Large-scale Recordings for Drug Screening in Brain Circuit Systems

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Brain function depends on a vast and complex network in which diverse types of neurons are interconnected. A number of studies have been conducted on the function of neuronal networks and neuronal ensembles, but the mechanisms underlying their system dynamics are poorly defined. One of the main reasons is a lack of strategies to address them appropriately.

Our current understanding of network information processing by neuronal networks has relied on compiling population statistics across different recording sessions, *i.e.*, inferring from pieces of evidence that are obtained by physiological and anatomical analysis of individual neurons and synapses or otherwise by bulk recording of averaged neuronal responses. In complex systems, however, individual units function together, exhibiting collective dynamics beyond linear expectations. Their integrative behavior cannot be explained by simply putting together the properties of individual units. Studies on network behaviors, therefore, require large-scale methods to simultaneously record from a population of individual neurons.

Over the past decade, large-scale imaging techniques have rapidly developed, including functional magnetic resonance imaging, positron-emission tomography, intrinsic optical signal imaging, and voltage-sensitive dye imaging. These methods are extensively used in studying different aspects of brain function, leading to discovery of many important regimes of neural information processing. Yet, one of the significant shortcomings of these techniques is their poor spatial resolution. They cannot capture network dynamics at the single-cell level.

As an alternative method, I have developed functional multineuron calcium imaging (fMCI), which can record from neuron populations with single-cell resolution. In other words, fMCI can reconstruct when, where, and how individual neurons are activated in a network of interest, although its strategy is somewhat invasive to living biosystems. For fMCI, brain tissue is bulk-loaded with calcium-sensitive fluorescence indicator, and the changes in fluorescence intensity are measured from the cell bodies of neurons. Unlike voltage-sensitive dyes, which usually undergo a small (<1%) change in fluorescence or photoabsorption during activity, commonly used calcium indicators show 2-30 % fluorescence changes in response to single action potentials. The fluorescence transients arise from calcium influx through one or more types of voltage-sensitive calcium channels, and thereafter the signal may be amplified by calcium release from intracellular stores. fMCI is based on the idea that if such spike-evoked calcium transients are simultaneously imaged from numerous neurons, they would serve as large-scale dataset of active neuronal networks.