

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 epilepsy¹. This project analyzes a previously developed biophysical model of the human R1648H sodium channel mutation, which has been implicated in forms of generalized epilepsy². Using computer simulations and dynamical systems analysis software³, 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 excitability⁵. Using a dynamical systems reduction protocol⁴, 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

1. Avanzini, G., and Franceschetti, S. (2003) Cellular biology of epileptogenesis. *Lancet Neurol.* 2, 33–42.
2. Clancy CE, Kass RS (2004) Theoretical investigation of the neuronal Na⁺ channel SCN1A: abnormal gating and epilepsy. *Biophys J* 86:2606 –2614.
3. Clewley R (2012) Hybrid Models and Biological Model Reduction with PyDSTool. *PLoS Comput Biol* 8(8): e1002628. doi:10.1371/journal.pcbi.1002628
4. Clewley, R., Rotstein, H.G., Kopell, N. (2005) A computational tool for the reduction of nonlinear ODE systems possessing multiple scales. *Multiscale Modeling and*

Simulation 4(3), 732–759

5. Xu J, Clancy CE (2008) Ionic Mechanisms of Endogenous Bursting in CA3 Hippocampal Pyramidal Neurons: A Model Study. PLoS ONE 3(4): e2056. doi:10.1371/journal.pone.0002056