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New technologies

Editorial Overview

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Our research group develops functional and anatomical imaging methods and applies them to problems in neuroscience.

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Our research group studies how neural circuits are assembled during development, and how they contribute to sensory perception.

Introduction

This issue of *Current Opinion in Neurobiology* is dedicated to reviewing advances in a wide range of technologies. The first set of five reviews deals with what one might call the 'hardware' side of mostly imaging methods, which are arranged in sequence of increasing length scales.

The first review, by Leapman, draws our attention to a number of advances in electron microscopy. Particularly exciting are the recent developments in electron cryotomography, which provide information about the molecular arrangement within the molecular machines that control, for example, synaptic signaling; those in energy-loss imaging, which put 'color' into electron micrography; and those in phase-contrast imaging, which avoid having to compromise between resolution and contrast when imaging phase objects in the electron microscope.

Next along the resolution axis are the new developments in light microscopy. Hell and co-workers review recent advances in high resolution optical microscopy, in which the dreaded Abbe diffraction barrier appears to finally have been broken in far-field imaging. Saturation based super-resolution methods could one day allow the imaging of living specimens at a spatial resolution that rivals that of the electron microscope. Less ambitious in terms of the reachable resolution but also quite promising are structured-illumination and double-objective interference methods.

The use of nonlinear contrast mechanisms to obtain structural contrast and functional signals is discussed by Mertz. Alongside some progress in physical instrumentation, Mertz also emphasizes how crucial many improvements in the area of novel functional fluorescent probes are.

Schnitzer and co-workers review progress in fiber-optical imaging modalities with particular emphasis on methods that could allow access to deeper parts of the brain where novel optical approaches, such as the use of special objective lenses, are needed.

Functional magnetic resonance imaging (fMRI) remains the only imaging technique available to measure activity throughout the brain. Friston and co-workers discuss and review novel ways of reducing the uncertainties that exist as to the exact source of the detected signals.

Even in the above five hardware reviews occasionally the 'probeware' is mentioned, and is the limiting factor in many cases. Fortunately, there has been spectacular progress in the area of protein-based sensors that can be used to probe the structure and function of cells and tissues. The review by Griesbeck summarizes the latest technology of biosensors that are based on

green fluorescent protein and other derivatives from design to application. The most important aspect of these fluorescent protein-based biosensors to neuroscience research is the ability to introduce their expression by genetic means virtually at will to specific cell types and/or subcellular compartments in transgenic animals, thus enabling physiological studies *in vivo*.

The nervous system contains a bewildering number of neurons; each of which has elaborate axonal and dendritic processes and makes numerous connections with other neurons. The power of visualizing isolated neurons in native tissue was first demonstrated by Ramon y Cajal's use of the Golgi method to investigate the organization of the nervous system. The review by Young and Feng discusses genetic methods of labeling isolated neurons. These modern analogs of the Golgi method have enabled the targeting of specific classes of neurons with a controlled frequency of labeling, and most importantly, labeling of neurons in living tissue with fluorescent proteins. These new developments mean that the changing structure and functional responses of individual neurons can be studied for days and weeks.

The final two reviews discuss methods to manipulate gene activity in developing and adult nervous systems. Zugates and Lee summarize genetic mosaic methods that have been used to investigate gene function in the nervous systems of genetic model organisms ranging from *Caenorhabditis elegans*, to *Drosophila*, zebrafish and mouse. By deleting genes in a small subset of cells in an organism, one can tease apart the functions of genes that are required in multiple developmental processes and cell types, and determine the cell-autonomy of gene action. By combining cell-specific gene knockout with labeling of those very cells, some of these mosaic methods enable the investigation of gene function during the morphological development of neurons, as well as deciphering the wiring logic and assembly mechanisms of neural circuits.

While so far only those working with the few established genetic model organisms can enjoy the full range of sophisticated manipulations, such as genetic mosaic analysis, the discovery and increasing use of RNA interference (RNAi) suggests that for some applications, a general gene manipulation method has be found that is easily adaptable to all organisms with a suitable gene transfer technology. The review by Zeringue and Constantine-Paton provides a current survey of RNAi uses. In addition to summarizing the technology and discussing the utility, the authors have also emphasized the precautions to be taken and the controls necessary during use.

We hope that this collection of reviews will be of use to scientists studying a wide range of neurobiological problems.