Abstract

The Hodgkin-Huxley model of the action potential makes the assumption that the intra- and extra-cellular concentrations of sodium and potassium remain constant. Creelman et al. (2000) presented a conductance-based neuron model with dynamic sodium and potassium concentrations, and an analysis of how these dynamics affected neuron behavior. The model predicts that changing certain concentrations will result in increased excitability and seizure-like behavior. This is supported by experiment (Jensen and Yaari 1997). Here, a small modification to the analysis by Creelman et al. (2000), involving new functional fits to the time-averaged ion currents for a more accurate reduction of the model for bifurcation and phase plane analysis. The reduced model does not exhibit the "fast" spiking that is attributed to the Hodgkin-Huxley mechanism.

MATLAB was used to find parameters so as to minimize the sum of squared difference between the fitted function and data generated from simulating the full model. To avoid getting stuck in local optima, it was necessary to provide MATLAB with the best human estimates of the parameters.

The resulting fits were combined with other assumptions to constitute the reduced model. These other assumptions included: a pump current, representing the sodium-potassium pump, maintaining the transmembrane concentration gradients, a glial contribution, which represents buffering of extracellular potassium, and a term that models diffusion. The new reduced model exhibits stable periodic trajectories for certain values of parameters, as expected. The new fits conform better to the generated data, both in general and in physiologically important regions. Nevertheless, discrepancies between the full model and the reduced model persist, most likely the results of small fitting errors.

Introduction

As for all biological systems, mathematical modeling of the neuron, an electrically excitable cell that constitutes a key component of nervous systems, can be very instructive. Models can provide testable predictions, inform potential treatments for disease, and guide theoretical explorations. The famous Hodgkin-Huxley model, a conductance based neuron model for which its authors won a Nobel Prize in 1963, is based on analogy between cell structures and electrical components (for example, the lipid bayer can be thought of as a capacitance).

A model neuron is depicted schematically on the left. The dark green area in the center is the interior of the neuron. The light green area is the extracellular space, and the black ring represents glial cells, which buffer potassium. There is also diffusion between the extracellular space and the "bath solution," in light blue. The colorful shapes that lie on the neuron membrane represent transmembrane ion transporters, responsible for giving the neuron its excitability.

The Hodgkin-Huxley model is (B), and tonic spiking (E), which in the reduced model is (B), and tonic spiking (E), which in the reduced model is (C).

Methods

Full Model

\[
\nu = \delta \left( I_{\text{in}} + I_{\text{out}} \right)
\]

\[
I_{\text{in}} = I_{\text{Na}} + I_{\text{K}} + I_{\text{Cl}} + I_{\text{pump}} + I_{\text{glia}}
\]

\[
I_{\text{Na}} = \frac{g_{\text{Na}} \left( V - E_{\text{Na}} \right)}{1 + \exp \left( \frac{V - E_{\text{Na}}}{\sigma} \right)}
\]

\[
I_{\text{K}} = \frac{g_{\text{K}} \left( V - E_{\text{K}} \right)}{1 + \exp \left( \frac{V - E_{\text{K}}}{\sigma} \right)}
\]

\[
I_{\text{Cl}} = \frac{g_{\text{Cl}} \left( V - E_{\text{Cl}} \right)}{1 + \exp \left( \frac{V - E_{\text{Cl}}}{\sigma} \right)}
\]

\[
I_{\text{pump}} = \frac{g_{\text{pump}} \left( V - E_{\text{K}} \right)}{1 + \exp \left( \frac{V - E_{\text{K}}}{\sigma} \right)}
\]

\[
I_{\text{glia}} = \frac{g_{\text{glia}} \left( V - E_{\text{Cl}} \right)}{1 + \exp \left( \frac{V - E_{\text{Cl}}}{\sigma} \right)}
\]

Reduced Model

\[
\frac{dV}{dt} = \frac{I_{\text{in}} - I_{\text{out}}}{C}
\]

\[
I_{\text{in}} = I_{\text{Na}} + I_{\text{K}} + I_{\text{Cl}} + I_{\text{pump}} + I_{\text{glia}}
\]

\[
I_{\text{Na}} = g_{\text{Na}} \left( V - E_{\text{Na}} \right)
\]

\[
I_{\text{K}} = g_{\text{K}} \left( V - E_{\text{K}} \right)
\]

\[
I_{\text{Cl}} = g_{\text{Cl}} \left( V - E_{\text{Cl}} \right)
\]

\[
I_{\text{pump}} = g_{\text{pump}} \left( V - E_{\text{K}} \right)
\]

\[
I_{\text{glia}} = g_{\text{glia}} \left( V - E_{\text{Cl}} \right)
\]

Nernst Equation

\[
V = \frac{E_{\text{Na}} g_{\text{Na}}}{g_{\text{Na}} + g_{\text{K}} + g_{\text{Cl}}}
\]

\[
V = \frac{E_{\text{K}} g_{\text{Na}}}{g_{\text{Na}} + g_{\text{K}} + g_{\text{Cl}}}
\]

\[
V = \frac{E_{\text{Cl}} g_{\text{Na}}}{g_{\text{Na}} + g_{\text{K}} + g_{\text{Cl}}}
\]

\[
I_{\text{pump}} = \frac{g_{\text{pump}} \left( V - E_{\text{K}} \right)}{1 + \exp \left( \frac{V - E_{\text{K}}}{\sigma} \right)}
\]

\[
I_{\text{glia}} = \frac{g_{\text{glia}} \left( V - E_{\text{Cl}} \right)}{1 + \exp \left( \frac{V - E_{\text{Cl}}}{\sigma} \right)}
\]

Ion Dynamics

\[
\frac{dE_{\text{Na}}}{dt} = \frac{E_{\text{Na}} - E_{\text{Na}}}{\tau_{\text{Na}}}
\]

\[
\frac{dE_{\text{K}}}{dt} = \frac{E_{\text{K}} - E_{\text{K}}}{\tau_{\text{K}}}
\]

\[
\frac{dE_{\text{Cl}}}{dt} = \frac{E_{\text{Cl}} - E_{\text{Cl}}}{\tau_{\text{Cl}}}
\]

Other Transmembrane Currents

\[
I_{\text{Na}} = \frac{g_{\text{Na}} \left( V - E_{\text{Na}} \right)}{1 + \exp \left( \frac{V - E_{\text{Na}}}{\sigma} \right)}
\]

\[
I_{\text{K}} = \frac{g_{\text{K}} \left( V - E_{\text{K}} \right)}{1 + \exp \left( \frac{V - E_{\text{K}}}{\sigma} \right)}
\]

\[
I_{\text{Cl}} = \frac{g_{\text{Cl}} \left( V - E_{\text{Cl}} \right)}{1 + \exp \left( \frac{V - E_{\text{Cl}}}{\sigma} \right)}
\]

\[
I_{\text{pump}} = \frac{g_{\text{pump}} \left( V - E_{\text{K}} \right)}{1 + \exp \left( \frac{V - E_{\text{K}}}{\sigma} \right)}
\]

\[
I_{\text{glia}} = \frac{g_{\text{glia}} \left( V - E_{\text{Cl}} \right)}{1 + \exp \left( \frac{V - E_{\text{Cl}}}{\sigma} \right)}
\]

The model reduction consists of replacing the time-dependent sodium and potassium currents with time-independent fitted currents.

Error Graph

This is a graph of fitting error for the potassium current. The x-axis is the potassium ratio multiplied by 300, and the y-axis is the sodium ratio multiplied by 300. Physiologically important regions, such as the low potassium ratio strip that represents quiescence, have fitting errors much below 1 mM/sec. Other regions, such as the area near the origin, are fit less accurately, but they are less realistic (the cell is unlikely to find itself in that state).

Bifurcation Diagram

The first part of the project involved "reducing" the full spiking model with dynamic ion concentrations to a model representing only the "slow" ion dynamics. The reduction was performed by time-averaging currents for fixed ion concentration, then fitting the current surfaces using MATLAB. Optimization of the fits involved a combination of human input and computer assistance.

The model exhibits stable periodic trajectories for certain values of parameters, as expected. The model conforms better to the generated data, both in general and in physiologically important regions. Nevertheless, discrepancies between the full model and the reduced model persist, most likely the results of small fitting errors.

Conclusions

- **Reducibility**: Improved agreement with full model (in some respects, but not onset kbath value).
- **Better automated fitting process in future?**
- **Greater flexibility with higher dimensionality?**

References