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Brain-wide interactions between neural circuits

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Larry Abbott is the William Bloor Professor of Theoretical Neuroscience at Columbia University. His research involves the computational modeling and mathematical analysis of neurons and neural networks. Analytic techniques and computer simulation are used to study how single neurons respond to their many synaptic inputs, how neurons interact to produce functioning neural circuits, and how large populations of neurons represent, store, and process information. He received his PhD in physics from Brandeis University in 1977 and worked in theoretical particle physics until 1988. His research in neuroscience started at Brandeis and now continues at the Zuckerman Mind, Brain and Behavior Institute at Columbia University.

Karel Svoboda is a Senior Group Leader at HHMI's Janelia Research Campus. Before Janelia, he was a postdoctoral member of technical staff at Bell Laboratories (until 1997) and a principal investigator at Cold Spring Harbor Laboratories (until 2006). Svoboda's work is at the intersection of neuronal biophysics and cognition. His goal is to identify core principles underlying information processing in neural circuits, with a current focus on how neural circuits implement planning and execution of voluntary movements in the context of decision-making. Svoboda is developing new methods to interrogate neural structure and function in intact brains.

For much of the history of systems neuroscience scientists have focused on linking the activity of neurons in individual brain areas to behavior. This research program has been successful in sensory neuroscience, where it has been used to identify and analyze discrete stages in sensory pathways that impose specific transformations to produce more refined sensory feature detectors. The same conceptual approach has been applied in the realm of cognition (place cells, mirror cells) and motor systems (coding for movement direction). However, a striking feature of neural connectivity is nested feedback loops, suggesting inherently multi-regional computations. Certain motor signals appear to be conveyed to areas throughout the brain. In addition, predictions about the sensory consequences of movement are sent from motor areas to sensory areas, where they may be compared to sensory input. As neuroscientists begin to probe more complex behaviors with large-scale recordings, understanding multi-regional neural circuits is coming into focus as a major goal of systems neuroscience. The articles in this collection review progress in analyzing multi-regional neural circuits, and they highlight conceptual and technical challenges for the future.

Small, genetically tractable model systems are leading the way in brain-wide analysis of neural computation and behavior. This is in part because cellular imaging can provide a comprehensive view of neural activity across large parts of small brains (Loring et al). Powerful tools to identify and access specific cell types for recording and manipulation, as well as synapse-level connectomics, provide the foundation for understanding how neural computations are implemented by structured neural circuits (Eshbach and Zlatic). With the development of richer behavioral assays, it is becoming possible to study the whole-brain basis of locomotion (Randi and Leifer), action-selection (Eshbach and Zlatic)(Cheong et al), multi-sensory integration (Eshbach and Zlatic), and navigation and learning (Eshbach and Zlatic) at a level of completeness that will remain out of reach in mammalian brains for at least the next decade. Studies in small model systems are addressing fundamental questions of what it means to understand a computation at the level of the whole brain. For example, analysis of whole brain activity in behaving C. elegans has revealed how populations of neurons act together as a dynamical system to control behaviors such as locomotion and sleep (Randi and Leifer; Biswas et al). Furthermore, small brains allow unbiased searches for neural correlates of particular behaviors, which has already led to unexpected discoveries, such as the role of glia in integration of information (Loring et al).

Multi-regional neural circuits are also being explored in model systems that have gained traction because of their specialist behavioral repertoire. For example, exploring the multi-regional neural circuits underlying vocal learning in zebrafinches has revealed mechanisms that had previously been studied in the context of stimuli-response associations (Chen and Goldberg).

These insights in turn are catalyzing research in rodents and primates, highlighting how researches across model systems inform each other.

Brain-wide analysis of neural computation is an active area in mice, turbocharged by great progress in mapping brain cell types (Winnubst et al) and multi-regional neural circuits. Studies in mice are perhaps most advanced in the context of innate behaviors (Sternson). For example, scientists have linked the activity of interoceptive sensory neurons that signal internal states to influence need-based behaviors. By using robust behavioral assays, such as feeding, and gain and loss of function manipulations, these studies have mapped chains of identified neurons from sensation to action.

Mice are routinely used in decision-making tasks in which sensory stimuli instruct specific movements for rewards. In these tasks, brain regions that innately relate to specific sensory and motor functions are linked through learning to the implementation of adaptive behaviors (Esmaeili et al). Decision-making involves multiple computations, such as action selection, short-term memory and movement execution, which are reflected in distinct cortical activity patterns. There is now evidence that changes in cortical activity patterns associated with these computations are controlled by midbrain and hindbrain circuits via the thalamus (Li and Mrsic-Flogel).

Selective visual attention refers to the use of specific visual information to guide behavior. Selective visual attention inherently involves interareal communication, for example feedback from the frontal eye fields to visual cortex. The coordination of cortical areas underlying selective visual attention also involves higher-order thalamus. In primates, lesions of the pulvinar produce an inability to filter distracting stimuli that compete with a target stimulus for neural representation. Simultaneous recordings in multiple brain regions, including cortex and thalamus, are beginning to reveal how the thalamus coordinates transmission of sensory information within and between cortical regions, in part by synchronizing cortical activity across brain regions (Kastner et al).

Selective visual attention for faces and gazes is a key component of social interactions. Primate brains have evolved to navigate their complex social world. Functional MRI (fMRI) can be used to map interactions between brain regions in a non-invasive manner. Using fMRI, the multi-regional neural circuits underlying both the analysis and participation in social interactions have been mapped in humans and non-human primates, ringing in an era of social neuroscience (Freiwald).

The dynamics of brain-wide multi-regional circuits holds clues for the diagnosis and treatment of neuropsychiatric disorders. In particular, resting-state fMRI (rsfMRI) is used to probe inter-regional interactions that occur when no task is performed. rsfMRI has defined networks of correlations between brain regions that are consistent across healthy subjects. rsfMRI is now being used to examine alterations in resting-state networks in mental disorders. In combination with new study designs and modern analytic methods, rsfMRI promises specific biomarkers for diverse neuropsychiatric conditions (Parkes et al).

Large-scale neurophysiological data have revealed that behavior-related neural activity is distributed in a redundant manner across multiple connected brain regions. These parallel representations interact with each other through interareal connections, but interactions differ across pairs of connected brain areas and across behavioral states. What are the mechanisms underlying flexible, interareal communication? As the availability of recordings from large populations of neurons across multiple brain areas increases, so does the need for analytical methods that can extract information about communication between brain areas.

Multiple papers in this collection review analytical methods that leverage population recordings to provide a rich description of inter-areal interactions. The approaches make use of correlations (Kang and Druckmann; Semedo et al), dimensionality reduction (Keeley et al; Kang and Druckmann), linear regression (Semedo et al), and coherence (Pesaran et al). Interesting hypotheses are being generated, including the idea that gating occurs when patterns of activity in one region are orthogonal to the input selectivity of another region (Semedo et al). Nevertheless, interarial signals are challenging to interpret, especially given that in most situations only a subset of inputs to any brain area are observed. Ideally results should be confirmed by perturbation experiments.

Understanding brain-wide circuit mechanisms of computation and behavior is a daunting task. Information flow across brain regions is flexible and organized in feedback loops. Although multi-regional circuits are increasingly becoming experimentally accessible, making sense of the experimental data will require testable theories that encapsulate well-defined principles. These theories are also needed to guide the design of future experiments. Fortunately, just as new experimental tools have greatly expanded our ability to study neural circuits, new theoretical tools have expanded our ability to model them. Machine learning techniques now allow models to be constructed that perform at least some tasks at human or even super-human levels (van Bergen and Kriegeskorte). This allows much more rigorous testing of model circuit function than could be done in the past.

Several papers in this collection highlight theory → experiment → theory loops across different domains. Data-driven models focused on large-scale recordings in small model systems now routinely propose algorithmic solutions to specific computations, as well as implementations of the computation at the level of defined neurons and cell types (Biswas et al; Perich and Rajan). Other models, based on large-scale anatomical databases now available for primates and mice, make functional predictions about the dynamic properties of feedforward and feedback projections in hierarchically organized neural circuits (Wang et al).

Understanding how multiple brain regions interact to produce behavior is a complex, multidisciplinary and multi-scale endeavor. Large-scale collaboration is still nascent in neuroscience. Many laboratories use idiosyncratic behavioral tasks and specialized procedures that are difficult to compare and combine across laboratories. Reuse of data, analysis software and models is rare. More mature fields, like astronomy, particle physics and genomics, have augmented their scientific ecosystems with large-scale collaborative science. This trend is also catching on in brain research. The Allen Institute and Janelia Research Campus have shown how coordinated and standardized atlassing and technology projects can produce foundational tools and resources for brain research.

Two papers in this collection highlight new initiatives to catalyze multidisciplinary collaborations for discovery science. The NIH “BRAIN Circuits” program was organized to build on the BRAIN Initiative’s investments in neurotechnologies and neuroanatomical resources to enable projects that are too large for individual laboratories, focusing on how neural circuits produce perceptions, motivations, and actions (Hsu et al). This program funds multi-laboratory collaborations that involve a mix of investigator-driven projects and team science. Data standards, data sharing and coordination within and even across teams are core features of this program.

The International Brain Laboratory (IBL) is a bottom-up model of collaborative science funded by the Simons Foundation and the Wellcome Trust. IBL is a collection of twenty laboratories, distributed over two continents, which have coalesced to study one standardized perceptual decision-making behavior in mice. The core project is to map neural activity and multi-regional interactions across the entire brain (Wool and IBL). Focused, investigator-initiated projects are then spawned from the core project. IBL may represent a model for large-scale collaborations in brain research.

It is not obvious if the brain can be understood on the basis of multi-area recordings and whole-brain anatomy, but it is clear that without these it cannot. This selection of papers captures both the excitement and challenges of a new frontier in neuroscience research.