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Informatics Resources for Electron Tomography

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Electron tomography, specifically cryoelectron tomography, was recently named one of the "runner up breakthroughs of the year" by *Science Magazine*[1], a tribute to its unique role in unraveling the macromolecular complexity of cells and tissues. Electron tomography is providing critical information in the range of μm^3 to nm^3, a resolution range where macromolecular complexes are situated in larger cellular and tissue domains. Although heralded as a "break through", electron tomography is well established and is moving from a specialized technique practiced by a few laboratories to a fairly routine, albeit compute intensive, and more widely available technology. It is just one example in the arsenal of techniques revolutionizing structural biology being driven by continued advances in high performance computing.

As cell-level electron tomography becomes more widely practiced, the tomographic community is working to increase both the speed and scope of tomographic reconstructions, e.g., by using computer controlled microscopes to automate data acquisition. As these efforts proceed, however, it is also necessary to develop resources for managing the resulting mountain of information and making these valuable and labor-intensive reconstructions available to the greater scientific community. In the molecular realm, large shared data repositories like the Protein Data Bank have been well established and are proving to be indispensable research tools. Once a critical mass of information has been assembled, scientists can begin to mine the data to uncover additional relationships among structures.

At the National Center for Microscopy and Imaging Research, we are developing several informatics-based approaches both to increase the throughput of large scale light and electron microscopic studies of cells and tissues and to house structural cell-level data in a shared data repository. For these studies, electron tomography of extended structures such as neuronal spiny dendrites and synaptic complexes is providing the necessary bridge between light and electron microscopy (Fig. 1). In combination with novel staining techniques, such as the recently developed tetracysteine technology for genetically engineered proteins for correlated analysis, we are using electron tomography to reveal the macromolecular specializations of complex tissues and cellular microdomains[3]. To enhance the efficiency of tomographic reconstruction, we have developed the Telescience Portal (www.ncmir.ucsd.edu /Telescience). The Telescience Portal provides access to an integrated suite of tomography tools, including easy access to remote microscopy, Grid-based reconstruction and visualization applications, and databases (see below). All are seamlessly integrated with distributed resources for computation, visualization, and data archival. Through the portal, users can acquire images from our JEM-4000EX Intermediate High Voltage Electron Microscope (IVEM) and our new JEM-3100EF energy filtering IVEM and perform all of the steps and computations necessary for end-to-end electron tomography.

For managing and mining cell level microscopic information, we have created the Cell Centered Database or CCDB, a web-accessible database for 3D reconstructions derived from light and electron microscopy, including electron tomography[4]. The CCDB (www.ncmir.ucsd.edu/CCDB) models the entire process of 3D reconstruction, from experiment to final analysis. Each data set consists of a set of raw imaging data, e.g., tilt or optical section series, 3D reconstructions, animations, segmented objects and any quantitative information extracted from that data set. Researchers are provided with a set of query forms through which they can search the available data based on descriptive information, e.g., reconstruction type or anatomical details, or by quantitative information on segmented objects, e.g., surface area and volume. The CCDB is available to outside users for deposition of appropriate data and may also be accessed through the Telescience Portal. The CCDB is one of series of databases that is being linked together as part of the newly created Biomedical Informatics Research Network (BIRN; www.nbirn.net), a new initiative from the National Institutes of Health designed to foster multi-institutional and multi-scale studies of human neurological disease. Through initiatives like the BIRN, the unique and important information obtained through electron tomography will be integrated with imaging at higher and lower scales.

References

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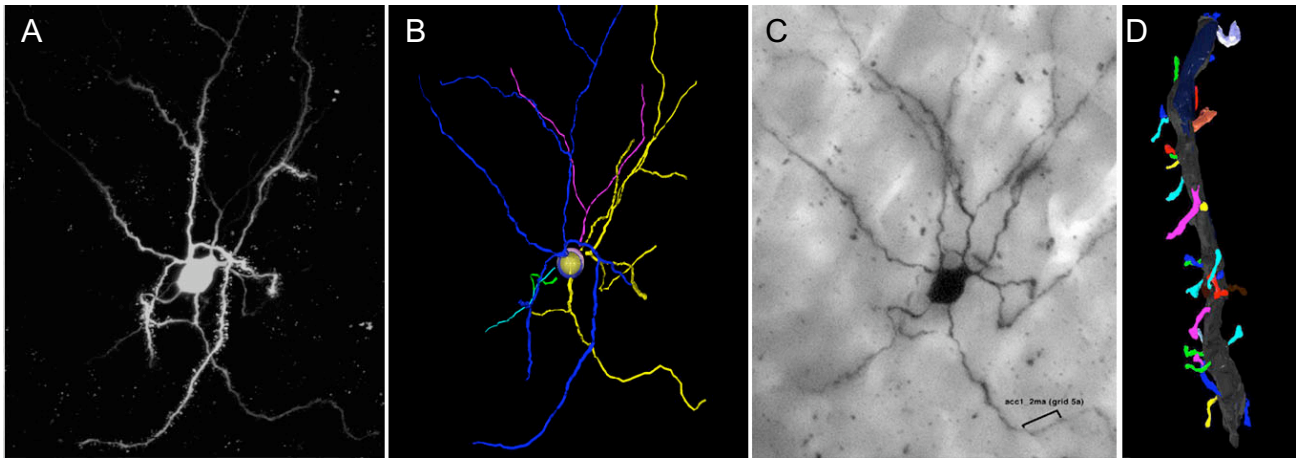

Fig. 1: Correlated light and electron microscopic imaging of a spiny neuron from the mouse nucleus accumbens. A) 3D reconstruction of spiny neuron injected with Alexa 568 and Lucifer Yellow from a series of optical sections acquired by multiphoton microscopy; B) Model of 3D branching structure of neuron shown in (A); C) Transmitted light image after fluorescence photooxidation to convert the fluorescence into an electron dense reaction product; D) Tomographic reconstruction of portion of spiny dendrite indicated by bracket in (C).

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