Title: A Computational Framework for Ultrastructural Mapping of Neural Circuitry

Running Head: A Framework for Mapping Neural Circuitry

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Referenced Abstract

Circuity mapping of metazoan neural systems is difficult because canonical neural regions are large, regional borders are uncertain (e.g. Lund et al. 2003), neuronal diversity is high (Masland 2001), and potential network topologies so numerous (Marc and Liu 2000; Chklovskii et al. 2004) that only anatomical ground truth can resolve them. Complete mapping of a specific network requires synaptic resolution, canonical region coverage (Reese 2008) and robust neuronal classification (e.g. Marc and Jones 2002; Micheva and Smith 2007, Lichtman et al., 2008). Though transmission electron microscopy (TEM) remains the optimal tool for network mapping, the process of building large serial section TEM (ssTEM) image volumes is rendered difficult by the need to pre-
cisely mosaic distorted image tiles, register distorted mosaics and browse massive datasets. Moreover, most molecular neuronal class markers are poorly compatible with optimal TEM imaging.

Our objective was to build a complete framework for circuitry mapping. This framework combines strong TEM-compliant small molecule molecular profiling (Jones et al. 2003) with automated large-scale image acquisition (Mastronarde 2005), automated image tile mosaicking and slice-to-slice image registration and gigabyte-scale image browsing in terabyte datasets for volume annotation. Specifically we show how molecular profiling of data sets and their resultant classification maps can be embedded into ssTEM data sets and how scripted acquisition tools (SerialEM), mosaicking and registration (ir-tools), and large slice viewers (MosaicBuilder) can be used to manage terabyte-scale volumes. These methods enable large-scale connectivity analyses of new and legacy data. In well-posed tasks (e.g. complete network mapping in retina), terabyte scale image volumes that previously would require decades of assembly can now be completed in months. Perhaps more importantly, the fusion of molecular profiling, SerialEM acquisition, ir-tools volume assembly and data viewers/annotators also allow ssTEM to be used as prospective tool for discovery in non-neural systems and a practical screening methodology for neurogenetics. Finally, this framework provides a mechanism for parallelization of ssTEM imaging, volume assembly, and data analysis across an international laboratory base, enhancing the productivity and skill of a large cohort of electron microscopists.

References


