Columbia Workshop on Brain Circuits, Memory and Computation

Thursday and Friday, March 21-22, 2019 | Davis Auditorium, CEPSR

Organizer and Program Chair: Aurel A. Lazar (Columbia University)

The goal of the workshop is to bring together researchers interested in developing executable models of neural computation/processing of the brain of model organisms. Of interest are models of computation that consist of elementary units of processing using brain circuits and memory elements. Elementary units of computation/processing include population encoding/decoding circuits with biophysically-grounded neuron models, non-linear dendritic processors for motion detection/direction selectivity, spike processing and pattern recognition neural circuits, movement control and decision-making circuits, etc. Memory units include models of spatio-temporal memory circuits, circuit models for memory access and storage, etc. A major aim of the workshop is to explore the integration of various sensory and control circuits in higher brain centers.

Program Overview

Thursday 09:00 AM - 05:30 PM

09:00 AM - 09:45 AM **Gero A. Miesenboeck** (University of Oxford), The Somnostat: Mechanisms for Balancing Sleep Need and Sleep

09:45 AM - 10:30 AM **Karla Kaun** (Brown University), Circuits that Encode and Predict Alcohol Associated Preference

10:30 AM - 11:00 AM Coffee Break

11:00 AM - 11:45 AM **Paul A. Garrity** (Brandeis University), Thermosensing in the Fly: from Genes to Cells to Behavior

11:45 AM - 12:30 PM **Richard Benton** (University of Lausanne), Olfactory Evolution in Drosophilids: Receptors, Neurons and Behaviours

12:30 PM - 02:00 PM Lunch Break

02:00 PM - 02:45 PM **Stephan Saalfeld** (HHMI Janelia), Better Connectome Reconstruction from Large Electron and Light Microscopy Volumes of the *Drosophila* Brain

02:45 PM - 03:30 PM **Anton Arkhipov** (Allen Institute of Brain Science), Data-Driven Modeling of the Cortex Based on a Systematic Experimental Platform

03:30 PM - 04:00 PM Afternoon Break

04:00 PM - 04:45 PM **Kristin Branson** (HHMI Janelia), Using Machine Vision and Learning to Discover How the Brain Generates Behavior

04:45 PM - 05:30 PM **Benjamin L. de Bivort** (Harvard University), The Neural Circuit Basis of Behavioral Individuality

Friday 09:00 AM - 05:30 PM

09:00 AM - 09:45 AM **Stephen F. Goodwin** (University of Oxford), Neural Circuits Underlying Sex-Specific Behaviours

09:45 AM - 10:30 AM **Gwyneth Card** (HHMI Janelia), Towards a Brain Architecture for Visual Behavior Selection

10:30 AM - 11:00 AM Coffee Break

11:00 AM - 11:45 AM **Venkatesh N. Murthy** (Harvard University), Decoding and Demixing Smells

11:45 AM - 12:30 PM **Kevin M. Franks** (Duke University), Recurrent Circuitry Stabilizes Cortical Odor Representations Despite Degraded Sensory Inputs

12:30 PM - 02:00 PM Lunch Break

02:00 PM - 02:45 PM **Aurel A. Lazar** (Columbia University), Building the Functional Map of the Fruit Fly Brain

02:45 PM - 03:30 PM **Srinivas C. Turaga** (HHMI Janelia), Connecting the Structure and Function of Neural Circuits

03:30 PM - 04:00 PM Afternoon Break

04:00 PM - 04:45 PM **Tim Jarsky** (Allen Institute of Brain Science), Microcircuitry of the Cortex: Connectivity, Strength, and Short-Term Plasticity

04:45 PM - 05:30 PM **Louis Scheffer** (HHMI Janelia), Completing the Fly Model?

The Somnostat: Mechanisms for Balancing Sleep Need and Sleep

Gero A. Miesenboeck, Centre for Neural Circuits and Behaviour, University of Oxford.

Sleep is vital and universal, but its biological function remains unknown. We seek to understand why we need to sleep by studying how the brain responds to sleep loss. Our studies in *Drosophila* have pinpointed neurons whose sleep-inducing activity switches on as sleep deficits accrue, revealed how this activity switch works, and furnished a molecular interpretation of sleep pressure, its accumulation, and its discharge.

Circuits that Encode and Predict Alcohol Associated Preference

Karla Kaun, Department of Neuroscience, Brown University.

The ability to associate a rewarding stimulus with a sensory cue from the environment is critical for an animal's ability to find food and mates. Mapping the circuits in which these associations are formed, then initiate an output response provides a scaffold for understanding how experiences can influence decisions. Drugs of abuse such as alcohol can induce lasting changes in these circuits to induce maladaptive behavioral decisions. Here we describe a how memories for the intoxicating properties of alcohol are acquired and expressed through different mushroom body circuits. Acquisition of odor-alcohol memories induce lasting molecular changes which affect plasticity within circuits important for memory expression. Expression of these memories requires a remarkably complex multi-level circuit whereby dopamine directly, and indirectly via the mushroom body, modulates the activity of glutamatergic and cholinergic output neurons. Moreover, trans-synaptic tracing the outputs of these neurons suggests convergent and divergent networks, providing an elaborate framework for integrating external content and internal state to coordinate an appropriate output response. Together this work provides a snapshot of how alcohol can affect the dynamic molecular and circuit mechanisms required for behavioral decisions.

Joint work with Kristin M. Scaplen[1], Mustafa Talay[2], Emily Petruccelli[3], Nicolas Ledru[4], Gilad Barnea[1], [1]Department of Neuroscience, Brown University, Providence, RI. [2]Department of Molecular and Cell Biology, Harvard University, Cambridge, MA. [3]Department of Biology, Southern Illinois University, Edwardsville, IL. [4]MSTP Program, Washington University, St Louis, MO.

Thursday 11:00 AM - 11:45 AM

Thermosensing in the Fly: from Genes to Cells to Behavior

Paul A. Garrity, Department of Biology, Brandeis University.

Temperature is a universal physical variable that affects all aspects of physiology. Among other vital functions, animals rely on their thermosensory systems to maintain appropriate body temperatures and avoid thermal extremes. Thermosensing in *Drosophila melanogaster* depends on multiple classes of thermosensors, which rely on diverse classes of molecular thermoreceptors, exhibit distinct thermal sensitivities and have distinct behavioral functions. How these thermosensory neurons encode temperature information and how the information they provide supports behavior remain largely open questions. I will present recent work in which we have identified a critical role for phasic thermosensors (sensory neurons which primarily respond to heating and cooling rather than hot or cold temperatures) in innocuous thermosensation in *Drosophila*. At the molecular level, we have identified the molecular receptors that confer thermosensitivity upon these neurons and found that these molecules are critically important for the morphogenesis of the elaborate sensory compartment involved in sensing temperature changes. At the behavioral level, we find that these phasic thermosensors are essential for mediating behavioral responses across a wide range of temperatures, consistent with their ability to respond robustly to small temperature changes at very different ambient temperatures. Together these findings begin to provide a consistent picture of thermosensory processing in the fly brain and raise questions concerning how phasic inputs might combine with other sensory inputs to drive behavior.

Thursday 11:45 AM - 12:30 PM

Olfactory Evolution in Drosophilids: Receptors, Neurons and Behaviours

Richard Benton, Center for Integrative Genomics, University of Lausanne.

My group is interested in understanding the structure, function and evolution of neural circuits. We exploit the olfactory system of *Drosophila melanogaster* as a model, which is well-described, experimentally accessible and dynamically evolving. Furthermore, genomic and growing genetic access to closely related, but ecologically diverse, drosophilids provides an unparalleled foundation for comparative studies of their olfactory circuits. I will present our recent work on the evolution of the olfactory pathways of *Drosophila* sechellia, an island endemic that displays extreme specialisation for the Morinda citrifolia "noni" fruit as a food source and breeding site. We have started to define the molecular basis by which D. sechellia's olfactory receptors are re-tuned to the odors of its host and – through development of novel neurogenetic tools in this species – how these different sensory pathways contribute to host-seeking behaviors.

Thursday 2:00 PM - 2:45 PM

Better Connectome Reconstruction from Large Electron and Light Microscopy Volumes of the *Drosophila* Brain

Stephan Saalfeld, HHMI Janelia Research Campus, Ashburn, VA.

At the resolution necessary to unambiguously extract the synaptic connectome, the brain of the fruit fly *Drosophila melanogaster* has a size of about 100 trillion voxels. Today, 3D electron microscopy (3D- EM) is the only available imaging method that provides this resolution.

Automatic reconstruction of neurons and synaptic connections has seen significant improvement over the last few years, in particular thanks to notable advances in machine learning. Our contribution to this improvement is threefold:

(1) We have generated the largest existing training data set for neuron reconstruction and synaptic partner detection from non-isotropic 3D-EM of the *Drosophila* brain. With secret test data of equal size, we have organized an ongoing public challenge for connectivity reconstruction in the *Drosophila brain* (`http://cremi.org`). (2) Together with collaborators, we have developed the leading neuron segmentation method for this dataset. Further evaluations and improvements are currently underway. (3) We developed the leading method for synaptic cleft detection and reconstructed all synaptic clefts in 3D-EM of the complete *Drosophila* brain. We generated a new, high-resolution statistical atlas of the *Drosophila* brain from resolution limited confocal microscopy images visualizing all synapses in the neuropils of the fly, and we automatically registered the synapse cloud of the EM volume with the light microscopy atlas such that neurons reconstructed in EM can be matched with sparsely labeled light microscopy images.

I will give a brief overview of the state of automatic connectome reconstruction in the fly brain and will discuss our ongoing efforts to improve upon the current state.

Data-Driven Modeling of the Cortex Based on a Systematic Experimental Platform

Anton Arkhipov, Allen Institute of Brain Science.

The Mindscope project at the Allen Institute for Brain Science aims to elucidate mechanisms underlying cortical function in the mouse, focusing on the visual system. This involves concerted efforts of multiple teams characterizing cell types, connectivity, and neuronal activity in behaving animals. An integral part of these efforts is the construction of models of the cortical tissue and cortical computations. We will discuss our current progress on this front. First, we built a computational pipeline to produce models of individual neurons based on slice electrophysiology and morphology reconstructions. Second, we used these models as building blocks for large simulations of cortical activity in response to visual stimuli. A highly realistic 230,000-neuron model of the mouse cortical area V1, receiving thalamocortical visual inputs, has been constructed at two levels of resolution: one using the biophysically detailed, compartmental neuron models and the other using point-neuron models. Third, we perform systematic comparisons of simulated responses to in vivo experiments and investigate the structure-function relationships in the models to make mechanistic predictions for experimental testing. To enable this work, we developed the software suite called Brain Modeling ToolKit (BMTK) and a modeling file format called SONATA. These tools, the models, and simulation results are all being made freely available to the community via the Allen Institute Modeling Portal.

Thursday 4:00 PM - 4:45 PM

Using Machine Vision and Learning to Discover How the Brain Generates Behavior

Kristin Branson, HHMI Janelia Research Campus, Ashburn, VA.

In this talk, I will overview our lab's work using machine vision and learning to analyze animal behavior from video in large-scale neuroscience experiments, including pose tracking, supervised behavior classification, and unsupervised behavior analysis.

The Neural Circuit Basis of Behavioral Individuality

Benjamin L. de Bivort, Department of Organismic and Evolutionary Biology, Harvard University.

Individuals animals vary in their behaviors even when their genetics and environment are held constant. The mechanisms underlying this variation is still largely uncharacterized, though we have made some progress in understanding genetic and circuit variants that lead a population of animals to exhibit high or low variability in behavior. These are key insights, but fall short of predicting the specific behavioral biases of individual animals. We term the causal biological features that determine individual behavioral biases "loci of individuality," and we have begun to search for them in the circuits that mediate sensory-evoked and spontaneous behaviors. We have found neural circuit elements, whose morphological properties predict behavioral biases. Specifically, the volume of axonal output arbors of central complex neurons that project to the Lateral Accessory Lobe correlates with changes in locomotor behavior in specific sensory contexts. We hypothesize that individual wiring variation in these neurons has a large effect on behavior because they lie at a bottleneck in the sensorimotor circuit, where stochastic fluctuations have an outsized effect on circuit outputs. Thus, we have found that individual variation in the structure of small numbers of neurons, in topologically critical circuit positions, predict individual behavioral biases in a sensory-context specific fashion.

Friday 9:00 AM - 9:45 AM

Neural Circuits Underlying Sex-Specific Behaviours

Stephen F. Goodwin, Centre for Neural Circuits and Behaviour, University of Oxford.

All animals must continuously sequence and coordinate behaviours appropriate to both their environment and internal state if they are to survive and reproduce. Dissecting the neural substrates that initiate, organize, and terminate these behavioural sequences is critical to understanding behaviour. Courtship behaviour in *Drosophila* has proven to be an outstanding model for understanding how a compact circuit coordinates these critical action sequences. Our group is interested in understanding how neural circuits are functionally assembled, and how they integrate information to generate appropriate sex-specific responses.

In the fly, sex-specific behaviours are hardwired into the nervous system via the actions of two sex determination transcription factors (TFs), Doublesex (Dsx) and Fruitless (Fru). We have focused our attention on neurons that express these TFs to find anatomical or molecular sex differences in neuronal populations in order to gain an entry point into the neural circuits underlying gender-typical behaviours and identify the neuronal nodes that control component behaviours and behavioural sequencing. We have focused on the role of neurons that express dsx. These dsx+ neurons control male courtship behaviour and aspects of female receptivity. Yet little is known about the specific role of dsx+ neurons in the brain, which are believed to control mating decisions. We identified a group of sexually-dimorphic dsx neurons that are critical to sensory integration in males and females. Importantly, the dimorphism we uncovered can alter connectivity and information flow between males and females.

Friday 9:45 AM - 10:30 AM

Towards a Brain Architecture for Visual Behavior Selection

Gwyneth Card, HHMI Janelia Research Campus, Ashburn, VA.

Selecting the right behavior at the right time is critical for animal survival. Animals rely on their senses to deliver information about the environment to sensory processing areas in the brain that extract relevant features and form the perceptual representations that guide behavior. We aim to uncover the organization of this feature space and the neural mechanisms by which these cues are translated into dynamic motor activity.

Our current focus is visually-driven behaviors of the fly. In particular, those driven by visual looming cues produced by an approaching predator or an imminent collision. The same looming stimulus can evoke a wide range of different behaviors, including a rapid escape jump, a slower, more stable takeoff sequence, or a landing response. We use whole-cell patch clamp physiology in behaving flies, calcium imaging, high-throughput/high-resolution behavioral assays, and genetic tools to examine the transformation of information from sensory to motor. I will discuss our recent work investigating the representation of ethologically-relevant visual features in the fly optic glomeruli and the mechanisms by which descending neurons read out this feature information to produce an appropriate behavioral choice.

Friday 11:00 AM - 11:45 AM

Decoding and Demixing Smells

Venkatesh N. Murthy, Department of Molecular and Cellular Biology, Harvard University.

Fluctuating mixtures of odorants, often transported in fluid environments, are detected by an array of chemical sensors and parsed by neural circuits to recognize odor objects that can inform behavioral decisions. Whether and how mice segment odor mixtures into individual components ("demix") remains unclear. We have found that mice can be trained to recognize individual odorants embedded in unpredictable and variable background mixtures with high degree of success [1]. Despite nonlinear interactions and variability in the representations of odor mixtures by odorant receptors [2], a simple linear feedforward decoding is sufficient to explain the performance of mice in this task [3]. Current experiments are aimed at understanding how the mouse brain represents information about odor mixtures to aid odor object identification and categorization.

Friday 11:45 AM - 12:30 PM

Recurrent Circuitry Stabilizes Cortical Odor Representations Despite Degraded Sensory Inputs

Kevin M. Franks, Department of Neurobiology, Duke University.

Animals must recognize familiar objects even when incoming sensory input may be noisy, degraded or incomplete. Theoretical studies have shown that this process, often called "pattern completion", can be implemented by recurrent cortical circuits within an autoassociative network. However, direct experimental evidence for this process has been lacking. Here, we recorded odor-evoked activity from simultaneous populations of neurons in mouse olfactory bulb and olfactory cortex before and after inducing anesthesia. We found that cortical odor representations remained stable across brain states even though upstream representations, in olfactory bulb, were markedly degraded under anesthesia. Odor representations were more robust in cortical pyramidal cells, which receive recurrent connections, than in semilunar cells, which do not. Furthermore, cortical odor representations became as state-dependent as those in olfactory bulb after blocking recurrent connections between pyramidal cells. Thus, we provide direct evidence for the crucial role of recurrent cortical circuitry in stabilizing sensory representations driven by degraded sensory input.

Building the Functional Map of the Fruit Fly Brain

Aurel A. Lazar, Columbia University, New York, NY.

I will describe the open interactive computing platform, called FlyBrainLab (FBL), designed for studying the function of executable circuits constructed from fly brain data. FBL provides easy access to biological data and brain circuit models of the Fruit Fly Brain Observatory (FFBO). FFBO lists a (i) hub for storing and integrating fruit fly brain data from multiple data sources worldwide, (ii) unified repository of tools and methods to build, emulate and compare brain models in health and disease, and (iii) an open framework for brain data processing and model execution. Furthermore, FFBO provides access to application tools for visualizing, configuring, simulating and analyzing computational models of brain circuits of the cell-type map, connectome, synaptome, and activity map using intuitive queries in plain English. FBL code and installation instructions are available on Github.

Friday 2:45 PM - 3:30 PM

Connecting the Structure and Function of Neural Circuits

Srinivas C. Turaga, HHMI Janelia Research Campus, Ashburn, VA.

In this talk, I will describe how we developed deep learning based computational tools to solve two problems in neuroscience: inferring the activity of a neural network from measurements of its structural connectivity, and inferring the connectivity of a network of neurons from measurements and perturbation of neural activity.

1. Can we infer neural connectivity from noisy measurement and perturbation of neural activity? Population neural activity measurement by calcium imaging can be combined with cellular resolution optogenetic activity perturbations to enable the mapping of neural connectivity in vivo. This requires accurate inference of perturbed and unperturbed neural activity from calcium imaging measurements, which are noisy and indirect. We built on recent advances in variational autoencoders to develop a new fully Bayesian approach to jointly inferring spiking activity and neural connectivity from in vivo all-optical perturbation experiments. Our model produces excellent spike inferences and predicts connectivity for mouse primary visual cortex which is consistent with known measurements.

2. Are measurements of the structural connectivity of a biological neural network sufficient to predict its function? We constructed a simplified model of the first two stages of the fruit fly visual system, the lamina and medulla. The result is a deep hexagonal lattice convolutional neural network which discovered well-known orientation and direction selectivity properties in T4 neurons and their inputs. Our work demonstrates how knowledge of precise neural connectivity, combined with knowledge of the function of the circuit, can enable in silico predictions of the functional properties of individual neurons in a circuit, leading to an understanding of circuit function from structure.

Friday 4:00 PM - 4:45 PM

Microcircuitry of the Cortex: Connectivity, Strength, and Short-Term Plasticity

Tim Jarsky, Allen Institute of Brain Science.

We seek to characterize the microcircuitry of the cortex in mouse and human using multipatch electrophysiology supplemented with 2-photon optogenetic circuit mapping. Using the approaches mentioned above, we quantify connection probability as a function of distance, synaptic strength, and short-term synaptic dynamics among the major classes of cortical neurons. We rely on the dimensionality reduction that modeling can provide to quantify and compare differences in synaptic dynamics. We intend to share the data so that accurate, integrative computer models of cortex can be made. This presentation will summarize our results to date and share how our data may be accessed.

Friday 4:45 PM - 5:30 PM

Completing the Fly Model?

Louis Scheffer, HHMI Janelia Research Campus, Ashburn, VA.

We are on the verge of having a full connectome of all neurons and their chemical synapses in *Drosophila*. But while necessary, this is not sufficient to model the fly's nervous system. Additional information includes gap junction varieties and locations, identities of neurotransmitters, receptor types and locations, neuromodulators and hormones (with sources and receptors), the role of glial cells, time evolution rules for synapses, and more. This talk will outline these missing pieces, look at methods by which the data might be obtained, and summarize existing efforts (where they exist) to get this needed information.