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Multiscale Computer Modeling of Spreading Depolarization in Brain Slices

Spreading depolarization (SD) is a slow-moving wave of neuronal depolarization accompanied by a breakdown of ion concentration homeostasis, followed by long periods of neuronal silence (spreading depression), and associated with several neurological conditions. We developed multiscale (ions to tissue lice) computer models of SD in brain slices using the NEURON simulator: 36,000 neurons (2 voltage-gated ion channels; 3 leak channels; 3 ion exchangers/pumps) in the extracellular space (ECS) of a slice (1 mm sides, varying thickness) with ion (K+, Cl−, Na+ 7) and O2 diffusion and equilibration with a surrounding bath. Glia and neurons cleared K+ from the ECS via Na+/K+ pumps. SD propagated through the slices at realistic speeds of 2–5 mm/min, which was augmented by 25–30% in models incorporating the effects of hypoxia or of propionate. In both cases, the speedup was mediated principally by ECS shrinkage. Our model allows us to make the following testable predictions: 1. SD can be inhibited by enlarging ECS volume; 2. SD velocity will be greater in areas with greater neuronal density, total neuronal volume, or larger/more dendrites; 3. SD is all-or-none: initiating K+ 13 bolus properties have little impact on SD speed; 4. Slice thickness influences SD due to relative hypoxia in the slice core, exacerbated by SD in a pathological cycle; 5. Higher neuronal spike rates and faster spread will be observed in the core than the periphery of perfused slice during SD.