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New technologies for neuroscience

Editorial overview

Atsushi Miyawaki and Mark J Schnitzer

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Atsushi Miyawaki

Laboratory for Cell Function Dynamics, Brain Science Institute RIKEN (The Institute of Physical and Chemical Research), 2-1 Hirosawa, Wako, Saitama 351-0198, Japan
e-mail: matsushi@brain.riken.go.jp

Atsushi Miyawaki is the head of the Laboratory for Cell Function Dynamics at RIKEN Brain Science Institute and is concurrently directing Advanced Technology Development Group at the same Institute. His laboratory has developed fluorescent tools for the visualization of the spatio-temporal regulation of biological functions inside neurons and brains.

Mark J Schnitzer

James H. Clark Center for Biomedical Engineering and Sciences, Departments of Biological Sciences and Applied Physics, Stanford University, 318 Campus Drive Stanford, CA 94305, USA
e-mail: mschnitzer@gmail.com

Mark Schnitzer is assistant professor of Biology and Applied Physics at Stanford University. His group is developing fluorescence optical imaging techniques, such as microendoscopy techniques involving fiber- and micro-optics, for studying populations of individual neurons in live animals over both short and long time scales. He is applying these techniques to studies of learning and memory as well as brain disease.

This issue of CONB focuses upon new technologies for neuroscience research. A number of exciting innovations have recently emerged, several of which are well suited to help neuroscientists investigate neural circuit function. These innovations include advances in genetic manipulation, imaging, and computational analysis.

The striking progress in genetics has led not only to scientific discoveries but also to novel genetic technologies. The technologies reviewed here can generally be applied to the intact nervous system and targeted to specific tissues, cell types, or subcellular compartments. The reviews cover advances in genetically encoded reporters, combinatorial approaches for controlling gene expression, and genetic means of silencing specific forms of neuronal activity. Collectively, these new techniques offer improved capabilities for observing and controlling neuronal function.

Genetically encoded reporters include neural activity sensors that allow visualization of circuit or system-level functions. Barth review reporters of immediate-early gene (IEG) include expression, sensors of voltage changes or ion flux, and detectors of pre-synaptic release. IEG reporters using green fluorescent protein (GFP) provide spatial maps of overall levels of neural activity over time scales ranging from minutes to hours. The temporal limitations of IEG-based reporters are often those that arise from the maturation and degradation of GFP. By comparison, sensors of fast signals such as neuronal spiking are typically limited by signal to noise ratio and dynamic range.

Methods for controlling gene expression in a selective and reproducible manner are also advancing. Conventional methods employ regulatory elements of endogenous genes to achieve the specificity of transgene expression, but researchers need to control expression patterns with more precise spatio-temporal resolution. Luan and White describe emerging combinatorial techniques that make transgene expression contingent not upon a single promoter but upon two or more promoters. They explain binary systems that use transcription factors and/or recombinase enzymes for intersectional or subtractive restriction of transgene expression.

A growing class of genetic technologies allows targeted disruptions of cellular dynamics. Tervo and Karpova review new approaches for the perturbation of specific neural functions. By comparison with classical lesion studies, genetic technologies can often be highly selective, since they are based on manipulations of ion channels, ion pumps, G-protein-coupled receptors, or modified pre-synaptic proteins in a manner that that can be localized to chosen subsets of neurons. Silencing of activity can be inducible and reversible, with light or small molecules serving as triggers. An import-

ant ongoing pursuit will be to achieve the integrated use of genetic silencing techniques with sensors of neuronal function.

Deisseroth and co-workers describe the combined use of optical techniques for controlling and imaging neuronal activity. Their system for multi-modal control and imaging exploits the distinct absorption spectra of the light-activated cation channel channelrhodopsin-2, the light-activated chloride pump halorhodopsin, and the voltage-sensitive dye RH-155 for exciting, inhibiting, and imaging neuronal activity across populations of cells. This review also covers recent advances in the development of optogenetic and chemical genetic approaches for controlling the activity of targeted cell types, with emphasis on applications to the study of neuropsychiatric disease.

Genetically encoded probes are not only important for optical studies but are also growing in utility for magnetic resonance imaging (MRI) of brain function. The review by Jasanoff describes progress in the design of the latter, as well in other types of contrast agents for visualizing brain activity-dependent parameters by MRI. Prominent among these contrast agents are those that are indicators of pH, metabolic processes, Ca^{2+}, Mn^{2+} (as a Ca^{2+} mimetic), and other ions.

The last two reviews discuss research areas in which technological progress hinges upon advances in both instrumentation and computational analysis. Smith describes the emerging field of neural circuit reconstruction, which is driving the creation of new transgenic tool mice, techniques for optical and electron microscopy, tissue handling and labeling methodologies, and computational algorithms for image segmentation. Smith concludes by arguing for the importance and coming feasibility of reconstructing the neural circuits within an individual whisker barrel of the rodent neocortex.

Churchland, Shenoy, and co-workers describe advances in large-scale, multi-electrode studies of the live mammalian brain. Multi-electrode recording techniques have existed for some time, but recent work has led to enhanced capabilities for achieving chronic recordings, including in the primate brain. Moreover, a key area of recent progress is in the advancement of computational techniques for analyzing both the variabilities and commonalities present in multi-neuronal activity patterns recorded across multiple trials of ostensibly similar behaviors. Analysis techniques for reducing the dimensionality of large data sets while identifying the primary correlates with behavioral performance are particularly vital.

Together, these reviews cover multiple areas of recent technological progress. We hope readers will find the material both informative and stimulating toward achieving further scientific progress.