Form and Function: Multi-scale Modeling of Electrophysiology in the Hippocampus

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Abstract

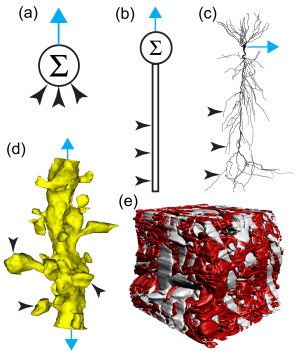

Figure 1: Multiple scales of Neuron Electrophysiology Models. Black arrowheads indicate synaptic input sites. Blue arrows indicate output sites.

Understanding the fundamental relationship between structure and function has long been an important goal in neuroscience. At all scales of analysis, the roles that geometric shapes and spatial interrelationships play in determining the functional abilities and constraints on brain activity are of paramount importance. Theoretical approaches have frequently been crucial to clarifying these structure/form-function relationships. With the help of computational modeling and simulations, questions of these relationships can be asked and answered in different levels. In general, finer modeling and simulations could answer questions at a finer level. Consider the example of a single pyramidal neuron in the mammalian brain. At one end of the spectrum, many models of neurons reduce the cellular structure down to a point (Fig. 1a). Such single compartment models are very efficient and can be appropriate to answer questions about networks of interconnected neurons but are inappropriate for understanding how single neurons integrate information from thousands of inputs impinging on dendrites. At the level of light microscopy, dendrites appear as cylindrical cables, and are typically modeled using the one-dimensional (1-D) cable equation or 1-D multi-compartment models (Fig. 1b). If one zooms closer into the structure, however, this simple cylindrical approximation further breaks

down (Fig. 1c). Electron microscopy has revealed that, at the scale of a few microns, realistic dendrites have considerable variation in cross-sectional area, dendritic spine morphologies, and intracellular organelles (Fig. 1d) (also [1, 3, 4]. How does this local variation in dendritic structure affect the local electrical signals in dendrites? Furthermore, spines, plentiful in the normal and healthy state, are frequently absent or misshapen in disease states (described below), but how do these structural differences affect function? Previous modeling of dendritic function has lacked sufficient information to explore the effects of variation in the physical relationships between dendrites, axons, glia, and extracellular space in the local neuropil. In terms of modeling, at the extreme opposite end of the spectrum from a single compartment model would be a three-dimensional (3-D) spatially realistic model of a whole neuron (Fig. 1e) that simulates the electrodiffusion of every discrete ion. The key, then, is to find the right middle ground where the functional implications of realistic small-scale structure within the neuropil can actually be studied. This requires a scalable modeling approach that maintains fidelity in the region of interest across multiple sizes of homogeneous domain. This talk shall describe several new computational strategies to incorporate structural features at multiple scales into realistic models of dendritic function[1, 5]. At the micron scale, variation in dendritic caliber and fluctuations in dendritic surface area due to spines and other irregularities are explored[2]. At the submicron scale the impact of organelles inside dendrites are incorporated. At the molecular scale, ion channel distribution is simulated. A fourth and important scale that we address is the realistic simulations of dendrites in relationship to their surrounding neuropil to provide a more nuanced understanding of how variation in structure, especially due to brain diseases and injuries, influences ephaptic function [1, 6].

References

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