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Construction of anatomically correct models of mouse brain networks☆

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Abstract

The *Mouse Brain Web* (MBW), a web-organized database, provides for the construction of anatomically correct models of mouse brain networks. Each web page in this database provides the position, orientation, morphology, and putative synapses for each biologically observed neuron. The MBW has been designed to support (1) mapping of the spatial distribution and morphology of neurons by type; (2) wiring of the network–synaptic assembly; (3) projection of neuron morphology and synapses to geometric multi-compartmental models; (4) search for motifs and basic circuits in the brain networks using customized web-crawlers; and (5) the mapping of anatomically correct networks to physiologically correct network simulations.

Keywords: Mouse brain networks; Web-based database; Neuron morphologies; Synaptic assembly; Network motifs

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1. Introduction

The mammalian brain is virtually unique in its structural complexity. It is estimated that a mouse cortex contains approximately 17 million neurons, which are interconnected by in the order of 10^{11} synapses [2]. To understand the intricate anatomical structure of the mouse brain requires analysis of the morphologies and connections of neurons at the cellular level. A neuroanatomical database enabling such analysis can serve as a starting point for discovering neural connectivity, much like sequence databases have served as a resource for protein and gene discovery.

The knife-edge scanning microscope (KESM) [6,7], capable of scanning an entire mouse brain in less than 1 month, generates at 250 nm sampling resolution a volume data set in the form of aligned serial sections. This technology makes it possible to collect whole brain data at sufficient level of detail to recover the full extent of neuronal morphology in 3D and to estimate synapses for further analyses. Knife-edge scanning microscopy is one of two available techniques [6,12] for scanning and reconstructing an entire mouse brain in three dimensions, that obviate the need to register the cut sections. KESM is also an order-of-magnitude faster than its alternative. From the data produced using the KESM, we have initiated the construction of the *Mouse Brain Web* (MBW) to provide a database of observed neurons in the mouse brain with sufficient neuroanatomical detail to enable discovery of neural connectivity and anatomically correct modeling of mouse brain networks.

In this paper, we summarize the data acquisition process that leads to the construction of the MBW. We describe the strategy and details of constructing a MBW database. We discuss how MBW can be utilized for functional modeling and network analysis.

2. Data acquisition

Data acquisition for construction of MBW comprises two stages: volume data acquisition and data reconstruction. During the volume data acquisition stage, a set of aligned serial sections is obtained from a mouse brain specimen embedded in a plastic block. The volume data set is then processed to retrieve its full 3D reconstruction. These two stages are described in detail elsewhere [4,5]. Here, we briefly summarize the two stages.

The KESM (Fig. 1) [6,7], an instrument of local design, uses repeated knife-edge scanning to generate a volume data set in the form of aligned serial sections from a specimen block (Fig. 2). KESM allows imaging the newly cut tissue just beyond the knife edge as a thin section is cut away by an ultramicrotome. Following the data acquisition protocol specified in [5], the acquired volume data set is organized into a set of *image stacks* for storage and processing. An *image stack* is a stack of square images that corresponds to a $(n \times n \times h)$ mm^3 sub-brain volume, where n is determined by an effective field of view of the microscope objective and stack thickness h is set uniform for the entire specimen block. For the $10\times$ objective, nominal values for n and h are 2.5 mm and 64 μm, respectively; for the $40\times$ objective, nominal values for n and h are 0.625 mm and 32 μm, respectively.

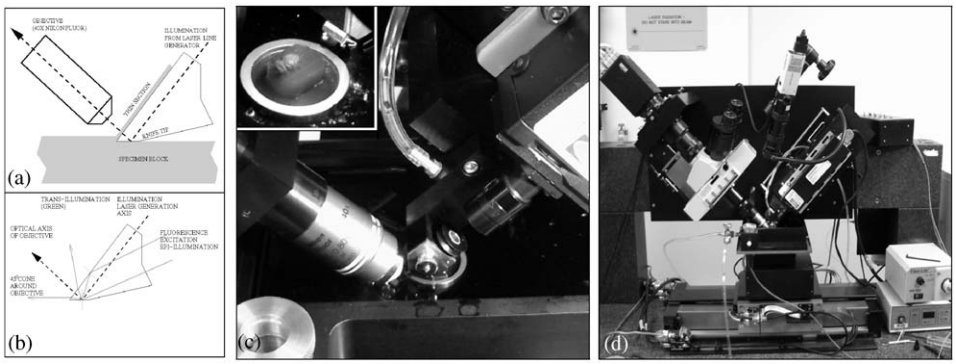

Fig. 1. The knife-edge scanning microscope. (a) Specimen undergoing sectioning by knife-edge scanner (thickness of section is exaggerated). (b) Diamond knife collimator supporting transmission illumination and fluorescence epi-illumination. (c) Close-up photo of the microscope (left; slanted) and the knife/epi-illumination assembly (right; slanted), submerged in the specimen tank. The inset shows a close-up view of the specimen and the diamond knife (on the right). (d) Photo of the KESM instrument showing the microscope (left; slanted), knife/epi-illumination assembly (right; slanted), and the stage (center; bottom). Currently, a white-light source is used.

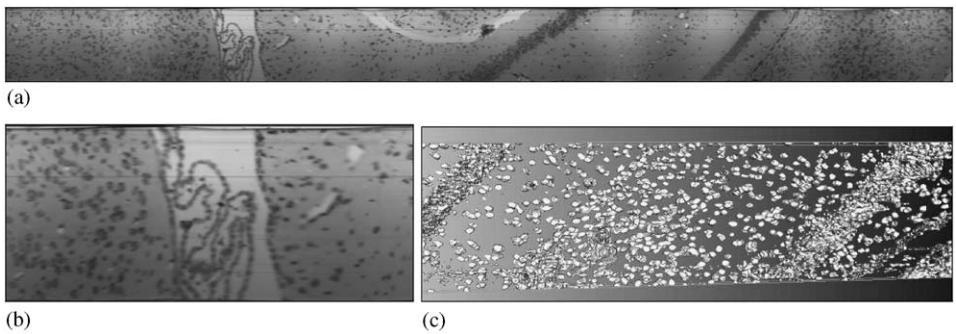

Fig. 2. Scanned mouse-brain sections. (a) Nissl-stained coronal section showing the lateral ventricle, hippocampus, and ventral part of the mouse cortex. (b) Magnified view of the lateral ventricle in (a). (c) 3D reconstruction of the hippocampal area shown in (a) from multiple aligned slices (generated using `Amira`).

The volume data set, organized into image stacks, is processed to retrieve its full 3D information by four serial stages of reconstruction: L-block segmentation [8], component analysis, neuron assembly, and synapse identification. Each reconstruction stage produces an equivalent data set at a higher level of description. We have designed a brain microstructure database system [4] to provide storage and access to microstructure data at these five levels of description: volume data, L-block coverings [8], volumes of interest, segment and neuron data, and brain network data.

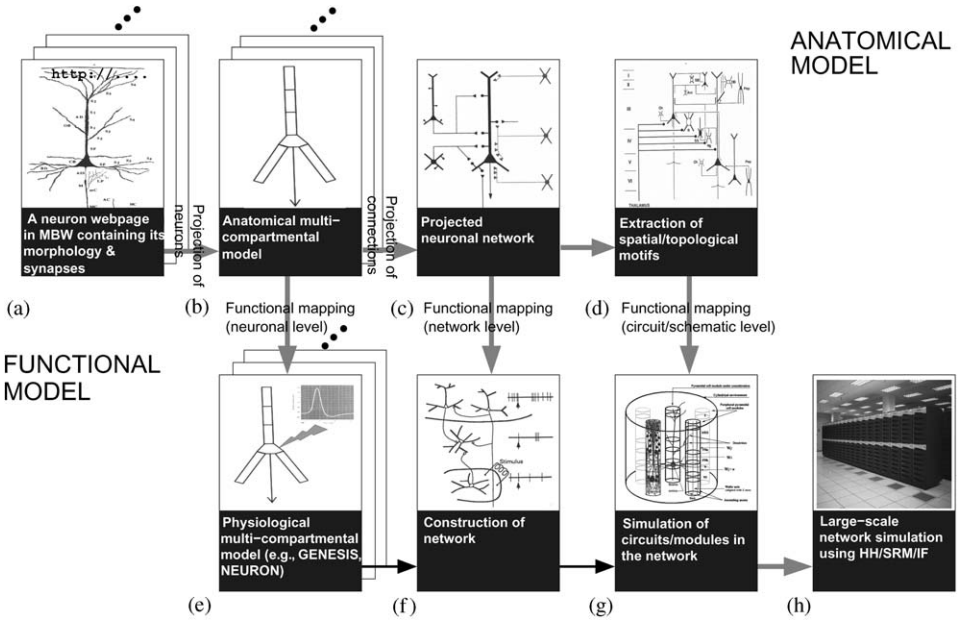

Fig. 3. Anatomically correct models of mouse brain networks and their functional simulation. (a) and (d) were adapted from [9]; (b) and (e) were adapted from [1]; (c) and (f) were adapted from [11]; (h) was adapted from [10].

3. Construction of MBW

Our motivation for constructing the MBW (Fig. 3) is to provide a database of observed neurons in the mouse brain, (1) to enable discovery of neural connectivity and anatomically correct modeling of mouse brain networks, and (2) to subsequently allow the mapping of anatomically correct networks to physiologically correct network simulation. The MBW database consists of web pages where a web page represents either (1) a $(n \times n \times h)$ mm^3 sub-brain volume as described in Section 2, or (2) an observed neuron and its processes. These two granularities of data representation per web page are characterized by the stained anatomy of the specimen.

A Nissl-stained specimen data set yields the full morphology of cell bodies, but not their processes. A MBW from a Nissl-stained specimen consists of web pages, where a web page represents a $(n \times n \times h)$ mm^3 sub-brain volume, where the nominal values for n and h are 2.5 mm and 64 μm, respectively. Each 0.4 mm^3, equivalent to 2.5 mm × 2.5 mm × 64 μm, sub-brain volume in the MBW is characterized by four types of information extracted from the brain microstructure database system: (1) unique identifier; (2) sub-brain volume index within the brain-based coordinate system; (3) position of each cell body within a brain-based local coordinate system; and (4) morphology of cell bodies within the sub-brain volume. The density of neurons in

the mouse brain is reported to be $9.2 \times 10^4/\text{mm}^3$ [2]. Our 0.4 mm^3 sub-brain volume would on average contain 3.7×10^4 neuron cell bodies. We estimate that each sub-brain volume in the MBW takes up approximately 3.7 MB, and that the MBW requires about 3 GB of storage for each Nissl-stained mouse.

Following the statistics reported in the literature regarding the neuronal types and their associated morphology [2,9,11], we estimate that each neuron in MBW takes up approximately 0.1 MB, exclusive of synapses. Taking into consideration that we expect to observe only 1% of total neurons from Golgi-stained and 16% GAT1-GFP labeled tissue, the MBW then requires about 11 TB of storage (including observed synapses) for pooled data from 4 Nissl-, 4 Golgi-, and 4 GAT1-GFP-stained mice.

Golgi-stained or GAT1-GFP labeled specimen data yields selected neurons in their full morphology. A MBW from such specimens consists of web pages where a web page represents an observed neuron. Each neuron in the MBW is characterized by five types of information [3] extracted from the brain microstructure database system: (1) a unique identifier; (2) position of its soma within a brain-based local coordinate system; (3) orientation of its 3D soma relative to the local coordinate system; (4) morphology of its dendrites and axons; and (5) putative synapses it makes with other neurons within the specimen. The data size required to describe each neuron in the MBW depends on its type, morphology, and observed synapses it makes with other neurons. The neuronal type determines the number of processes emanating from the soma and whether the dendritic processes have spines. The morphology determines the number of segments needed to represent each axonal/dendritic process. On average each neuron in mouse cortex is pre-synaptic to 7000–8000 neurons and post-synaptic to 6000–10000 neurons, and multiple synapses between the same two neurons are rare [2].

The neuronal data and the sub-brain volume data that constitute a web page in the MBW are derived from our brain microstructure database system via an XML schema [4]. The derived XML files are converted to HTML for display in the MBW. The web-based organization of the MBW database makes it accessible and also provides an interface to the database. The text-based XML tags makes the database searchable, and the hyperlinks between HTML files can be used to search for connectivity patterns using customized web-crawlers.

4. Discussion

The methods and results presented in this paper form a foundation for constructing the MBW database which supports (1) mapping of the spatial distribution and morphology of neurons by type; (2) wiring of the network–synaptic assembly; (3) projection of neuron morphology and synapses to geometric multi-compartmental models; (4) search for motifs and canonical circuits in the brain networks using customized web-crawlers; and (5) the mapping of anatomically correct networks to physiologically correct network simulations. These five stages are designed to be fairly independent so that each stage does not depend too much on the immediate availability of data from the previous stage. Thus, we are currently tackling each stage in parallel to reduce development time.

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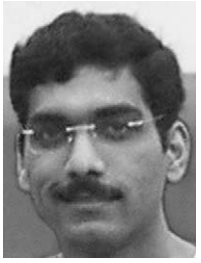

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