Spatially Realistic and Reduced Electrophysiology Models Dervied From EM Reconstruction

UT Austin: Andrew Gillette[1], Radhakrishna Bettadapura[1], Sk. Fahad Chowdhury[1], John Edwards[1], Ajay Gopinath[1], Jose Rivera[1], Bharadwaj Subramanian[1], Alexander Rand[1], Clifton Rumsey[1,2], Qin Zhang[1], Daniel Johnston[2], Kristen Harris[2], Chandrajit Bajaj[1]

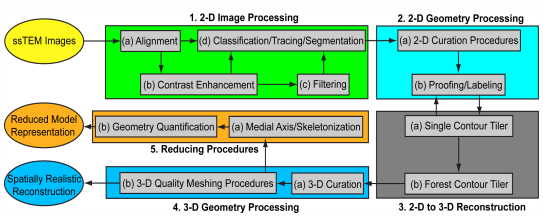
SALK: Tom Bartol, Daniel Keller, Justin Kinney, Terry Sejnowski

1 = Computational Visualization Center, 2 = Center for Learning and Memory

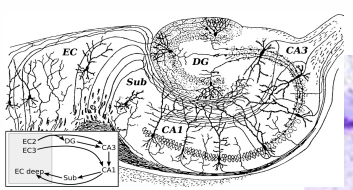
Research Goals

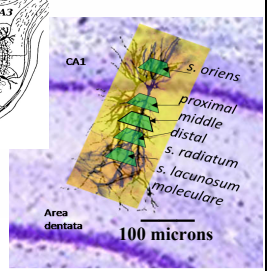
Construct spatially realistic structural models of neuronal processes, organelles, and extracellular space. From stacks of ssTEM images, we extract contours for all neuronal processes (dendrites, axons, glia) and internal organelles (mitochondria, endoplasmic reticulum, etc). Contours are tagged, curated, and meshed into surfaces representing the cellular or organelle 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 and biochemical signaling in dendrites. We use a suite of tools to construct appropriately reduced domain models from these spatially realistic quantifications suitable for incorporation into the NEURON and MCELL simulation environments.



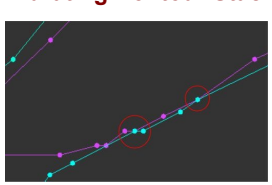
I: Hippocampal Image Stacks

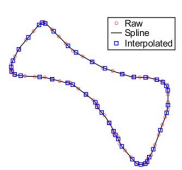




Samples are acquired from the CA1 and CA3 hippocampal regions of a rat brain. Pyramidal cells in each strata appear in parallel configurations.

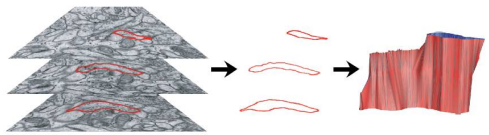
II: Curating Contour Stacks



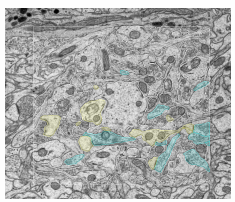


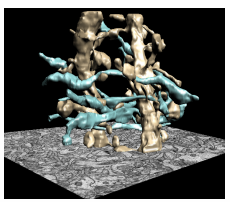
On the left, 2D curation has detected and removed intersections at the indicated locations. On the right, a sample of how splines are used to resample the contours.

III: 3D Neuropil Reconstruction

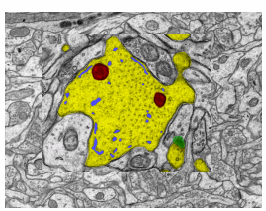


Extracted contours are tiled using the ContourTiler algorithm [BCL'96], incorporated into Volume Rover [CVC].

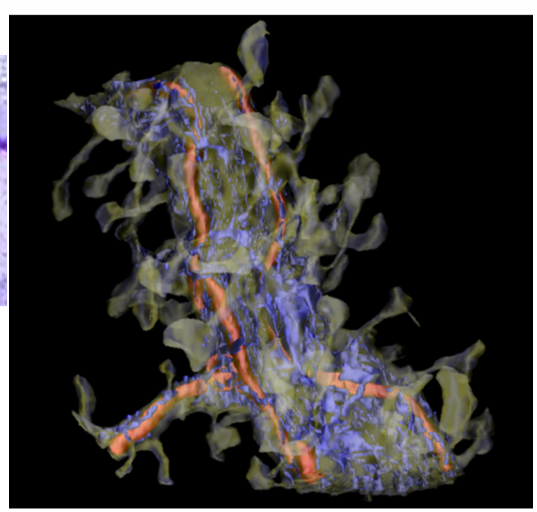




Contours of two dendrites (yellow) and a few axons (blue) are shown along with the associated reconstructed surfaces. The various processes come in close proximity to each other but intersections are avoided by quality branched forest meshing [BGG'08].

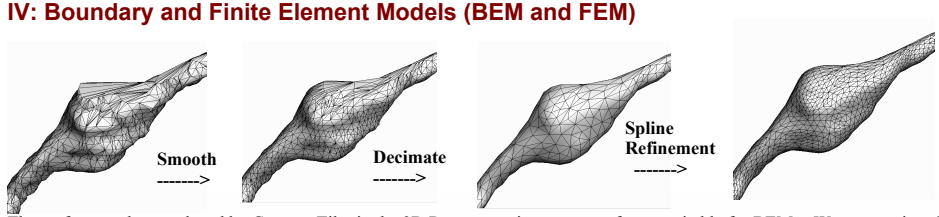


Mitochondria (red), endoplasmic reticulum (blue) and postsynaptic density (green) are shown in this zoomed in view. Image segmentation methods help in the identification of these regions [BYA'03, YB'04].

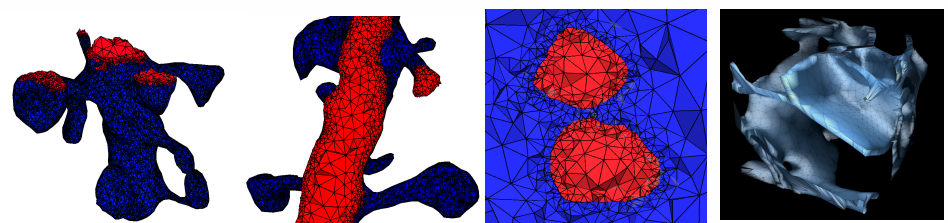


The apical dendrite has been made transparent, revealing the organelles nested within.

IV: Boundary and Finite Element Models (BEM and FEM)



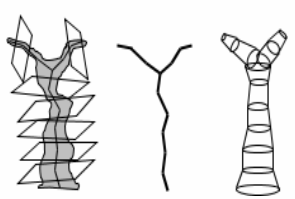
The surface meshes produced by Contour Tiler in the 3D Reconstruction step are often unsuitable for BEMs. We use a suite of tools incorporated into the VolumeRover software package to smooth, decimate, and refine by fitting algebraic splines.

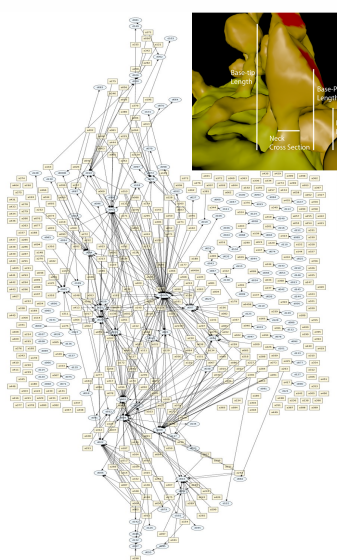


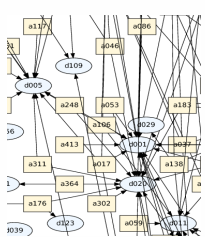
We use the conforming Delaunay volume mesher DIR3 to create tetrahedralizations that restrict to the refined surface meshes [RW'08]. This provides a mesh of cell interiors as well as extracellular space for use in FEMs. On the left, a volume mesh of a dendrite and its spines is shown with two different 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.

V: NEURON Models

We use information gleaned from the surface and volume meshes to create spatially accurate reduced models for input to the NEURON circuit modeling environment. All processes are chunked into compartments and linked according to their spatial relation. The resistivity in each compartment is adjusted based on the proportion of the region occupied by organelles.







We use synapse data to identify connections between specific axons and dendrites. By collecting this information in a graph structure, we can visualize the wiring connectivity. Merging geometric measurements from the meshes with the graph data will yield a circuit diagram for the entire neuropil volume.

Acknowledgements

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