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Neural Modeling of Channelopathies to Elucidate Neural Mechanism of Neurodevelopmental Disorders

Neurodevelopmental disorders (NDDs) such as epilepsy, autism spectrum disorder, and developmental delays vary greatly clinically and effect a large portion of the population. Despite this variability, NDDs share common pathophysiological characteristics: the hallmark of these disorders is imbalanced excitatory inhibitory input (E/I), which during development leads to dysfunction in neuronal circuits. Brain channelopathies are particularly useful in studying the E/I imbalance mechanism because their function can be linked to neuronal excitability. Changes in neuronal ion channels disrupting electrical activity, has been highly associated with NDDs. Channelopathies can cause an increase or decrease in the excitability of neurons, which can result in a change in the number of functional channels or in channel biophysics. Using a previously published primary motor cortex (M1) model, we utilize a large-scale, highly detailed biophysical neuronal simulation to investigate how channel mutations affect individual and network neuronal activity. We specifically look at how these channelopathies affect the excitability of layer 5 pyramidal neurons because they are particularly sensitive to E/I imbalance. The stimulations provide a detailed mechanistic understanding of the role channelopathies play in the E/I imbalance and will allow us to better understand therapeutic targets that specifically target disease symptoms. Using the M1 cortical column simulation, we can measure how channel biophysical changes affect the overall excitability of the network in a time and cost-efficient manner. This model will allow us to realistically examine how NDDs alter the intrinsic excitability of each neuron and the network as a whole. This will provide a tool to investigate the underlying neuronal mechanisms of NDDs affecting many children worldwide and will allow us to stimulate how novel therapeutics can return excitability to neurotypical levels and ultimately be translated clinically.