CellPress

Setting the Stage for the Next Generation of Neuroscience

Neuroscientists share their vision—spanning from the nanoscale to complex social behavior—for what is needed to take on the big challenges of the field.

Understanding Social Behavior

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Social behaviors play a crucial role in the reproduction, survival, and physical and mental health of animals, and they can be impaired in many mental disorders. Extraordinary progress has been made toward understanding their underlying mechanisms, but many challenges remain. Social interactions involve reciprocal feedback between two or more individuals who make decisions simultaneously, making social behavior inherently complex and highly context dependent. Establishing a foundation concerning the definition, measurement, and interpretation of behavioral motifs and elements is essential. At present, these may vary substantially across contexts, conditions, and even labs, but it is crucial to have unifying criteria based on objective, quantifiable measurements. Studying behaviors using sophisticated data-acquisition tools with advanced machine-learning algorithms begins to address this issue. Another challenge is in understanding how circuit components within and across brain regions synergize to process social information computationally and how this is modulated by highly variable contexts. Recording and manipulating activities of larger neural ensembles with higher spatiotemporal precision—and across brain structures—will provide new insights. All these challenges emphasize the necessity of acquiring and interpreting large-scale, high-dimensional datasets and closely collaborating across fields including, but not limited to, various areas of biology, mathematics, and engineering. Through these efforts, we will establish conceptual and theoretical frameworks that help us understand social interactions in both normal and diseased conditions.

Cell Biology in the Circuit Age

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Is cell biology needed to understand how the brain works? Triggered by advances in systems neuroscience, this question has become a flashpoint regarding the future of neuroscience. But the dispute is shortsighted, as even optimally charted circuits cannot be understood without knowing the functional characteristics of the neurons and synapses involved. We need a complementation of brain connectomes with detailed maps of the functional cell biology in the interconnected neurons. We need functional "synaptomes." This is a fascinating perspective to cell biologists and an obligation. We require comprehensive, quantitative models of the protein and organelle machinery in all neuronal subcompartments linked to their key functional features. The objective should be nerve cell models that predict the diverse functional characteristics of neurons and their synapses *in vivo*. Breakthroughs in cell biology—such as genome editing, single-cell transcriptomics, spatially resolved proteomics, super-resolution microscopy, and *in situ* cryo-electron microscopy—bring this within reach so that cell-type-specific gene expression and sub-compartment-specific protein expression, localization, and stoichiometry can be charted. Combined with cell-type- and synapse-type-specific functional analyses based on highly selective genetic perturbations, this will yield the cell-biological understanding that is required to decipher the function of connectomes in health and disease—and to understand how the brain works.

Neural Dynamics across Timescales

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One of our greatest challenges in neuroscience is coalescing increasingly complex experimental data into powerful theories. Successful theories ought to explain phenomena at multiple timescales, ranging from fast neuronal ring dynamics to slower changes in gene expression. In between lies the activity of neuromodulators, which confer computational flexibility and tune neural circuits in every part of the nervous system. One context in which rigorous theories to bridge these timescales have developed is decision making. These theories have largely occupied the domain of fast timescales, but have begun to incorporate slower dynamics. Certain neuromodulatory cells, such as those in the mammalian midbrain that release dopamine, have been studied in this framework. Most of the diffusely projecting neuromodulatory cells await deeper explanation, however. Moreover, it is unclear why there are so many different neuromodulators. One possibility is that the combinatorial dynamics of multiple neuromodulators allow target circuits to implement the model (for example, how to form a decision policy) most appropriate for a given environment. Approaching this problem without a theory would lead to a combinatorial explosion in the number of experiments required to test all possible interactions. It is thus a critical, and exciting, time in the field to be building on work done over the last few decades to generate more mature theories for neural dynamics.

Neuronal Assemblies and Memory

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Neuronal assemblies are groups of neurons that can be recruited together and activated synchronously through synaptic connections. Individual assemblies and their dynamics are thought to represent neuronal counterparts of memories, but how assembly structure (neuronal composition and connectivity) relates to assembly function in memory is an open question. Currently, learning-related neuronal assemblies are mainly investigated through two approaches. One type addresses the dynamics of activity in large sets of neurons with, for example, repeated calcium imaging experiments in behaving animals. The other type addresses functional roles of "memory neuron" assemblies using genetic tagging and/or manipulation experiments of learning-related "memory neurons" based on the expression of activity-regulated genes (cFos, Arc). Yet we currently lack conceptual frameworks to relate the resulting findings to each other. It seems unlikely that expression of genes such as cFos or Arc can simply be accounted for by activity in neurons. Conversely, it is not clear how to causally relate activity patterns in defined groups of neurons to learning and memory. Current evidence suggests that local memory-related neuronal assemblies might consist of partially overlapping subgroups of neurons with different roles. Experimental approaches that will manage to relate activity patterns in large groups of neurons, neuronal subpopulations and learning-related gene expression within neuronal assemblies will likely lead to fundamental advances in how learning and memory are implemented in the brain.

Decoding States and Contexts

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It's an exciting time in neuroscience—advances are enabling unprecedented precision, wherein connectivity is mapped with high spatiotemporal control, cells are profiled at the single nucleus level, and subcellular dynamics are imaged intravitally. As we gain a deeper understanding of the way the nervous system regulates behavior, the need to illuminate how it reacts under diverse conditions becomes more pressing. Pioneering studies have shown that behaviors and circuit activities are "state- and -context dependent": environmental stimuli specify neuronal signaling, differences in internal states in and beyond the brain evoke distinct neural responses, and interactions between external contexts and genetic programs underlie many neurological disorders. However, what exactly are these states and contexts? Which ones produce meaningful neurobiological outcomes? And what are their molecular underpinnings? The future holds the opportunity to uncover how external contexts determine internal states and to identify convergent biological signatures that can classify the seemingly infinite factors that inform molecular "state" and "context." Some may be unexpected, like the disorienting yet stunning microbiome, which adapts to external stimuli and modifies host physiology in ways that impact immunity, metabolism, sensation, and behavior. Incisive studies on states and contexts will inspire a richer understanding of how the nervous system responds to our varied interactions with the world.

Nanoscale Neuroscience

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Recent technological development for exploring neural mechanisms across multiple dimensions inspires us to imagine how we can solve the inner workings of the brain. A goal that unifies many neuroscientists is to improve human life through understanding brain function and curing brain disease. To reach this goal, I argue, it is essential to develop precise insight at the scale at which the brain's fundamental components, proteins and lipids, operate. Unless we have detailed knowledge of the dynamic actions of key molecular machines, we will unlikely be able to stop neurodegeneration and to reconstruct the making of memories, for example. Hence, basic molecular neuroscience, empowered by new technology, needs to be a major focus in the future with the goal to systematically dissect key nanoscale processes. New genetic and sequencing techniques enable unprecedented control and understanding of cell types and cell states. Super-resolution microscopy allows the studying of molecular assemblies with striking accuracy. Cryo-electron tomography will soon make it possible to visualize protein structures and complexes at near-atomic resolution within a neuron, maintaining essential context for understanding protein function. Once we can study molecular machines at work with nanoscale precision in the living brain and connect new insights with studies of circuit wiring and function, boundaries that prevent the development of new treatments for brain disease may become borders to be crossed.