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Transformative Research in Neural Engineering: Foreword / Editors' Commentary (Volume 3)

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Neural engineering is in the midst of a renaissance. The main goal of neural engineering is to develop solutions to neurological, neurosurgical, and rehabilitative problems. As neuroscientists and neural engineers, we are in an early period of discovery where we are defining the limitations both technologically and biologically of how we can fundamentally alter the function of the nervous system. This issue of *Critical Reviews in Biomedical Engineering* is volume three of a three volume series focused on neural engineering. The theme of this issue is "Transformative Research in Neural Engineering."

Indeed, biomedical engineering efforts have brought us to the precipice of innovative neurotechnology altering our world in ways previously unimaginable. Yet unanswered questions abound: What are the regenerative limits of the nervous system? Can noninvasive (external) interfaces ever provide sufficient resolution to control neuronal function? Will "electrodes" ultimately be the final solution for electrical interface, or will optogenetics play a role? Can biomaterials or biohybridization ever remove the inflammatory or foreign-body response? Will cell replacement strategies fundamentally alter repair following injury or mitigate age-related deficits? Successful programs will address these questions as they evolve, utilizing new technology and discoveries to create solutions for the neural engineering challenges of the twenty-first century.

As with most biomedical engineering endeavors, a successful neural engineering research program should be interdisciplinary, able to integrate emerging technologies, and advanced by hypothesis-driven studies. Neural engineering projects represent the quintessential cross-disciplinary biomedical engineering endeavor, often drawing from various areas, such as neuroscience, neurology, and neurosurgery as well as multiple engineering subspecialties such as electrical, mechanical, and materials science. Ambitious neural engineering projects will continue to transform the field, bringing together multidisciplinary technical expertise found in schools of engineering with clinical and neuropathophysiological knowledge present in schools of medicine. These teams must collectively provide the requisite expertise for a given complex problem, but be mutually dependent to maximize the perspectives and capabilities of the team. Such collaborations require the skills, knowledge, and full engagement of each individual, and often must be formed across universities. Such multidisciplinary, mutually dependent teams are needed in order to shift paradigms and allow us to transform how the nervous system heals, ages, and interfaces with complex technologies.

However, research using such multidisciplinary teams often creates unique challenges. These teams, by definition, require neuroscientists or clinicians interacting with biomedical engineers. For instance, common neural engineering projects involve technology development and implementation for sustained interfacing (e.g., electrical, microfluidic) with neural tissue/cells. For these projects, neuroscientists handling neural systems or neurobiological aspects must communicate effectively with the engineering teams charged with instrumentation (e.g., electrode array, signal processing) or material design and fabrication. In particular, although different investigators communicate nearly identical

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project objectives, the course each would chart to achieve those objectives or the particular design criteria are often vastly different, typically elevating their area of expertise and under-recognizing the challenges inherent in the areas of others. Moreover, the language within these teams is often fundamentally different: to electrical engineers, *plating* means depositing a thin layer of material on a surface; to neuroscientists, this might mean adding cells to culture; even the word *cell* may have different meanings, as in a power source to a traditional engineer, versus the fundamental units of life to a biological scientist. Although these are highly simplified examples, they provide important insights into communication across the multidisciplinary teams necessary to advance any cutting-edge neural engineering endeavor. Thus, effective leadership in any ambitious cross-disciplinary project requires not only communication of a common vision, but assurance that the team members are working in concert to achieve common goals and communicating effectively.

The articles presented in volume three of this special neural engineering issue of *Critical Reviews in Biomedical Engineering* present cutting-edge neurotechnology capable of advancing hypothesis-driven neuroscience to address fundamental questions. These articles present novel platforms and microsystems that have been specifically engineered to address key neurobiological questions, which in some cases had previously been unanswerable. For instance, neural interface technologies are vastly increasing our understanding of how the brain works at a cellular and systems level. Such projects are critically important to advance neuroscience, and require a strong foundation in engineering fundamentals and biomedical concepts, and an ability to integrate across disciplines to work with clinicians, scientists, and engineers with wide-ranging backgrounds.

The first article is "Microfluidic and Compartmentalized Platforms for Neurobiological Research," by Dr. Anne M. Taylor and Dr. Noo Li Jeon. Dr. Taylor is an Assistant Professor in the Joint Department of Biomedical Engineering at University of North Carolina–Chapel Hill and North Carolina State University. Dr. Jeon is a Professor of Mechanical and Aerospace Engineering at Seoul National University in South Korea. Their work has focused on developing microscale devices for applications in neurobiology. They pioneered novel compartmentalized microfluidic culture platforms, which have multiple uses including for the controlled study of axonal biology and synaptic plasticity. Notably, this neurotechnology permitted testing of fundamental neurobiological questions that had previously been ambiguous or unanswerable, such as the character of local axonal mRNA translation. Their article presents this technology within a larger context of compartmentalized and/or microfluidic platforms used in neuroscience research.

The next two articles are a series on neural tissue engineering. The first in this series, "Neural Tissue Engineering and Biohybridized Microsystems for Neurobiological Investigation In Vitro (Part 1)," presents our work to tissue-engineer three-dimensional (3-D) nervous tissue constructs and biohybridized interface microsystems. These 3-D cellular constructs may provide a more realistic environment to study basic neurobiological phenomena, and microfluidically or microelectrically active interface platforms provide exquisite microenvironmental control. This work began in the laboratory of Dr. Michelle C. LaPlaca, an Associate Professor of Biomedical Engineering at the Georgia Institute of Technology, who has also been a leader in traumatic brain injury and spinal cord injury biomechanics, in vitro neural interfacing, and stem-cell-based neural tissue engineering strategies.

The final article, "Neural Tissue Engineering for Neuroregeneration and Biohybridized Interface Microsystems In Vivo (Part 2)," presents our work to engineer living neural tissue outside the body for specific applications inside the body. For neuroregeneration, these living constructs are effectively "pre-engineered" in vitro prior to implantation in order to recapitulate the geometry of neural tissue damaged or lost following injury. Moreover, tissue engineering strategies may be employed to biohybridize neural interface components for improved integration with neural cells/tissue. This work builds on seminal contributions by Dr. Douglas H. Smith, a Professor of Neurosurgery at the University of Pennsylvania and director of Penn's Center for Brain Injury and Repair, who is a world-renowned expert in neurotrauma, clinical applications of neurotechnology, and neural tissue engineering. Notably, Dr. Smith led efforts to discover the process of axonal "stretch-growth," which may be exploited to engineer robust tracts of living axons up to several centimeters long.

In closing, the articles in this volume epitomize an effective balance between innovative technology development and traditional hypothesis-driven research. Moreover, the author teams are advancing neuroscience by applying fundamental engineering principles and quantitative metrics to complex neural engineering applications. These facets are necessary to substantially advance our understanding of brain function at the cellular, network, and systems levels.