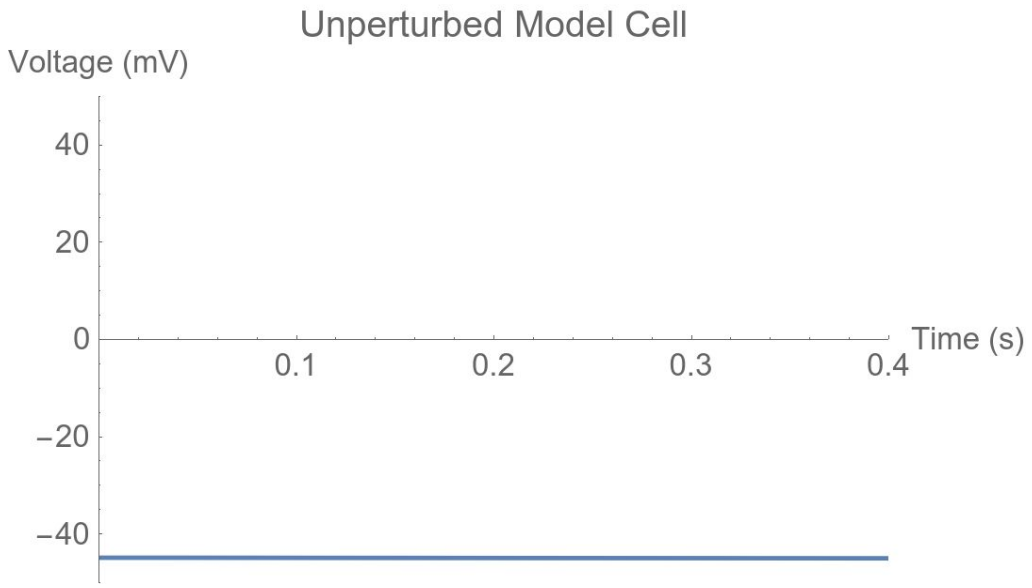
Discussion

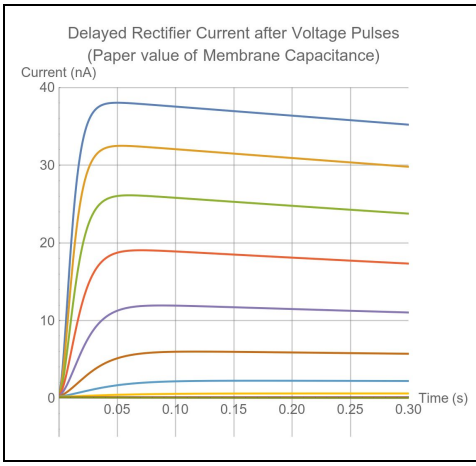
It perhaps makes the most sense to begin discussing our results in relation to the discrepancies with the paper's results. In biological data as well as the original results, tonic firing is expected at a baseline voltage of -45 to -50 mV -- that is, the model should give regular, unceasing action potentials without perturbations such as voltage clamp or current clamp conditions (Wang 2014). Also noted in the paper is that the sodium current should drive this behavior, while contributing mildly to the resting voltage of the cell. This informs a reading of the section describing the sodium current equations, which claims "the parameters were chosen to obtain firing of action potentials when the differential equations were integrated" in the full model cell (Buchholtz pg. 336). When the model is recreated entirely faithful to the values and equations as described in the paper, without the presence of any sort of perturbation, the following graph is obtained:



This presents a problem. A number of questions arose about the paper: it gives two relaxation parameters for the sodium current, for example, in line with other steady-state

equations which lack a voltage-dependent relaxation and instead use a scalar value for relaxation. However, the sodium steady-state equations have Hodgkin-Huxley form voltage-dependent relaxation equations, and the reported parameters do not appear to be used anywhere. Indeed, their scalar values (10000 and 500 for activation and inactivation, respectively) are orders of magnitude different from those given by the stated equations, which range from zero to one. Using these values in lieu of the equations does not illuminate the model any further.

Another issue arises in the given membrane capacitance, 1.7nF. The paper states this value was chosen in order to obtain accurate behavior from the model cell after construction. Indeed, biologically observed values can differ depending on the measurement method, as Golowasch revisited in a 2009 paper (Golowasch 2009). My partner and I worked through the units on individual currents, however, and found that a value of 1700 gave accurate behavior of the individual currents -- otherwise, they vary significantly from what is expected.



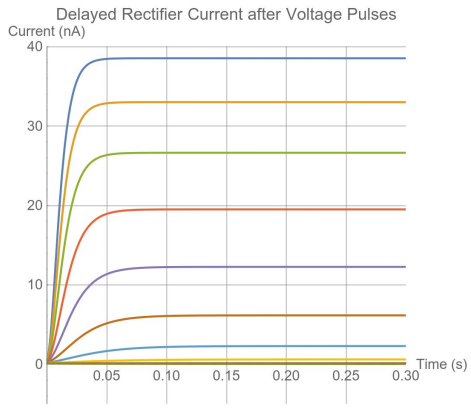


Figure 1A without *(left)* and with *(right)* the altered membrane capacitance.

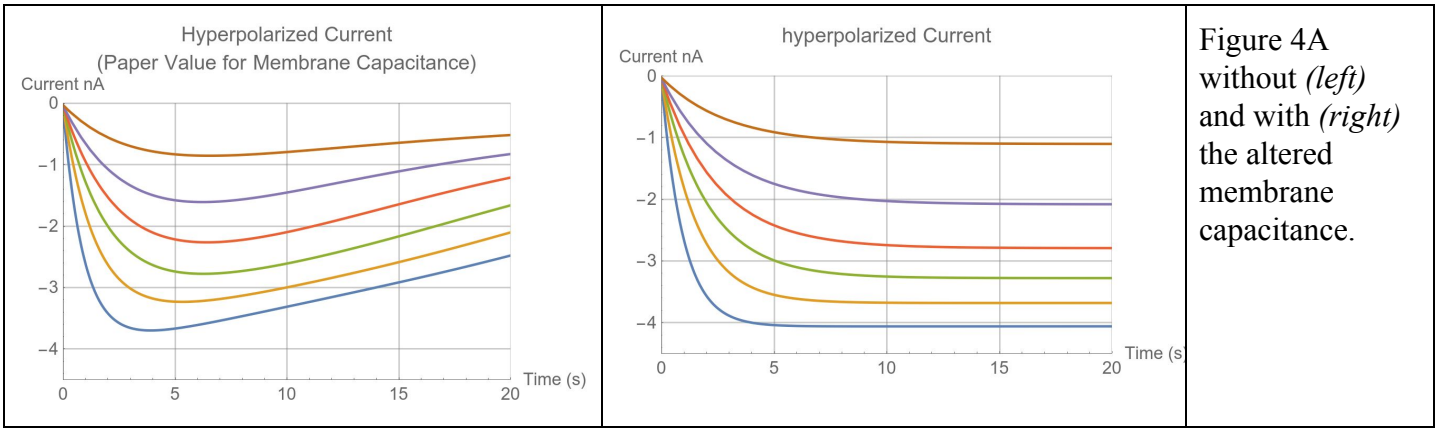


Figure 4A without *(left)* and with *(right)* the altered membrane capacitance.

I bring up these two errant details because they are stated in the paper to be critical to appropriate model performance, yet are presented in an unclear, conflicting fashion.

Original Hypothesis

The paper achieves its stated goal of creating and comparing model data to biological data in part by selectively altering parameter values for the sodium current (which generates action potentials) and the membrane capacitance (which approximates the model to represent where in the cell biological measurements were taken) such that the model was useful to their purposes. What my partner and I have found through our reconstruction is that the model is incredibly sensitive to these parameters and their respective equations to the point that apparent errors in the paper render accurate reconstruction quite difficult.

This has a direct implication to our hypothesis. While troubleshooting the model, my partner and I created models with the currents most important to the creation of action potentials, the delayed rectifier, sodium, and leak currents. The sodium and rectifier currents swing back and forth in dominance between hyperpolarized and depolarized values, which is the fundamental relationship underlying the previously described tonic action potentials. Other currents play critical roles in the cell's response to voltage and current clamp scenario, but those

identified above ought to satisfy our hypothesis that the cell could be broken down into components to better understand the behavior of the cell. However, the sensitive dependencies on particular values and the lack of biological reasoning for the selection of those values makes it useless to attempt to understand the behavior of selected components of the model.

Similar Models and Future Work

The natural next step is to attempt to find our own parameter values that coerce accurate behavior from the model. Mathematica offers the Manipulate tool which allows us to directly search for these values. A reasonable (and likely) plan of action would be to first resolve our model incorporating the delayed rectifier, sodium, and leak currents by themselves. Good examples of neurons modeled in Mathematica can be found in chapter seven of Dr. Hillel Chiel's textbook, *Dynamics of Biological Systems*, (Chiel 2019) as well as directly from the Wolfram Foundation (Marom 2012) (Neske 2011).

That option of simplification exists, but over the years the scope of the field has increased, including in several directions indicated by the paper. A notable example is cable theory, which accounts for the fact that most neurons are not isopotential across their dendrites. An example of this produced by Golowasch in 2009 would be an excellent next step in the study of these systems, especially since it is a two-compartment model, a noted simplification in the paper (Golowasch 2009) (Buchholtz 1992 pg. 338).

Just as in class we examined growth of cells and growth of animal populations as two different, yet closely interrelated problems, the field of neuroscience is able to consider larger networks of neurons in their own models. One of the authors listed in the model paper has done exactly that in a 2018 paper, *Sloppy morphological tuning in identified neurons of the*

crustacean stomatogastric ganglion. Here, the potential for variability between neural network constructs in different specimens and species is explored with an eye for cable theory and statistical testing. The thought of connecting these variations to a model cell is alluring, especially considering the finding that neuronal structures do not obey wiring optimization principles, instead being "governed by a space-filling mechanism that outweighs the cost of inefficient wiring" (Otopalik 2018).

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