Utilizing biophysically accurate computational models of NaV1.2 to simulate mutations and therapeutics in neonatal and adult neurons and neuronal networks.

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***Abstract*:**

Dysfunction of *SCN2A*, the gene encoding $Na_V1.2$, is implicated in a spectrum of severe neurological disorders including infantile epileptic encephalopathies, autism spectrum disorder, and intellectual disability. The high number of unique *SCN2A* mutations renders the traditional approach of developing biological models for each variant unfeasible. Therefore, we leveraged *in silico* modeling to simulate a *SCN2A* mutations and drugs that would be prohibitive in a conventional laboratory setting. We utilized Hodgkin-Huxley equations to model channel kinetics for multiple *SCN2A* mutations, then integrated them into reconstructions of layer 5 pyramidal neurons with complex morphological features. To understand $Na_V1.2$ dysfunction at the system level, our neuron model was incorporated into a cortical column model with over 10,000 interconnected neurons and more than 30 million synapses to investigate network dynamics. Some $Na_V1.2$ mutations exhibit different properties in their neonatal versus adult isoforms. To address this, we constructed an immature neuron model to simulate a neuron undergoing early development. It features a smaller morphology with fewer dendritic branches and different distribution of ion channels compared to the adult neuron. Using our computational models, we aim to accurately predict disease states that can be altered using therapeutics personalized to each child's genetic diagnosis.

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