Analyzing a Neuron Model with 4-Aminopyridine-induced Bursting using Genetic Programming

Jeremy Owen
Mentor: John R. Cressman

Abstract
Mathematical modeling of the neuron has proven successful in providing testable predictions and guiding future experimental work on neuronal behavior. It is sometimes desirable to separate two very different timescales in such a model—to reduce it in order to better study behavior on just one timescale. For example, in Cressman et al. (2009) [1], a modified Hodgkin-Huxley model with dynamic ion concentrations was reduced to remove fast spiking. In order to analyze the novel ion dynamics occurring several orders of magnitude slower, a modification of the model in [1] to mimic the effect of the potassium channel blocker 4-aminopyridine (4-AP) is investigated with the help of symbolic regression by genetic programming. The modified model predicts that the presence of a potassium channel blocker such as 4-AP lowers the threshold at which neuronal bursting occurs. This prediction corresponds to 4-AP-induced seizure inducing effects. While this result is interesting in and of itself, it is expected that the technique used in this research—model reduction by symbolic regression via genetic programming—will be applicable to the analysis of other models.

Introduction
Neurons can exhibit a range of different behaviors:

- Spontaneous Spiking
- Bursting
- Tonic Spiking

Similarly, the model studied in this project exhibits different kinds of behavior depending on the parameter values used. The potassium channel blocker 4-aminopyridine (4-AP) is known to induce seizures in experimental brain slice preparations. In this project, a modification of the model from Cressman et al. (2009) was made to incorporate the effects of 4-AP, with the expectation that the modification would result in increased excitability or seizures at both concentrations of potassium that are normal in vivo. To analyze the 4-AP model, a reduction was performed using techniques similar to those discussed in Cressman et al. (2009), with one innovation—a bio-inspired optimization technique called genetic programming (GP) was used to automate the most laborious part of the process. GP entails evolving tree-like structures, which can be functions or computer programs, to accomplish a certain goal. In this case, GP was used for symbolic regression—building a function to fit some data. A GP algorithm was implemented in Wolfram Mathematica for this purpose. The key components of the implementation, as with any GP algorithm, were procedures to "memorize" a functional expression, to "crossover" two expressions, mixing terms or other aspects of the expressions, and to "select" the best expressions from the pool of evolved expressions.

Methods

- **Full Model**
  - Hodgkin-Huxley model with dynamic ion concentrations

- **Reduced Model**
  - Modified Hodgkin-Huxley model

To analyze the model, a model reduction had to be performed. The technique used was the same as that used by Cressman et al. (2009), with one innovation—the surface-fitting was done using genetic programming, not only finding parameters to optimize a functional form, but actually constructing the functional form from basic functional building blocks. All the surfaces to be fitted resembled the diagram above. The blue region is very flat, and is joined to the rest of the curve at a very sharp rise. To accurately fit the surfaces, the algorithm was directed to fit the flat part (corresponding to resting) and the curved part (corresponding to bursting) separately.

Comparison of Fitted Curve and Data

The GP-generated fit, red, compared to the potassium current, blue, for a given value of the sodium ratio. Note the step near 0.06, which corresponds to the transition from resting to bursting in the model.

**Model Equations**

- **Hodgkin-Huxley**
- **Nernst Equation**
- **Other Transmembrane Currents**

The model reduction consists of replacing the time-dependent sodium and potassium currents with time-independent fitted currents. To incorporate 4-AP in the model, a constant $\frac{26.64}{[K]}$ was multiplied to the potassium voltage-gated conductance.

Time-Averaged Potassium Current of "No 4-AP" Model

The model equations are as follows:

- $\frac{dV}{dt} = \frac{g_{Na}V(V-E_{Na})}{C_m} + \frac{g_{K}V(V-E_{K})}{C_m} - I_{ext}$
- $I_{Na} = \frac{g_{Na}m^3h(V-E_{Na})}{C_m}$
- $I_{K} = \frac{g_{K}V(V-E_{K})}{C_m}$

**Phase Plane Diagrams for Various Parameter Values**

- **A**
- **B**
- **C**

The bifurcation diagram compares the with 4-AP (in red) and without 4-AP (in blue) models. The diagram shows that with 4-AP, bursting starts earlier in the $KB$ parameter, and that the oscillations are smaller in amplitude.

**Bifurcation Diagram**

The numerical solution of a system of differential equations will describe the time evolution of several variables (one for each equation) from an initial state. To visualize a solution, we can plot each variable against time, or, we may choose to plot variables against each other, as in a parametric plot. This is called a phase portrait or phase plane diagram.

- Four phase portraits are shown above and to the left, showing the evolution of the sodium and potassium concentrations over time. The orange line is the potassium nullcline, where the gradient of the potassium concentration is zero, and green line is the sodium nullcline. The white line is the solution trajectory.

**Results**

- **A**
- **B**
- **C**

This bifurcation diagram compares the with 4-AP (in red) and without 4-AP (in blue) models. The diagram shows that with 4-AP, bursting starts earlier in the $Kbath$ parameter, and that the oscillations are smaller in amplitude.

**Conclusions**

- Increased automation of reduction in future, perhaps using island model?
- 4-AP-induced seizures might require external stimulation of neuron, as model does not show intrinsic bursting at resting potassium concentrations.
- Possible future modification of the model—specific channelopathies believed to be implicated in epilepsy?

**References**


Jeremy Owen

Analyzing a Neuron Model with 4-Aminopyridine-induced Bursting using Genetic Programming

Jeremy Owen
Mentor: John R. Cressman

Abstract
Mathematical modeling of the neuron has proven successful in providing testable predictions and guiding future experimental work on neuronal behavior. It is sometimes desirable to separate two very different timescales in such a model—to reduce it in order to better study behavior on just one timescale. For example, in Cressman et al. (2009) [1], a modified Hodgkin-Huxley model with dynamic ion concentrations was reduced to remove fast spiking. In order to analyze the novel ion dynamics occurring several orders of magnitude slower, a modification of the model in [1] to mimic the effect of the potassium channel blocker 4-aminopyridine (4-AP) is investigated with the help of symbolic regression by genetic programming. The modified model predicts that the presence of a potassium channel blocker such as 4-AP lowers the threshold at which neuronal bursting occurs. This prediction corresponds to 4-AP-induced seizure inducing effects. While this result is interesting in and of itself, it is expected that the technique used in this research—model reduction by symbolic regression via genetic programming—will be applicable to the analysis of other models.

Introduction

Neurons can exhibit a range of different behaviors:

- Spontaneous Spiking
- Bursting
- Tonic Spiking

Similarly, the model studied in this project exhibits different kinds of behavior depending on the parameter values used. The potassium channel blocker 4-aminopyridine (4-AP) is known to induce seizures in experimental brain slice preparations. In this project, a modification of the model from Cressman et al. (2009) was made to incorporate the effects of 4-AP, with the expectation that the modification would result in increased excitability or seizures at both concentrations of potassium that are normal in vivo. To analyze the 4-AP model, a reduction was performed using techniques similar to those discussed in Cressman et al. (2009), with one innovation—a bio-inspired optimization technique called genetic programming (GP) was used to automate the most laborious part of the process. GP entails evolving tree-like structures, which can be functions or computer programs, to accomplish a certain goal. In this case, GP was used for symbolic regression—building a function to fit some data. A GP algorithm was implemented in Wolfram Mathematica for this purpose. The key components of the implementation, as with any GP algorithm, were procedures to "memorize" a functional expression, to "crossover" two expressions, mixing terms or other aspects of the expressions, and to "select" the best expressions from the pool of evolved expressions.

Methods

- **Full Model**
  - Hodgkin-Huxley model with dynamic ion concentrations

- **Reduced Model**
  - Modified Hodgkin-Huxley model

To analyze the model, a model reduction had to be performed. The technique used was the same as that used by Cressman et al. (2009), with one innovation—the surface-fitting was done using genetic programming, not only finding parameters to optimize a functional form, but actually constructing the functional form from basic functional building blocks. All the surfaces to be fitted resembled the diagram above. The blue region is very flat, and is joined to the rest of the curve at a very sharp rise. To accurately fit the surfaces, the algorithm was directed to fit the flat part (corresponding to resting) and the curved part (corresponding to bursting) separately.

Comparison of Fitted Curve and Data

The GP-generated fit, red, compared to the potassium current, blue, for a given value of the sodium ratio. Note the step near 0.06, which corresponds to the transition from resting to bursting in the model.

**Model Equations**

- **Hodgkin-Huxley**
- **Nernst Equation**
- **Other Transmembrane Currents**

The model reduction consists of replacing the time-dependent sodium and potassium currents with time-independent fitted currents. To incorporate 4-AP in the model, a constant $26.64 \ln [K]$ was multiplied to the potassium voltage-gated conductance.

Time-Averaged Potassium Current of "No 4-AP" Model

The model equations are as follows:

- $\frac{dV}{dt} = \frac{g_{Na}V(V-E_{Na})}{C_m} + \frac{g_{K}V(V-E_{K})}{C_m} - I_{ext}$
- $I_{Na} = \frac{g_{Na}m^3h(V-E_{Na})}{C_m}$
- $I_{K} = \frac{g_{K}V(V-E_{K})}{C_m}$

**Phase Plane Diagrams for Various Parameter Values**

- **A**
- **B**
- **C**

The bifurcation diagram compares the with 4-AP (in red) and without 4-AP (in blue) models. The diagram shows that with 4-AP, bursting starts earlier in the $Kbath$ parameter, and that the oscillations are smaller in amplitude.

**Results**

- **A**
- **B**
- **C**

This bifurcation diagram compares the with 4-AP (in red) and without 4-AP (in blue) models. The diagram shows that with 4-AP, bursting starts earlier in the $Kbath$ parameter, and that the oscillations are smaller in amplitude.

**Conclusions**

- Increased automation of reduction in future, perhaps using island model?
- 4-AP-induced seizures might require external stimulation of neuron, as model does not show intrinsic bursting at resting potassium concentrations.
- Possible future modification of the model—specific channelopathies believed to be implicated in epilepsy?

**References**