State of the Art and Future Challenges in Neural Engineering: Neural Interfaces: Foreword / Editors' Commentary (Volume 1)

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We are honored to serve as guest editors for this timely special three volume series of *Critical Reviews in Biomedical Engineering* focused on neural engineering. Neural engineering is a research area that applies engineering principles and specialized technology to investigate neurological function and to repair, replace, or enhance the nervous system. The field of neural engineering has expanded rapidly, in particular over the last decade. Indeed recent growth in neural engineering is illustrated by the recent increase in related conferences and publications. There are two dedicated conferences: first, the International Institute of Electrical and Electronics Engineers (IEEE), Engineering in Medicine and Biology Society (EMBS) Neural Engineering Conference, and second, the Neural Interfaces Conference. In addition, many large scientific conferences are dedicating tracks to neural engineering, including the IEEE EMBS, the Biomedical Engineering Society (BMES), the Society for Neuroscience, and the National Neurotrauma Society. A *Pubmed* search of "neural engineering" produced 7677 hits, 914 published in 2010, 1016 in 2009, and more than half of that total since 2006. Three journals have been devoted to neural engineering: the *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, the *Journal of Neural Engineering*, and the *Journal of NeuroEngineering and Rehabilitation*. Neural engineering has also become a priority area for National Science Foundation (NSF) research investment. The NSF Directorate for Engineering (ENG) has called for adaptive systems technology "particularly in the area of neural engineering, an emerging field that bridges molecular, cellular, systems, cognitive, and behavioral neuroscience with engineering, physics, chemistry, mathematics, and computer science." In particular, the Division of Chemical, Bioengineering, Environmental, and Transport Systems (CBET) Biomedical Engineering program has a standing call for proposals under the theme of neural engineering. This focus, growth, and investment in neural engineering hold tremendous promise to improve human health in a transformational fashion.

Neural engineering reaching its full potential relies on enhancing our understanding of neurological function, developing novel neurotechnology, and translating these to clinical applications. However, the expectations placed on twenty-first century biomedical researchers are tremendous, particularly in neural engineering. Effective researchers must have an eye on true translational research, including intellectual property protection and commercialization potential. These realities have created a new generation of entrepreneur-scientists who co-exist in the worlds of novel technology development, working towards commercialization, while also contributing to the fundamental knowledge of the field. For instance, novel neurotechnology is developed to aid patients or to visualize specific phenomena; however, it is also either indirectly or directly used to address key scientific questions. Moreover, this generation of biomedical engineers is keenly aware of intellectual property protection to facilitate the propagation of custom techniques, platforms, materials, hardware, and software. Interestingly, in the realm of neural-interface platforms, there is no consensus about what are the best techniques to functionally integrate and/or com-

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municate with neural tissue. We will likely see a continued expansion of these tools and techniques for many years before there is eventually a distinct minority that have widespread translation into humans. This may define the materials and "language" with which we interface with the nervous system, influencing the development and compliance of subsequent technologies.

The future of neural engineering represents almost unlimited possibilities to repair and perhaps enhance the human condition. The author teams in this three-volume special issue are at the forefront of traditional and emerging themes in neural engineering. The overarching theme of these issues is to capture the state of the art in neural engineering, while defining specific challenges the field must overcome for substantial advancement. The main theme of volume one is "Neural Interfaces," with a focus on multidisciplinary engineering-based strategies for neural-electrical interfaces and deficit mitigation. The focus of volume two is "Strategies for Nervous System Repair", and presents comprehensive articles summarizing the key discussion points from a workshop held at the 2009 Biomedical Engineering Society Annual Meeting in Pittsburgh, PA, titled "Tissue Engineering of the Nervous System: Approaches and Strategies for the Repair of Peripheral and Spinal Cord Injuries." The theme of volume three is "Transformative Research", presenting cutting-edge approaches and neurotechnology capable of advancing hypothesis-driven neuroscience. Across all three volumes, there are several instances where new technologies were developed to address important neurobiological questions that have been previously unanswerable.

An interesting subtheme in these articles is the intersection of neuroscience and engineering, as our interdisciplinary authorship teams in many cases consist of biomedical engineers, neuroscientists, and clinicians. We feel this diversity gives this special issue on neural engineering proper biomedical and clinical perspective. It is critical for successful biomedical research to have the proper perspective of the final application at the systems level; here we define perspective as "the faculty of seeing all the relevant data in a meaningful relationship." Accordingly, biomedical engineers need a perspective that is inherently interdisciplinary, as it draws on the underlying systems biology, pathophysiology, and clinical applications and limitations. Moreover, the complexity of neural engineering is daunting: the intricacies of standard and emerging neurotechnology driven by interfacing with the exquisitely complex nervous system. It is extremely difficult, if not impossible, for a single individual to posess a sufficient mastery of these areas, hence the need for interdisciplinary teams to tackle the most challenging issues in neural engineering.

The opening article of volume one is "Brain-Machine Interfaces: Electrophysiological Challenges and Limitations," by Dr. Bradley C. Lega, Dr. Mijail D. Serruya, and Dr. Kareem A. Zaghloul. Drs. Lega and Serruya are residents in Neurosurgery and Neurology, respectively, at the University of Pennsylvania. Dr. Zaghloul is a Neurosurgeon and Academic Clinician at the National Institutes of Health. These clinicians have been at the forefront of implanting neural-electrical interface technology in human patients to address often devastating neurological disorders and to mitigate deficits. Their article presents a thorough overview of historical and current clinical interface technology. Interestingly, the underlying mechanism(s) by which several of these successful techniques actually work have yet to be defined; however, the authors present some intriguing and compelling hypotheses that may be tested to understand these mechanisms of action, and thereby drive the development of next-generation interface technology that is even more targeted for clinical effectiveness.

Many engineered solutions to nervous system disorders involve some type of implanted material such as temporary regenerative biomaterial scaffolds or chronic electrodes for neural interface. Accordingly, neural engineers must often deal with the body's response to foreign materials. The second article, "The Challenge of Integrating Materials into the Central Nervous System," addresses key issues regarding the inflammatory and foreign-body responses upon the introduction of engineered materials, authored by Dr. Patrick A.

Tresco, Professor in the Department of Bioengineering and Associate Dean for the College of Engineering at the University of Utah. A central theme in Dr. Tresco's work involves understanding the brain tissue response to implants that vary in their physical and chemical properties. Dr. Tresco is a leader in the field of neural engineering, including developing biomaterial technologies for the reconstruction, replacement, and repair of damaged central nervous system, including seminal work on targeting nerve outgrowth.

The third article is entitled "In Vitro Microelectrode Array Technology and Neural Recordings," written by Dr. Yoonkey Nam and Dr. Bruce C. Wheeler. Dr. Nam is an Assistant Professor in the Department of Bio and Brain Engineering at KAIST in the Republic of Korea. Dr. Wheeler is a Professor in the Department of Biomedical Engineering at the University of Florida. Drs. Nam and Wheeler apply cutting-edge electrical engineering techniques to neuroscience in order to better understand basic neurophysiology of small neuronal networks, ultimately providing insights into the functioning of the brain. Dr. Wheeler has been a leader in neural engineering for over 20 years. His work has influenced the fabrication of microelectrode arrays (MEAs), neural signal processing, electrophysiology of brain slices, as well as pioneering micropatterning techniques to control cell growth, especially neurons, in culture. Their article offers tremendous insights into the history, basic function, and capabilities of MEA technology to study neuronal networks.

The final article presents technology for "Wireless Microstimulators for Neural Prosthetics" by Dr. Mesut Sahin and Dr. Victor Pikov. Dr. Sahin is an Assistant Professor in the Department of Biomedical Engineering at the New Jersey Institute of Technology. Dr Sahin is a leader in neural prosthetic technology for the brain and spinal cord, in particular optical stimulation, photodiodes, neural electrode materials, and signal processing. Dr. Victor Pikov at the Huntington Medical Research Institutes is a neurophysiologist and cell/molecular biologist applying cutting-edge neural engineering techniques. In particular, he has significantly advanced the use of electromagnetic irradiation at millimeter range for stimulating neuronal activity, and he is involved in using high-density silicon probes to assess hyperexcitability as well as optogenetics to allow light-induced neuronal activation in the central nervous system. Their article discusses wireless, or "untethered," neural interface components, an extremely promising strategy to potentially facilitate long-lasting neural implants. Notably this strategy may mitigate some issues driving or exacerbating the inflammatory and foreign-body response detrimental to chronic performance in these devices. Interestingly, their research also explores the benefits of interfacing with the spinal cord rather than the brain.

The making of a true expert requires honed perspective, which takes many years to develop and involves a mastery of the underlying knowledgebase and principles, as well as applied first-hand experience. Such mastery of the engineering principles, the technological capabilities, and knowledge of the basic and systems neuroscience and clinical applications is requisite for advancement in neural engineering. We hope that our author teams provide insightful perspective and subject area mastery to make these articles powerful benchmarks for the current state and future prospects for specific facets of neural engineering.