Lecture Notes in Mathematics
1860

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Tutorials in Mathematical Biosciences I

Mathematical Neuroscience

Mathematical Biosciences Subseries

Springer

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Lecture Notes in Mathematics

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   - a subject index: as a rule this is genuinely helpful for the reader.

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Lecture Notes in Mathematics 1860

Preface

This is the first volume in the series "Tutorials in Mathematical Biosciences". These lectures are based on material which was presented in tutorials or developed by visitors and postdoctoral fellows of the Mathematical Biosciences Institute (MBI), at The Ohio State University. The aim of this series is to introduce graduate students and researchers with just a little background in either mathematics or biology to mathematical modeling of biological processes. The first volume is devoted to Mathematical Neuroscience, which was the focus of the MBI program in 2002-2003; documentation of this year's activities, including streaming videos of the workshops, can be found on the website http://mbi.osu.edu.

The use of mathematics in studying the brain has had great impact on the field of neuroscience and, simultaneously, motivated important research in mathematics. The Hodgkin-Huxley model, which originated in the early 1950s, has been fundamental in our understanding of the propagation of electrical impulses along a nerve axon. Reciprocally, the analysis of these equations has resulted in the development of sophisticated mathematical techniques in the fields of partial differential equations and dynamical systems. Interaction among neurons by means of their synaptic terminals has led to a study of coupled systems of ordinary differential and integro-differential equations, and the field of computational neurosciences can now be considered a mature discipline.

The present volume introduces some basic theory of computational neuroscience. Chapter 2, by David Terman, is a self-contained introduction to dynamical systems and bifurcation theory, oriented toward neuronal dynamics. The theory is illustrated with a model of Parkinson's disease. Chapter 3, by Bard Ermentrout, reviews the theory of coupled neural oscillations. Oscillations are observed throughout the nervous systems at all levels, from single cell to large network: This chapter describes how oscillations arise, what pattern they may take, and how they depend on excitory or inhibitory synaptic connections. Chapter 4 specializes to one particular neuronal system, namely, the auditory system. In this chapter, Alla Borisyuk provides a self-contained

introduction to the auditory system, from the anatomy and physiology of the inner ear to the neuronal network which connects the hair cells to the cortex. She describes various models of subsystems such as the one that underlies sound localization. In Chapter 1, I have given a brief introduction to neurons, tailored to the subsequent chapters. In particular, I have included the electric circuit theory used to model the propagation of the action potential along an axon.

I wish to express my appreciation and thanks to David Terman, Bard Ermentrout, and Alla Borisyuk for their marvelous contributions. I hope this volume will serve as a useful introduction to those who want to learn about the important and exciting discipline of Computational Neuroscience.

August 27, 2004 Avner Friedman, Director, MBI

Contents

Introduction to Neurons
Avner Friedman 1
1 The Structure of Cells 1
2 Nerve Cells 6
3 Electrical Circuits and the Hodgkin-Huxley Model 9
4 The Cable Equation 15
References 20

An Introduction to Dynamical Systems and Neuronal Dynamics
David Terman 21
1 Introduction 21
2 One Dimensional Equations 23
2.1 The Geometric Approach 23
2.2 Bifurcations 24
2.3 Bistability and Hysteresis 26
3 Two Dimensional Systems 28
3.1 The Phase Plane 28
3.2 An Example 29
3.3 Oscillations 31
3.4 Local Bifurcations 31
3.5 Global Bifurcations 33
3.6 Geometric Singular Perturbation Theory 34
4 Single Neurons 36
4.1 Some Biology 37
4.2 The Hodgkin-Huxley Equations 38
4.3 Reduced Models 39
4.4 Bursting Oscillations 43
4.5 Traveling Wave Solutions 47

5 Two Mutually Coupled Cells 50
5.1 Introduction 50
5.2 Synaptic Coupling 50
5.3 Geometric Approach 51
5.4 Synchrony with Excitatory Synapses 53
5.5 Desynchrony with Inhibitory Synapses 57
6 Activity Patterns in the Basal Ganglia 61
6.1 Introduction 61
6.2 The Basal Ganglia 61
6.3 The Model 62
6.4 Activity Patterns 63
6.5 Concluding Remarks 65
References 66

Neural Oscillators
Bard Ermentrout 69
1 Introduction 69
2 How Does Rhythmicity Arise 70
3 Phase-Resetting and Coupling Through Maps 73
4 Doublets, Delays, and More Maps 78
5 Averaging and Phase Models 80
5.1 Local Arrays 84
6 Neural Networks 91
6.1 Slow Synapses 91
6.2 Analysis of the Reduced Model 94
6.3 Spatial Models 96
References 103

Physiology and Mathematical Modeling of the Auditory System
Alla Borisyuk 107
1 Introduction 107
1.1 Auditory System at a Glance 108
1.2 Sound Characteristics 110
2 Peripheral Auditory System 113
2.1 Outer Ear 113
2.2 Middle Ear 114
2.3 Inner Ear. Cochlea. Hair Cells. 115
2.4 Mathematical Modeling of the Peripheral Auditory System 117
3 Auditory Nerve (AN) 124
3.1 AN Structure 124
3.2 Response Properties 124
3.3 How Is AN Activity Used by Brain? 127
3.4 Modeling of the Auditory Nerve 130

4 Cochlear Nuclei 130
4.1 Basic Features of the CN Structure 131
4.2 Innervation by the Auditory Nerve Fibers 132
4.3 Main CN Output Targets 133
4.4 Classifications of Cells in the CN 134
4.5 Properties of Main Cell Types 135
4.6 Modeling of the Cochlear Nuclei 141
5 Superior Olive. Sound Localization, Jeffress Model 142
5.1 Medial Nucleus of the Trapezoid Body (MNTB) 142
5.2 Lateral Superior Olivary Nucleus (LSO) 143
5.3 Medial Superior Olivary Nucleus (MSO) 143
5.4 Sound Localization. Coincidence Detector Model 144
6 Midbrain 150
6.1 Cellular Organization and Physiology of Mammalian IC 151
6.2 Modeling of the IPD Sensitivity in the Inferior Colliculus 151
7 Thalamus and Cortex 161
References 162

Index 169

Introduction to Neurons

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Summary. All living animals obtain information from their environment through sensory receptors, and this information is transformed to their brain where it is processed into perceptions and commands. All these tasks are performed by a system of nerve cells, or neurons. Neurons have four morphologically defined regions: the cell body, dendrites, axon, and presynaptic terminals. A bipolar *neuron* receives signals from the dendritic system; these signals are integrated at a specific location in the cell body and then sent out by means of the axon to the presynaptic terminals. There are neurons which have more than one set of dendritic systems, or more than one axon, thus enabling them to perform simultaneously multiple tasks; they are called *multipolar neurons*.

This chapter is not meant to be a text book introduction to the general theory of neuroscience; it is rather a brief introduction to neurons tailored to the subsequent chapters, which deal with various mathematical models of neuronal activities. We shall describe the structure of a generic bipolar neuron and introduce standard mathematical models of signal transduction performed by neurons. Since neurons are cells, we shall begin with a brief introduction to cells.

1 The Structure of Cells

Cells are the basic units of life. A cell consists of a concentrated aqueous solution of chemicals and is capable of replicating itself by growing and dividing. The simplest form of life is a single cell, such as a yeast, an amoeba, or a bacterium. Cells that have a nucleus are called *eukaryotes*, and cells that do not have a nucleus are called *prokaryotes*. Bacteria are prokaryotes, while yeasts and amoebas are eukaryotes. Animals are multi-cellular creatures with eukaryotic cells. A typical size of a cell is 5–20μm (1μm = 1 micrometer = 10^{-6} meter) in diameter, but an oocyte may be as large as 1mm in diameter. The human body is estimated to have 1014 cells. Cells may be very diverse as they perform different tasks within the body. However, all eukaryotic cells have the same basic structure composed of a nucleus, a variety of organelles

and molecules, and a *plasma membrane*, as indicated in Figure 1 (an exception are the red blood cells, which have no nucleus).

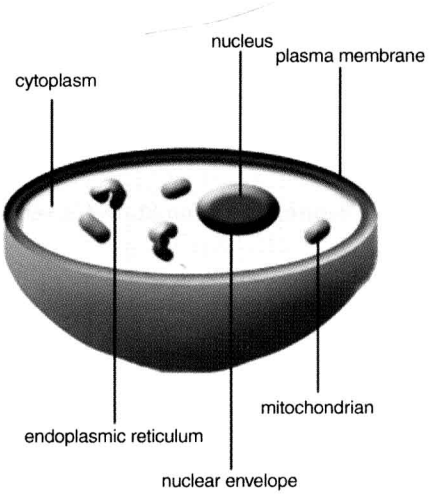

Fig. 1. A cell with nucleus and some organelles.

The DNA, the genetic code of the cell, consists of two strands of polymer chains having a double helix configuration, with repeated nucleotide units A, C, G, and T. Each A on one strand is bonded to T on the other strand by a hydrogen bond, and similarly each C is hydrogen bonded to T. The DNA is packed in chromosomes in the nucleus. In humans, the number of chromosomes in a cell is 46, except in the sperm and egg cells where their number is 23. The total number of DNA base pairs in human cells is 3 billions. The nucleus is enclosed by the nuclear envelope, formed by two concentric membranes. The nuclear envelope is perforated by *nuclear pores*, which allow some molecules to cross from one side to another.

The cell's plasma membrane consists of a lipid bilayer with proteins embedded in them, as shown in Figure 2. The *cytoplasm* is the portion of the cell which lies outside the nucleus and inside the cell's membrane.

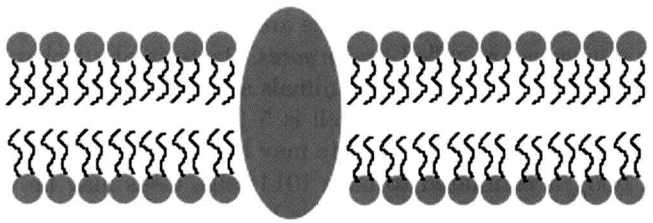

Fig. 2. A section of the cell's membrane.

An *organelle* is a discrete structure in the cytoplasm specialized to carry out a particular function. A *mitochondrion* is a membrane-delineated organelle that uses oxygen to produce energy, which the cell requires to perform its various tasks. An *endoplasmic reticulum* (ER) is another membrane-bounded organelle where lipids are secreted and membrane-bound proteins are made. The cytoplasm contains a number of mitochondria and ER organelles, as well as other organelles, such as *lysosomes* in which intra-cellular digestion occurs. Other structures made up of proteins can be found in the cell, such as a variety of filaments, some of which serve to strengthen the cell mechanically. The cell also contains amino acid molecules, the building blocks of proteins, and many other molecules.

The *cytoskeleton* is an intricate network of protein filaments that extends throughout the cytoplasm of the cell. It includes families of *intermediate filaments*, *microtubules*, and *actin filaments*. Intermediate filaments are rope-like fibers with a diameter of 10nm and strong tensile strength (1nm=1 nanometer=10^{-9} meter). Microtubules are long, rigid, hollow cylinders of outer diameter 25nm. Actin filaments, with diameter 7nm, are organized into a variety of linear bundles; they are essential for all cell movement such as crawling, engulfing of large particles, or dividing. Microtubules are used as a "railroad tract" in transport of vesicles across the cytoplasm by means of motor proteins (see next paragraph). The motor protein has one end attached to the vescicle and the other end, which consists of two "heads", attached to the microtubule. Given input of energy, the protein's heads change configuration (conformation), thereby executing one step with each unit of energy.

Proteins are polymers of amino acids units joined together head-to-tail in a long chain, typically of several hundred amino acids. The linkage is by a covalent bond, and is called a *peptide bond*. A chain of amino acids is known as a *polypeptide*. Each protein assumes a 3-dimensional configuration, which is called a *conformation*. There are altogether 20 different amino acids from which all proteins are made. Proteins perform specific tasks by changing their conformation.

The various tasks the cell needs to perform are executed by proteins. Proteins are continuously created and degraded in the cell. The synthesis of proteins is an intricate process. The DNA contains the genetic code of the cell. Each group of three letters (or three base pairs) may be viewed as one "word". Some collections of words on the DNA represent *genes*. The cell expresses some of these genes into proteins. This translation process is carried out by several types of RNAs: *messenger* RNA (mRNA), *transfer* RNA (tRNA), and *ribosomal* RNA (rRNA). Ribosome is a large complex molecule made of more than 50 different ribosomal proteins, and it is there where proteins are synthesized. When a new protein needs to be made, a signal is sent to the DNA (by a *promoter* protein) to begin transcribing a segment of a strand containing an appropriate gene; this copy of the DNA strand is the mRNA. The mRNA molecule travels from the nucleus to a ribosome, where each "word" of three letters, for example (A, C, T), called a *codon*, is going to be translated into

one amino acid. The translation is accomplished by tRNA, which is a relatively compact molecule. The tRNA has a shape that is particularly suited to conform to the codon at one end and is attached to an amino acid corresponding to the particular codon at its other end. Step-by-step, or one-by-one, the tRNAs line up along the ribosome, one codon at a time, and at each step a new amino acid is brought in to the ribosome where it connects to the preceding amino acid, thus joining the growing chain of amino acids until the entire protein is synthesized.

The human genome has approximately 30,000 genes. The number of different proteins is even larger; however cells do not generally express all their genes.

The cell's membrane is typically 6–8nm thick and as we said before, it is made of a double layer of lipids with proteins embedded throughout. The lipid bilayer is hydrophobic and selectively permeable. Small nonpolar molecules such as O_2 and CO_2 readily dissolve in the lipid bilayer and rapidly diffuse across it. Small uncharged polar molecules such as water and ethanol also diffuse rapidly across the bilayer. However, larger molecules or any ions or charged molecules cannot diffuse across the lipid bilayer. These can only be selectively transported across the membrane by proteins, which are embedded in the membrane. There are two classes of such proteins: *carrier proteins* and *channel proteins*. Carrier proteins bind to a solute on one side of the membrane and then deliver it to the other side by means of a change in their conformation. Carrier proteins enable the passage of nutrients and amino acids into the cell, and the release of waste products, into the extracellular environment. Channel proteins form tiny hydrophilic pores in the membrane through which the solute can pass by diffusion. Most of the channel proteins let through only inorganic ions, and these are called *ion channels*.

Both the intracellular and extracellular environments include ionized aqueous solution of dissolved salts, primarily $NaCl$ and KCl, which in their disassociated state are Na^+, K^+, and Cl^- ions. The concentration of these ions, as well as other ions such as $Ca2^+$, inside the cell differs from their concentration outside the cell. The concentration of Na^+ and $Ca2^+$ inside the cell is smaller than their concentration outside the cell, while K^+ has a larger concentration inside the cell than outside it. Molecules move from high concentration to low concentration ("downhill" movement). A pathway that is open to this movement is called a *passive* channel or a *leak* channel; it does not require expenditure of energy. An *active transport* channel is one that transports a solute from low concentration to high concentration ("uphill" movement); such a channel requires expenditure of energy.

An example of an active transport is the sodium-potassium pump, pumping $3Na^+$ out and $2K^+$ in. The corresponding chemical reaction is described by the equation

$$ATP + 3Na_i^+ + 2K_e^+ \rightarrow ADP + P_i + 3Na_e^+ + 2K_i^+$$

In this process, energy is expended by the conversion of one molecule ATP to one ADP and a phosphate atom P.

Another example of active transport is the calcium pump. The concentration of free $Ca2^+$ in the cell is 0.1μM, while the concentration of $Ca2^+$ outside the cell is 1mM, that is, higher by a factor of 10^4 (μM=micromole=10^{-6} mole, mM=milimole=10^{-3} mole, mole=number of grams equal to the molecular weight of a molecule). To help maintain these levels of concentration the cell uses active calcium pumps.

An important formula in electrophysiology and in neuroscience is the *Nernst equation*. Suppose two reservoirs of the same ions S with, say, a positive charge Z per ion, are separated by a membrane. Suppose each reservoir is constantly kept electrically neutral by the presence of other ions T. Finally, suppose that the membrane is permeable to S but not to T. We shall denote by $[S_i]$ the concentration of S on the left side or the inner side, of the membrane, and by $[S_o]$ the concentration of S on the right side, or the outer side, of the membrane. If the concentration $[S_i]$ is initially larger than the concentration $[S_o]$, then ions S will flow from inside the membrane to the outside, building up a positive charge that will increasingly resist further movement of positive ions from the inside to the outside of the membrane. When equilibrium is reached, $[S_o]$ will be, of course, larger than $[S_i]$ and (even though each side of the membrane is electrically neutral) there will be voltage difference V_s across the membrane. V_s is given by the Nernst equation

$$V_s = \frac{RT}{ZF} \ell n \frac{[S_o]}{[S_i]}$$

when R is the universal gas constant, F is the Faraday constant, and T is the absolute temperature. For $Z = 1$, temperature=37°C,

$$V_s = 62 \log_{10} \frac{[S_o]}{[S_i]} .$$

By convention, the membrane potential is defined as the difference: The outward-pointing electric field from inside the membrane minus the inward-pointing electric field from outside the membrane.

The ions species separated by the cell membrane, are primarily K^+, Na^+, Cl^-, and $Ca2^+$. To each of them corresponds a different Nernst potential. The electric potential at which the net electrical current is zero is called the *resting membrane potential*. An approximate formula for computing the resting membrane potential is known as the Goldman-Hodgkin-Katz (GHK) equation.

For a typical mammalian cell at temperature 37°C,

S	$[S_i]$	$[S_o]$	V_s
K^+	140	5	−89.7 mV
Na^+	5–15	145	+90.7 – (+61.1)mV
Cl^-	4	110	−89mV
Ca^{2+}	1–2	2.5–5	+136 – (+145)mV

where the concentration is in milimolar (mM) and the potential is in milivolt. The negative V_s for $S = K^+$ results in an inward-pointing electric field which drives the positively charged K^+ ions to flow inward. The sodium-potassium pump is used to maintain the membrane potential and, consequently, to regulate the cell volume. Indeed, recall that the plasma membrane is permeable to water. If the total concentration of solutes is low one side of the membrane and high on the other, then water will tend to move across the membrane to make the solute concentration equal; this process is known as *osmosis*. The osmotic pressure, which drives water across the cell, will cause the cell to swell and eventually to burst, unless it is countered by an equivalent force, and this force is provided by the membrane potential. The resting potential for mammalian cells is in the range of -60mV to -70mV.

2 Nerve Cells

There are many types of cells in the human body. These include: (i) a variety of epithelial cells that line up the inner and outer surfaces of the body; (ii) a variety of cells in connective tissues such as fibroblasts (secreting extracellular protein, such as collagen and elastin) and lipid cells; (iii) a variety of muscle cells; (iv) red blood cells and several types of white blood cells; (v) sensory cells, for example, rod cells in the retina and hair cells in the inner ear; and (vi) a variety of nerve cells, or neurons.

The fundamental task of neurons is to receive, conduct, and transmit signals. Neurons carry signals from the sense organs inward to the central nervous system (CNS), which consists of the brain and spinal cord. In the CNS the signals are analyzed and interpreted by a system of neurons, which then produce a response. The response is sent, again by neurons, outward for action to muscle cells and glands.

Neurons come in many shapes and sizes, but they all have some common features as shown schematically in Figure 3.

A typical neuron consists of four parts: *cell body*, or *soma*, containing the nucleus and other organelles (such as ER and mitochondria); branches of *dendrites*, which receive signals from other neurons; an *axon* which conducts signals away from the cell body; and many branches at the far end of the axon, known as *nerve terminals* or *presynaptic terminals*. Nerve cells, body and axon, are surrounded by *glial cells*. These provide support for nerve cells, and they also provide insulation sheaths called *myelin* that cover and protect most of the large axons. The combined number of neurons and glial cells in the human body is estimated at 10^{12}.

The length of an axon varies from less than 1mm to 1 meter, depending on the type of nerve cell, and its diameter varies between 0.1μm and 20μm.

The dendrites receive signals from nerve terminals of other neurons. These signals, tiny electric pulses, arrive at a location in the soma, called the *axon hillock*. The combined electrical stimulus at the hillock, if exceeding a certain

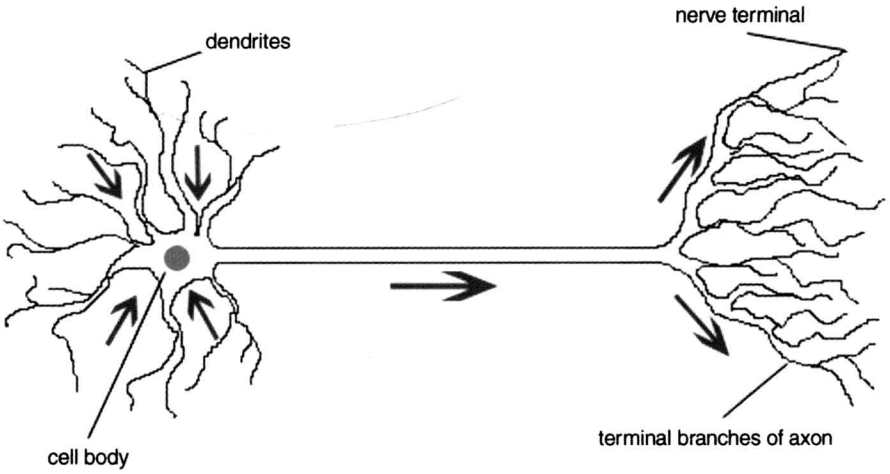

Fig. 3. A neuron. The arrows indicate direction of signal conduction.

threshold, triggers the initiation of a traveling wave of electrical excitation in the plasma membrane known as the *action potential*. If the plasma membrane were an ordinary conductor, then the electrical pulse of the action potential would weaken substantially along the plasma membrane. However, as we shall see, the plasma membrane, with its many sodium and potassium active channels spread over the axon membrane, is a complex medium with conductance and resistance properties that enable the traveling wave of an electrical excitation to maintain its pulse along the plasma membrane of the axon without signal weakening. The traveling wave has a speed of up to 100m/s.

A decrease in the membrane potential (for example, from −65mV to −55mV) is called *depolarization*. An increase in the membrane potential (for example, from −65mV to −75mV) is called *hyperpolarization*. Depolarization occurs when a current is injected into the plasma membrane. As we shall see, depolarization enables the action potential, whereas hyperpolarization tends to block it. Hence, a depolarizing signal is *excitatory* and a hyperpolarizing signal is *inhibitory*.

The action potential is triggered by a sudden depolarization of the plasma membrane, that is, by a shift of the membrane potential to a less negative value. This is caused in many cases by ionic current, which results from stimuli by neurotransmitters released to the dendrites from other neurons. When the depolarization reaches a threshold level (e.g., from −65mV to −55mV) it affects voltage-gated channels in the plasma membrane. First, the sodium channels at the site open: the electrical potential difference across the membrane causes conformation change, as illustrated in Figure 4, which results in the opening of these channels.

When the sodium channels open, the higher Na^+ concentration on the outside of the axon pressures these ions to move into the axon against the