Report from Dagstuhl Seminar 18481

High Throughput Connectomics

Edited by

Moritz Helmstaedter[1], Jeff Lichtman[2], and Nir Shavit[3]

1 **MPI for Brain Research – Frankfurt am Main, DE,** moritz.helmstaedter@brain.mpg.de
2 **Harvard University – Cambridge, US,** jeff@mcb.harvard.edu
3 **MIT – Cambridge, US,** shanir@csail.mit.edu

Abstract

The structure of the nervous system is extraordinarily complicated because individual neurons are interconnected to hundreds or even thousands of other cells in networks that can extend over large volumes. Mapping such networks at the level of synaptic connections, a field called connectomics, began in the 1970s and has recently garnered general interest thanks to technical and computational advances that offer the possibility of mapping mammalian brains. However, modern connectomics produces 'big data' that must be analyzed at unprecedented rates, and will require, as with genomics at the time, breakthrough algorithmic and computational solutions. This workshop will bring together key researchers in the field, and experts from related fields, in order to understand the problems at hand and provide new approaches towards the design of high throughput systems for mapping the micro-connectivity of the brain.

Seminar November 25–30, 2018 – http://www.dagstuhl.de/18481
2012 ACM Subject Classification Computing methodologies → 3D imaging, Applied computing → Biological networks, Computing methodologies → Image processing, Computing methodologies → Image segmentation
Keywords and phrases Big Data, Connectomics, Distributed Computing, Machine Learning, Parallel Computing
Digital Object Identifier 10.4230/DagRep.8.11.112
Edited in cooperation with Daniel R. Berger

1 Executive Summary

Nir Shavit (MIT – Cambridge, US)

Our workshop brought together experts in the computational aspects of connectomics. A week of lectures and work-group meetings in a lively and collegial environment led to a collection of interesting conclusions. One big idea that was put forth in the meeting was the gargantuan effort of reconstructing a complete mouse brain. Another was to completely map the white matter connectivity of a mammalian brain. We also discussed which techniques/pipelines we should continue to pursue as a community. In that vein one big conclusion was that you have to have both the engineers and software working on a pipeline; distributing software only is not sufficient (you need dedicated engineers to run the software, it can't be based just on grad students). Zeiss reported on a multibeam 331 beam microscope that was in the making. There were also discussions on quality measures and metrics for connectomics reconstruction, and on developing standardized datasets for segmentation training and comparison of algorithms

(scaling up from current day small datasets). Finally, there were discussions on the ethics and policies in the area going forward – Should we rely more on industrial partners to provide compute power and storage, or is it better to keep most of the research in universities and non-for-profit research institutes.

Introduction

The sheer complexity of the brain means that sooner or later the data describing brains must transition from something that is rather easily managed to something far less tractable. This transition appears to now be underway. The accumulation of ever-bigger brain data is a byproduct of the development of a number of new technologies that provide digitized information about the structural organization (anatomy) and the function of neural tissue. These new collection approaches bring novel data into neuroscience that potentially bears on many poorly understood aspects of the nervous system. Fundamental scientific questions such as the way learned information is instantiated in the brain and how brains change over the course of development and aging are likely to be usefully addressed in the coming decades as large data sets mapping networks of neurons at high resolution become available.

Mapping networks of neurons at the level of synaptic connections, a field called connectomics, began in the 1970s with a the study of the small nervous system of a worm and has recently garnered general interest thanks to technical and computational advances that automate the collection of electron-microscopy data and offer the possibility of mapping even large mammalian brains. However, modern connectomics produces 'big data', unprecedented quantities of digital information at unprecedented rates, and will require, as with genomics at the time, breakthrough algorithmic and computational solutions.

Unfortunately the generation of large data sets is actually the easy part. Our experience in the nascent field of connectomics indicates that there are many challenges associated with the steps after data acquisition, that is, the process of turning the data into a mineable commodity. This workshop will focus on addressing these challenges by bringing together researchers developing algorithms and deploying software systems that enable high-throughput analysis of connectomic data.

While high-throughput connectomics must tackle many of the problems that occur in big data science and engineering, tremendous differences in data size, computational complexity, and the problem domain will require novel computational frameworks, algorithms, and systems. Input image data in connectomics is reaching, even in its initial stages, petabytes in size at a terabytes-per-hour rate, and currently requires millions of cycles of computation per pixel. Such data is not easily moved or stored, and so on-the-fly analysis of the data as it comes off the microscope is the most likely future solution. Achieving the kind of throughput that will allow us to process the data at the rate at which it is being generated necessitates a three orders of magnitude reduction in cycles per pixel, compared to the status quo. Furthermore, there is locality to the data. Unlike other big data problems, which can often be represented as independent key-value pairs spread across many machines, reconstruction of neural circuits requires frequent data exchanges across adjacent image regions. Buffering all the data in machine memory is infeasible, as is data replication on multiple servers. That means one cannot rely on Moore's law and parallelism across data centers to solve this problem–we need to be smarter.

In a nutshell, a connectomics data set is a collection of images taken on a volume of brain tissue that has been sectioned into many thousands of small slices, each only a few

tens of nanometers thick. These slices are then imaged using custom electron microscopes to produce an image stack that will in the near future reach petabytes in size. Using one of the standard electron microscopy pipeline approaches, the key computational problems that must be addressed in order to turn the raw acquired digitized images into a useful form of "onnectivity graph" are stitching, alignment, neuron reconstruction, and synapse detection. Each digitized image tile needs to be stitched together with neighboring tiles to form a composite image of a slice. Then, the stitched slice image is aligned with the previous and subsequent slice images. Despite being mostly similar, image alignment is challenging because typically a conveyor belt collects the slices and each may rotate a few degrees, or stretch depending on its thickness. Fortunately, because of the high image resolution, alignment is practical, as axons and dendrites are readily visible in cross-section and can be traced from one section to the next. A second challenge is that, once the image data is aligned, the sectioned objects must be individuated. In these data sets, the objects are neurons and other cellular entities that are interwoven in the three-dimensional space of the sample tissue. The reconstruction of neural processes as they pass from one section to the next is directly related to the computer vision problem of obtaining a segmentation of an image series, that is, the labeling of pixels in the images according to which cell they belong to.

Although considerable progress has been achieved in computer-based image segmentation in the last few years, reliable automatic image segmentation is still an open problem. Automating the segmentation of connectomic data is challenging because the shapes of neural objects are irregular, branching, non-repeating and intertwined. Moreover, the actual number of different objects and their synaptic interconnections in a volume of brain tissue is unknown and, at the moment, even difficult to estimate or bound. Segmentation of a standard electron microscopy image is further complicated by the fact that the range of pixel intensity values of cell membranes overlaps with that of other organelles. Thus, simple thresholding to find cell boundaries does not work.

In the eyes of many, the term big data is synonymous with the storage and analysis of massive collections of digital information. The "big" refers to the size of the input sets, typically ranging in the tens or even hundreds of terabytes, and arriving at rates of several tens or hundreds of gigabytes per second. In connectomics, the size of the input set is at the high end of the big data range, and possibly among the largest data ever acquired. Images at several nanometers resolution are needed to accurately reconstruct the very fine axons, dendrites, and synaptic connections. At this resolution, a cubic mm is about 2 petabytes of data. A complete rat cortex including some white matter might require 500 cubic mm and thus would produce about an exabyte (1000 petabytes) of data. This amount is far beyond the scope of storage that can be handled by any system today (as a reference point, consider that Walmart or Aldi's database systems manage a few petabytes of data). A complete human cortex, 1000-times that of a rodent, will require a zetabyte (1000 exabytes) of data, an amount of data approaching that of all the information recorded in the world today. Obviously this means that the goal of connectomics will not be to acquire complete human brains and that for the near future one must consider reconstructions of neuronal substructures as opposed to whole brains. Moreover, it is clear that as we go beyond a few millimeters, one cannot store the raw data: it must be analyzed on the fly as it comes off the microscope and then discarded, keeping the physical tissue sample for re-imaging if needed.

What is this on-the-fly acquisition rate? The new multi-beam electron microscopes currently produced by Carl Zeiss LLC have a staggering throughput approaching 400 sections per day or a terabyte of data per hour, placing them at the far end of the big data rate spectrum. This rate, if it can be matched with appropriate reconstruction algorithms, will

allow researchers to process a cubic mm of rodent brain, that is, 2 petabytes of data, in about 6 months operating 24 hours a day, 7 days a week. Whatever computational pipeline is used to extract the connectomics graph from the image data, it will eventually have to work on the fly, at the pace of the microscope that generates this data.

The algorithms and computational techniques for developing such high throughput connectomics pipelines are the target of this workshop. The massive amounts of storage and computation require expertise not only in computational neurobiology, machine learning, and alignment techniques, but also in parallel computation, distributed systems, and storage systems. There are several groups of researchers around the world that specialize in collecting the electron microscopy datasets, and several that engage in developing matching computational pipelines. Our aim is to bring these researchers together for an extended 5-day brainstorming session. We will also invite some top researchers in related fields such as machine learning, computer vision, distributed systems, and parallel computing. Our goal for this meeting is to both build an understanding of the state of the art in high-throughput connectomics pipelines, and to brainstorm on how to move the field forward so that high throughput connectomics systems become widely available to neurobiology labs around the world.

Concretely, we would like to come out of this workshop with a hierarchical plan for future connectomics systems that solve existing systems' problems. We will begin the workshop by having workgroups discuss these problems in existing systems and then dedicate the latter part to collectively working out solutions. We will consider three levels:

1. The system layer: how data is stored, moved around and computed on in a distributed and parallel fashion.
2. The pipeline layer: how processing progresses from stitching through alignment and reconstruction.
3. The algorithm layer: the specific machine learning and error detection and correction algorithms used in various pipeline stages to bring the datasets to analyzable connectivity graphs.

Our plan is to discuss each of these in detail, with the hope of concluding the workshop with a coherent plan on how to proceed.

Relation to previous Dagstuhl seminars

To the best of our knowledge there have been no similar Dagstuhl seminars in the past. The field of connectomics is a young cutting edge big data research area that will have important implications on both computation in the sciences (and in particular on the use of large scale machine learning in the sciences) and on artificial intelligence (through the development of new neural network models based on the neurobiological discoveries this research may lead to). We believe it is important for modern computer science to engage in such interdisciplinary applications of computing and algorithms and we are therefore eager to initiate this new seminar direction.

2 Table of Contents

Working groups

3 Overview of Talks

3.1 VAST – Efficient Manual and Semi-Automatic Labeling of Large 3D Image Stacks

Daniel R. Berger (Harvard University – Cambridge, US)

Recent developments in serial-section electron microscopy allow the efficient generation of very large image datasets but analyzing such data poses challenges for software tools. Here we introduce VAST (Volume Annotation and Segmentation Tool) [1], a freely available utility program for generating and editing annotations and segmentations of large volumetric image (voxel) data sets. It provides a simple yet powerful user interface for real-time exploration and analysis of large data sets even in the Petabyte range.

References

1 Berger D. R., Seung, H. S., & Lichtman, J. W. (2018). *VAST (Volume Annotation and Segmentation Tool): efficient manual and semi-automatic labeling of large 3D image stacks.* Front Neural Circuits. 2018; 12: 88.

3.2 A Complete Electron Microscopy Volume of the Brain of Adult Drosophila melanogaster

Davi Bock (Howard Hughes Medical Institute – Ashburn, US)

In this talk Davi Bock described a new electron microscopic dataset of the complete adult fruit fly brain [1], and collaborative efforts to reconstruct the circuits in it.

References

1 Zheng Z., Lauritzen J. S., Perlman E., Robinson, C. G., Nichols M., Milkie D., Torrens O., Price J., Fisher C. B., Sharifi N., Calle-Schuler S. A., Kmecova L., Iqbal J.Ali I. J., Karsh B., Trautman E. T., Bogovic J. A., Hanslovsky P., Jefferis G. S. X. E., and Bock D. D. (2018). *Complete Electron Microscopy Volume of the Brain of Adult Drosophila melanogaster*. Cell, Volume 174, Issue 3, 26 July 2018, Pages 730–743.e22

3.3 Drosophila larva EM

Albert Cardona (University of Cambridge, GB)

Albert talked about the analysis of circuitry in his drosophila larva EM dataset. [1]

References

1 Gerhard, S., Andrade, I., Fetter, R. D., Cardona, A., and Schneider-Mizell, C. M., (2017). *Conserved neural circuit structure across Drosophila larval development revealed by comparative connectomics*. eLife 2017;6:e29089.

3.4 Analysis Infrastructure

Forrest Collman (Allen Institute for Brain Science – Seattle, US)

This talk described the data analysis pipeline of the large-scale 3D electron microscopy study of mouse cortex currently done at the Allen Brain Institute in Seattle. This includes alignment, automatic segmentation, and proofreading.

3.5 Towards a neuronal wiring diagram of a cubic millimeter of mouse cortex

Nuno Maçarico da Costa (Allen Institute for Brain Science – Seattle, US)

This talk described an ongoing project at the Allen Institute for Brain Research in Seattle, which aims at reconstructing the neuronal wiring diagram of a cubic millimeter of mouse cortex from serial-section transmission electron microscopy data. Nuno also presented first results of reconstructed basket and chandelier neurons.

3.6 Beyond Connectomics

Winfried Denk (MPI für Neurobiologie – Martinsried, DE)

This talk addressed the possibility to understand the wiring diagram of the brain by unraveling how genes drive proteins, which in turn drive brain development and neuronal wiring. For this it would be very helpful to know where each protein is in the nervous system, over time. This can to some extent be approached with electron microscopy. Winfried showed that the location and orientation of individual protein structures (for example, ribosomes) can be identified in Cryo-EM image volumes by template matching [1].

References

1 Rickgauer J.P., Grigorieff N., and Denk, W (2017). *Single-protein detection in crowded molecular environments in cryo-EM images*. eLife 2017;6:e25648 DOI: 10.7554/eLife.25648

3.7 Multi-modal parcellation using mesoscale connections

Eva Dyer (Georgia Institute of Technology – Atlanta, US)

This talk discussed methods to analyze high-resolution 3D x-ray datasets (micro-CT) of brain sections to find cell bodies, blood vessels and more.

3.8 Connectivity determines neural computations in the olfactory bulb

Rainer W. Friedrich (FMI – Basel, CH), Christel Genoud (FMI – Basel, CH), and Adrian Wanner (Princeton University, US)

We measured odor-evoked activity in the olfactory bulb (OB) of a zebrafish larva by multi-photon calcium imaging and subsequently reconstructed all 1047 neurons and their synaptic connections by serial block face scanning electron microscopy (SBEM) and manual annotation. This comprehensive dataset allowed us to assess the contribution of neuronal connectivity to transformations of distributed neuronal activity patterns. The OB receives sensory input from the nose via an array of discrete input channels, the olfactory glomeruli. Each glomerulus is activated by a specific spectrum of ligands, and each odor is represented by a specific pattern of activation across the glomerular array. However, these combinatorial odor representations are suboptimal because chemically similar odorants evoke highly overlapping activity patterns that are difficult to distinguish by a simple classifier. Neuronal circuits within the OB decorrelate such overlapping odor representations and thereby facilitate odor classification. Previous work showed that this pattern decorrelation requires specific network connectivity that is likely to depend on the tuning curves of individual neurons. We found that the larval olfactory bulb contains a "core circuitry" that corresponds to the superficial interneuron network in the adult olfactory bulb and shows similarities to the insect antennal lobe. Long-range inter-glomerular projections are not random but organized by the identity of olfactory glomeruli. Interneurons connect ensembles of neurons responding to odorants with specific physico-chemical features through specific connectivity motifs. Analyses using matrix algebra suggested that this connectivity can, at least in part, account for the pattern decorrelation observed in the OB. Consistent with this conclusion, the connectivity reproduced experimentally observed dynamics of neuronal activity and the associated computations when implemented in a simple biophysical network model. Further analyses of the model demonstrated that the observed connectivity motifs were essential for pattern decorrelation and other computations. The wiring diagram therefore contains specific structure that removes predictable correlations from odor-evoked input patterns and supports additional computations. Hence, our "dense functional connectomics" approach revealed multisynaptic connectivity motifs in the OB that are computationally relevant and difficult to analyze by other approaches. This connectivity mediates fundamental neuronal computations that support the classification of odor-evoked activity patterns.

3.9 Circuit reconstruction in flies

Jan Funke (Howard Hughes Medical Institute – Ashburn, US) and Julia Buhmann (Universität Zürich, CH)

We present an automated method for the identification of synaptic partners in insect brains. The main idea of the method published in [1] is the direct identification of voxels that are pre-and postsynaptic to each other using a 3D U-Net. With an extension of the model of [1], we present preliminary results on a larger cutout of the FAFB dataset. We show that our method is scalable and produces qualitatively promising results.

References

1 Buhmann, J., Krause, R., Lentini, R. C., Eckstein, N., Cook, M., Turaga, S., & Funke, J. (2018). *Synaptic partner prediction from point annotations in insect brains.* MICCAI

3.10 EM pipeline at FMI

Stephan Gerhard (FMI – Basel, CH)

A connectomics pipeline consists of a number of stages, including sample preparation, data acquisition, alignment, segmentation, proofreading, circuit analysis & visualization and data dissemination. Often, these stages are conceived as a feedforward process and feedback pathways are not often considered. I introduced the Volume Image Environment VIME (github.com/vime, unpublished), a Python-based, client-server framework for data management and linear and non-linear alignment procedures. Importantly, VIME can be interfaced with SBEMimage, a novel data acquisition software for SBEM datasets [1] enabling on-the-fly alignment and a feedback path to control acquisition based on quality control metrics from alignment. I introduced the results of processing an adult zebrafish olfactory bulb dataset with alignment in VIME, and with Google's Flood-Filling-Networks subsequently for segmentation. The size of extracted supervoxels is impressive, superseding any manual skeletonization approaches. Further stages in the pipeline are anticipated to use tools such as Neuroglancer and CATMAID for proofreading, circuit analysis and visualization. Finally, I introduce a novel web-based platform for large-scale comparative connectomics – BrainCircuits.io. Initially, the platform indexes connectomics publications and links to publicly available image dataset for browsing. The platform is maintained and further developed by a newly formed company – UniDesign Solutions (https://unidesign.solutions) – which also provides additional connectomics services to the community.

References

1 Titze B., Genoud C., and Friedrich R. W. (2018). *SBEMimage: Versatile Acquisition Control Software for Serial Block-Face Electron Microscopy.* Front Neural Circuits. 2018; 12: 54.

3.11 Commodity Connectomics and Applications to Bioinspired Robotics

William Gray Roncal (Johns Hopkins Univ. – Baltimore, US)

This talk gave an overview of the work related to large-scale connectomics done at the Applied Physics Lab (APL) Intelligent Systems Center at Johns Hopkins University, including the SABER pipeline, data storage, processing, and public outreach.

3.12 Dense connectomic reconstruction in layer 4 of the somatosensory cortex

Moritz Helmstaedter (MPI for Brain Research – Frankfurt am Main, DE)

The dense circuit structure of the mammalian cerebral cortex is still unknown. With developments in 3-dimensional (3D) electron microscopy, the imaging of sizeable volumes of neuropil has become possible, but dense reconstruction of connectomes from such image data is the limiting step. Here, we report the dense reconstruction of a volume of about 500,000 μm^3 from layer 4 of mouse barrel cortex, about 300 times larger than previous dense reconstructions from the mammalian cerebral cortex. Using a novel reconstruction technique, FocusEM, we were able to reconstruct a total of 0.9 meters of dendrites and about 1.8 meters of axons investing only about 4,000 human work hours, about 10-25 times more efficient than previous dense circuit reconstructions. We find that connectomic data alone allows the definition of inhibitory axon types that show established principles of synaptic specificity for subcellular postsynaptic compartments. We find that also a fraction of excitatory axons exhibit such subcellular target specificity. Only about 35% of inhibitory and 55% of excitatory synaptic subcellular innervation can be predicted from the geometrical availability of membrane surface, revoking coarser models of random wiring for synaptic connections in cortical layer 4. We furthermore find evidence for enhanced variability of synaptic input composition between neurons at the level of primary dendrites in cortical layer 4. Finally, we obtain evidence for Hebbian synaptic weight adaptation in at least 24% of connections; at least 35% of connections show no sign of such previous plasticity. Together, these results establish an approach to connectomic phenotyping of local dense neuronal circuitry in the mammalian cortex. [1]

References

1 Motta, A., Berning, M., Boergens, K. M., Staffler, B., Beining, M., Loomba, S., Schramm, C., Hennig, P., Wissler, H, and Helmstaedter, M. (2018). *Dense connectomic reconstruction in layer 4 of the somatosensory cortex*. https://doi.org/10.1101/460618, https://www.biorxiv.org/content/early/2018/11/03/460618

3.13 Challenges for automated reconstruction

Michal Januszewski (Google Switzerland – Zürich, CH)

Significant advancements in automated reconstruction of neural tissue have been made in the last few years, yet much further progress is needed in order for the community to be able to tackle continuously increasing datasets. In my talk, I will try to highlight a number of issues that seem to be very important, but often do not receive sufficient attention. In particular, I will discuss the problems of acceptable error rates, practical proofreading time optimization and its relation to compute cost of automated processing, storage costs and interaction of compression methods with downstream processing, as well as alignment automation and data nonuniformity at large scales.

3.14 From electron microscopy images to a connectome

Joergen Kornfeld (MPI für Neurobiologie – Martinsried, DE)

Reconstruction and annotation of volume electron microscopy data sets of brain tissue is challenging but can reveal invaluable information about neuronal circuits. Significant progress has recently been made in automated neuron reconstruction as well as automated detection of synapses and the morphological classification of these reconstructions. Here, we present a complete computational analysis pipeline, starting with an aligned electron microscopy data set, and leading to a richly annotated connectivity matrix, including detailed semantic information about the location of dendritic spines and their presynaptic partners.

3.15 Whole organism segmentation without connectome

Anna Kreshuk (EMBL – Heidelberg, DE)

This talk described the efforts to do automatic segmentation analysis of cells in a large electron-microscopic dataset of a marine worm.

3.16 Sensorymotor circuitry in the fly peripheral nervous system

Wei-Chung Allen Lee (Harvard Medical School – Boston, US)

Wei showed data and results of his project to reconstruct the neuronal circuitry in the fly nerve cord from a large-scale EM volume and x-ray microCT data.

3.17 Mammalian Connectomes

Jeff Lichtman (Harvard University – Cambridge, US)

One looming challenge of connectomics is whether it will scale to volumes that comprise a mammalian brain. The mouse brain is about 500 cubic millimeters. If cut at a section thickness of 30 nm and imaged at 4 x 4 nm in-plane pixels, then this volume would require acquiring about 1 exabyte of data. This could be done in a number of ways but if the aim is to complete such a project in 5 years or less, all of them require parallelizing data acquisition. One way to do this is to section the volume first (such as on tape) and then distribute the imaging tasks by distributing the tape to multiple electron microscopes. To speed data acquisition further one can also parallelize the data acquisition from each microscope by use of multiple beam scanning devices (such as Zeiss' mSEM). For example, 24 multiple beam scanning electron microscopes each acquiring 42 TB per day could acquire an exabyte in 2 years 9 months. Storage of the data, stitching and alignment of the digital images, segmentation of cells and synapse and circuit reconstruction, and finally data sharing would require an extensive computer infrastructure and sophisticated AI technologies. Proof of concept computational pipelines for all these steps already exist in the Jain group at Google, Seung group at Princeton, and the Helmstaedter group at Frankfurt MPI among others. It thus seems feasible to do a project on this scale. A discussion ensued about how such a project might come about and what technical hurdles remain.

3.18 Ad hoc proofreading and analysis workflows using the Neuroglancer Python integration

Jeremy Maitin-Shepard (Google Research – Mountain View, US)

The Neuroglancer Python integration provides a way to use Neuroglancer as an interactive visualization library from Python, with the ability to overlay in-memory and on-the-fly generated volumes over existing volumes, define custom actions for keyboard and mouse events, and display annotations. Common use cases include manually annotating a set of objects/object fragments as one of several classes, displaying convolutional network inference results, visualizing the progress of a flood filling network-type algorithm, interactively viewing synaptic partner information, interactively splitting under-segmented objects using an agglomeration graph, and creating scripted videos.

3.19 Cross-Classification Clustering (3C): An Efficient Multi-Object Tracking Technique for 3-D Instance Segmentation in Connectomics

Yaron Meirovitch (Harvard University – Cambridge)

Pixel-accurate tracking of objects is a key element in many computer vision applications, often solved by iterated individual object tracking or instance segmentation followed by object matching. Here we introduce *cross classification clustering* (3C), a new technique that simultaneously tracks all objects in an image stack. The key idea in cross-classification is to efficiently turn a clustering problem into a classification problem by running a logarithmic number of independent classifications, letting the cross-labeling of these classifications uniquely classify each pixel to the object labels. We apply the 3C mechanism to achieve state-of-the-art accuracy in connectomics. Our reconstruction system introduces an order of magnitude scalability improvement over the best current methods for neuronal reconstruction, and can be seamlessly integrated within existing single-object tracking methods like flood-filling networks to improve their performance. This scalability is crucial for the real-world deployment of connectomics pipelines, as the best performing existing techniques require computing infrastructures that are beyond the reach of most labs.

3.20 Reconstructing subcellular microcircuits with circuit scale 3D electron microscopy

Josh Morgan (Washington University, US)

Many neurons have neurites that are both pre- and postsynaptic. These input/output neurites mean individual cells can contain multiple subcellular pathways for signal processing. Characterizing these subcellular pathways requires connectome analysis tools that take the precise spatial distribution of synapses into account. Applying this approach to the local interneurons of the mouse lateral geniculate nucleus reveals three types of output processes in the same neuron, each generating distinct synaptic motifs.

3.21 Dense Projectomes and Analysis of Connectomes

R. Clay Reid (Allen Institute for Brain Science – Seattle, US)

In the first part of this talk Clay described the idea to image dense projectomes, comprised of all myelinated axons running between different brain areas in whole brains, by confocal optical imaging using a fluorescent stain for myelin. In the second part he discussed the idea to use the similarity between real neuronal networks and machine learning models (e.g., convolutional networks) to analyze and understand the relationship between brain circuitry and function.

3.22 Whole-Brain Projectomes

R. Clay Reid (Allen Institute for Brain Science – Seattle, US)

In this talk Clay gave more detail about his proposal to analyze all myelinated projection axons in complete mammalian brains with light microscopy.

3.23 The value of connectomes in poorly explored species

Kerrianne Ryan (Dalhousie University – Halifax, CA)

The report of the connectome of the tadpole larva of the basal chordate *Ciona intestinalis* has enhanced our knowledge of its nervous system and its value as a biological model. The analysis of this connectome revealed features of synaptic organization, novel neurons and neuronal types, clarified sensory relay organization to the motor complex and enabled identification of homologous circuits with those of vertebrates. These analyses and explorations into the reported connectome have helped to promote this model species within the world of neuroscience, and have impacted the research in chordate neurobiology by providing testable hypotheses, and a comprehensive and detailed network of cells and connections. High throughput connectomics techniques can now be applied to test hypotheses and conditions in this developing nervous system alongside genetic tools.

3.24 Status report + Paintera

Stephan Saalfeld (Howard Hughes Medical Institute – Ashburn, US)

Stephan talked about his current projects, including 'N5', a hierarchical tensor storage API with backends to filesystem, cloud-storage, and HDF5 that allows parallel writing of chunked data [1]. He showed their synaptic cleft detection method on the complete Drosophila brain imaged with serial section transmission EM [2, 3], their new Drosophila brain atlas [4] bridging between light and EM, and 'Paintera' [5], a tool they are developing for manual image painting and proofreading on large data sets.

References

1 https://github.com/saalfeldlab/n5
2 Heinrich, L., Funke, J., Pape, C., Nunez-Iglesias, J., and Saalfeld, S. (2018). *Synaptic Cleft Segmentation in Non-Isotropic Volume Electron Microscopy of the Complete Drosophila Brain.* In: Medical Image Computing and Computer Assisted Intervention – MICCAI 2018, 317–25. https://doi.org/10.1007/978-3-030-00934-2_36.
3 Zheng, Z., Lauritzen, J. S., Perlman, E., Robinson, C. G., Nichols, M., Milkie, D., Torrens, O., et al. (2018). *A Complete Electron Microscopy Volume of the Brain of Adult Drosophila Melanogaster.* Cell 174, no. 3 (July 26, 2018): 730-743.e22.

4 Bogovic, J. A., Otsuna, H., Heinrich, L., Ito, M., Jeter, J., Meissner, G. W., Nern, A., et al. (2018). *An Unbiased Template of the Drosophila Brain and Ventral Nerve Cord.* BioRxiv, July 25, 2018, 376384. https://doi.org/10.1101/376384.
5 https://github.com/saalfeldlab/paintera

3.25 Ontogeny, phylogeny, and connectomics

Aravinthan D.T. Samuel (Harvard University – Cambridge, US)

Developmental biology and evolutionary biology are interwoven. Adaptive changes in an animal's anatomy and behavior, which confer fitness in an evolutionary sense, can occur as modulations of developmental programs. This is probably also true of neural circuits and brain connectivity, and could be studied through connectomics applied to animals across their developmental time courses and across their phylogenetic neighbors. Given the current pipelines for connectomics, it makes most sense to pursue this endeavor with small animals like nematodes and flies. Here, I argue for connectomics focused on small invertebrates to pursue such fundamental questions in biology.

3.26 Publishing and Simulation

Louis Scheffer (Howard Hughes Medical Institute – Ashburn, US)

In science, when you publish, the data should be available, and the analysis reproducible. This is challenging with large connectomics data sets. Currently we rely on the graciousness of the authors, but we should likely move to centralized analysis and storage, as genetics did long ago. Another use of completed connectomes is simulation. This seems simple, but in practice is much more than re-formatting. You must pick a subset of data, extrapolate to portions of neurons outside your volume, find synapse models, and figure out input vectors and observables. The raw models from EM are more complex than needed and make simulation slow without adding accuracy. We need fairly sophisticated model order reduction to make this practical.

3.27 The Dynamic Connectome

Jochen Triesch (Goethe-Universität Frankfurt am Main, DE)

Experiments from recent years suggest that the connectome is quite dynamic [1]. On the one hand, learning processes have been shown to induce systematic changes to the connectome. On the other hand, even under basal conditions there is substantial turnover of synaptic connections. Nevertheless, the connectome also has stable features such as the lognormal-like

distribution of postsynaptic density surface area, which is a good proxy for synaptic efficacy. I will discuss self-organizing recurrent neural network models (SORNs), that try to reproduce and explain the dynamic and stable features of the connectome. Interestingly, a recent model from this family can also capture experiments on sequence learning in rodent visual cortex and predicts specific learning-induced changes to the connectome. [2]

References

1 Rumpel, S., & Triesch, J. (2016). *The dynamic connectome*. e-Neuroforum, 22(3), 48-53.
2 Klos, C., Miner, D., & Triesch, J. (2018). *Bridging structure and function: A model of sequence learning and prediction in primary visual cortex*. PLoS computational biology, 14(6), e1006187.

3.28 The network topology of neural sequences in retrosplenial cortex

Adrian Wanner (Princeton University, US)

Working memory, the ability to temporarily hold multiple pieces of information in mind for manipulation, is central to virtually all cognitive abilities. Preliminary data from the Tank lab at the Princeton Neuroscience Institute shows choice-specific activity sequences in posterior cortical neurons in a delayed match to sample task, which can be interpreted as working memory related neural activity. I aim to comprehensively dissect the neural circuit underlying these sequential activity patterns by combining *in-vivo* functional imaging in mice performing working memory tasks in a virtual-reality setting with subsequent large-scale electron microscopy (EM) based circuit reconstruction. Thereby I focus on retrosplenial cortex, which is of special interest because working memory related activity sequences are more linear in this part of cortex than in other cortical areas. The neurons that participate in these sequences are typically hundreds of microns apart from each other. Reconstructing the underlying microcircuit therefore requires the acquisition of cubic millimeter sized EM volumes. Staining such large volumes with high contrast homogeneously is still very challenging and unreliable. To facilitate the development of new staining protocols and to monitor the staining process in precious functionally characterized tissue blocks, I developed a novel X-ray assisted staining procedure [1], that uses temporally resolved high-resolution X-ray imaging to monitor the diffusion and staining of heavy metals into the tissue – enabling to control the staining process in much more detail. In collaboration with the Allen Institute of Brain Science in Seattle, we recently built a custom low cost high-throughput transmission electron microscopy (TEM) pipeline. Our pipeline features an automated reel-to-reel system for grid tape (Harvard University/Luxel Inc.) section feed [2] and a prototype of CRICKET, a TEM beam scanner developed by Voxa Inc. In combination with a novel 50 megapixel camera system from AMT Inc, that comes with a specialized integrated scintillator-lens system, we routinely reach acquisition rates above 250 MHz.

References

1 Provisional patent application no. 62/760,329
2 Own, C., Murfitt, M., Own, L., & Cushing, J. (2017). *Developments in Reel-to-Reel Electron Microscopy Infrastructure*. Microscopy and Microanalysis, 23(S1), 32-33. doi:10.1017/S1431927617000848

3.29 Achieving the next order of magnitude in imaging speed with multibeam scanning electron microscopes

Dirk Zeidler (Carl Zeiss – Oberkochen, DE) and Anna Lena Eberle (Carl Zeiss – Oberkochen DE)

With the introduction of a 61-beam multibeam SEM in 2014, the limiting element in connectomics studies has shifted from data acquisition to data processing. As data processing capabilities have increased since, we have recently developed a 91-beam multibeam SEM that provides a 50% increase in throughput at similar resolution. These instruments are currently used for data acquisition at sample sizes of about 1 mm side length or below. Nevertheless, future large-scale studies with sample volumes of possibly several cm^3 will soon require higher throughput. We will report on latest results on the development of our multibeam technology. We will show results on recent resolution improvements at the latest 91-beam tool, and first results on our 331-beam demonstrator. We will also show roadmaps on reducing overhead and further improving resolution and scan speed.

4 Working groups

4.1 Alignment

Working group participants

Alignment and stitching of image stacks is one of the major steps in the pipeline of data processing for large-scale electron microscopy. This workgroup addressed current challenges and solutions. A typical alignment approach involves several stages such as: 1) Stitching montage tiles into 2D section. 2) Rough alignment of sections (Often SIFT to affine). 3) Fine non-linear warping. For small volumes (<1TB) ImageJ plugins and a standard workstation can adequately align. Very large volumes may require tile management software, cluster computing (or custom high powered workstations), and human supervision/correction. Alignment code is available from Github distributions from Stephan Saalfeld, Janelia, Sebastian Seung, Google and others. Notably, good alignment of large volumes still requires human expertise in tweaking parameters, human management moving data through the alignment pipeline, and human corrections of alignment errors. Both Forrest Coleman and Stephan Gerhard have alignment pipelines they are reasonably satisfied with. Forrest stressed the value of having managing tiles and transformations using the Render web service (from Janelia). Using this framework, a range of alignment solutions can be tested and integrated into the data processing pipeline.

4.2 Cell Types

Working group participants

Often, addressing biological questions using large electron-microscopic datasets involves the identification of different cell types. This workgroup discussed methods of identification, and the general question of what constitutes a 'cell type' in the first place. Cell types could, for example, be defined as the centers of clusters in a feature space spanning synaptic connectivity and morphology, a more flexible concept than the hopeless attempt of drawing sharp boundaries where none might exist. There was a general consensus that large-scale connectomics will allow us to focus more on individual neurons and how they interact with their synaptic partners, which should provide a better understanding of how similar neurons as individuals are.

4.3 Combining EM connectomics with non-EM techniques

Working group participants

This working group discussed what other techniques might be helpful to integrate with EM connectomes. The main division is between other techniques applied to the same animal, versus other techniques applied to other animals of the same type, but then cross-referenced to EM.

Techniques that can be applied in the same animal:

- Calcium (activity measurement) and other imaging
- X-ray of block
- Dye fill or other labelling such as nanobodies
- Electrophysiology (on same volume before prep)
- Labelled lines in same value

Techniques that can be applied across different animals:

- Corresponding genetic lines
- RNA expression data
- Papers/literature on cell type
- Links to other atlases
- Lineage and successors
- Gap junctions and other stuff not visible in EM

4.4 Error Metrics

Working group participants

Current machine learning methods can produce automatic segmentations of cells and their processes in 3D electron microscopic image datasets, but with non-zero error rates. Also, an error estimate ('loss function') is an important parameter used in training models in machine learning; often, training is done by adaptation of model parameters to minimize the error between the output of the model and the desired output ('ground truth'). Therefore, robust error metrics are needed to compare the performance of different automatic segmentation methods, and to train the segmentation algorithms.

Used metrics include: axon/dendrite run length, variation of information, Rand index, graph edit distance, and network integrity. There was some discussion about the differences between what was useful for a loss function vs. an error metric. Stefan Saalfeld argued that error metrics really aren't the core problem right now, and that having easy access to test data is more the limiting factor. He pointed out that techniques that work on specific data (i.e., CREMI challenge) are often failing on different data.

4.5 Full pipeline design

Working group participants

Currently the analysis of large electron microscopic data sets is done with a large variety of tools developed by many labs independently, each of which can deal with one or several parts of the whole analysis pipeline. This workshop discussed the possibility of combining efforts and coming up with a framework for tool integration, to reduce redundant programming efforts and to improve usability. It was felt that the pipeline should be developed and improved as an integrated product and software, and that it should be based on an open source framework, such as Fiji (ImageJ). However, even if such a framework existed, labs may still need a systems programmer to adapt it to their specific needs; so a 'full pipeline design' may have to consist of the combination of a software package and a hired programmer. Alternatively, it may be helpful if particularly useful features (like the 'flight mode' in Knossos) could be made available to the community and integrated in other tools.

4.6 Long-Term Storage

Working group participants

Current electron microscopic data sets can be very large (exceeding one Petabyte), which means that storage is expensive, especially if the data should be widely accessible and held for a long time.

There was no consensus about whether data should be made available beyond 5 years. Cost could be reduced by only storing compressed raw data, and it may in some cases be possible and cheaper to re-acquire the data if necessary. The usefulness of data for science could be quantified by a metric of # of scientists/megabytes. There should maybe be a public of notice when data is retired, or a defined data retiring plan. Ultimately, a timeline for storage and availability of the data produced in a scientific project could be specified in grant proposals, and the cost could be covered by the project's budget.

4.7 Proofreading Tools

Working group participants

Proofreading is one of the major parts of a typical data analysis pipeline of electron-microscopic image volume datasets. After segmentation of objects of interest with automatic methods, often human experts review and correct the result. This workgroup discussed current needs and currently available tools. These include:

- TrakEM2
- CATMAID
- Mojo/Dojo
- Knossos
- WebKnossos
- pyKnossos
- Eyewire
- NeuTu
- Raveler
- Ilastik
- Paintera
- VAST
- Neuroglancer

It was noted that as the quality of automatic segmentation results improves, finding errors may become inefficient because too much data has to be screened by experts to find errors. In that case targeted proofreading may help.

4.8 Raw Data Quality

Working group participants

The quality of image data acquired with electron microscopes can have profound effects on the more challenging data processing downstream, like image alignment and segmentation. For example, errors in automatic segmentation are often caused by defects in the image data. This workgroup addressed the need for image quality metrics to ensure optimal downstream processing.

Nobody could agree what the right quality was and intuitions collided. However, everybody agreed that we needed to know this and there was a consensus to collect a FIB (focused ion beam) dataset of mouse cortex at a resolution of 4 nm isotropic and 25 micrometer cube. Then this dataset would be degraded to different voxel sizes, anisotropies and signal to noise to estimate what would be the minimal conditions to collect a dataset.

There was some discussion about having reference volumes of varying section thickness, etc. Winfried Denk argued that it was going to be very hard to evaluate all those. There was some disagreement whether you can simulate different qualities by adding shot noise and simulating different aspect ratios. Some people aren't sure that would work. Clay Reid asked how much it would cost to acquire and how much to do ground truth segmentation of the dataset. People agreed that it would be money well spent.

Different researchers had different intuitions about what resolution is good enough. Sectioners feel comfortable with a section thickness of 25-40 nm. FIBers feel 10 nm is correct. However there is no data to draw upon yet, because ground truthing is boring and tedious and expensive.

4.9 Scalable analysis of connectomes, representation beyond graphs

Working group participants

This workgroup looked at the queries biologists would like to make of connectomes. Many of these involve information other than just the graph of connections. We listed a number of different queries and tasks users would like to perform. The numbers after each topic are number of people (of about 20) who would use this feature. Features marked with '##' need information beyond the graph:

- Link to other databases on the same species (All) ##
- Query by cell type
- List/table/query of all inputs and outputs
- Violations of Peter's rule (contact vs number/size of synapses) (5) ##
- Find pathways from A to B (all)
- Motifs, possibly local, beyond triplets (10)
- Shape based searches (all) ##
- Build realistic electrical models (4). Simulators include: Neuron (3) ##; Nest (1); Genesis (0); Brian (2); Dipty (2).
- Local fixed points (as determined by specific local motifs) (5)
- Contact area (all) ##
- Detection of bundles and assignment of neurons to bundles (all) ##
- Connectome differences, between connectomes and between subsets of same connectome (6).
- All the above, but: Interactive (6); Filterable (all).
- Staff, user community, etc. to get help on constructing efficient queries, etc. (6) ##
- Metadata curation (cell names, names of spines/necks, etc) (6) ##
- Ultrastructure information (subcellular segmentation). Run additional analysis on a selected subset (all) ##
- Confidence numbers (5)

- Correlation to functional imaging obtained beforehand (8) ##
- Biases in sampling (1)
- Overall metrics (density of neurons, synapses, branch points, etc) (all) ##
- Import into other tools (10) ##
- Complex queries on big systems paid for by the connectome project) (2) ##
- Running queries in the cloud (paid for by user): ##;
- – Should be possible, achieved by storing a copy in the cloud (all);
- – Should be easy (5)
- Natural language queries (4) ##
- Connection to proofreading (for double checking, looking for other cell characteristics, etc) (all) ##
- Log files and other methods to check operation of queries, find FAQ, etc. (6) ##

4.10 Synaptic Strength

Working group participants

Electron microscopy delivers static images of the structure of nervous systems, but not direct information of functional properties of the cells. Some parameters may however be inferred from the images. An important one is synaptic strength, which informs about the connection strength between neurons. Important image parameters include the size of the synaptic cleft and the number of neurotransmitter vesicles at the synapse.

In the fly Albert Cardona reported that in the larva there is a linear correlation between number of synapses and summed synapse area implying that all the synapses are the same size. Jeff Lichtman argued that this may change when an animal matures. Lou Scheffer reported that in the mushroom body there is variability of synapse size. He also reported that inactive/silent synapses do not disappear. A discussion followed on silent synapses in the mammalian brain, with no resolution, as we don't know if there are really silent synapses and if there are we don't know how they look at the EM level.

There was also an interesting discussion on electrical synapses. Kevin Briggman has data from the retina that shows if you prepare tissue with preservation of extracellular space, the appositions that are left and are not chemical synapses correlates with cell types that have electrical synapses. A discussion followed that it would be interesting to do the same in the cortex.

There was also a discussion of the roles of vesicle density and spine neck shape, without resolution.

4.11 Whole Brain Projects

Working group participants

As EM datasets now reach a scale of cubic millimeters of tissue and data sizes of Petabytes, it may soon become feasible to prepare and image larger brains in their entirety with electron-microscopic resolution. This workshop explored the feasibility of imaging whole mammalian brains, in particular a whole mouse brain.

5 Panel discussions

5.1 Final Discussion Transcript

Seminar participants

Winfried Denk thanked the organizers, most of who had left, for a meeting he enjoyed that much and which was that productive. Lou Scheffer said that he realized that people made serious thoughts about the whole mouse brain, which he thought to be 10-15 years away. Adrian Wanner stated that the atmosphere was really special, with new energy, more motivation, and people feeling more optimistic. Nir Shavit said that he thinks that we will have some graphs that we can analyze very soon. He thinks this community is fun, since people are working hand in hand towards the same end.

- Forrest: What makes things transfer? transmission of information and methods
- Will: Where does it make sense to compete and where does it make sense to collaborate
- Nir: Next Dagstuhl seminar?
- Winfried: One has always the desire to have the users/biologists, but it doesn't work, because of little common interest in each specific system. Once we reach the shores of graphs we will reach nirvana? But how to translate graphs into biological meaning? That may be the next difficult thing, and may make sense for a next meeting – theoretical neuroscientists and people who generate connectomes, even people who have no vested interest in neuroscience. Right now the methods discussion still dominates, but may be resolved in 2-3 years
- Nir: One could get a few of the top theorists in machine learning, it would be fascinating to expose them to things we know and they don't, to help them to incorporate biological insights. They view the connectome as a random graph, which is far away from reality, anchoring them to what a connectome really is
- Forrest: Connectome graph challenge for theorists? Solve practical problems on large graphs where the correct result is known?
- Joergen: Large-scale simulation community?
- Winfried: Question about challenges: Challenges provide a good endpoint, but in a phase when developing methods they may limit ideas, and may not work that well
- Winfried: We should focus on what they can do for us rather than what we can do for them, to develop our field. We need the input from the graph field, but modeling is not that useful for us
- Lou: Modeling can help us
- Winfried: Modelers will come whereever they can find data
- Nir: Challenge how to find motifs
- Jochen: Graph theorists don't think about dynamics of graphs
- Lou: Finding motifs in graphs with errors
- Winfried: Have we forgotten anything we need?
- Dirk: One direction: Small animal; use larger and larger animals; Other direction: Make portion of large brain larger. How to run large projects? How to talk to funding agencies? Talk to people who do that.
- Ask mathematicians for a new view on things, let in mathematicians, may solve a lot of problems by sitting there with a big cup of coffee and finding the small glitch in the method, a tiny glitch may have a large effect

- Winfried: We don't have enough to eat for a mathematician, we'd have to pay them
- Kerrianne: Some mathematicians already get very excited
- Winfried: Do we need people to run large projects in hierarchical settings (scary)? More important is a cottage industry of a number of small groups making progress on different problems, which may be in danger if there is a large project
- Joergen: Include the genomics part
- Winfried: Which approach advances the field more, the small projects developing different methods, or the big project? But 1 cubic millimeter is too small if one can't find the source of an axon of interest. Localized computation, but the cost function of behavior is global, so one has to be able to put it in a global context, which requires high resolution and global context
- Lou: That is the advantage of a small animal!
- Winfried: The fly work is crucial to make clear why connectomes are useful, which can be used as an argument
- Lou: Why is it that a child can learn what a tiger is in 3 examples, but machine learning takes a million?
- Winfried: The bane of modeling of the last 30 years is that you make assumptions and then something interesting happens and then you sit on this pile of rubble. Once you have the circuit diagram you can build theories on solid ground. Set the theorists free by constraining the theorists
- Julia: Should we have a large-scale segmentation benchmark? Maybe from two different techniques and two different model organisms, as a test case
- Lou: This needs a secret test set, so difficult to do
- Winfried: It would be ideal if my competitor did it, so they would be slowed down, but is it necessary for progress? We're not held back by the lack of this, usually
- Daniel: It could attract people from outside?
- Winfried: 7 years ago I would have agreed, but not necessary any more, there are enough talented people in the field
- Nir: MNist, imagenet have been extreme drivers of development; large datasets could be beneficial and would allow progress, also for the development of measures / metrics
- Jochen: Competition vs. benchmark: benchmarks are low-maintenance
- Michal: A volume size of 25 microns^3 is the lower bound
- Stefan: Computer vision conferences are full of talented people who are virtually unaware of our field; but yes, organizing such a challenge is major distraction
- Winfried: In the spirit of challenges, for the whole mouse brain: What preparation to choose, what imaging method to choose? Quantitative way – lowest error rate: All camps provide a reasonable volume with training data, and the decision to use one method or another is based on evidence rather than opinions. This requires thought to prevent to game this competition but is important. We should first analyze how error rates of different approaches compare.

Participants

- Daniel R. Berger
Harvard University – Cambridge, US
- Davi Bock
Howard Hughes Medical Institute – Ashburn, US
- Kevin Briggman
Max-Planck-Gesellschaft – Bonn, DE
- Julia Buhmann
Universität Zürich, CH
- Albert Cardona
University of Cambridge, GB
- Forrest Collman
Allen Institute for Brain Science – Seattle, US
- Nuno Maçarico da Costa
Allen Institute for Brain Science – Seattle, US
- Winfried Denk
MPI für Neurobiologie – Martinsried, DE
- Eva Dyer
Georgia Institute of Technology – Atlanta, US
- Rainer W. Friedrich
FMI – Basel, CH
- Jan Funke
Howard Hughes Medical Institute – Ashburn, US
- Christel Genoud
FMI – Basel, CH
- Stephan Gerhard
FMI – Basel, CH
- William Gray Roncal
Johns Hopkins Univ. – Baltimore, US
- Moritz Helmstaedter
MPI for Brain Research – Frankfurt am Main, DE
- Michal Januszewski
Google Switzerland – Zürich, CH
- Joergen Kornfeld
MPI für Neurobiologie – Martinsried, DE
- Anna Kreshuk
EMBL – Heidelberg, DE
- Julia Kuhl
MPI für Neurobiologie – Martinsried, DE
- Wei-Chung Allen Lee
Harvard Medical School – Boston, US
- Jeff Lichtman
Harvard University – Cambridge, US
- Jeremy Maitin-Shepard
Google Research – Mountain View, US
- Yaron Meirovitch
Harvard University – Cambridge, US
- Josh Morgan
Washington University, US
- R. Clay Reid
Allen Institute for Brain Science – Seattle, US
- Kerrianne Ryan
Dalhousie University – Halifax, CA
- Stephan Saalfeld
Howard Hughes Medical Institute – Ashburn, US
- Aravinthan D.T. Samuel
Harvard University – Cambridge, US
- Louis Scheffer
Howard Hughes Medical Institute – Ashburn, US
- Nir Shavit
MIT – Cambridge, US
- Jochen Triesch
Goethe-Universität Frankfurt am Main, DE
- Xueying Wang
Harvard University – Cambridge, US
- Adrian Wanner
Princeton University, US
- Casimir Wierzynski
Intel – Santa Clara, US
- Dirk Zeidler
Carl Zeiss – Oberkochen, DE