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Contents

Preface

In the last decade of the 20th century, the "Decade of the Brain", the scientific community put forth a concerted effort towards understanding the nervous system. Although experimental neurophysiological approaches provided many advances, it became increasingly evident that mathematical and computational techniques would be required to achieve a comprehensive and quantitative understanding of neural system function. "Computational Neuroscience" emerged to complement experimental neurophysiology. Simultaneously, fueled by engineering breakthroughs, the last two decades have seen a phenomenal rise in our ability to probe the nervous system and to influence neural system activity across scales of complexity and states of disease. Devices that use focused electrical stimulation to activate neural circuits are now routinely used to restore hearing to the deaf and to alleviate the symptoms of Parkinson's disease, while emerging technologies will provide amputees with the ability to feel with their artificial limb. In the first decade of the 21st century, this new engineering paradigm that links living with non-living systems to investigate, intervene and harness neural plasticity to counter disease and disablement emerged in the form of "Neural Engineering".

This book presents a window into the convergence of Computational Neuroscience and Neural Engineering. Over the past two decades it has been my privilege to be enriched by the flourishing of both Computational Neuroscience and Neural Engineering and to have the opportunity to dialogue with neuroscientists, mathematicians, physicists, and engineers from around the world. Two summers have played an important role in my personal engagement with these fields. One was a summer at Woods Hole, attending the 'Methods in Computational Neuroscience Course'. Here, I listened to John Rinzel present phase space analyses methods, talked to Ron Calabrese about leech heart interneurons that I modeled, heard about the newly devised 'Dynamic Clamp' from Eve Marder, talked about 'Consciousness' with Christof Koch and others on the beach at night, and met a neuroscientist who became my postdoctoral mentor - Avis Cohen. It was Avis who suggested a summer at Telluride at the 'Neuromorphic Engineering' workshop. There, I listened to Rodney Douglas and Misha Mahowald, once again Christof Koch, and got introduced to the world of engineers trying to capture the biological neuron in hardware. It is not surprising then, that as a biomedical engineer fascinated by the two fields, I have sought to find a practical interface that is driven by the merger of the software and hardware models of neurons with the nervous system itself. It is at the summer courses that I met many of my fellow scientists and engineers who have over the years sought similar goals, some of who have contributed to this book.

Growth of such a transdisciplinary effort required a concerted investment by many institutions that were guided by people with foresight and boldness. Dennis Glanzman and Yuan Liu from the National Institutes of Health, USA and Kenneth Whang from the National Science Foundation, USA have played an unrelenting role in supporting programmatic growth of Computational Neuroscience and the research effort of several investigators. The Collaborative Research in Computational Neuroscience Program has supported a wide range of research efforts that underlie the development of biohybrid systems and has allowed me to seek new knowledge in spinal organization for motor control after spinal cord injury. The book and I have also benefitted from transdisciplinary dialogue on biohybrid systems and neuromorphic design at a series of workshops that we conducted with support through the Science of Learning Centers program at the National Science Foundation, USA under Soo-Siang Lim. Grace Peng from the National Institutes of Health has been a steady champion of programmatic growth in neural engineering and has been a supporter of the efforts of many, including me, in bringing technology to the people that stand to benefit from this technology. Most interestingly, Elmar Schmeisser from the Army Research Office saw promise in our work on neuromorphic control of spinal interfaces in the lamprey as the basis for a novel approach to control powered or thoses for people with lower limb dysfunction. It was a presentation of these multiple related areas of research that caught the attention of Wiley and I thank them for inviting me to develop a book to present our ideas about this emerging field of biohybrid systems. The growing interest in this topic motivated my colleagues and meto develop a book for a cross-section of scientists and engineers. We hope that this book will enhance the communication between computational neuroscientists and neural engineers and bring to attention the exciting new applications that biohybrid systems could offer clinicians who are eager to deliver new solutions to their clients. It has been my pleasure to have worked with the authors of the different chapters and their teams in the writing of the book. I thank them for their effort and for their enthusiasm, not only in penning their own chapters, but also in providing helpful critiques of others.

I must thank my brother Vikram who has over the many years shared with me many of his management skills that have allowed me to juggle multiple projects and work across academic-clinical-industrial partnerships. My parents, Sarla and Padam, are a steady source of support and guidance. My husband Jimmy and son Nikhar, who are both contributors to this book, have been my sounding boards, have withstood my immersion in various projects, but most importantly have been a never-ending source of joy and companionship. Finally, I am forever indebted to my doctoral thesis advisor, Peter Katona who fostered inquiry across boundaries, supported my inquisitiveness and nurtured my foray into new realms.

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1

Merging Technology with Biology

Ranu Jung

1.1

Introduction

The most important trend in recent technological developments may be that technology is increasingly integrated with biological systems. Many of the critical advances that are emerging can be attributed to the interactions between the biological systems and the technology. The integration of technology with biology makes us more productive in the workplace, makes medical devices more effective, and makes our entertainment systems more engaging. Our lives change as biology and technology merge to form biohybrid systems.

This book describes some of the recent advances and some of the key challenges faced by engineers and scientists developing biohybrid systems that interface nerves, muscles, and machines. Modern computers have high computational capacity and high rates of internal information transfer between components; similarly, neurobiological systems have high computational capacity and high interconnectivity of neural structures. Some of the key developments in biohybrid systems have been in opening lines of communication between the engineered and the biological systems. Real-time communication between a nervous system and a device is now possible, but full and reliable integration is still far from reality. In order to achieve more complete integration, some of the key challenges in biohybrid system development are to improve the quality, quantity, and reliability of the information that can be transferred between the engineered and the biological systems.

As we move forward in developing biohybrid systems, we can leverage a second key trend in recent technological developments: technology is increasingly being designed to be adaptive in its capabilities. The breakthrough about to be achieved is to close the loop in a manner that utilizes the adaptive capabilities of electronic and mechatronic systems in order to promote adaptation in the nervous system.

Biohybrid Systems: Nerves, Interfaces, and Machines, First Edition. Edited by Ranu Jung.

1.2
NeuroDesign

The nervous system functions by generating *patterns of neural activity.* These patterns underlie sensation and perception as well as control of movement, cardiovascular, endocrine, immune, and other systems. Nonlinearities and dynamical states that span scales of physical form and time are key features of the patterns that emerge from the living nervous system. Biohybrid interfaces can be developed to (1) access these neural activity patterns, (2) influence the neural activity patterns, or (3) fundamentally alter the pattern formation mechanisms (i.e., promote plasticity) (Figure 1.1). This development can be accomplished through the process of "NeuroDesign." One aspect of NeuroDesign is that the man-made abiotic systems to access or influence the neural patterns can be devised to embody the design principles of the nervous system. Here, the fundamental structure and/or operation of the technological system are based on an understanding of nervous system function. A second aspect of NeuroDesign is the process of engineering the nervous system itself. The concept here is a deliberate approach to mold and modify the structure and function of the nervous system to obtain a specific objective. In the short timescale, this can be thought of as "influence" or control of neural system function, in the medium timescale as "adaptation," and in the long timescale as "plasticity or learning" of the nervous system. In closing the loop between the nonliving and the living, NeuroDesign also allows us to merge technology and science. This merger opens new opportunities for use of technological innovation for scientific investigation and a continuous modulation of biological activity to achieve desired function.

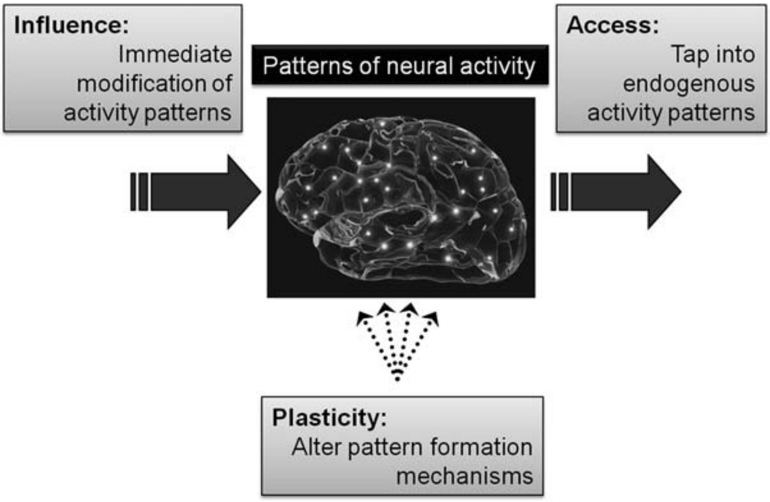

Figure 1.1 Biohybrid systems can access the patterns of neural activity, influence this pattern in real time, and induce plasticity by altering the pattern formation mechanisms. Brain image from http://www.getfreeimage.com/image/77/human-brain-and-neuron-impulses.

The primary challenge is to design biohybrid interfaces that can access and capture the biosignatures of the living system through limited spatiotemporal sampling and influence the inherently adaptive biological system through punctate intervention. For promoting plasticity, the challenge is to promote learning by influencing the core biochemical machinery in a desired manner.

1.3
The NeuroDesign Approach

Figures 1.2 and 1.3 illustrate the approach to NeuroDesign. The three features of this approach are (1) integration between the exogenous human designed system and the endogenous living system (2) biomimicry in the design of the exogenous system, and (3) the fact that an intervention that exerts its direct influence at one scale has an overall effect that spans multiple scales. The exogenous system performs both neurosensing and neuroactivation. By designing engineered systems that are biomimetic, we are able to produce systems with some of the robustness and versatility of biological systems and that potentially facilitate functional integration with the endogenous biological system. The nature and degree of biomimicry that

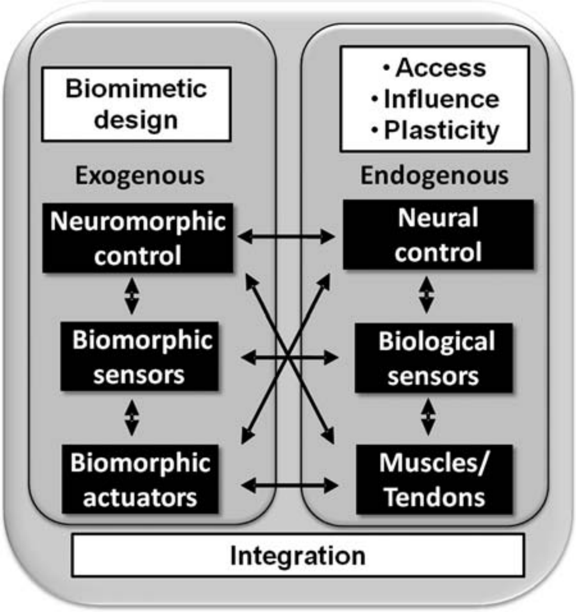

Figure 1.2 "NeuroDesign" integrates man-made systems with biological systems to access information, influence the activation of the biological system in real time, and/or promote long-term plasticity in the biological system. Bidirectional communication at multiple points of interface offers opportunities for closed-loop control of coadaptive systems. Biomimetic approaches are often used in the design of the exogenous system.

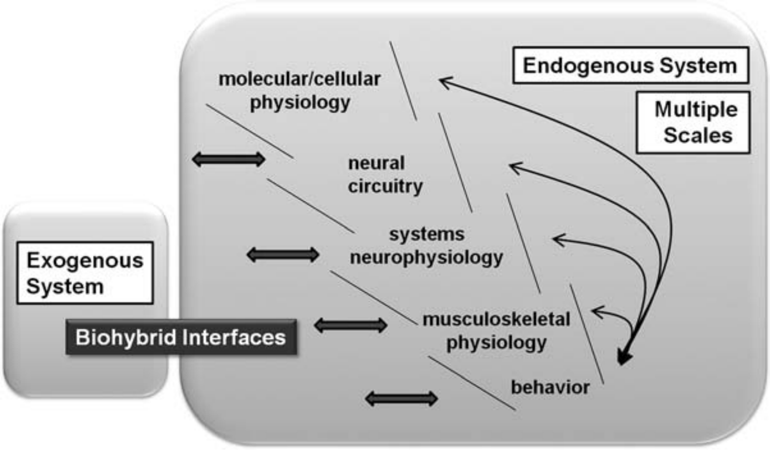

Figure 1.3 Biohybrid interfaces between exogenous man-made systems and endogenous biological systems can occur at one or more junctions along multiple scales of form and complexity. The effects of the interface at any one scale are propagated along the chain of scales.

could be used in the design of the exogenous system depend on the objective for which the biohybrid is developed. That is, when using a closed-loop system to discover ion channels at the cellular level, neuromimicry at the cellular level leads to utilization of computational models of neurons with details of ion channels. On the other hand, the development of systems for closed-loop rhythmic control of the neuromusculoskeletal system utilizes the concept of pattern generators in the nervous system to design the exogenous system.

Biohybrid systems can effect outcomes at multiple scales, at the behavioral scale (function), electrophysiological scale (synaptic learning), morphological scale (form), or molecular scale (genes/proteins/sugars). An interface that acts at one scale influences the entire chain (Figure 1.3). Thus, changes brought about at the molecular microlevel affect the pattern of activation across scales and ultimately influence behavior on a macroscale. On the other end, intervention at the macroscale for, for example, electrical stimulation of peripheral nerves after incomplete spinal cord injury to provide repetitive movement therapy, can promote motor recovery perhaps by promoting neuroplasticity at the molecular level [1–4].

Biohybrid systems can thus facilitate investigation of the intact and diseased living systems to efficiently replace damaged biological systems and to effectively interact with the residual biological components with the promise of repair.

1.4
Neuromorphic Control of a Powered Orthosis for Crutch-Free Walking

The use of NeuroDesign in the deployment of biohybrid systems can be illustrated by the following example of a powered orthotic and prosthetic system that is driven by a

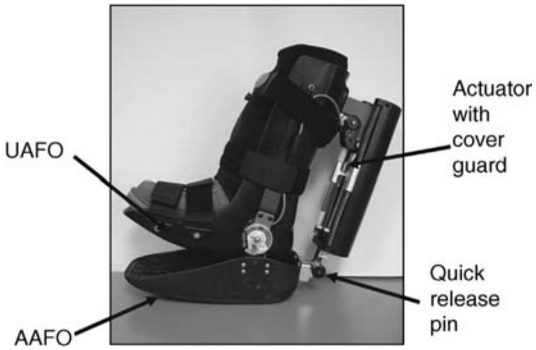

Figure 1.4 Prototype of a fixed universal ankle–foot orthosis (UAFO) attached to an AAFO. The prototype device is designed for use by combat troops. Quick release pins on the top and bottom can be used to easily separate the actuator from the AAFO.

neuromorphic controller that was designed using biomimetic NeuroDesign principles [5]. This biohybrid system (patent pending) is designed to allow "crutch-free" walking by a person with a tibial fracture of the lower limb. For this system, two objectives must be met: (1) the injured lower limb must be stabilized; and (2) the person must be able to walk under voluntary control. To achieve the former, the orthotic system illustrated in Figure 1.4 was designed. This device consists of a fixed-ankle orthosis that is used to stabilize or immobilize the injured lower limb. The fixed-ankle orthosis is encased by an actuated (powered) false-foot orthosis and the combined device forms an actuated articulated false-foot orthosis (AAFO). This AAFO is designed to permit the person to walk with a stabilized lower limb with minimal load bearing on the injured limb.

In order to achieve the second objective and provide voluntary control of the false foot, it was necessary to access information about the intent of the person to walk and then appropriately control the cyclic movement of the AAFO during walking. The inspiration for the design of this control system scheme was drawn from the control of movement in biological systems. Networks of neurons in the spinal cord of vertebrates are capable of producing rhythmic neural output that in turn controls a well-orchestrated sequence of muscle activation for cyclic control of locomotion [6]. The activity of these spinal pattern generators is usually initiated and terminated by descending voluntary control signals from the brain. The pattern generators also receive feedback from sensors in actuated muscles and tendons during the entire gait cycle. The neural organization of this biological system was mimicked in the design of the control system used for the AAFO.

An electronic circuit was designed to implement a neural network pattern generator that could be used as the controller (Figure 1.5). The biomimetic architecture of the pattern generator circuit was based on knowledge of connectivity of neurons within the spinal cord of the lamprey, a primitive vertebrate [7, 8]. Computational models of individual neurons were implemented in a circuit made from analog very large scale integrated (aVLSI) components and discrete electronic components [9, 10]. This pattern generator is capable of autonomously generating