Electrophysiological Models Derived from EM Reconstructions

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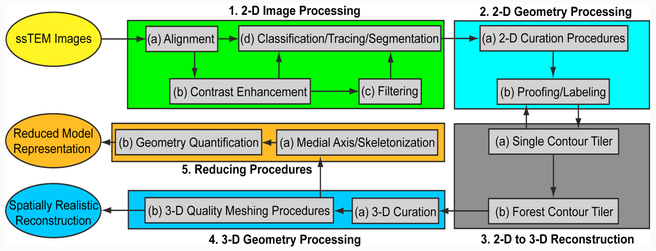
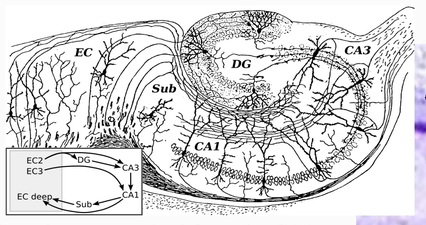
Research Goals

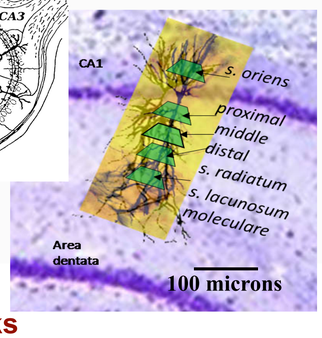
Construct spatially realistic structural models of neuronal processes, organelles, and extracellular space. From stacks of ssTEM images, we extract contours for all neuronal processes (dendrites, axons, glia) and internal organelles (mitochondria, endoplasmic reticulum, etc). Contours are tagged, curated, and meshed into surfaces representing the cellular or oranelle boundaries in 3D. A conforming Delaunay method is used to construct volumetric meshes of the interiors as well as of extracellular space.

Quantify structural properties of spatially realistic models and construct appropriately reduced domain models. Reconstruction and modeling tools are used to quantify the variation in surface area and volume of axons, dendrites, glia, extracellular space, synapses, and core subcellular organelles (smooth endoplasmic reticulum, endosomal compartments, Golgi and spine apparatus, and mitochondria) that could impact electrical signaling in dendrites. We use a suite of tools to construct domain models from these spatially realistic quantifications suitable for incorporation into the NEURON simulation environment….



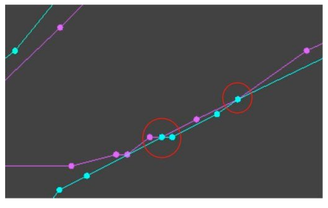
I: Hippocampal Image Stacks

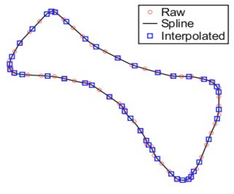




Samples are acquired from the CA1 and CA3 hippocampal regions of a rat brain. Pyramidal cells in each strata appear in parallel configurations.

II: Curating Contour Stacks

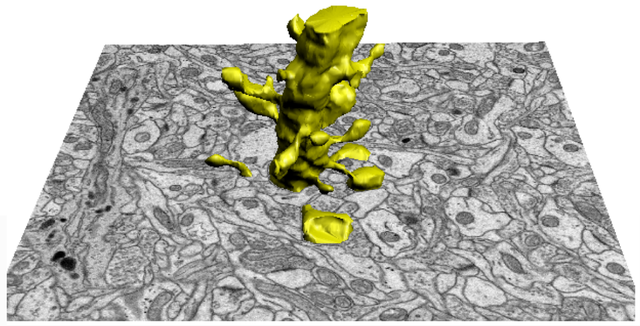


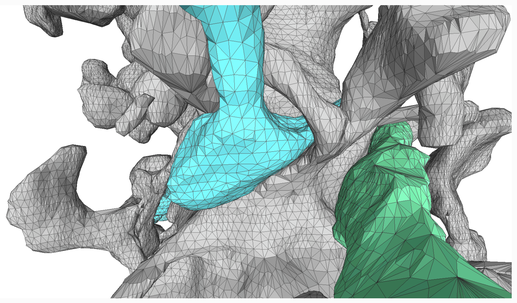


On the left, 2D curation has detected and removed intersections at the indicated locations. On the right, a sample of how splines are used to resample the contours.

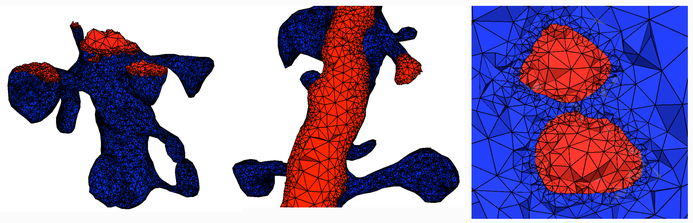
III: 3D Neuropil Reconstruction

Extracted contours are tiled using the ContourTiler algorithm [BCL'96, EB'10], incorporated into Volume Rover [CVC]. Single component reconstructions are guaranteed to be topologically correct and watertight. Post-reconstruction corrections guarantee that there are no intersections between components.

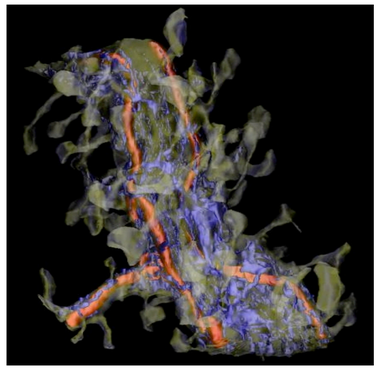




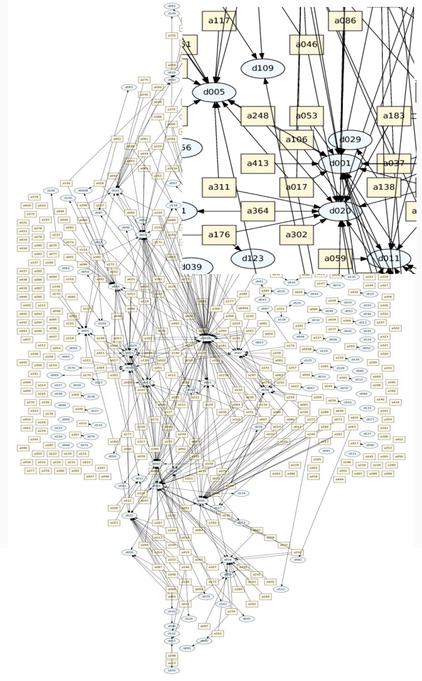
The surface meshes produced by Contour Tiler in the 3D Reconstruction step are often unsuitable for BEMs. We use a suite of tools incorporated into the VolumeRover software package to smooth, decimate, and refine by fitting algebraic splines.



We use the conforming Delaunay volume mesher DIR3 to create tetrahedralizations that restrict to the refined surface meshes [RW'08]. This provides a mesh of cell interiors as well as extracellular space for use in FEMs. On the left, a volume mesh of a dendrite and its spines is shown with two different cut plane views. The mesh respects features that occur in close proximity as the third visualization illustrates. On the right, a mesh of a cubic micron of extracellular space created at SALK reveals the tortuous 3D nature of the region where ions and neurotransmitters diffuse.



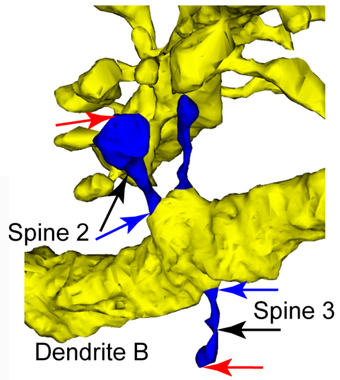
The apical dendrite has been made transparent, revealing the organelles nested within. A model including intra- and extra-cellular components can provide for more realistic simulations.

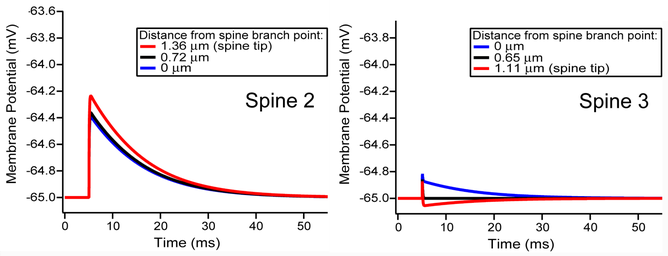


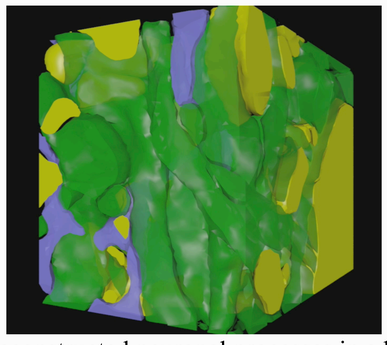
We use synapse data to identify connections between specific axons and dendrites. The resulting graph structure reveals complicated connectivity. Merging geometric measurements from the meshes with the graph data will yield a circuit diagram for the entire volume.

IV: Simulations

Ephaptic effects: an action potential is initiated at each of the three locations pointed to on spines 2 and 3. The resulting extracellular potential is plotted below as a function of time for indicated extracellular locations.







Visualizing all reconstructed neuronal processes in a block emphasizes the need to understand ephaptic and other geometry-related electrophysiological effects.

Acknowledgements

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