

Mathematics for Neuroscientists

神经科学中的数学

Fabrizio Gabbiani and Steven James Cox



神经科学研究与进展

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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—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，远远胜过了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 Matthews 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.

目 录

前言	xi	5.5 超极化激活的非特异性阳离子电流	59
1. 简介	1	5.6 总结与参考资料来源	60
1.1 如何使用本书	2	5.7 练习题	61
1.2 大脑简介	2	6. 被动电缆理论	67
1.3 基础数学知识	4	6.1 离散的被动电缆公式	67
1.4 计量单位	7	6.2 特征向量扩展的精确求解	69
1.5 参考资料来源	8	6.3 数值分析法	71
2. 被动等电位细胞	9	6.4 被动电缆公式	73
2.1 简介	9	6.5 突触输入	78
2.2 能斯特电位	11	6.6 总结与参考资料来源	81
2.3 膜电导	12	6.7 练习题	82
2.4 膜电容与电流平衡	12	7. 傅立叶级数与变换	87
2.5 突触电导	14	7.1 傅立叶级数	87
2.6 总结与参考资料来源	15	7.2 离散的傅立叶变换	89
2.7 练习题	16	7.3 连续傅立叶变换	94
3. 微分方程	21	7.4 协调离散与连续傅立叶变换	95
3.1 精确求解	21	7.5 总结与参考资料来源	98
3.2 矩量法	23	7.6 练习题	98
3.3 拉普拉斯变换	25	8. 被动树突野	103
3.4 数值分析法	27	8.1 离散的被动树突野	103
3.5 突触输入	28	8.2 特征向量扩展	105
3.6 总结与参考资料来源	29	8.3 数值分析法	107
3.7 练习题	29	8.4 被动树突公式	110
4. 主动等电位细胞	33	8.5 (树突电缆的) 等效圆柱体	111
4.1 延迟整流钾离子通道	34	8.6 (树突) 分支的特征函数	113
4.2 钠离子通道	36	8.7 总结与参考资料来源	115
4.3 Hodgkin-Huxley 公式	37	8.8 练习题	115
4.4 瞬时钾离子通道	40	9. 主动树突野	119
4.5 总结与参考资料来源	43	9.1 主动的均一电缆	120
4.6 练习题	43	9.2 主动均一电缆的相互作用	122
5. 半主动等电位细胞	49	9.3 主动非均一电缆	125
5.1 半主动模型	49	9.4 半主动电缆	130
5.2 数值分析法	51	9.5 主动树突野	134
5.3 特征向量扩展的精确求解	54	9.6 总结与参考资料来源	136
5.4 持续钠电流	58	9.7 练习题	136

10. 简化的单神经元模型	143	14.2 主成分分析与动作电位发放的归类	226
10.1 漏电的整合—发放神经元	143	14.3 突触可塑性与主成分	228
10.2 簇放电神经元	146	14.4 通过均衡截断方法精简神经元模型	230
10.3 簇放电神经元的简化模型	147	14.5 总结与参考资料来源	233
10.4 总结与参考资料来源	152	14.6 练习题	233
10.5 练习题	153	15. 动作电位发放波动的定量分析	237
11. 概率与随机变量	155	15.1 动作电位发放的时间间距柱形统计图与变异系数	238
11.1 事件与随机变量	155	15.2 动作电位不应期	239
11.2 符合二项式分布的随机变量	157	15.3 动作电位发放数分布与法诺因子	240
11.3 符合泊松分布的随机变量	159	15.4 更新过程	240
11.4 符合高斯分布的随机变量	159	15.5 返回图与经验相关因子	243
11.5 累计分布函数	160	15.6 总结与参考资料来源	245
11.6 条件概率	161	15.7 练习题	246
11.7 独立随机变量的加和	162	16. 随机过程	251
11.8 随机变量的变换	163	16.1 定义与一般特性	251
11.9 随机向量	164	16.2 高斯过程	252
11.10 指数与伽玛分布的随机变量	167	16.3 点过程	254
11.11 齐次泊松过程	168	16.4 非均一泊松过程	257
11.12 总结与参考资料来源	170	16.5 频谱分析	259
11.13 练习题	170	16.6 总结与参考资料来源	262
12. 突触传递与量子释放理论	175	16.7 练习题	262
12.1 突触的基本结构与生理	175	17. 膜噪声	267
12.2 量子释放的发现	177	17.1 两状态通道模型	267
12.3 突触释放的复合泊松模型	178	17.2 多状态通道模型	270
12.4 与实验数据的对比	180	17.3 Ornstein-Uhlenbeck 过程	271
12.5 中枢系统突触的量子分析	181	17.4 突触噪声	272
12.6 突触传递的易化、增强与抑制	183	17.5 总结与参考资料来源	275
12.7 短时程突触可塑性的模型	186	17.6 练习题	275
12.8 总结与参考资料来源	189	18. 能量谱与互相关分析	279
12.9 练习题	190	18.1 互相关与互相干	279
13. 神经元钙流信号	193	18.2 估计量偏倚与方差	280
13.1 电压门控型钙离子通道	195	18.3 能量谱的数值估计	282
13.2 胞内钙离子的扩散、缓释与再摄取	198	18.4 总结与参考资料来源	286
13.3 电镜所揭示的钙离子释放	201	18.5 练习题	286
13.4 树突小棘的钙离子	209	19. 自然光信号与光（电）转导	291
13.5 突触前钙离子和神经递质释放	213	19.1 波长与光强	291
13.6 总结与参考资料来源	217	19.2 自然光信号的空间特性	293
13.7 练习题	217		
14. 奇异值分解算法及其应用	223		
14.1 奇异值分解算法	223		

19.3	自然光信号的时间特性	293	24.5	Fisher 线性判断	351
19.4	光电转导模型	294	24.6	总结与参考资料来源	354
19.5	总结与参考资料来源	297	24.7	练习题	354
19.6	练习题	298	25. 神经元反应与心理物理学的关联研究		
20. (动作电位) 发放率编码与早期视觉					355
	299	25.1	单光子检测	355
20.1	平均自发放电的定义	299	25.2	信号检测理论与心理物理学	359
20.2	视觉系统和视觉刺激	300	25.3	运动检测	361
20.3	视网膜神经节细胞的空间感受野	301	25.4	总结与参考资料来源	363
20.4	感受野结构的特性描述	303	25.5	练习题	364
20.5	感受野时空特性	306	26. 群体编码		367
20.6	静态非线性	308	26.1	笛卡尔坐标系	367
20.7	总结与参考资料来源	308	26.2	过度完整表达	369
20.8	练习题	309	26.3	框架	370
21. 简单细胞与复杂细胞模型		311	26.4	最大似然估计	372
21.1	简单细胞模型	311	26.5	估计误差与克拉美罗界	374
21.2	不可分离的感受野	318	26.6	上丘的群体估计	375
21.3	复杂细胞感受野	320	26.7	总结与参考资料来源	376
21.4	运动-能量模型	321	26.8	练习题	378
21.5	Hubel-Wiesel 模型	321	27. 神经网络		381
21.6	视觉信息的多尺度表征	322	27.1	Hopfield 网络	382
21.7	总结与参考资料来源	323	27.2	漏电的整合发放网络	383
21.8	练习题	323	27.3	具有可塑性突触的漏电整合发放网络	389
22. 随机估计理论		327	27.4	基于 Hodgkin-Huxley 模型的网络	392
22.1	最小平均平方差估计	327	27.5	具有可塑性突触的 Hodgkin-Huxley 模型	397
22.2	高斯信号的估计	329	27.6	基于发放率的网络	398
22.3	线性非线性模型	331	27.7	脑图和自组织模型图	401
22.4	总结与参考资料来源	332	27.8	总结与参考资料来源	403
22.5	练习题	332	27.9	练习题	404
23. 反相关分析与动作电位发放解码		335	28. 练习题解答		409
	335	参考文献		473
23.1	反相关	335	索引		483
23.2	刺激重构	338			
23.3	总结与参考资料来源	340			
23.4	练习题	340			
24. 信号检测理论		343			
24.1	检测假设	343			
24.2	理想决策规则	346			
24.3	ROC 曲线	348			
24.4	多维高斯信号	348			

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(俞洪波 译)

Full Contents

Preface xi

1. Introduction 1

- 1.1 How to Use This book 2
- 1.2 Brain Facts Brief 2
- 1.3 Mathematical Preliminaries 4
- 1.4 Units 7
- 1.5 Sources 8

2. The Passive Isopotential Cell 9

- 2.1 Introduction 9
- 2.2 The Nernst Potential 11
- 2.3 Membrane Conductance 12
- 2.4 Membrane Capacitance and Current Balance 12
- 2.5 Synaptic Conductance 14
- 2.6 Summary and Sources 15
- 2.7 Exercises 16

3. Differential Equations 21

- 3.1 Exact Solution 21
- 3.2 Moment Methods* 23
- 3.3 The Laplace Transform* 25
- 3.4 Numerical Methods 27
- 3.5 Synaptic Input 28
- 3.6 Summary and Sources 29
- 3.7 Exercises 29

4. The Active Isopotential Cell 33

- 4.1 The Delayed Rectifier Potassium Channel 34
- 4.2 The Sodium Channel 36
- 4.3 The Hodgkin-Huxley Equations 37
- 4.4 The Transient Potassium Channel* 40
- 4.5 Summary and Sources 43
- 4.6 Exercises 43

5. The Quasi-Active Isopotential Cell 49

- 5.1 The Quasi-Active Model 49
- 5.2 Numerical Methods 51
- 5.3 Exact Solution via Eigenvector Expansion 54
- 5.4 A Persistent Sodium Current* 58

- 5.5 A Nonspecific Cation Current that is Activated by Hyperpolarization* 59
- 5.6 Summary and Sources 60
- 5.7 Exercises 61

6. The Passive Cable 67

- 6.1 The Discrete Passive Cable Equation 67
- 6.2 Exact Solution via Eigenvector Expansion 69
- 6.3 Numerical Methods 71
- 6.4 The Passive Cable Equation 73
- 6.5 Synaptic Input 78
- 6.6 Summary and Sources 81
- 6.7 Exercises 82

7. Fourier Series and Transforms 87

- 7.1 Fourier Series 87
- 7.2 The Discrete Fourier Transform 89
- 7.3 The Continuous Fourier Transform 94
- 7.4 Reconciling the Discrete and Continuous Fourier Transforms 95
- 7.5 Summary and Sources 98
- 7.6 Exercises 98

8. The Passive Dendritic Tree 103

- 8.1 The Discrete Passive Tree 103
- 8.2 Eigenvector Expansion 105
- 8.3 Numerical Methods 107
- 8.4 The Passive Dendrite Equation 110
- 8.5 The Equivalent Cylinder* 111
- 8.6 Branched Eigenfunctions* 113
- 8.7 Summary and Sources 115
- 8.8 Exercises 115

9. The Active Dendritic Tree 119

- 9.1 The Active Uniform Cable 120
- 9.2 On the Interaction of Active Uniform Cables* 122
- 9.3 The Active Nonuniform Cable 125
- 9.4 The Quasi-Active Cable* 130
- 9.5 The Active Dendritic Tree 134
- 9.6 Summary and Sources 136
- 9.7 Exercises 136

10. Reduced Single Neuron Models	143	14.5 Summary and Sources	233
10.1 The Leaky Integrate-and-Fire Neuron	143	14.6 Exercises	233
10.2 Bursting Neurons	146	15. Quantification of Spike Train Variability	237
10.3 Simplified Models of Bursting Neurons	147	15.1 Interspike Interval Histograms and Coefficient of Variation	238
10.4 Summary and Sources	152	15.2 Refractory Period	239
10.5 Exercises	153	15.3 Spike Count Distribution and Fano Factor	240
11. Probability and Random Variables	155	15.4 Renewal Processes	240
11.1 Events and Random Variables	155	15.5 Return Maps and Empirical Correlation Coefficient	243
11.2 Binomial Random Variables	157	15.6 Summary and Sources	245
11.3 Poisson Random Variables	159	15.7 Exercises	246
11.4 Gaussian Random Variables	159	16. Stochastic Processes	251
11.5 Cumulative Distribution Functions	160	16.1 Definition and General Properties	251
11.6 Conditional Probabilities*	161	16.2 Gaussian Processes	252
11.7 Sum of Independent Random Variables*	162	16.3 Point Processes	254
11.8 Transformation of Random Variables*	163	16.4 The Inhomogeneous Poisson Process	257
11.9 Random Vectors*	164	16.5 Spectral Analysis	259
11.10 Exponential and Gamma Distributed Random Variables	167	16.6 Summary and Sources	262
11.11 The Homogeneous Poisson Process	168	16.7 Exercises	262
11.12 Summary and Sources	170	17. Membrane Noise*	267
11.13 Exercises	170	17.1 Two-State Channel Model	267
12. Synaptic Transmission and Quantal Release	175	17.2 Multistate Channel Models	270
12.1 Basic Synaptic Structure and Physiology	175	17.3 The Ornstein-Uhlenbeck Process	271
12.2 Discovery of Quantal Release	177	17.4 Synaptic Noise	272
12.3 Compound Poisson Model of Synaptic Release	178	17.5 Summary and Sources	275
12.4 Comparison with Experimental Data	180	17.6 Exercises	275
12.5 Quantal Analysis at Central Synapses	181	18. Power and Cross Spectra	279
12.6 Facilitation, Potentiation, and Depression of Synaptic Transmission	183	18.1 Cross Correlation and Coherence	279
12.7 Models of Short-Term Synaptic Plasticity	186	18.2 Estimator Bias and Variance	280
12.8 Summary and Sources	189	18.3 Numerical Estimate of the Power Spectrum*	282
12.9 Exercises	190	18.4 Summary and Sources	286
13. Neuronal Calcium Signaling*	193	18.5 Exercises	286
13.1 Voltage-Gated Calcium Channels	195	19. Natural Light Signals and Phototransduction	291
13.2 Diffusion, Buffering, and Extraction of Cytosolic Calcium	198	19.1 Wavelength and Intensity	291
13.3 Calcium Release from the ER	201	19.2 Spatial Properties of Natural Light Signals	293
13.4 Calcium in Spines	209	19.3 Temporal Properties of Natural Light Signals	293
13.5 Presynaptic Calcium and Transmitter Release	213	19.4 A Model of Phototransduction	294
13.6 Summary and Sources	217	19.5 Summary and Sources	297
13.7 Exercises	217	19.6 Exercises	298
14. The Singular Value Decomposition and Applications*	223	20. Firing Rate Codes and Early Vision	299
14.1 The Singular Value Decomposition	223	20.1 Definition of Mean Instantaneous Firing Rate	299
14.2 Principal Component Analysis and Spike Sorting	226	20.2 Visual System and Visual Stimuli	300
14.3 Synaptic Plasticity and Principal Components	228	20.3 Spatial Receptive Field of Retinal Ganglion Cells	301
14.4 Neuronal Model Reduction via Balanced Truncation	230	20.4 Characterization of Receptive Field Structure	303
		20.5 Spatio-Temporal Receptive Fields	306

20.6	Static Nonlinearities*	308	26.4	Maximum Likelihood	372
20.7	Summary and Sources	308	26.5	Estimation Error and the Cramer–Rao Bound*	374
20.8	Exercises	309	26.6	Population Coding in the Superior Colliculus	375
			26.7	Summary and Sources	376
			26.8	Exercises	378
21.	Models of Simple and Complex Cells	311			
21.1	Simple Cell Models	311	27.	Neuronal Networks	381
21.2	Nonseparable Receptive Fields	318	27.1	Hopfield Networks	382
21.3	Receptive Fields of Complex Cells	320	27.2	Leaky Integrate-and-Fire Networks	383
21.4	Motion-Energy Model	321	27.3	Leaky Integrate-and-Fire Networks with Plastic Synapses	389
21.5	Hubel–Wiesel Model	321	27.4	Hodgkin–Huxley Based Networks	392
21.6	Multiscale Representation of Visual Information	322	27.5	Hodgkin–Huxley Based Networks with Plastic Synapses	397
21.7	Summary and Sources	323	27.6	Rate Based Networks	398
21.8	Exercises	323	27.7	Brain Maps and Self-Organizing Maps	401
			27.8	Summary and Sources	403
			27.9	Exercises	404
22.	Stochastic Estimation Theory	327	28.	Solutions to Selected Exercises	409
22.1	Minimum Mean Square Error Estimation	327	28.1	Chapter 2	409
22.2	Estimation of Gaussian Signals*	329	28.2	Chapter 3	411
22.3	Linear Nonlinear (LN) Models*	331	28.3	Chapter 4	413
22.4	Summary and Sources	332	28.4	Chapter 5	414
22.5	Exercises	332	28.5	Chapter 6	416
			28.6	Chapter 7	419
23.	Reverse-Correlation and Spike Train Decoding	335	28.7	Chapter 8	421
23.1	Reverse-Correlation	335	28.8	Chapter 9	422
23.2	Stimulus Reconstruction	338	28.9	Chapter 10	422
23.3	Summary and Sources	340	28.10	Chapter 11	423
23.4	Exercises	340	28.11	Chapter 12	428
			28.12	Chapter 13	430
24.	Signal Detection Theory	343	28.13	Chapter 14	431
24.1	Testing Hypotheses	343	28.14	Chapter 15	433
24.2	Ideal Decision Rules	346	28.15	Chapter 16	436
24.3	ROC Curves*	348	28.16	Chapter 17	442
24.4	Multidimensional Gaussian Signals*	348	28.17	Chapter 18	445
24.5	Fisher Linear Discriminant*	351	28.18	Chapter 19	452
24.6	Summary and Sources	354	28.19	Chapter 20	453
24.7	Exercises	354	28.20	Chapter 21	453
			28.21	Chapter 22	455
25.	Relating Neuronal Responses and Psychophysics	355	28.22	Chapter 23	458
25.1	Single Photon Detection	355	28.23	Chapter 24	459
25.2	Signal Detection Theory and Psychophysics	359	28.24	Chapter 25	464
25.3	Motion Detection	361	28.25	Chapter 26	466
25.4	Summary and Sources	363	28.26	Chapter 27	470
25.5	Exercises	364			
			References	473	
26.	Population Codes*	367	Index	483	
26.1	Cartesian Coordinate Systems	367			
26.2	Overcomplete Representations	369			
26.3	Frames	370			

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Introduction

OUTLINE

1.1 How to Use this Book	2	1.4 Units	7
1.2 Brain Facts Brief	2	1.5 Sources	8
1.3 Mathematical Preliminaries	4		

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

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

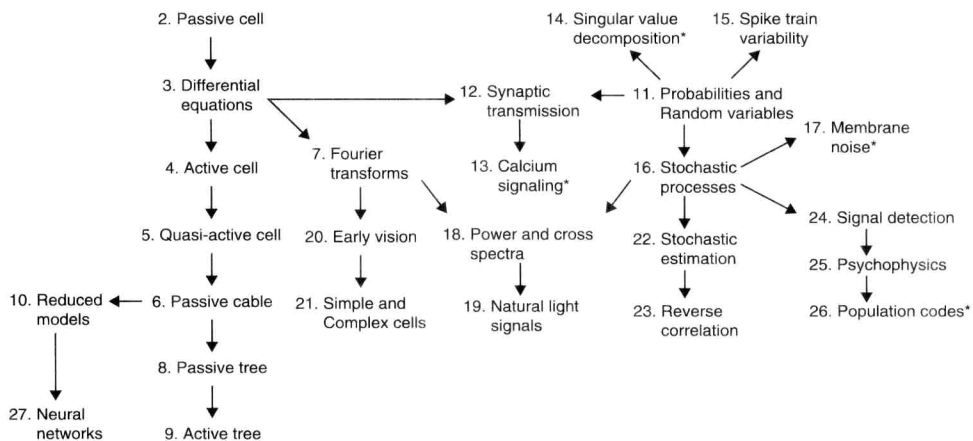


FIGURE 1.1 Chapter dependencies. Each arrow points to a chapter that depends significantly on the content of the current chapter. The asterisk is used to denote chapters that cover advanced material.

(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 zebra finches, 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, $\{0, 1, 2, \dots\}$, 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

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

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 $a \leq x \leq b$. The semiclosed (or semiopen) intervals $[a, b)$ and $(a, b]$ are the set of numbers x such that $a \leq x < b$ and $a < x \leq b$, respectively.

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

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

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

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