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GSURC Abstract
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Hyperexcitability of individual neurons is a hallmark feature of many brain diseases. For example, neuronal hyperexcitability has been implicated as a potential mechanism of seizure generation in epilepsy[1]. This project analyzes a previously developed biophysical model of the human R1648H sodium channel mutation, which has been implicated in forms of generalized epilepsy[2]. Using computer simulations and dynamical systems analysis software[3], we elucidate the physiological mechanisms by which this mutation causes hyperexcitability when incorporated into model neurons. First, we compare steady-state properties and response to voltage changes of the wild-type (normal) versus the mutant channel. We illustrate the tendency of the mutant channel to inactivate at a slower rate than its wild-type counterpart.

To understand how the mutation alters the action potential waveform, we incorporate each channel into a generic Hodgkin-Huxley model neuron with three ionic currents (sodium, potassium, and leak). We discover that the mutation induces subtle increases in spike-base width and refractory period of this simple Hodgkin-Huxley neuron. Then we implement each sodium channel model into a more complex, physiologically relevant model of a CA3 hippocampal pyramidal neuron and confirm that the mutation increases cellular excitability[5]. Using a dynamical systems reduction protocol[4], we then explicate precisely how the mutation causes an increase in excitability of the pyramidal neuron. These findings not only confirm the hyperexcitability of the mutant neuron but also provide a detailed mechanistic explanation of how a slight modification in sodium channel kinetics changes the macroscopic features of the neuronal action potential.

References

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