Mathematical Modeling of a Central Nervous System Catecholaminergic Cell Line

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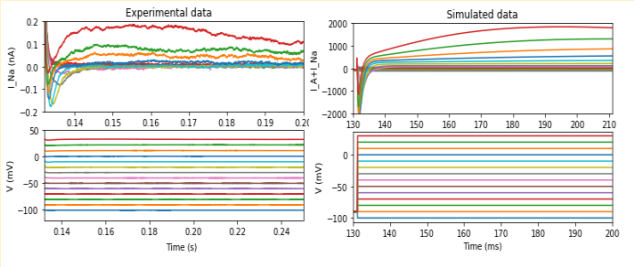
Abstract / Introduction

Neurons are brain cells that produce electrical signals called action potentials (APs) to communicate with each other and transmit information about the external world or the internal brain state. Different types of neurons use different combinations of voltage-gated ionic currents to produce APs, and the interaction of these currents can be complex. CAD cells are a type of neuron for which the AP generation mechanism has not been extensively studied. We are using mathematical modeling to characterize the ionic currents within CAD cells and understand how these cells generate APs.

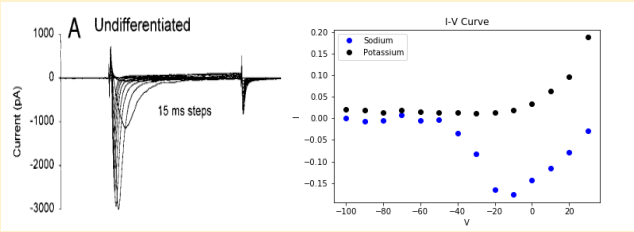
Results

When we used the original parameters, the model did not match up to the data. We had to adjust the time constants in the A-current equation to get a graph that was comparable to the actual lab results.



A comparison between the experimental data from the lab and simulations of a voltage-clamp experiment including the Hodgkin-Huxley Na^+ current and a modified version of the Connor-Stevens transient K^+ current.

We then used the voltage-clamp data to construct an I-V curve, and we found that our CAD cells exhibit much more potassium current than the CAD cells the Wang and Oxford paper

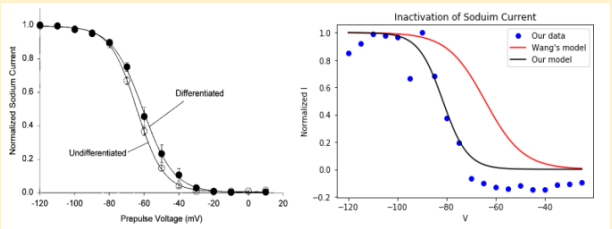


Left: I-V curve from Wang and Oxford (2000), showing sodium current (white triangles) and potassium current (black dots). **Right**: I-V curve from our data, showing much more potassium current (black dots) relative to our sodium current (blue dots) than the Wang and Oxford data. Note that our currents are expressed in different units than theirs.

We also used the varying prepulses lab results and compared it to the findings of Wang and Oxford, found the peak sodium current for each prepulse and plotted it as a function of the prepulse voltage. We then fit a curve to these points using the equation:

$$I_{Na(norm)} = 1/\{1 + \exp[(V - V_{0.5})/k]\}$$

In Wang's data, he had $V_{0.5}$ = -64.3 mV and k = 7.7 mV. However, these parameters did not fit our data, so we changed the parameters to better fit ours. Our fit has $V_{0.5}$ = -81.2 mV and k = 5.0 mV.



Significance

CAD cells are catecholaminergic, meaning that when they fire action potentials they release catecholamine neurotransmitters such as dopamine, adrenaline, and noradrenaline. Disruptions in the release of catecholamines are associated with nervous system disorders such as Parkinson's disease and mental illness. The mathematical model of CAD cell electrical activity that we are building could potentially be used in future research aimed at modulating ion channels to treat nervous system disorders.

Objectives

- Simulate canonical neuronal models such as Hodgkin-Huxley and Connor-Stevens to gain a general understanding of membrane excitability
- Analyze voltage-clamp data from CAD cells provided by the Golowasch lab
- Create a mathematical model by fitting to the CAD cell data
- Use the model to explain why the CAD cells in the Golowasch lab do not fire action potentials, in contrast to the CAD cells in the Wang and Oxford (2000) paper that do fire action potentials

Methods

We used the equations and parameters given by Hodgkin-Huxley's model found in the Ermentrout and Terman (2010) textbook and made adjustments as necessary.

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n = (n_\infty(V) - n)/\tau_n(V),$$
$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m = (m_\infty(V) - m)/\tau_m(V),$$
$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h = (h_\infty(V) - h)/\tau_h(V).$$

If $X = n, m,$ or h, then

$$X_\infty(V) = \frac{\alpha_X(V)}{\alpha_X(V) + \beta_X(V)} \quad \text{and} \quad \tau_X(V) = \frac{1}{\alpha_X(V) + \beta_X(V)}. \qquad (1.42)$$

We used Python to solve the model equations and plot the solutions. The function odeint, a differential equation solver found in the SciPy library, was used to solve the ODEs given the initial values.

The Golowasch lab used patch-clamp electrophysiology to record ionic currents from CAD cells that would assist us in our research.

We will compare our data to previous studies of these cells, in particular Wang and Oxford (2000)

Conclusions / Future Directions

- We found that the CAD cells in the Golowasch lab express more potassium current (relative to the sodium current) than in the Wang and Oxford paper
- We found that the CAD cells in the Golowasch lab have a sodium current that inactivates at more hyperpolarized voltages than in the Wang and Oxford paper
- Both of these results potentially explain why the CAD cells in the Golowasch lab do not fire action potentials, whereas they do in the Wang and Oxford paper

References / Acknowledgements

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Equations and graphs referenced from Ermentrout, Bard and Terman, David (2010), *Mathematical Foundations of Neuroscience,* Springer, pages 23, 24, 25, 50, and Wang, Haibin, and Oxford, Gerry (2000). "Voltage-Dependent Ion Channels in CAD Cells: A Catecholaminergic Neuronal Line That Exhibits Inducible Differentiation." *Journal of Neurophysiology,* 84:2888-95.

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