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.

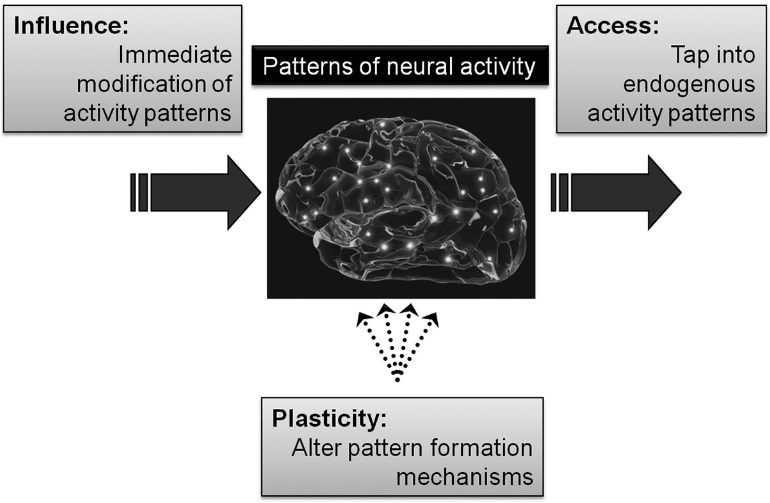

Figure 1.1 Biohybrid systems can access the patterns of neural activity, influence this pattern in real time, and induce plasticity by altering the pattern formation mechanisms. Brain image from http://www.getfreeimage.com/image/77/human-brain-and-neuron-impulses.

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

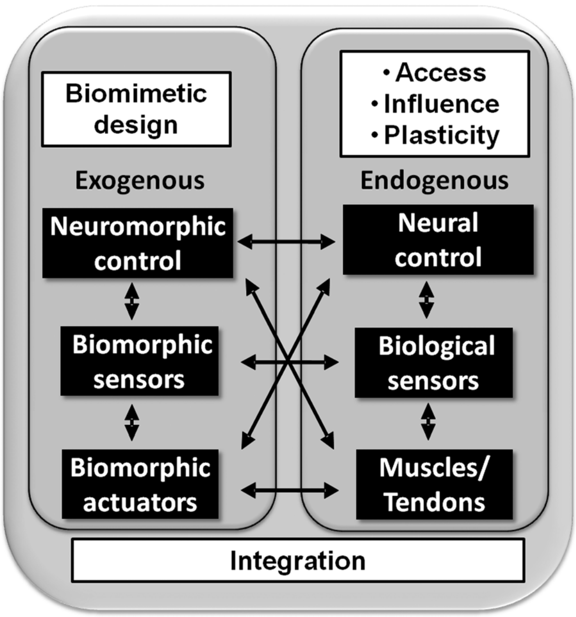

Figure 1.2 "NeuroDesign" integrates man-made systems with biological systems to access information, influence the activation of the biological system in real time, and/or promote long-term plasticity in the biological system. Bidirectional communication at multiple points of interface offers opportunities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

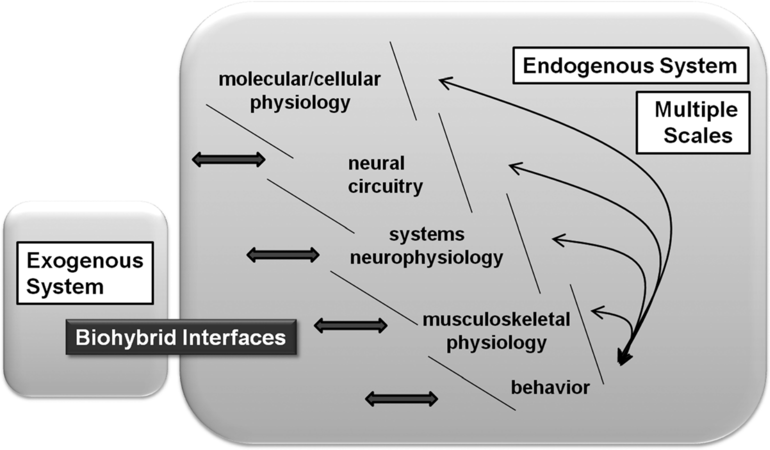

Figure 1.3 Biohybrid interfaces between exogenous man-made systems and endogenous biological systems can occur at one or more junctions along multiple scales of form and complexity. The effects of the interface at any one scale are propagated along the chain of scales.

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

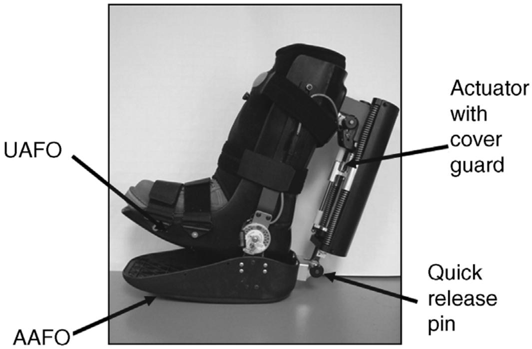

Figure 1.4 Prototype of a fixed universal ankle–foot orthosis (UAFO) attached to an AAFO. The prototype device is designed for use by combat troops. Quick release pins on the top and bottom can be used to easily separate the actuator from the AAFO.

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

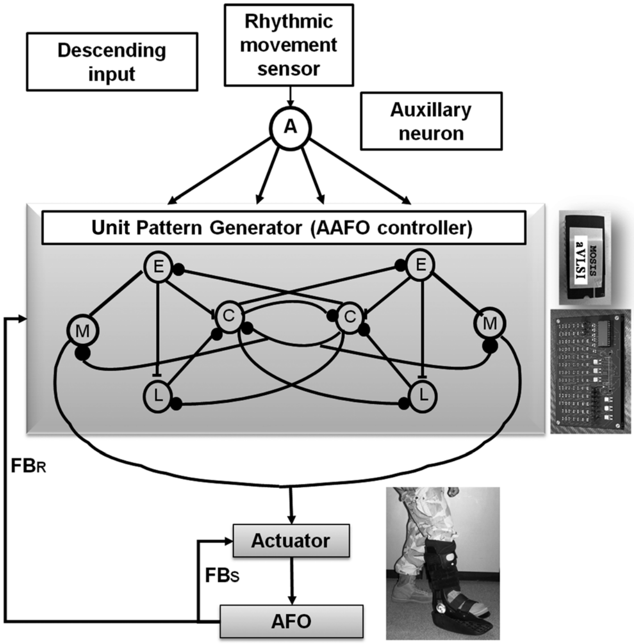

Figure 1.5 Biohybrid neuromorphic orthotic control system. The rhythmic movement sensor captures intent to move and provides periodic descending signals to entrain the unit pattern generator controller, which provides the cyclic voltage output needed to actuate the AFO. Sensors on the AFO provide local feedback (FB_S) to the actuator for control of position and ankle stiffness; sensors also provide input to the pattern generator where it may reset the rhythm in the presence of perturbation (FB_R).

cyclic voltage output that drives the AAFO. Biological pattern generators can be entrained by impinging cyclic rhythms. Their rhythm can also be reset if a perturbation of sufficient strength is applied at a particular phase of the rhythm. For example, the spinal pattern generator of the lamprey can be entrained by mechanosensory signals as well as reset by perturbations to stop and start anew [11]. Sensors mounted on the leg or AAFO provide cyclic input to the electronic pattern generator controlling the AAFO. In this manner, voluntary control of gait initiates and terminates cyclic actuation of the AAFO. Once initiated, the cadence of the AAFO matches the user's self-selected walking speed. Sensors mounted on the AAFO also provide two types of feedback signals. One set of signals feeds back position information to the actuator of the articulated ankle for local control, while another set of signals feeds information on external perturbation to the pattern generator and resets the cyclic control of the AAFO.

The importance of having an actively controlled AAFO instead of just a passively controlled ankle–foot orthosis (AFO) becomes apparent during walking (Figure 1.6). When operating in passive mode (without active control), the false foot dorsiflexes during stance phase (at approximately 40% of the gait cycle) and does not actively plantar flex at the ankle during push-off (at approximately 60% of the gait cycle). With

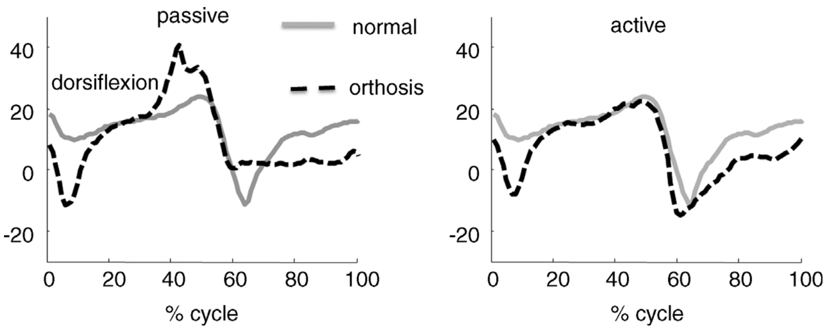

Figure 1.6 Ankle kinematics (in degrees of dorsiflexion) during a typical normalized gait cycle (heel strike to heel strike) with no orthosis (normal), passive orthosis (left), and active AAFO (right). Active control of the orthosis corrects the excessive dorsiflexion during stance phase (at 40%) and provides more plantarflexion at push-off (at 60%).

active control that is automatically timed by the entrained pattern generator, this dorsiflexion is prevented and the ankle more closely follows the normal ankle movement pattern.

Thus, this example shows how a neuromorphic design of a control system for a powered orthosis can function as a biohybrid device at the macroscale. It offers "crutch-free walking" to a person with an injured lower limb.

1.5 Frontiers of Biohybrid Systems

The greatest promise of biohybrid systems lies in promoting plasticity in the nervous system, thereby contributing to recovery and repair of lost biological function whether it ensues because of trauma, disease, or aging. This will be achieved as the closed loop becomes adaptive with adaptation occurring in both the biological and the engineered components. The greatest challenge is to design engineered systems whose adaptation enables the system to customize itself to each individual and to account for changes in the biological system as the two systems coadapt ([12–18].

As discussed and presented by multiple examples in this book, patterns of activity of the biological system could be accessed using advanced adaptive technology that responds to a biological system that is nonstationary and dynamic, and functions across multiple time- and spatial scales and multiple modalities. The design of the control system will be guided by the structural and functional constraints observed in biological systems, and allow for real-time learning, stability, and error correction that accounts for the biological systems features and takes into account the paucity of inputs to influence the biological system. The frontier lies in being able to harness the adaptive technology to promote plasticity and synergistic learning with the biological system on a long timescale under coadaptive conditions. Optimizing the technology will necessitate an approach that looks beyond the technology in isolation and looks beyond the technology as it interacts with the biological system in its current state.

Here, the design of effective technology must consider its adaptive interaction with a biological system that is continuously changing.

Endogenous compensatory learning of the biological system on short and long timescales and the physical constraints of interaction will provide challenges to this synergistic learning. It is likely that there exist windows of opportunity that may be critical periods for induction of sustained learning. Learning in the merged systems will have occurred when there are carryover effects beyond the time period when the technology is interacting with the biological systems. Future biohybrid systems may have the ability to self-wean when necessary. The biohybrid systems will thus allow us to discover the principles governing activity-dependent learning in living systems, to develop novel approaches to sense the dynamic changes in the adaptive living system and the environment, and to deliver novel adaptive technology that encourages appropriate plasticity in biological systems.

1.6 Chapter Organization

The book chapters are divided into three sections. Together, the chapters illustrate the principle approaches of NeuroDesign and present practical applications of the use of biohybrid systems for scientific interrogation and medical intervention. The first three chapters present the principles that can be used for development of biohybrid systems. Chapter 2 presents the principles of computational neuroscience. Computation complements mathematical theory and is often used to understand and reengineer the neural code represented by the rich repertoire of neural activity patterns under natural as well as experimental conditions. This chapter introduces basic physiology of neurons and presents mathematical models for excitable cells. It also presents general formalisms in neuronal modeling and briefly captures models for plasticity. The ability to embody these equivalent mathematical models for neural cells and synapses in silicon using neuromorphic electronic design principles is presented in Chapter 3. Fundamental devices and circuits that can emulate neuronal behavior at the single cell level as well as more complex circuits are presented. The chapter also discusses the advantages of using a neuromorphic approach in the design of the hardware. Chapter 4 presents principles of signal processing. It specifically examines the use of point process theory for understanding the neural code and illustrates the bounds placed by this theory in the rational design of interfaces for biohybrid systems for neurosensing and neurostimulation.

The next three chapters discuss biohybrid systems that interface at the single cell level. Chapter 5 presents the role of dynamic clamp in biomimetic and biohybrid living-hardware systems. The concepts of the dynamic clamp experimental technique are discussed and illustrated. The technique utilizes artificial synapse interfaces between single cells and computational models of those cells to investigate the fundamental biochemistry of neuronal activation. Also presented are examples of use of such biohybrid systems for specific neuronal gain control by manipulating synapses. Approaches by which the actual interface between individual neurons and sensing transducers can be enhanced by surface modification of the hardware at nanoscales that mimic biology are presented in Chapter 6. This section wraps up with Chapter 7, which introduces real-time computing for the development of the artificial neurons utilized in dynamic clamp studies. It also presents an easy-to-learn and easy-to-use technique for performing biohybrid systems analysis and presents the use of a biohybrid system to control the heartbeat in a leech though dynamic clamp.

The last section of the book consists of four chapters on biohybrid systems that interface at a macroscale and present the potential for closed-loop control of complex systems using such interfaces. Chapter 8 on biomimetic adaptive control algorithms presents the use of biomimetic features including computational models of excitable neurons, network architectures derived from biological systems, and learning algorithms inspired by synaptic learning mechanisms for the design of adaptive control algorithms. The chapter also discusses factors that should be considered in the design of closed-loop control systems in the context of coadaptation of the interfaced systems. Chapter 9 builds on Chapter 3 by presenting applications that utilize neuromorphic hardware for audition and vision and a system to control the neuromuscular skeletal system after spinal cord injury. In Chapter 10, a new approach to control cardiac function by interfacing with the nervous system is presented. It discusses the precautionary measures that will be necessary in the design of a closed-loop system. Finally, a biohybrid system with an adaptive smart sensor to measure neural activity of pancreatic cells cultured on multielectrode arrays is presented in Chapter 11. The chapter also presents the initial building blocks for a closed-loop implantable system for measuring blood-borne glucose for the management of diabetes.

Acknowledgment

Neuromorphic controlled powered orthosis case study supported by STTR Contract No. W911NF-05-C-0122 from Army Research Office to Advensys, LLC (PI: R. Jung; Contributions t case study by S.V. Jung, V. Darbhe, B. Srimattirumalaparle, D. Meller and S. Phillips at Advensys LLC and J. J. Abbas, J. Jolly and T. Sugar at Arizona State University.).

References

1 Thuret, S., Moon, L.D.F., and Gage, F.H. (2006) Therapeutic interventions after spinal cord injury. *Nat. Rev. Neurosci.*, **7**, 628–643.

2 Lynskey, J., Belanger, A., and Jung, R. (2008) Activity dependent plasticity in spinal cord Injury. *J. Rehabil. Res. Dev.*, **45** (2), 229–240.

3 Al-Majed, A.A., Neumann, C.M., Brushart, T.M., and Gordon, T. (2000) Brief electrical stimulation promotes the speed and accuracy of motor axonal regeneration. *J. Neurosci.*, **20**, 2602–2608.

4 Jung, R., Belanger, A., Kanchiku, T., Fairchild, M., and Abbas, J.J. (2009) Neuromuscular stimulation therapy after incomplete spinal cord injury promotes recovery of interlimb coordination during locomotion. *J. Neural Eng.*, **6**, 055010.

5 Jung, R., Jung, S.V., and Srimattirumalaparle, B. (2010) Neuromorphic controlled powered orthotic and prosthetic system. USPTO 201002806289 A1.

6 Gillner, S. (2006) Biological pattern generation: the cellular and computational logic of networks in motion. *Neuron*, **52**, 751–766.

7 Grillner, S., Wallen, P., Brodin, L., and Lansner, A. (1991) Neuronal network generating locomotor behavior in lamprey: circuitry, transmitters, membrane properties, and simulation. *Annu. Rev. Neurosci.*, **14**, 169–199.

8 Buchanan, J.T. (1992) Neural network simulations of coupled locomotor oscillators in the lamprey spinal cord. *Biol. Cybern.*, **66**, 367–374.

9 Jung, R., Kiemel, T., and Cohen, A.H. (1996) Dynamic behavior of a neural network model of locomotor control in the lamprey. *J. Neurophysiol.*, **75**, 1074–1086.

10 Jung, R., Brauer, E.J., and Abbas, J.J. (2001) Real-time interaction between a neuromorphic electronic circuit and the spinal cord. *IEEE Trans. Neural Syst. Rehabil. Eng.*, **9** (3), 319–326.

11 McClellan, A.D. and Jang, W. (1993) Mechanosensory inputs to the central pattern generators for locomotion in the lamprey spinal cord: resetting, entrainment, and computer modeling. *J. Neurophysiol.*, **70** (6), 2442–2454.

12 Jung, R. (2007) Adaptive learning technology. Final Workshop Report on "Future Challenges for the Science and Engineering of Learning, National Science Foundation, USA, July 23–25, 2007" (http://www.nsf.gov/sbe/SLCWorkshopReportjan08.pdf).

13 Viadaurre, C., Sannelli, C., Muller, K.-R., and Blankertz, B. (2011) Machine-learning-based coadaptive calibration for brain–computer interfaces. *Neural Comput.*, **23** (3), 791–816.

14 Gage, G.J., Ludwig, K.A., Otto, K.J., Ionides, E.L., and Kipke, D.R. (2005) Naive coadaptive cortical control. *J. Neural Eng.*, **2**, 52–63.

15 Wang, W., Collinger, J., Perez, M., Tyler-Kabara, E., Cohen, L., Birbaumer, N., Brose, S., Schwartz, A., Boninger, M., and Weber, D. (2010) Neural interface technology for rehabilitation: exploiting and promoting neuroplasticity. *Phys. Med. Rehabil. Clin. North Am.*, **21** (1), 157–178.

16 Riess, J. and Abbas, J.J. (2001) Adaptive control of cyclic movements as muscles fatigue using functional neuromuscular stimulation. *IEEE Trans. Neural Syst. Rehabil. Eng.*, **9**, 326–330.

17 Dobkin, B.H. (2003) Do electrically stimulated sensory inputs and movements lead to long-term plasticity and rehabilitation gains? *Curr. Opin. Neurol.*, **16**, 685–691.

18 Fairchild, M., Kim, S.J., Iarkov, I., Abbas, J. J., and Jung, R. (2010) Repetitive hindlimb movement using intermittent adaptive neuromuscular electrical stimulation in an incomplete spinal injury rodent model. *Exp. Neurol.*, **223**, 623–633.