

Preface

Understanding the function and organization of billions of neurons and trillions of connecting synapses in the human brain is a tremendous challenge requiring coordinated efforts from scientists from many different research areas. This belief has motivated both the European Union and the United States to invest billions of dollars in long-term, multidisciplinary projects—the “Human Brain” flagship project and the “Brain Initiative,” respectively—involving hundreds of scientists and technologists to build a comprehensive picture of the human brain. To achieve this goal, new technologies and approaches for interrogating neuronal circuits will be needed, as well as innovative approaches to handle an exponentially increasing amount of physiological data.

Strategies for recording and stimulating neurons in the central and peripheral nervous systems have been investigated since the eighteenth century, with Luigi Galvani’s first electrophysiology experiments. After more than two centuries, the current methodologies and tools allow simultaneous interaction with only a relatively small number of cells. As a result, although it has been possible to elucidate the mechanisms and roles of specific groups of neurons and areas of the brain, we have no available techniques to systematically monitor thousands of functional links that each neuron forms with other neurons. Thus, we lack a clear understanding of large-scale integration in the brain.

Neuroscientists need new tools that enable recording or stimulation at high spatial and temporal resolution and for extended periods of time. Ideally, such devices should be able to interface—with high fidelity and low invasiveness—a large number of neurons to record, perturb, and control their electrical activity. Nanoscience and nanotechnology can play a key role in improving the performance of existing tools and in developing new ideas and experimental approaches to create detailed maps of the human brain. Indeed, reducing the size of electrophysiology probes down to the nanoscale minimizes their invasiveness and increases their spatial resolution; furthermore, more sophisticated electrical, mechanical, and optical functionalities can be merged in miniaturized devices thanks to advanced nanofabrication protocols.

This book provides an overview of the different ways in which the “nano-world” can be beneficial for neuroscientists. The volume encompasses the latest developments in the field of micro- and nanotechnology applied to neuroscience, discussing technological approaches applied to both *in vitro* and *in vivo* experiments. A variety of different nanotechnologies are presented that include nanostructured electrodes and their electrical, mechanical, and biochemical properties, active and passive 2D and 3D multielectrode arrays (MEAs), nanoscale transistors for subcellular recordings, and an overview on methods, tools, and applications in optogenetics.

Advances in electrode technology including improvements in the mechanical adhesion of cells on electrodes and the realization of novel, minimally invasive extracellular and intracellular recording approaches are reported. Electrodes are still the most common tools in neuroscience for bidirectional communication with the brain because of their simple fabrication, long-term stability, and large bandwidth, enabling the registration of action potentials as well as low-frequency field potentials (LFPs). Nanotechnology has dramatically improved their spatial resolution by exploiting surface micromachining and technologies derived from CMOS integrated circuits (IC). In addition, three-dimensional shaping, optimized electrode–electrolyte–neuron interfaces, surface functionalization by means of inorganic (e.g., carbon nanotubes) or organic materials, and cell-engulfment strategies for in-cell recording and stimulation have significantly increased their signal-to-noise ratio.

Arrays of electrodes have also become a key methodology in neuroscience for studying the function of neuronal networks and for the development of brain–machine interfaces (BMIs) and neural prostheses. Advances in semiconductor technologies and surface- and bulk-micromachining techniques have doubled the number of electrodes on the same substrate and the number of neurons that can be recorded simultaneously every 7 years. Nanotechnologies and nanostructuring capabilities have opened novel perspectives for multielectrode arrays. In fact, electrode arrays have progressed towards massively parallel single-unit recordings, at the same time taking advantage of low-power microelectronics to implement on-board circuits for conditioning, multiplexing, and wireless transmission of the recorded signals. Real-time operation is now reported for novel *active* multielectrode arrays based on CMOS technologies composed of several thousand electrodes. The impressive fabrication approaches of 2D and 3D MEAs on different substrates and their *in vitro* and *in vivo* applications developed during the last decades are reviewed in this book.

At the nanoscale, it is also possible to probe neurons with subcellular resolution, to follow the propagation of electrical signals in axons and dendrites. Such applications have been demonstrated with nanowire-based field effect transistors (FETs). The volume reports on 3D-distributed self-organized nano-FETs produced by bottom-up approaches and on their use in subcellular and high-frequency recordings. Substrate-free nanoscale electrical probes that could penetrate into living tissues or artificial tissue constructs, allowing electrical recording and mapping of cellular activities in a 3D microenvironment, are reported.

Defined as one of the breakthroughs of the decade, optogenetics is still at its infancy, but its capability for controlling neural activity rapidly and reversibly is already revolutionizing behavioral and neurophysiological analysis in animal models, both for understanding the function of the healthy brain and in brain disease. Nanotechnologies are having a major impact in this fast-growing field; indeed, novel micro- and nanotools that target light-sensitive proteins in multiple single neurons are making possible investigations of causal relationships in neural networks. In the last chapter of the book, new optogenetic approaches are discussed, including new ways in which nano- and microtechnologies can advance optogenetic approaches.

The book focuses specifically on fabrication strategies, to offer a comprehensive guide for developing and applying micro- and nanostructured tools for neuroscientific applications. It is intended as a reference both for neuroscientists and nanotechnologists on the latest developments in neurotechnological tools.

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