ABSTRACT FACE PAGE

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The brain as tissue — simulation of ischemic effects in single cell and in networks

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INTRODUCTION

In this research, we address the limitations of abstract models of brain circuitry by developing multiscale simulations that incorporate the extracellular space and glial cells, providing a more comprehensive representation of the brain. We focus on the effects of two crucial factors for brain health: oxygenation and potassium level control.

METHODS

We developed NEURON/NetPyNE simulator models to investigate ion homeostasis at subcellular and tissue scales in both in vitro and in vivo conditions. At the subcellular scale, we optimized a CA1 pyramidal neuron model to maintain ion homeostasis under physiological conditions. For our *in vitro* slice model, we considered oxygen diffusion into the slice with 90,000 neurons/mm3. Our *in vivo* model used histologic images of a 2.0 x 2.3cm cross-section of the human cortical plate in V1 with immunostaining for CD34 to determine the locations of 918 capillaries. These loci provided the sources of oxygen for a cortical microcircuit.

RESULTS

Our subcellular modeling predicted greater calcium accumulation in basal dendrites, making them more vulnerable to excitotoxicity. In contrast, the distal-apical dendrites suffered more chloride influx, a cause of dendritic beading. Our *in vitro* simulation provided a model of spreading depression (SD), which propagated at 2-4 mm/min, increasing by as much as 50% in models incorporating hypoxia or propionate effects. Our model produced testable predictions: SD can be inhibited by enlarged extracellular space volume; SD velocity will be greater in areas with greater neuronal density; SD is all-or-none.

CONCLUSIONS

Our multiscale modeling approach incorporating the extracellular space and glial cells provides valuable insights into the interplay between brain circuitry and critical factors for brain health. By bridging the gap between abstract models and the complexities of the brain parenchyma, our research offers promising avenues for optimizing brain health and contributes to the advancement of computational neuroscience.