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Polina Anikeeva is the Class of 1942 Associate Professor of Materials Science and Engineering, and an Associate Director of the Research Laboratory of Electronics at the Massachusetts Institute of Technology. Her group has created flexible multifunctional fibers capable of electrophysiological recoring, optical neuromodulation, and delivery of genes and drugs into the mammalian brain and spinal cord. In addition, her group has demonstrated that magnetic nanomaterials can wirelessly transduce magnetic fields into thermal and chemical stimuli to neurons in deep brain.

In this issue of CONB we highlight recent developments in tools to interrogate neuronal function across species ranging from fruit flies to humans, spatial scales spanning individual synapses to entire brains, and temporal resolution from milliseconds to months.

The articles dedicated to dynamic probing of neural function can be arranged in order of increasing temporal precision, spatial resolution, and invasiveness. The discussion of advanced hardware suitable for whole-brain functional magnetic resonance imaging (fMRI) in human subjects by Polimeni and Wald is complemented by the review by Jasanoff *et al.* of recent developments in fMRI contrast agents that permit monitoring of not only hemodynamic response but also release of neurochemicals in the rodent brain.

Tanter *et al.* offer an overview of rapidly progressing field of functional ultrasound (fUS) imaging of blood flow that, in part due to their efforts, has recently enabled non-invasive hemodynamic mapping of the entire rodent brain with resolution approaching the dimensions of neurons. Akin to fUS imaging, the developments in focused ultrasound technology discussed by Tyler have permitted non-invasive modulation of neural activity in deep brain structures in rodents and, importantly, in the cortex of human subjects.

Optical functional imaging approaches that take advantage of cell-type specificity afforded by genetically encoded activity indicators remain unrivaled in their ability to monitor dynamics of individual synaptic boutons or entire brain regions with temporal precision approaching timescales of single action potentials. This cluster of papers opens with an article by Hillman *et al.* who introduce the reader to high-speed three-dimensional swept confocally aligned planar excitation (SCAPE) imaging that enables imaging of entire cortical surfaces in rodents offering insight into emerging network patterns and their coupling to hemodynamics. Yang and Yuste then follow with a perspective on two-photon (2P) holographic imaging that takes advantage of spatial light modulator optics, genetically encoded fluorescent Ca^{2+} indicators, and engineered microbial rhodopsins and enables simultaneous recording or manipulation of multiple regions in the rodent cortex. Emiliani *et al.* discuss how the development of parallel holographic 2P excitation hardware approaches goes in stride with advancement of image encoding algorithms and the discovery and engineering of microbial rhodopsins with faster kinetics. The optical cluster culminates with a review by Rodriguez and Ji, who offer insight into the aberration corrective optics typically used in astronomy and astrophysics to permit functional imaging with single-bouton resolution in behaving animals.

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Liqun Luo is the Ann and Bill Swindells Professor in the School of Humanities and Sciences at Stanford University, and an Investigator of the Howard Hughes Medical Institute. His research group uses *Drosophila* and mice to study how neural circuits are assembled during development, and how they are organized in adults to process information. To facilitate these studies, his group has also developed widely used genetic tools to label and manipulate specific neuronal populations. Dr. Luo authored *Principles of Neurobiology*, a textbook for teaching neuroscience research to undergraduate and graduate students.

Despite the advances in optical techniques and fluorescent activity indicators (see below), electrophysiological methods remain essential to unequivocally probe neuronal spiking, subthreshold, and local field potentials in arbitrary deep brain structures that continue to challenge approaches relying on light. This year marks 60th anniversary of Strumwasser's pioneering report of extracellular recording of action potentials in the brain of a ground squirrel. The explosion of micro- and nano-fabrication techniques over the past five decades has delivered a wealth of alternatives to the insulated wires used by Strumwasser. State-of-the-art electrophysiological probes now combine recording with optical stimulation and drug delivery as described in a review by Stieglitz *et al.*, and can be integrated with wireless and even fully implantable flexible antennae compatible with complex behaviors as detailed by Gutruf and Rogers. Advances in integrated circuit design have permitted simultaneous electrical recording and stimulation owing to electrical artifact rejection algorithms reviewed by Muller *et al.* Similarly, complementary metal-oxide-semiconductor (CMOS) processing enabled unprecedented resolution and channel count in miniature electrophysiological probes – Neuropixels highlighted by Steinmetz *et al.*

The interactions of the implanted hardware with the neural tissue continue to pose challenges to long-term recording and modulation of neuronal dynamics at least in part due to chemical and mechanical mismatch between the devices and the biological matter. Scaini and Ballerini propose that nanomaterials with dimensions of biomolecular complexes may offer biocompatible interfaces with neural tissues, while Lieber *et al.* show how mesh and nanowire based electronics can deliver bio-attractive electrophysiological recording interfaces. Finally, Maharbiz and the team review an alternative approach to electrophysiological recording that relies on ultrasonic readout from millimeter scale piezoelectric motes 'neural dust' that in principle could be dispersed within neural tissue.

The advances in optical and electrophysiological techniques are delivering increasing quantities of neural data. Paninski and Cunningham review computational approaches, such as decoding tools and dimensionality reduction techniques, necessary for extracting meaningful information from these massive datasets.

While much of the tools discussed above have been used to record activity of neurons in specific brain regions, each region contains a mixture of different cell types with diverse physiological response properties and functions. An increasingly widely used approach to tease apart this complexity is to optically image neuronal activity from genetically defined cell types. This approach requires genetically encoded activity indicators, as well as genetic access to specific cell types. Two groups of reviews highlight recent advances on these topics.

On the activity indicator front, Plastisa and Pieribone discuss the promises and challenges of developing genetically encoded voltage indicators — promises because voltage indicators could allow simultaneous recording of membrane potentials of many closely packed neurons of a specific type, challenges because the current state-of-the-art indicators still suffer from low signal-to-noise in comparison with genetically encoded Ca^{2+} indicators. Li summarizes recent advances on genetically encoded indicators for neurotransmitters and neuromodulators, focusing on those that use G-protein-coupled receptors as their activation results in lower magnitude and slower changes of membrane potential compared to ionotropic receptors and thus is more difficult to monitor by electrophysiology. Deo and Lavis

expand on the discussion of fluorescence indicators for imaging neuronal activity by comparing chemical-based and genetically encoded indicators, as well as hybrid systems that can combine the advantages of the two. Combined use of genetically encoded indicators and advanced microscopy has enabled whole-brain functional imaging in the transparent zebrafish larvae during sensory processing and motor action, as reviewed by Vanwalleghem *et al.*

On the genetic access front, Huang summarizes current strategies to genetically access neurons based on cell types, in particular germline engineering approaches to target neurons based on expression of specific markers and their intersections. Tasic discusses how recent explosion of single-cell RNA-sequencing has expanded our ability to identify cell type-specific markers and help define neuronal cell types. These approaches are complemented by viral vector engineering discussed by Sun and Schaffer, which allow access of neurons based on their axonal projection patterns, for example. Okano reviews recent advance in making genetically modified non-human primates, such that the genetic strategies discussed above can in principle be applied to investigate the function and dysfunction of primate nervous systems.

Genetic targeting of neuronal types enables the investigations of not only their physiological response properties but also their anatomical connections, so that the activity of neurons can be investigated in the context of neural circuits. Zeng summarizes recent advances in brain-wide mesoscale connectome — the connections between specific neuronal types across different brain regions — at the levels of neuronal populations as well as individual cells. The microscale connectome traditionally tackled by serial electron microscopy followed by labor-intensive manual image processing, has benefitted from advances in computational image analysis aided by advances in machine learning as discussed by Kornfeld and Denk. These sophisticated approaches have now been complemented by clever light microscopic methods, such as expansion microscopy highlighted by Karagiannis and Boyden, with added information about localization of specific protein and RNA molecules.

The final three pieces extend the reaches of neurotechnology to development, cell biology, and modeling human brain disorders. Ma *et al.* review tools for tracing neuronal lineages from traditional viral based to those that utilize modern genome editing and single-cell RNA sequencing techniques. Shuo *et al.* discuss how proximity labeling has enabled mapping of the proteome of specific subcellular compartments, such as the synaptic cleft, to discover new proteins and new protein interactions that mediate specific cell biological processes. Şentürk and Bellen outline an effective strategy to tackle human neurological diseases in fruit flies. Nearly 75% of human disease genes have functional homologues in flies, and rich genetic tools in flies can help study pathophysiology of disease-associated genes and even identify new ones.

'Progress in science depends on new techniques, new discoveries, and new ideas, probably in that order.' This Syndey Brenner quote appears in several pieces in this issue. We hope that the new techniques discussed in this issue will help CONB readers to make new discoveries and generate new ideas.