Bin He *Editor*

Neural Engineering

Second Edition

Springer

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Preface

There has been tremendous progress in the engineering of tools, which interact with the nervous systems—from signal detection and processing to restoration and enhancement of functions. Neural engineering (or its equivalent, neuroengineering) is a rapidly expanding interdisciplinary field bridging neuroscience and engineering. Neural engineering spans cellular, tissue, and systems level research and has become a core discipline within biomedical engineering and beyond. It is our intent to provide a comprehensive review of the principles, concepts, theories, methods, and state-of-the-art research in selected areas of neural engineering. This book is aimed at serving as a textbook for undergraduate and graduate level courses in neural engineering within a biomedical engineering or bioengineering curriculum. It is also suitable as an introduction to engineers or neuroscientists who are interested in entering the field of neural engineering or acquiring knowledge about the current state of the art in this rapidly developing field.

Chapter 1 provides a general introduction to human neuroanatomy and neurophysiology. The chapter was written mainly for readers with backgrounds in engineering and the physical sciences. Readers who are familiar with neuroanatomy and neurophysiology may skip this chapter, but this chapter will be useful for those who have not previously been exposed to these topics. The chapter includes over 60 original figures drawn for educational purposes.

Brain–computer interface or brain–machine interface technologies have been an important area of research in neural engineering and involve neural sensing, decoding, modeling, computation, and control. Chapter 2 provides an introduction and comprehensive review of the concepts, principles and methods of brain–computer interface technology. Using various recorded brain signals that reflect the "intention" of the brain, brain–computer interface systems have been shown to control an external device, a computer, or a robot. This chapter reviews the history, system structure, signal acquisition, signal processing, performance evaluation, and major applications of noninvasive brain–computer interface systems. Chapter 3 reviews the concept of neural prosthetic devices and recent developments in neurorobotics. These range from using the activity of peripheral nerves or muscles to acquire a control signal to implanting devices directly into the brain or central nervous system to extract command signals from populations of neurons. This chapter focuses on neuroprosthetic devices that use recording microelectrodes in the brain to capture information from populations of neurons to create a command signal for a device or machine that can then restore useful functions to the patient. Chapter 4 discusses the principles for model estimation that are relevant to brain–machine interface systems, as well as a review of successful implementations. This chapter specifically reviews methods and models that are based on a population of single-unit activity, where action potential timings from a single cell are used in estimating continuous kinematic variables.

An important aspect of neural engineering is to properly analyze and interpret the neural signals—a step that plays a vital role for sensing and controlling neural prostheses and other neural interfacing devices, as well as understanding the mechanisms of neural systems. Chapter 5 provides a comprehensive review of EEG signal processing. After a general overview of EEG, time, frequency, and wavelet signal processing techniques are reviewed in detail. These signal processing techniques are also applicable for processing other neural signals.

Computational models of neural systems provide a quantitative perspective in neurophysiology and neural engineering by coupling experimental observations to mathematical formulations. Chapters 6–8 deal with neural modeling, which is an important tool for understanding neural mechanisms. Chapter 6 provides an introduction to neural modeling, laying the foundation for several basic models and surveying key topics. These include the properties of electrically excitable membranes, the Hodgkin–Huxley model, and how such a model can be extended to describe a variety of excitable membrane behaviors, including axonal propagation, dendritic processing, and synaptic communication. Chapter 6 also covers mathematical models that replicate basic neural behaviors through more abstract mechanisms and explores efforts to extend single-neuron models to the network level. Chapter 7 discusses modeling techniques for neural information processing with selected application examples. Reviewed topics include: the known properties of neural information processes, ranging from cellular to system levels, generic multi-scale modeling techniques for the dynamics of neural systems, and selected model examples of a neural information process. The examples presented include sensory perception and neural control of baroreflex. Chapter 8 focuses on the bidomain modeling of excitable neural tissues. An understanding of the mechanisms of excitation and propagation of neural activation is desirable, and mathematical models of electrical stimulation can help predict localized activation in desirable regions of tissue, and conversely, regions where undesirable activation may occur.

Neuromodulation is one of the important areas in neuroengineering research and has rapidly become an important option in treating a variety of neurological and mental disorders. Chapter 9 provides an in-depth coverage of transcranial magnetic stimulation, a noninvasive neuromodulation technique that is based on electromagnetic induction principles. This technique creates electrical fields inside the body, which can depolarize neurons in the central nervous system and peripheral nervous system, leading to the firing of action potentials. Chapter 10 provides an overview of neurological disorders and various neuromodulation techniques, as well as the applications that are currently being used to treat clinical problems.

Neuroimaging has played an important role in understanding neural functions and aiding in clinical diagnoses and treatments. Recent developments in functional neuroimaging have led to important tools for better understanding, as well as aiding in the restoration of, neural functions. Chapters 11–13 cover three important approaches on neuroimaging. Chapter 11 provides an introduction to the principles of magnetic resonance imaging (MRI) and functional MRI, as well as a detailed look at the physiological source of the fMRI signal. This chapter covers the physics of nuclear magnetic resonance, image formation and contrast mechanisms; an overview of functional MRI; and experiment design, data analysis and modeling of the functional MRI. Chapter 12 reviews the basic principles and applications of electrophysiological neuroimaging. Applying the electromagnetic theory and signal processing techniques, electrophysiological neuroimaging provides spatio-temporal mapping of source distributions within the brain from noninvasive electrophysiological measurements, such as electroencephalogram (EEG) and magnetoencephalogram (MEG). Knowledge of such spatio-temporal dynamics of source distribution associated with neural activity aids in the understanding of the mechanisms of neural systems and provides a noninvasive probe of the complex central nervous system. Multimodal neuroimaging, which integrates functional MRI and EEG/MEG, is also discussed. Chapter 13 covers functional and causal connectivity analysis and imaging with the goal of not only discovering where brain activity occurs but also how neural information processing is performed. The concepts of functional and causal connectivity are introduced, and mathematic models behind the causality analysis are presented. Causal connectivity approaches using various signals are also introduced.

The retina represents an important component of the peripheral nervous system. Chapters 14 and 15 discuss retinal bioengineering and prostheses. The mathematical modeling of neural responses in the retinal microenvironment as well as the restoration of retinal function, is reviewed. The retina has long served as a model for understanding complex parts of the nervous system, but is also simpler than other parts of the brain due to the lack of significant feedback from the brain to the retina.

The translation of neuroscience discoveries to clinical applications represents one of the unique features of neural engineering research. The following chapters cover various medical aspects of neural engineering. Chapter 16 deals with peripheral neural interfacing. This chapter examines the possibility of detecting peripheral nerve signals and using these voluntary signals to restore function in patients with stroke, amputation or paralysis. Applying source localization and imaging techniques that were heavily developed in EEG/MEG source imaging, this chapter presents the capability of the estimation of electrical source signals from recordings made by an array of electrodes for peripheral neural interfacing. Chapter 17 discusses neural system prediction, in particular the prediction of epileptic seizures. It provides an overview of the various techniques for quantifying and predicting seizure activities, which may allow for proper intervention and control of the impending seizure. Chapter 18 provides a review of a cognitive prosthesis designed to restore the ability to form new long-term memories—a memory capability lost after damage to the hippocampal formation and surrounding temporal lobe brain structures. This chapter also describes recent studies demonstrating that the same device and procedures that are used to restore lost hippocampal memory function can also be used to enhance memory capability in otherwise normal animals.

Chapter 19 provides an overview of neural tissue engineering, which describes the potential for repairing injury to the nervous system. This chapter discusses the differences and challenges in treating injuries of central and peripheral nervous systems, and the current methodologies that are being employed to enhance the endogenous regenerative potential and plasticity. The discussion includes the state-of-the-art in facilitating repair and rehabilitation by means of biochemical and cellular therapies as well as by electrical stimulation of neuromuscular tissue.

Through this collection of carefully selected chapters, we wish to provide a general picture of neural engineering to outline the fundamental underpinnings that will make it a core discipline in biomedical engineering, as well as to convey the exciting aspects of neural engineering. Neural engineering not only represents an interface between neuroscience and engineering, but, more importantly, has led to great advancements in basic and clinical neurosciences which would not have been possible without the integration with engineering.

This book is a collective effort by researchers and educators who specialize in the field of neural engineering. I am very grateful to them for taking the time out of their busy schedules and for their patience during the entire process. It should be noted that the field of neural engineering is developing rapidly and there are many worthwhile topics that could not be included in this book, as the book aims to serve as textbook for a semester-long neural engineering course. Nevertheless, our intention is to provide a general overview that covers important areas of neural engineering research.

I would like to thank a number of colleagues who served as reviewers of all chapters included in the book; most chapters were peer-reviewed multiple times. These colleagues include Aviva Abosch, Ardalan Aarabi, Riccardo Barbieri, Marom Bikson, James Carey, Andrey Dmitriev, Dominique Durand, Laura Frishman, Elias Greenbaum, James Hickman, Bo Hong, Leonidas Jassemidis, Matt Johnson, Jennifer Kang-Mieler, Erin Lavik, Mikhail Lebedev, Frank Lehmann-Horn, Tay Netoff, Marco Marcolin, Bradley Roth, Wim Rutten, Justin Sanchez, Allen Song, Stephen Helms Tillery, Shanbao Tong, Edward Vigmond, John White, Wei Wu, and Nanyin Zhang.

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Contents

Chapter 1
Introduction to Neurophysiology

Paul A. Iaizzo

Neurophysiology is a critical and exciting topic to study and understand in great detail for those working in any field associated with neuroengineering—basic or applied research, device design and development, and/or neurology or neurosurgical clinical subspecialties. The purpose of this chapter is to provide a general introduction to neurophysiology with more detailed information on several selected topics and to offer a high level overview of the workings of the human central nervous system (CNS). One can explore other sources to find in-depth discussions related to many of the topics introduced in this chapter, as well as learn the specifics of state-of-the-art neuroengineering concepts related to each topic.

1 Overview of Neurons, Synapses, Neuronal Circuits, and Central Nervous System Anatomy

Cells within the CNS are like most other cells in the human body and contain various components/organelle, including surface membranes (which contain ion channels and biochemical receptors), nuclei (containing chromosomes and DNA), mitochondria, ribosomes, endoplasmic reticulum, Golgi complexes, lysosomes, etc. The cell populations defined as nerve cells (*neurons*) are considered as the functional units within the *human nervous system*; see Fig. 1.1. These cells also typically have dendrites, axons, and axon terminals. Neurons under resting conditions have an electrical potential across their plasma membranes, with the inside of these cells being negatively charged with respect to the outside (extracellular spaces). This is defined as the *resting membrane potential*, which ranges between −40 and −70 mV in healthy neurons; by convention, the extracellular fluid is assigned a voltage of zero.

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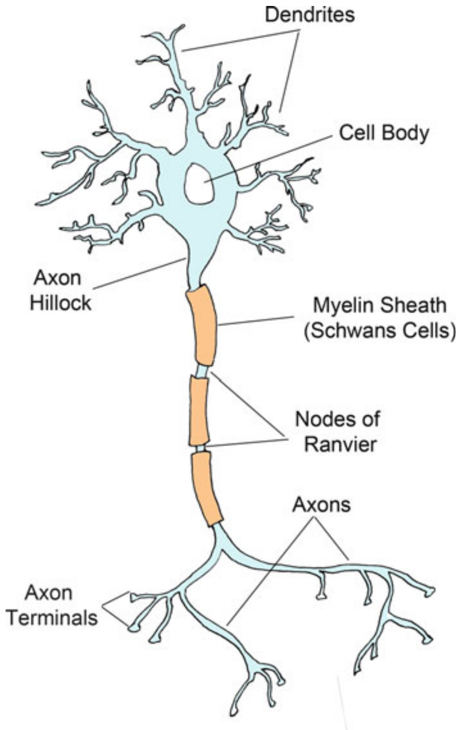
Fig. 1.1 Although nerve cells throughout the central nervous system take hundreds of unique forms and shapes, most of the cells have common cellular components. Shown here are the major structural features of an idealized neuron: dendrites (receiving synapses from other cells), the cell body, the axon hillock, myelination, axons, and the axon terminals (forming synapses onto other cells)



In general, the resting membrane potential can be considered to hold steady, unless altered by changes in local electrical currents. These potentials exist due to an excess of negative ions inside the cells and an excess of positive ones on the outside. One can consider that it is the distribution of three major mobile ions across a neuron's plasma membrane that sets up the possibility for a change in potential (1) Na^+ with 145 mmol/L extracellular and 15 mmol/L intracellular concentrations; (2) Cl^- with 100 mmol/L extracellular and 7 mmol/L intracellular concentrations; and (3) K^+ with 5 mmol/L extracellular and 150 mmol/L intracellular concentrations. The excess of charged ions collect near the plasma membrane, and their movement during excitation of the cell underlies the development of an *action potential*, which then propagates from the point of excitation along the surface membranes (e.g., down a neuron's axon). See Fig. 1.2 for definitions of excitation states.

If the concentration gradient for any ion is known, then the relative equilibrium potential across the plasma membrane for that ion can be calculated by means of the *Nernst equation*, i.e., one can estimate the electrical potential necessary to balance a given ionic concentration gradient across a membrane (the net flux for this ion is zero). The Nernst equation is:

$$E_{\text{ion}} = \frac{61}{Z} \log\left(\frac{C_{\text{out}}}{C_{\text{in}}}\right),$$

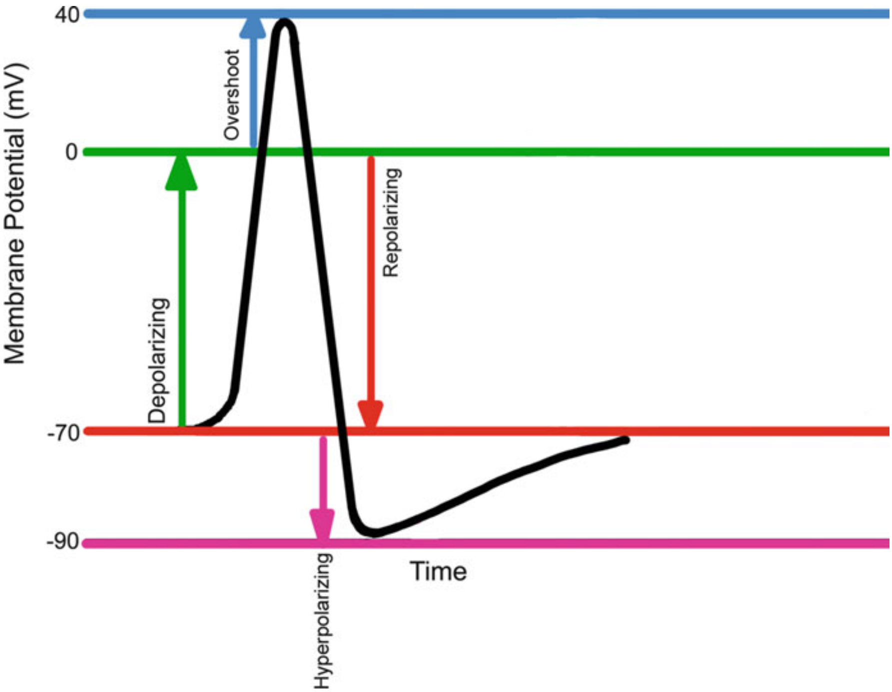


Fig. 1.2 Shown here is a general action potential waveform. Depolarizing, repolarizing, hyperpolarizing, and overshoot changes in membrane potential are shown in relation to the resting membrane potential (*horizontal red line*)

where E_{ion} is the equilibrium potential for a given ion (mV); C_{in}, the intracellular concentration of the ion; C_{out}, the extracellular concentration of the ion; Z, the valence of the ion; and 61 is a constant value that takes into account the Universal gas constant, temperature (37°C), and Faraday's electrical constant. If each one of these three main ions become totally permeable across a given membrane, then $E_{Na} = +60$ mV, $E_K = -90$ mV, and $E_{Cl} = -80$ mV. Note that nerve cells have negative resting membrane potentials, suggesting that it is primarily determined by either the chloride or potassium ion distributions. Yet, by measurements of ion movements, it has been shown that chloride ions are typically passively distributed across a given neuron's surface membrane, and thus chloride currents have negligible roles under resting conditions. This leaves potassium as the dominant ion species in determining the overall resting membrane potentials in most nerve cells. It should be noted that neurons typically contain a variety of ion-selective channels within their surface membranes, with differing neuron types having unique compositions. The term *gating* is used to refer to the triggered openings of such channels. More specifically, voltage-gated ion channels respond to changes in local membrane potentials of a given cell, and ligand-gated ion channels are those that respond to specific biochemical factors (receptor activated by agonists). Note that spontaneously active ion channels will

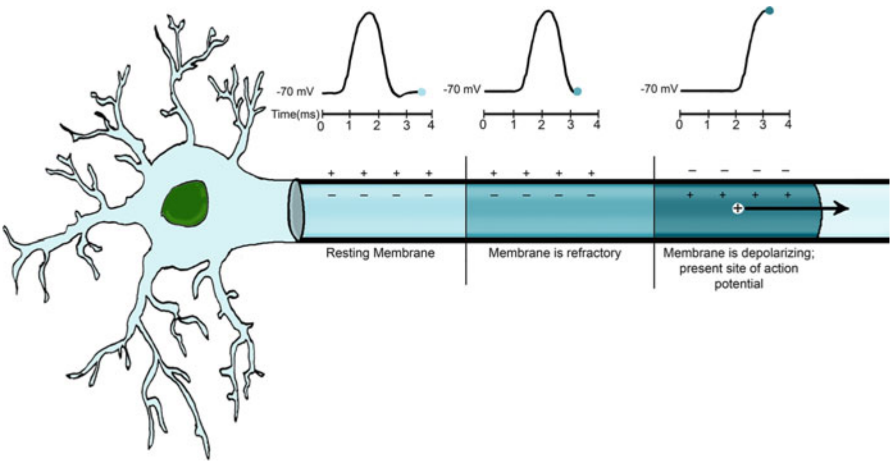


Fig. 1.3 Shown here is the schematic representation of the one-way propagation of an action potential down a nerve cell's axon. Local currents generated within the cell body subsequently resulted in an action potential being generated in the far left region of the axon (known as the axon hillock). This excitation then propagated to the middle region of the axon which, in turn, activated the voltage-gated Na channels in the *dark blue* (*far right*) portion of the axon, i.e., the action potentials propagated rapidly down the axon. As in the initial segments of the axon membranes, the Na current becomes near zero and the initiated voltage-gated K current will allow for repolarization back to the original resting membrane potential (e.g., −70 mV)

elicit random frequencies of opening and closing, whereas leak channels seem to be more continuously open (though only allowing typically low ion flows). In addition to classifications based on control mechanisms, channels are also classified by their ion selectivities (e.g., Na^+, K^+, Ca^{2+}, or cation nonspecific) and/or the directions in which such ions pass through them (e.g., inward or outward). Action potentials are elicited in nerve cells due primarily to transient changes in the cellular permeabilities of both Na^+ and K^+ ions. An initial local electrical depolarization (i.e., the surface membrane reaches a threshold voltage of ~ +10 to +30 mV above the given resting potential) then causes the transient openings of voltage-dependent Na channels. This brief (1–2 ms) increase in sodium permeability (conductance) further depolarizes the cell and drives the membrane potential toward the sodium equilibrium potential; shortly (within approximately 1 ms) these channels are actively inactivated. This depolarization, in turn, activates voltage-gated K channels, which allows for efflux from the cell and thus drives the membrane potential back towards the potassium equilibrium potential (more negative); see Fig. 1.2. This excitation can also be considered as typically self-propagating (excite adjacent cell membrane areas, e.g., action potential propagation down the nerve axon); see Fig. 1.3.

Importantly, neurons form connections between themselves (e.g., via synapses, chemical, or electrical), and this is the primary mechanism for information transfer within the CNS (Figs. 1.4 and 1.5). Nevertheless, there are other cell populations beyond neurons that make up the CNS that are known to be vital for its proper function.