

Preface

The human brain is a terrifically complicated structure. Nearly 100 billion neurons use trillions of synapses to communicate with one another, releasing a large and only partially catalogued variety of neurotransmitters that can exert very different effects depending on the neuroanatomical and physiological context. Activity in this network is driven by millisecond-duration action potentials, and the precise, relative timing of these events in different cells fundamentally determines the functional outcome. Even if we were able to account for all of these features, neuronal plasticity and regeneration would make any description we might derive only a snapshot of a temporally varying structure. Somehow, this mass of complexity allows us to perceive and interact with our environment in dynamic and appropriate ways. Systems neuroscientists, who seek to understand the cellular principles governing network function and behavior, have their work cut out for them.

The great technical difficulty in studying the brain, even in the simplified context of a model organism, has meant that insights into brain function often quickly follow technological advances. If that holds generally true, then we should expect the coming decade to be among the most illuminating periods in the history of neuroscience, as the last several years have seen an explosion of powerful new methods for studying the brain. The invention of optogenetics has given us a means to manipulate genetically defined populations of cells with a high degree of spatial and temporal precision and, in some cases, to do so without any invasive surgery. New microscopy techniques, coupled with an increasingly robust set of fluorescent calcium and voltage indicators, allow us to record activity in many cells simultaneously using a noninvasive optical readout. New ways to acquire and analyze electron microscopy data from large volumes of tissue are starting to provide complete physical wiring diagrams that will help constrain our models of circuit function. In addition, an ever-expanding set of molecular tools promises to help us identify molecular signatures of discrete neuronal subtypes, and to correlate those features with the cells' functional properties. In a very short period of time, the field has gained the ability to study how many identified single neurons work together in large groups to shape behavior.

While these new technical capabilities have already begun to provide important biological insight, there have also been significant lags in realizing their full

potential. There are two straightforward reasons for this. One is that it simply takes time for researchers to overcome the inevitable technical hurdles that accompany new methods, and the recent techniques, while powerful, also tend to be somewhat complex. The other reason derives from the sheer abundance of new tools. There are now dozens of optogenetic reagents and optical stimulation methods in the literature. The same goes for functional indicators and microscopy techniques. Predicting which tools will best address a particular biological question (or even which will do the job they are advertised to do) can be a daunting task, and often limits an investigator's willingness to adopt a new approach until a sufficiently large number of studies have shown it to be worthwhile.

This book addresses both of these issues while discussing the directions that several key technical areas are now moving in, and highlighting specific examples of how molecular and optical tools have helped us to understand neural circuit function. It is intended to form part of the ongoing discussion between tool-builders and other neuroscientists seeking to stay ahead of the curve in adopting new techniques. It should additionally serve as a useful, if dense, primer for students and other individuals looking to understand the methodological driving forces behind modern neuroscience.

In Chap. 1, Robert Marc and colleagues discuss progress in EM connectomics, where they and others are seeking to build high-resolution maps of neuronal connectivity that will be foundational to labs interested in physiology and behavior. In Chap. 2, Paul Bonthuis and Chris Gregg examine the problem of heterogeneity in neuronal populations, with regard to the ways that new expression profiling techniques might help us to define and identify distinct subclasses of cells within complex tissues. Chapters 3–5 focus on the development of optical tools for fluorescently labeling neurons and recording calcium signals (Chap. 3), neuronal voltage imaging (Chap. 4), and manipulating neural activity with wavelength-shifted rhodopsin variants (Chap. 5). The following three chapters explore specific aspects of these methods in the context of three model organisms: Using optogenetics (and especially red-shifted optogenetic activators) to study physiology and behavior in *Drosophila melanogaster* (Chap. 6); using optical tools to monitor and manipulate neuronal activity in freely-behaving *C. elegans* (Chap. 7); and applying a variety of techniques to understand sensorimotor physiology and behavior in zebrafish (Chap. 8). Chapter 9, by Dinu Albeanu's group, discusses the principles behind methods for spatially structuring the illumination light used in optogenetics experiments, and Chap. 10, by Matt Smear, illustrates the unique insight into olfactory circuits that he and his colleagues have derived by combining functional imaging, optogenetics, and behavior.

The ongoing work of these authors and many other technical innovators will define the kinds of experiments we do for years to come. I hope it inspires the reader to take advantage of the incredible opportunities we now have to understand the brain.

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