Expanding NEURON to bridge electrophysiology, chemical, and network models: simulations of ischemic stroke

Adam JH Newton[1,2], Robert A McDougal[1], Carl Tropper[3], Alexandra H Seidenstein[2,4], William W Lytton[2,5]
[1] Department of Neuroscience, Yale University, New Haven CT 06520, USA
[2] Department Physiology & Pharmacology, SUNY Downstate, Brooklyn, NY 11203, USA
[3] Department of Computer Science, McGill University Montreal, Quebec, Canada
[4] NYU School of Engineering, 6 MetroTech Center, Brooklyn, NY 11201, USA
[5] Kings County Hospital Center, Brooklyn, NY 11203, USA
E-mail: adam.newton@yale.edu

The brain distributes information processing across systems at different spatial and temporal scales. Electrophysiological mechanisms govern the integration of signals from across the dendritic arbor to trigger action potentials in the axon in a matter of milliseconds. Although much remains to be learned, these mechanisms are relatively well accessible for experimental investigation and simulation. By communicating with each other in an adaptive way, neurons form a network that can learn to generate a given output for a given input. Although less experimentally tractable than studying individual neuron dynamics, network dynamics remain tractable for computational study using the same techniques as for single cells. Subsequently the NEURON platform traditionally focused on electrophysiology and network simulations. In 2013, NEURON introduced support for reaction-diffusion simulations with the NRxD module, which has allowed models to probe; intracellular calcium dynamics in dystonia, extracellular potassium in spreading depression and persistent neuronal activity via HCN channels.

We introduce the NEURON simulator (neuron.yale.edu) and discuss recent progress in NRxD. We are moving run-time code to C from Python; tests suggests an approximately 10x speedup as a result. We have developed an interface using NEURON's rxd.plugins module to connect NEURON to the stand-alone stochastic solver NTW. In our current development code we have implemented support for parallel extracellular reaction-diffusion. Extracellular reaction-diffusion is essential to capture the distal effects of neuromodulators and spillover of neurotransmitters. A macroscopic view of the extracellular space (ECS) is characterised by its tortuosity (reduced diffusion due to obstructions) and its volume fraction (typically ~20%). The addition of reactions allows the ECS be modeled as an active medium, to account for enzymatic degradations, transporters or glial buffering. NEURON enables this macroscopic model of tissue to be coupled with detailed biophysical models of cells.

An example of Multiscale Modeling and multiphysics modeling that makes full use of these new tools is ischemic stroke. This modeling requires coupling of electrophysiology with complex intracellular molecular alterations, and consideration of network properties in the context of bulk tissue alterations mediated by extracellular diffusion. Occlusion of a blood vessel in the brain triggers a cascade of changes, including: 1. synaptic glutamate release, related to excitotoxicity; 2. elevated extracellular potassium, leading to spreading depression; 3. cell swelling, reducing the extracellular volume and increasing the tortuosity; 4. production of reactive oxygen species, which give rise to inflammation. These cascades occur over multiple time-scales, with the initial rapid changes in cell metabolism and ionic concentrations trigging several damaging agents that may ultimately leads to cell death. NRxD provides a platform where detailed neurons models coupled to macroscopic model of tissue capture both the rapid intracellular changes and slower diffusive signalling involved ischemic stroke.

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