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Dynamics of Biological Systems

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Term Paper Proposal

Timothy and I plan to recreate the model present in *Mathematical Model of an Identified Stomatogastric Ganglion Neuron* by Frank Buchholtz, Jorge Golowasch, Irving R. Epstein, and Eve Marder of the departments of Chemistry and Biology, and Center for Complex Systems at Brandeis University. Their paper describes the ionic currents in the LP neuron of *Cancer borealis* with the intention of explaining "how each of the membrane currents in a neuron that is part of a functional network contributes to its dynamical properties" (332). We hypothesize that the interactions between the identified currents in a single-compartment, isopotential model can be isolated and connected to biophysical data despite the impossibility of measuring these currents experimentally and the relative simplicity of the model.

The paper presents 6 ionic currents and a leak current, each with between two and four factors governed themselves by equations. However, this is greatly simplified by the presentation of three standard equations: current, rate, and voltage-dependence. Although each of the six currents has several equations governing it, they are often equations of the same form, differing only in their stated parameters. The delayed rectifier features its own equation, a rate equation, and a voltage-dependence equation, for example, but all three are standard equations as described above. Because the same equation could be used for all of these with a simple pure function to replace all with appropriate parameters, I will count these standard equations only

once. The Ca^{2+}-activated outward current introduces two additional equations governing activation and inactivation and their dependence on concentration of the ion, which is itself governed by a single equation. The fast Na^{+} current complicates the standard equations enough to justify their inclusion in our state variable count, adding three additional equations representing its instantaneous activation (hence the name). The currents are summed into a final differential equation describing membrane potential. This brings us to a total of 16 distinct equations governing the state of the system. The parameters are all given in a table, totalling 72, with additional commonly known constants used, such as Faraday's constant.

The instantaneous activation of the fast Na^{+} current is one of the simplifications the model makes. The model is single compartment, when it is believed that the cell actually has more than one. The equations themselves are simplified to be more similar to Hodgkin-Huxley equations, which although it prevents detailed description, it follows the data rather well and may cover for the variability inherent in biological systems. The Ca^{2+} buffering system is on a much shorter time scale than is found in biological data -- the system corresponds to averages of [Ca] throughout the entire volume of the cell, and so does not give an accurate definition of actual kinetics. On the whole the model still performs remarkably in matching the data compared. Importantly, the model overshoots action potentials despite following them rather well, and has capacitance lower than measured values. This leads to perhaps the most important wrinkle in the model: it only represents a smaller area of the cell's total surface, the action-potential initiation zone.

Since the three standard equations are present throughout, they will appear first in an attempt to recreate the model. Parameters will need to be entered for the equations they are

useful in: due to the nature of the currents, almost all parameters are only relevant to one equation. It may prove useful to set up the entries by ionic current, so that each one will have its parameters defined in a first cell and its equations called in a second. The standard equations will be called and given their values for the individual currents. For those currents whose equations are specific as outlined above, additional equations will be defined. It will prove useful to have a separate definition of the Ca^{2+} buffering system as well. Finally, the current equations will be summed by the membrane capacitance equation.

The paper describes its methods of simulating current clamp and voltage clamp experiments, and graphs its model curves overlapped with biological data. All of these graphs should be reproducible following the paper's outlined procedures. The paper itself is extended in a follow up paper, which explores additional currents, the effects of peptides on the neuron, and comparing blocking currents in the model with known biological methods of blocking specific currents. We can follow those lines by choosing currents without biological data to block, and observing what happens to the model under those conditions. This may allow us to make predictions about neuron behavior in extreme cases not yet observable through experiment. Varying parameters such as volume and background [Ca] will allow us to see how the currents might be affected by size, particularly in the interplay between the two [Ca] reliant currents and the others. These extensions will have interesting consequences for our hypothesis in that they will allow us to observe interactions that may not be possible in experimental settings. However, due to the relative simplicity of the model and despite its strong performance in matching biological data, the model cannot be trusted to make definitive claims from; rather, it may prove a useful launchpad and compass for future modelling and experimentation.

References

Buchholtz, F., Golowasch, J., Epstein, I. R., & Marder, E. (1992). Mathematical model of an identified stomatogastric ganglion neuron. Journal of Neurophysiology, 67(2), 332-340. doi:10.1152/jn.1992.67.2.332