ALLEN INSTITUTE *for*
BRAIN SCIENCE

Human Brain Project
Education Programme

3rd HBP School – Future Neuroscience
The Multiscale Brain: From Genes to Behaviour

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Speaker Abstract Collection

Alphabetical order according to presenting author

List of Abstracts (in alphabetical order)

Genetic dissection of neural circuits

Bakken, Trygve
Allen Institute

The human cortex is composed of billions of neurons whose coordinated activity produces thought and action. In order to understand this complex circuit, we must simplify our representation of it, and over 100 years of research has categorized neurons based on their shape, connections, electrical properties, and genetic markers. However, the full diversity of human cortical cell types remains unknown. Recent technological advances have enabled gene expression profiling of single cells and nuclei using RNA-sequencing. Nuclei have less RNA content and give noisier estimates of gene expression than whole cells but allow a less biased survey of transcriptomic cell types in human cortex. We applied single nucleus RNA-seq to study the diversity of Layer 1 inhibitory neurons and to target von Economo neurons, a rare type found in large-brained social mammals that has a distinct shape and is restricted to Layer 5 of a few frontal cortical areas. Iterative clustering revealed multiple subtypes of inhibitory and excitatory neurons, including a putative von Economo type. This work demonstrates the utility of single nucleus RNA-sequencing for documenting the diversity of cell types in the adult human neocortex.

Human Brain Atlasing

Bzdok, Danilo
RWTH Aachen

Over the past century and an half, human brain mapping consisted in pinning small functionally responsive areas within the brain. However the real extent of these areas and their eventual overlap remains unknown. The challenge now facing neuroscience is to define boundaries for functionally responsive areas at the group and the individual level. Many approaches parcellating the brain in areas with different features became recently available including post-mortem and in vivo architectonics, tractography-based connectivity, functional coactivation, and resting state functional connectivity. However, what these methods really measure and what conclusion can be drawn, are not yet fully clear to the scientific community. This course addresses this need and is intended for a large audience of research scientist.

Synaptic mapping

Collman, Forrest
Allen Institute

Synapses of the mammalian CNS are diverse in size, structure, molecular composition, and function. Synapses in their myriad variations are fundamental to neural circuit development, homeostasis, plasticity, and memory storage. Unfortunately, quantitative analysis and mapping of the brain's heterogeneous synapse populations has been limited by the lack of adequate single-synapse measurement methods. Electron microscopy (EM) is the definitive means to recognize and measure individual synaptic contacts, but EM has only limited abilities to measure the molecular composition of synapses. I'll describe conjugate array tomography (AT), a volumetric imaging method that integrates immunofluorescence and EM imaging modalities in voxel-conjugate fashion. We will illustrate the use of conjugate AT to advance the proteometric measurement of EM-validated single-synapse analysis in studies of mouse and human cortex.

Structure, function, behaviour

De Vries, Saskia
Allen Institute

In order to explore how features of the sensory environment are represented by cortical circuits, the Allen Institute for Brain Science has recently released the first survey of neural activity in the living brain, the ALLEN Brain Observatory. Using high-throughput 2-photon calcium imaging, we have systematically recorded the responses of over 18,000 neurons in the awake mouse cortex to a wide range of visual stimuli, including gratings, sparse noise, natural images and movies. In my talk I will explore the single cell and population level responses found in this data set, and explore what these responses can tell us about sensory processing in the cortical circuit.

Building biophysically-constrained models of large-scale phenomena in the brain

Alain Destexhe
UNIC, CNRS, Gif sur Yvette, France, and The European Institute for Theoretical Neuroscience (EITN), Paris

Propagating waves are large-scale phenomena widely seen in the nervous system, in both anesthetized and awake or sleeping states. Recently, the presence of propagating waves at the scale of microns

to millimeters was demonstrated in the primary visual cortex (V1) of macaque monkey. Using a combination of voltage-sensitive dye (VSD) imaging in awake monkey V1 and model-based analysis, we showed that virtually every visual input is followed by a propagating wave (Muller et al., Nat Comm 2014). The wave was confined within V1, and was consistent and repeatable for a given input. Interestingly, two propagating waves always interact in a suppressive fashion, and sum sublinearly. This is in agreement with the general suppressive effect seen in other circumstances in V1 (Bair et al., J Neurosci 2003; Reynaud et al., J Neurosci 2012).

To investigate possible mechanisms for this suppression we have designed mean-field models to directly integrate the VSD experiments. Because the VSD signal is primarily caused by the summed voltage of all membranes, it represents an ideal case for mean-field models. However, usual mean-field models are based on neuronal transfer functions such as the well-known sigmoid function, or functions estimated from very simple models. Any error in the transfer function may result in wrong predictions by the corresponding mean-field model. To palliate this caveat, we have obtained semi-analytic forms of the transfer function of more realistic neuron models. We found that the same mathematical template can capture the transfer function for models such as the integrate-and-fire (IF) model, the adaptive exponential (AdEx) model, up to Hodgkin-Huxley (HH) type models, all with conductance-based inputs.

Using these transfer functions we have built "realistic" mean-field models for networks with two populations of neurons, the regular-spiking (RS) excitatory neurons, showing spike frequency adaptation, and the fast-spiking (FS) inhibitory neurons. This mean-field model can reproduce the propagating waves in V1, due to horizontal interactions, as shown previously using IF networks. This mean-field model also reproduced the suppressive interactions between propagating waves. The mechanism of suppression was based on the preferential recruitment of inhibitory cells over excitatory cells by afferent activity, which acted through the conductance-based shunting effect of the two waves onto one another. The suppression was negligible in networks with identical models for excitatory and inhibitory cells (such as IF networks). This suggests that the suppressive effect is a general phenomenon due to the higher excitability of inhibitory neurons in cortex, in line with previous models (Ozeki et al., Neuron 2009).

Work done in collaboration with Yann Zerlaut (UNIC) for modeling, Sandrine Chemla and Frederic Chavane (CNRS, Marseille) for in vivo experiments. Supported by CNRS and the European Commission (Human Brain Project).

Mouse whole brain modelling

Erö, Csaba
EPFL

Most large-scale models in computational neuroscience result from a "one-time heroic effort" rather than from a systematic repeatable process. Moreover, they typically focus on one or a few brain regions which are then described as networks of randomly or topologically connected neurons. These models are constrained by parameters that the scientific community considers plausible. While many interesting features of networks can be predicted by this approach, biological networks exhibit more variability in cell placement, types, and wiring with possible functional consequences. Here, we present a semi-automatic workflow that integrates different data-sets and generates models, ready to be simulated and validated. It allow researchers to routinely build models by entering a virtuous cycle of data-integration, model-generation, validation and model refinement.

The Blue Brain Project

Hill, Sean
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Abstract NOT PROVIDED

Defining disease signatures

Kherif, Ferath
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Abstract NOT PROVIDED

Brain-wide single neuron reconstructions

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Neuron is the basic unit of the brain, the human brain generally contains approximately one hundred billion neurons, and neurons with different functions have different sizes, shapes and locations, and even neighbouring neurons of the same cell type differ in their morphologies. Thus, the reconstruction of exactly fine morphology of neuron is becoming the fundamental work for further comprehension of the brain. In this report, we will first review the development history of neuron reconstruction methods, especially neuronal labeling techniques and imaging techniques. Then, we will show how to achieve the brain-wide single neuron reconstructions in Visible Brain-wide Networks (VBN) project, including neuronal labeling techniques, brain-wide micro-optical imaging with landmarks and big data analysis. In addition, the techniques adopted in VBN project and the up to date mainstream techniques will be compared to give students a more comprehensive understanding of the advantages and disadvantages of each method. We will finally discuss the opportunities and challenges of brain-wide single neuron reconstructions from different perspectives.

Human cellular morphology and electrophysiology

Mansvelder, Huibert
VU Amsterdam

While the human neocortex is many times more extended than the rodent neocortex, and its computational power much larger, we have very little understanding of the properties of the elementary building blocks of information processing, the neurons. Our knowledge on neuronal structure and function is primarily based on brains of laboratory animals. Whether it translates to human neocortex is not known. In this talk, I will discuss the methods to obtain data on morphology and function of human neocortical microcircuits and share some striking results of how human neurons behave very differently from rodent neurons. I will also discuss how the interaction between detailed biophysical models of these human neurons and testing these on actual data of human neuronal circuits are vital to understand human neocortical circuitry function.

Using whole-brain and single-cell gene expression to identify and characterize cell types

Menon, Vilas
Allen Institute, Janelia

A major effort in neuroscience has been to identify and characterize the building blocks, or cell types, that comprise the nervous system. Various data modalities such as gene expression, electrophysiology, morphology, response properties, and connectivity have led to the classification of neurons into various classes with distinct properties. Recently, advances in single-cell RNA-sequencing methods have led to large-scale characterization of multiple neuronal types in various regions of the brain. This lecture will explore the various transcriptomic neuronal types that have been identified in the mouse over the past five years, and relate them to the Allen Brain Atlas, a brain-wide in situ atlas of the adult mouse. The interplay between single-cell transcriptomics and brain-wide in situ characterization methods is a powerful combination to identify and localize cell types, and is critical in generating hypotheses about potential downstream cellular phenotypes.

Whole brain morphofunctional imaging

Pavone, Francesco
LENS

We are interested in the correlations between morphology of brain connections and functionality, which is one of the major issues in neuroscience in the comprehensions of many pathologies and mechanisms of behavior and computation. Elucidating the neural pathways that underlie brain function is also one of the greatest challenges in neuroscience.

Nowadays, there are several imaging techniques offering a complementary approach to visualize intact neural networks. Each of those offers a different strategy and furnish complementary information on the role of neural components.

We will describe different approaches enabling to move from single neuron details to whole brain imaging both on functional and morphological point of view.

Some examples of correlative microscopies, combining linear and non linear techniques will be described. Particular attention will be devoted to neural plasticity after damage as neurobiological application.

Mesoscale mapping

Waters, Jack
Allen Institute

We are interested in the organization and functional activity of neocortical areas in the mouse. Using a widefield microscope with a large enough field of view to include much of the mouse neocortex, we are able to monitor cortical activity through the intact skull neocortex in GCaMP6-expressing mice and perturb activity in localized regions of cortex is opsin-expressing mice. I will describe some of our recent results, examining the organization of mouse visual areas and the activities and roles of neocortical areas during presentation of visual stimuli and visually-guided behaviours.