The Open Synaptome Project: Toward a Microscopy-Based Platform for Single-synapse Analysis of Diverse Populations of CNS Synapses

*Stephen J Smith[1], Randal Burns[2], Mark Chevillet[3], Ed Lein[1], Guillermo Sapiro[5], William Seeley[6], James Trimmer[7], Joshua Vogelstein[4], Richard Weinberg[8] // [1]Allen Inst. For Brain Sci., Seattle, WA; [2]Computer Sci., [3]Applied Physics Lab., [4]Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; [5]Electrical and Computer Engin., Duke Univ., Durham, NC; [6]Univ. of California, San Francisco, CA; [7]Univ. of California, Davis, CA; [8]Cell Biol. and Physiol., Univ. of North Carolina, Chapel Hill, NC

Abstract

New light and electron microscopy methods are now enabling the first structural and molecular measurements across large CNS synapse populations at the single-synapse level. Accumulating evidence that CNS synapses are highly diverse in structure, protein composition, function, and neuropathologic susceptibility points to an urgent need for integrated "synaptomic" survey tools. The Open Synaptome Project (OSP; http://neurodata.io/modalities/at and http://smithlab.stanford.edu) is an endeavor of a consortium of investigators at the Allen Institute, Johns Hopkins, Johns Hopkins Applied Physics Laboratory, UNC Chapel Hill, Duke, UC Davis and UC San Francisco aimed at building broadly accessible foundations for single-synapse analysis of CNS synapse populations. Our current efforts concentrate on advancing and disseminating methods for Array Tomography (AT) immunofluorescence microscopy, as these seem especially suitable for high-throughput proteometric analysis of the diverse and volumetrically dense synapse population encountered in the mammalian CNS. Given the importance of mouse models of human brain function and human mental and neurological disorders, the OSP's initial work focuses on neocortical structures in mouse and human. The goal is to build an open and broadly useful platform to more quantitatively understand similarities and differences between CNS synapse populations in those species. The OSP's present work includes efforts to (1) improve methods for preparing specimens of mouse and human neocortex for AT analysis, (2) expand and validate synapse-relevant antibody panels, (3) develop faster and more automated ATomo imaging methods, (4) deploy advanced petascale image database methods, (5) improve methods for automated synaptomic analysis of AT image datasets, (6) develop cell-biologically principled taxonomies of mouse and human synapse types, and (7) establish web portals for sharing of methods, data, taxonomies, and other resources across broad communities of synapse biologists and for any other neuroscientists grappling with basic mechanisms and disorders of synaptic network function. This poster describes OSP status in each of these areas.

Approach: Overview of the Synaptome Project

To create new methods and models for understanding and exploiting synapse diversity and for measuring synaptic population profiles, we are developing the seven "workstreams" schematized here into an integrated pipeline:.

We are a multidisciplinary consortium sharing common interests in synaptic circuit neuroscience, but with special areas of strength and activity as follows:

Stephen J Smith (Allen Institute)	Synapses, Circuits, Microscopy
Randal Burns (Johns Hopkins)	Big data, machine architecture, data sharing
Ed Lein (Allen Institute)	Transcriptomics, circuits, neuron types
Guillermo Sapiro (Duke)	Image processing, machine learning
William Seeley (UCSF)	Neurology, human neuroanatomy
James Trimmer (UC Davis)	Neuronal ion channels, antibody technology
Joshua Vogelstein (Johns Hopkins)	Statistics, machine learning, data sharing
Mark Chevillet (JHU/APL)	System engineering, circuits, data sharing
Richard Weinberg (UNC, Chapel Hill)	Synapses, tissue technology

1. Tissue: Collection, fixation and curation of brain specimens from mice, from human neurosurgical excisions (Lein) and from human autopsies; Tissue processing and resin embedding; Cutting and array fabrication.

2. Reagents: Antibody generation; Automated antibody screening, panel optimization and specificity validation.

3. Imaging: Staining and array tomography (AT) image acquisition; Streaming from client to petascale data cluster.

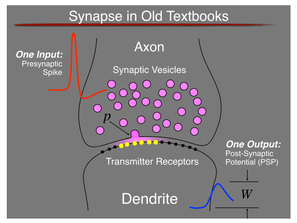
4. Computing: Streaming image data ingestion, storage and analysis on petascale data cluster.

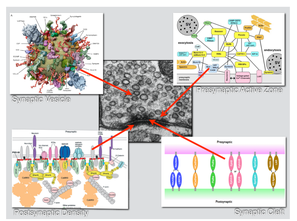
5. Vision: Robustly automated image processing and machine vision services; synaptic protein punctum and neuronal cytoskeleton segmentation.

6. Statistics: Inference of synapse taxonomies from high-dimensional synapse data; testing of cell-biological hypotheses relating synapse molecular diversity to parent neuron diversity.

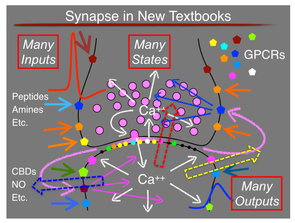
7. Access: Resource and data sharing amongst consortium, pilot users and broad communities of basic and clinical synaptic neuroscientists; hosting of web resources for an "Open Synaptome Project" for open access to synaptomic expertise, services and data.

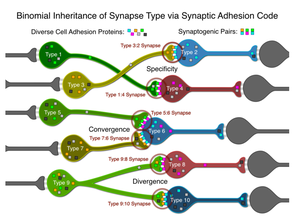
Why do we need Synaptomes?



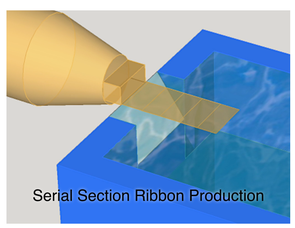


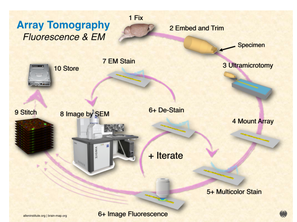
Synapses are Complex and Diverse!

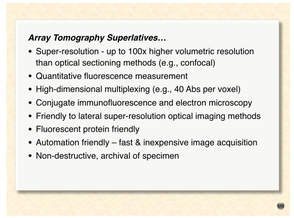


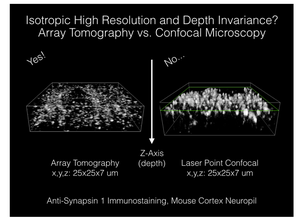


What is Array Tomography?

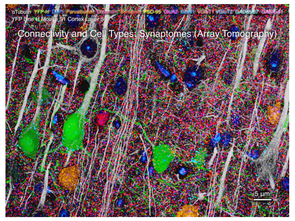


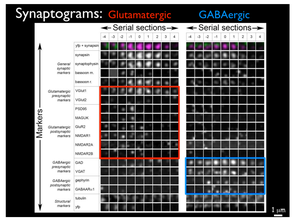


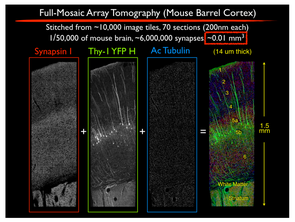


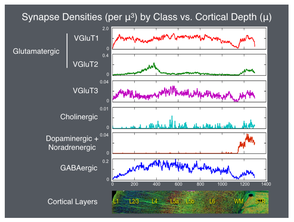


Visualizing and Measuring Individual Synapses by Array Tomography

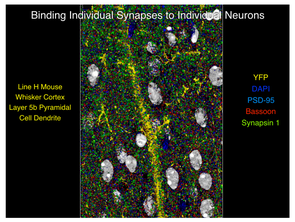


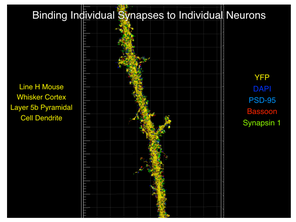




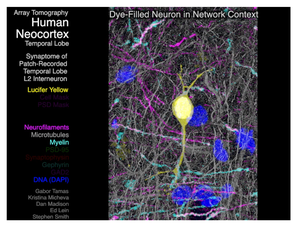


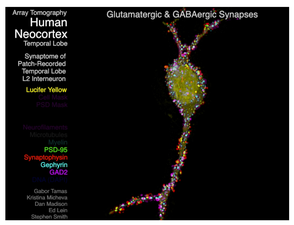
Binding Synapses to Sparse YFP-Expressing Mouse Neurons



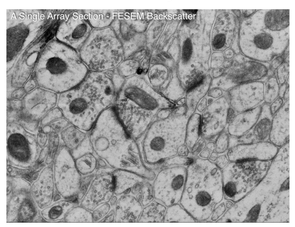


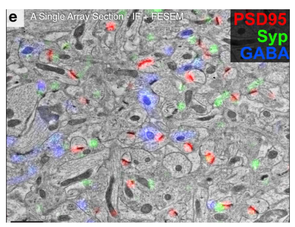
Binding Synapses to Dye-Filled Human Neurons



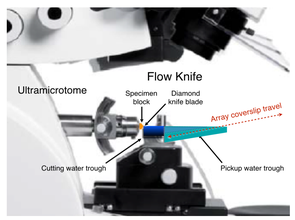


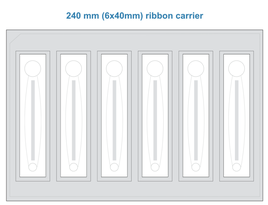
EM Validation of Synapse Detection

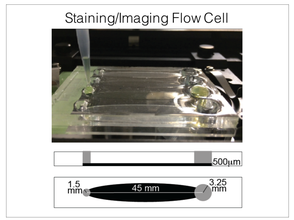


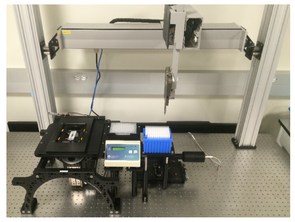


Automating and Accelerating Array Tomography

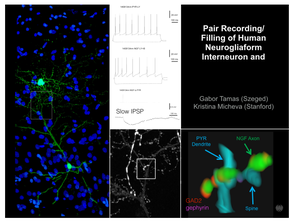




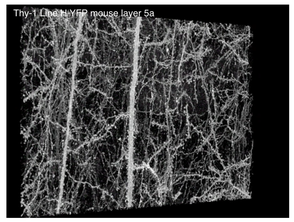




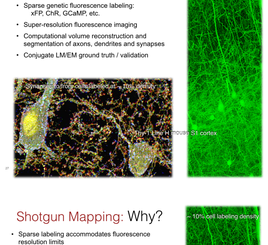
Electophysiology + AT Human

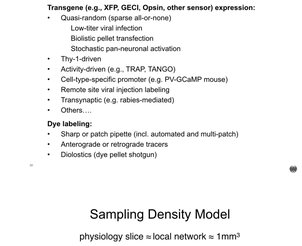


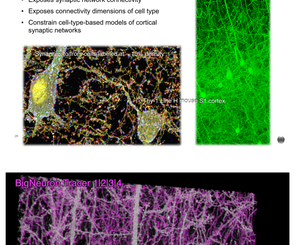
Resolving Sparse Filaments

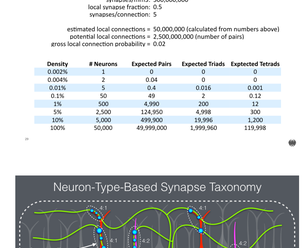


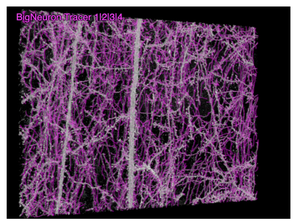
Sparse "shotgun" labeling for Neuron-Type-Based Synapse Taxonomy

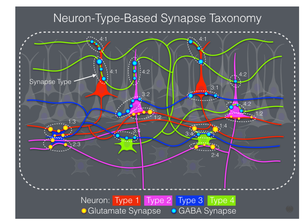












Other SfN 2015 Open Synaptome Project Posters

Topics touched upon by this poster, and many other efforts of the Open Synaptome Project, are treated in much more depth by the following posters. Even though the first is at a time now gone by, we hope you can visit and enjoy the rest!

Tuesday, Oct 20, 2015, 8:00 AM -12:00 PM 544.16/DD52
Web visualization of massive neuroscience datasets using the open connectome project. A. D. Baden, K. A. Lillaney, W. Gray Roncal, J. T. Vogelstein, R. Burns

Tuesday, Oct 20, 2015, 1:00 PM - 5:00 PM 638.06/DD52
Open connectome project: Lowering the barrier to entry big data neuroscience. J. T. Vogelstein, S. J. Smith, W. Gray Roncal, R. Vogelstein, R. Burns, K. A. Lillaney, A. D. Baden, G. Kiar, P. Manavalan

Wednesday, Oct 21, 2015, 8:00 AM -12:00 PM 735.01/DD33
Synaptomes of electrophysiologically characterized human neocortical neurons. K. D. Micheva, A. Ko, E. Lein, D. V. Madison, A. Dijkstra, W. Seeley, S. J. Smith, G. Tamas, J. Ting, N. A. O'Rourke

Wednesday, Oct 21, 2015, 8:00 AM -12:00 PM 735.02/DD34
An integrated imaging and staining platform for cubic millimeter scale array tomography. F. C. Collman, S. Davis, O. Gliko, T. M. Keenan, K. Parker, L. E. Ostroff, S. J. Smith

Wednesday, Oct 21, 2015, 8:00 AM -12:00 PM 735.03/DD35
Scalable, automated synapse detection using the open connectome project. W. R. Gray Roncal, A. K. Simhal, J. T. Vogelstein, F. Collman, M. A. Chevillet, R. Burns, G. Sapiro, G. D. Hager

Acknowledgements

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Conflicting Interest Disclosure

Stephen Smith has a founder's financial interest in Aratome, LLC, a Menlo Park CA startup company that is commercializing array tomography products and services.

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