapters 16 and 18 introduce stochastic processes and methods of spectral analysis. These results can be applied at the microscopic level to describe single channel gating properties, Chapter 17, and at the macroscopic level to describe the statistical properties of natural scenes and their impact on visual processing, Chapter 19. Finally the chapters on population codes and networks, Chapters 26 and 27, address the coding and dynamical properties of neuronal ensembles.

To ease the reading of the text, we have relegated all references to the **Summary and Sources** section located at the end of each chapter. These reference lists are offered as pointers to the literature and are not intended to be exhaustive.

1.2 BRAIN FACTS BRIEF

The brain is the central component of the nervous system and is incredibly varied across animals. In vertebrates, it is composed of three main subdivisions: the forebrain, the midbrain, and the hindbrain. In mammals and particularly in humans, the cerebral cortex of the forebrain is highly expanded. The human brain is thought to contain on the order of 100 billion (10^{11}) nerve cells, or neurons. Each neuron "typically" receives 10,000 inputs (synapses, §2.1) from other neurons, but this number varies widely across neuron types. For example: granule cells of the cerebellum, the most abundant neurons in the brain, receive on average four inputs while Purkinje cells, the output neurons of the cerebellar cortex, receive on the order of 100,000. In the mouse cerebral cortex, the number of neurons per cubic millimeter has been estimated at 10^5, while there are approximately 7×10^8 synapses and 4 km of cable (axons, §2.1) in the same volume. Brain size (weight) typically scales with body size, thus the human brain is far from the largest. At another extreme, the brain of the honey bee is estimated to contain less than a million (10^6) neurons within a single cubic millimeter. Yet the honey bee can learn a variety of complex tasks, not unlike those learned by a macaque monkey for instance. Although it is often difficult to draw comparisons across widely different species, the basic principles underlying information processing as they are discussed in this book appear to be universal, in spite of obvious differences in implementation. The electrical properties of cells (Chapter 2), the generation and propagation of signals along axons (Chapters 4 and 9), and the detection of visual motion (Chapters 21 and 25) or population codes (Chapter 26), for instance, are observed to follow very similar principles across very distantly related species.

Information about the environment reaches the brain through five common senses: vision, touch, hearing, smell, and taste. In addition, some animals are able to sense electric fields through specialized electroreceptors. These include many species of fish and monotremes (egg-laying mammals) like the platypus. Most sensory information is gathered from the environment passively, but some species are able to emit signals and register their perturbation by the environment and thus possess active sensory systems. This includes bats that emit sounds at specific frequencies and hear the echoes bouncing off objects in the environment, a phenomenon called echolocation. In addition some species of fish, termed weakly electric, possess an electric organ allowing them to generate an electric field around their body and sense its distortion by the environment, a phenomenon called electrolocation.

Ultimately, the brain controls the locomotor output of the organism. This is typically a complex process, involving both commands issued to the muscles to execute movements, feedback from sensors reporting the actual state of the musculature and skeletal elements, and inputs from the senses to monitor progress towards a goal. So efficient is this process that even the tiny brain of a fly is, for instance, able to process information sufficiently fast to allow for highly acrobatic flight behaviors, executed in less than 100 ms from sensory transduction to motor output.

To study the brain, different biological systems have proven useful for different purposes. For example, slices of the rat hippocampus, a structure involved in learning and memory as well as navigation, are particularly adequate for electrophysiological recordings of pyramidal neurons and a detailed characterization of their subcellular properties, because their cell bodies are tightly packed in a layer that is easy to visualize. The fruit fly *Drosophila melanogaster* and the worm *Caenorhabditis elegans* (whose nervous system comprises exactly 302 neurons) are good models to investigate the relation between simple behaviors and genetics, as their genomes are sequenced and many tools are available to selectively switch on and off genes in specific brain structures or neurons. One approach that has been particularly successful to study information processing in the brain is "neuro-ethological," based on the study of natural behaviors

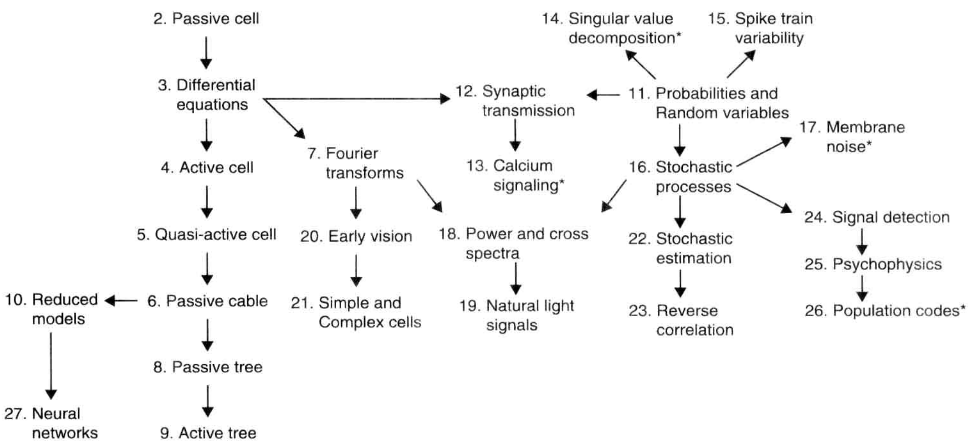

FIGURE 1.1 Chapter dependencies. Each arrow points to a chapter that depends significantly on the content of the current chapter. The asterisk is used to denote chapters that cover advanced material.

(ethology) in relation to the brain structures involved in their execution. Besides the already mentioned weakly electric fish and bats, classical examples, among many others, include song learning in zebrafinches, the neural control of flight in flies, sound localization in barn owls, and escape behaviors in a variety of species, such as locust, goldfish, or flies.

1.3 MATHEMATICAL PRELIMINARIES

MATLAB. Native MATLAB functions are in typewriter font, e.g., `svd`. Our contributed code, available on the book's web site, has a trailing `.m`, e.g., `bepswI.m`.

Numbers. The counting numbers, $\{0,1,2,\ldots\}$, are denoted by $\mathbb{N}$, while the reals are denoted by $\mathbb{R}$ and the complex numbers by $\mathbb{C}$. Each complex number, $z \in \mathbb{C}$, may be decomposed into its real and imaginary components. We will write

$$z = x + iy, \quad \text{where} \quad x = \Re(z), \quad y = \Im(z), \quad \text{and} \quad i \equiv \sqrt{-1}.$$

Here x and y are each real and $\equiv$ signifies that one side is defined by the other. We denote the complex conjugate and magnitude of z by

$$z^* \equiv x - iy \quad \text{and} \quad |z| \equiv \sqrt{x^2 + y^2},$$

respectively.

Sets. Sets are delimited by curly brackets, $\{\}$. For example the set of odd numbers between 4 and 10 is $\{5,7,9\}$.

Intervals. For $a,b \in \mathbb{R}$ with $a < b$ the open interval (a,b) is the set of numbers x such that $a < x < b$. The closed interval $[a,b]$ is the set of numbers x such that $a \le x \le b$. The semiclosed (or semiopen) intervals $[a,b)$ and $(a,b]$ are the set of numbers x such that $a \le x < b$ and $a < x \le b$, respectively.

Vectors and matrices. Given n real or complex numbers, $x_1, x_2, \ldots, x_n$, we denote their arrangement into a vector, or column, via bold lower case letters,

$$\mathbf{x} = \begin{pmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{pmatrix}. \tag{1.1}$$

The collections of all real and complex vectors with n components are denoted $\mathbb{R}^n$ and $\mathbb{C}^n$, respectively. The transpose of a vector, $\mathbf{x}$, is the row,

$$\mathbf{x}^T = (x_1 \; x_2 \; \cdots \; x_n),$$

and the conjugate transpose of a vector, $\mathbf{z} \in \mathbb{C}^n$, is the row

$$\mathbf{z}^H = (z_1^* \; z_2^* \; \cdots \; z_n^*).$$

We next define the inner, or scalar, or "dot," product for $\mathbf{x}$ and $\mathbf{y}$ in $\mathbb{C}^n$,

$$\mathbf{x}^H \mathbf{y} \equiv \sum_{j=1}^{n} x_j^* y_j,$$

and note that as

$$\mathbf{z}^H \mathbf{z} = \sum_{i=1}^{n} |z_i|^2 \ge 0$$