**C43**

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**Human capillary identification used to simulate spreading depression in control and ischemic neocortical microcircuits**

Spreading depolarization (SD) is a wave of neuronal depolarization that propagates through gray matter at 2-7mm/min: a brief period of hyperexcitability at the wavefront is followed by spreading depression, neuronal silence from depolarization block; as well as by disruption of ion homeostasis. Blood vessels play a key role in SD as the source of the energy needed for ion pumps. Multiple mechanisms underlie SD initiation and propagation which we explored using simulation.

NEURON/RxD/NetPyNE were used: point neurons with Hodgkin-Huxley style ion channels augmented with homeostatic mechanisms, including Na+/K+-ATPase, NKCC1, KCC2, and dynamic volume changes. We simulated the intracellular and extracellular concentrations of Na+, K+, Cl-, and O2. The contribution of astrocytes was modeled as the O2-dependent clearance of K+. The evolutional-optimization Python framework Optuna was used to find parameters in simulating 13,000 neurons representing ~1 mm3 of mouse cortex.

Oxygen sources in the model were determined using histologic images showing capillary locations from human tissue: a 2.0 x 2.3 cm cross-section of the V1 cortex was immunostained for CD34. This identified 918 capillaries with mean density of 199.6/cm2 and capillary cross-sectional area of 16.7±11.9μm2. For simulation, we used a biased random walk to expand the 2D cross-section of capillaries to a 3-dimensional distribution of oxygen sources. SD was reliably triggered in this model by a bolus of extracellular K+ applied to cortical layer 4. Our model showed neurons closer to capillaries were more able to maintain homeostasis and physiological firing. We also found that neuronal depolarization occurred in all cortical layers, with pathological activity spreading both through extracellular K+ diffusion and through network connectivity.