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Retinal connectomics: Towards complete, accurate networks

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ABSTRACT

Connectomics is a strategy for mapping complex neural networks based on high-speed automated electron optical imaging, computational assembly of neural data volumes, web-based navigational tools to explore 10^{12}–10^{15} byte (terabyte to petabyte) image volumes, and annotation and markup tools to convert images into rich networks with cellular metadata. These collections of network data and associated metadata, analyzed using tools from graph theory and classification theory, can be merged with classical systems theory, giving a more completely parameterized view of how biologic information processing systems are implemented in retina and brain. Networks have two separable features: topology and connection attributes. The first findings from connectomics strongly validate the idea that the topologies of complete retinal networks are far more complex than the simple schematics that emerged from classical anatomy. In particular, connectomics has permitted an aggressive refactoring of the retinal inner plexiform layer, demonstrating that network function cannot be simply inferred from stratification; exposing the complex geometric rules for inserting different cells into a shared network; revealing unexpected bidirectional signaling pathways between mammalian rod and cone systems; documenting selective feedforward systems, novel candidate signaling architectures, new coupling motifs, and the highly complex architecture of the mammalian A_{II} amacrine cell. This is but the beginning, as the underlying principles of connectomics are readily transferrable to non-neural cell complexes and provide new contexts for assessing intercellular communication.

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[1] Percentage of work contributed by each author in the production of the manuscript is as follows: Marc, 40%; Jones, 10%; Watt, 10%; Anderson, 15%; Lauritzen, 25%.

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1. Connectomics

A new field like connectomics brings with it much uncertainty, contention and new terminologies. The uncertainly derives in part from the fact that connectomics blends new methods (fast electron optical imaging, image processing algorithms, dataset assembly methods, database architectures, hardware configurations) and new interpretive frameworks (graph theory, computational complexity theory, classification theory). Contention arises in part from concerns that claims of improved network analysis may be overstated; that discovery may not reasonably scale with cost; and that some theoretical underpinnings are disputed.

As the field is not mature, many neuroscientists have opinions on its merits and how its discourses ought to be framed. A recent issue of Nature Methods (Volume 10, No 6, June 2013) contains many of these debates and they are not repeated here except to note that the arguments for and against connectomics are elegantly summarized by Morgan and Lichtman (2013). However, this review is not nor is it intended to be balanced. Rather it presents our experience with connectomics technology and discovery. Finally, graph theory, classification theory, electron optics and computational management of large datasets all involve unfamiliar conceptual frameworks and terminologies. This review is not intended to remedy understanding of all those areas, but will provide directions to the primary literature, textbooks and technical overviews. The review formally ends at Section 3. Sections 4.1–4.3 provides a detailed list of critical definitions and references. We encourage the reader to refer to them as needed. Sections 4.5 and 4.6 provide deeper explorations of network theory and classification forming the underpinning of modern connectomics, including arguments supporting the essential role of connectomics in achieving complete understanding of retinal networks.

1.1. Introduction

A connectome is a complete graph of a neural network. In principle, it is not an approximation or even a statistical average. It is a comprehensive list of every connection in a defined neural region. In practice, no studies have achieved this completeness, but unlike previous anatomical efforts, the goal is clear and the technical path straightforward. We expect completeness from community efforts, not from one lab. Connectomics efforts include macroscalestudies of connectivity across the brain (Marcus et al., 2011; Sporns et al., 2005; van den Heuvel and Sporns, 2011), mesoscale optical studies of connections between defined brain regions (Kleinfeld et al., 2011; Oberlaender et al., 2011), as well as nanoscale electron optical studies of synaptic connectivity, e.g. the vertebrate retina (Anderson et al., 2011b; Briggman et al., 2011). Fine-scale, ultrastructural connectome assembly has become possible due to high-speed automated electron optical imaging, including scanning electron microscope (SEM) and transmission electron microscope (TEM) imaging. Connectome analysis has become possible due to the development of large-scale annotation and database mining tools such as Viking and Connectome Viz (Anderson et al., 2011a).

1.2. Connectomics versus legacy anatomy

Why do we need a new approach to ultrastructural connectivity analysis at all? Don't we already know all the fundamental networks of retina? The answer to that is: No (Marc et al., 2012a; Anderson et al., 2011a: Lauritzen et al., 2012a,b; Briggman et al., 2011). We do not even really know if we have classified all retinal neurons, including bipolar, amacrine and ganglion cells and it is clear from new cell-specific genetic techniques that even well-known cells may have surprising roles in vision (Beier et al., 2013; Huberman and Niell, 2011; Rivlin-Etzion et al., 2011). So what is wrong with legacy analyses using traditional electron microscopy? Basically, legacy anatomy is ponderously slow and limited by the capacity of a single human observer to select and capture an image. Given the proliferation of new genetic models and new understanding of pathologic rewiring in the retina (Jones et al., 2011, 2003), high throughput ultrastructure is an essential advance. Previous TEM montaging efforts produced only arrays of single images for humans to track as stacks of photographs or low resolution digital files. For neuroscience, this meant that legacy ultrastructural anatomy, which (albeit heroic in scope) actually delivered only a broad-brush concepts and only fragments of retinal networks at best (Calkins and Sterling, 1996, 2007; Calkins