Assessing the functional significance of errors and omissions by automated network reconstruction in phantom data generated with NETMORPH

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Automated serial 3D reconstruction from stacks of neurohistological images is a must in order to include long-range connections between brain regions, and can proceed by threading together regions of interest in successive images into cell trajectories, then into viable dendrites, axons, or somata. Reconstructin has to deal with problems of illumination, aligment, knife chatter, incomplete staining, constraints on the number of simultaneous stains, smear noise and more. Ultimately, reconstruction aimed at a functional model requires more than structure. To emulate original activity dynamics, a model needs to know the biophysical properties of the individual neurons and synapses, as well as neuromodulatory conditions.

It is difficult to validate the performance of the computational algorithms used at this scale, since there is no comparable stack of histological slice images that contains a fully described neuronal network. In order to address this problem, we developed the "SLICE" module for the NETMORPH platform (`http://Neural-Engineering.org`). The free software platform NETMORPH (`http://netmorph.org`) provides the novel capability to simulate the development of neuron morphology in large-scale neuronal networks in 3D. Neuronal morphogenesis is simulated from the perspective of the individual growth cones of neural fiber. With NETMORPH , it is possible to simulate the detailed neuronal structure of thousands of neurons at successive stages of network development. It is also possible to simulate functional activity in those networks throughout simulated development, since the functional attributes of all components can be determined by the modeler. NETMORPH is poised to become an invaluable and unique tool for fundamental research of neuronal network development and to investigate the underlying causes of functional deficits in abnormal brain development (e.g. Autism, Fragile-X syndrome) and brain disease (e.g. Alzheimer's).

The SLICE module extracts virtual slices from a volume of NETMORPH generated network structure and applies image processing to produce "phantom" images with resolution, content and artifacts that resemble those of real images of histological slices. Specific problematic features, such as missing or distorted data due to illumination or staining problems can be included explicitly. Any number of these stacks of phantom images can be generated to provide a statistically meaningful number of samples for the validation of reconstruction algorithms. Reconstructed structure and simulated activity can be compared directly with original NETMORPH generated structure and its function.

In a prominent discussion on the computational neuroscience mailing list "comp-neuro", Robert Cannon compared the problem of understanding the brain with a problem in astrophysics concerning the transition of many stars from dwarfs to giants for the last tenth of their active lives. A set of equations and known physical data suffice to implement a computer model that replicates this and behaves much like a real star. A number of intuitive, easily communicated and elegant explanations were attempted and published, but could not be used to address "what-if" questions. Such high-level models were insensitive to quantitative details, while the computational models clearly show that stars are sensitive to those details. Elegant explanations assume a smoothness that may not be justified.

If this applies to neuroscience then understanding may only be sharable in terms of working models: a "proddable brain" equivalent with which to investigate "what-if" questions. A convergence of new methods used in the neuroscientific study of function and dysfunction, and in the development of neuroprostheses suggests that the time is ripe to start creating large-scale high-resolution proddable brain models. Investigators such as Henry Markram have taken this as a call to action (Nature Reviews, vol.7, Feb.2006). At the Blue Brain Project, anatomically diverse neurons are simulated within microcircuits that are embedded in simulated local circuitry of regions of the whole brain.

Creating a proddable brain that is biologically accurate, but composed of modules generalized from studies of many sample specimens is complicated, since a primary feature of the neurophysiology is its drive to specialize the circuitry based on individual experiences, the much vaunted plasticity of the brain. A model that replicates an individual brain can also provide the proddable brain model.

At last year's SFN meeting, Sebastian Seung energized the crowd when he introduced "connectomics", the study of the structure of neuronal fiber and the distribution and abundance of synaptic connections among neurons in the brain. That involves scanning and reconstructing large volumes of neural tissue at a resolution between 5 and 300 nanometers, depending on the technology used: Knife-Edge Scanning Microscopy (KESM, Bruce McCormick, Yoonsuck Choe, `http://research.cs.tamu.edu/bnl/static/kesm.html`), Automatic Tape-Collecting Lathe Ultramicrotome (ATLUM, Ken Hayworth, Jeff Lichtman, `http://www.mcb.harvard.edu/lichtman/ATLUM/ATLUM_web.htm`), Serial Block-Face Scanning Electron Microscopy (SBFSEM, Winfried Denk, `http://www.technologyreview.com/player/07/11/19Singer/1.aspx`).

KESM has the lowest voxel resolution but specializes in high-throughput, cutting consecutive serial block sections of neural tissue with a custom-made diamond knife and imaging the newly cut section just beyond the knife edge before the tissue deforms. KESM scanning of a complete mouse brain is now feasible. SBFSEM can provide a full description of the distribution of synaptic connections within a scanned volume. These technologies promise to turn neuroscience into a true quantitative physical science.

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