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Dynamics of Biological Systems

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Model Plan

Hypothesis

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. We will test this hypothesis by using the model to do voltage clamp experiments that isolate individual currents which are, biologically, impossible to clamp and/or measure directly. Of particular interest is the Fast Na^+ current, for which biological data does not exist. We will ensure the accuracy of the results by comparing overall model reactions to stimuli for which similar reaction data is available for biological experiments.

Table 1: Parameters

Conductance	**Maximum Conductance (µS)**	**Reversal Potential (mV)**	**Rate Constant (s^{-1})**	**Half-Maximal Potential (mV)**	**Step Width (mV)**	**Other Parameters**
Delayed Rectifier	$\bar{g}_d = 0.35$	$E_k = -80$	$C_n = 180$	$V_n = -25$ $V_{kn} = 10$	$S_n = -17$ $S_{kn} = -22$	
Ca^{2+}-Activated Outward	$\bar{g}_{0(Ca)} = 3.2$	$E_k = -80$	$K_{0a} = 600$ $K_{0b} = 35$ $K_{Ca} = 360$	$V_{a01} = 0$ $V_{a02} = -16$	$S_{a01} = -23$ $S_{a02} = -5$	$f = 0.6$ mV/µM $c_1 = 2.5$ µM $c_2 = 0.7$ µM $c_3 = 0.6$ µM $[Ca^0] = 0.05$ µM $c_{iCa} = 300$ µM/nC
A-Current	$\bar{g}_A = 2.2$	$E_k = -80$	$K_A = 140$ $K_{A1} = 50$ $C_{A2} = 3.6$	$V_A = -12$ $V_B = -62$ $V_{A2} = -40$ $V_X = 7$	$S_A = -26$ $S_B = 6$ $S_{A2} = -12$ $S_X = -15$	
Ca^{2+}	$\bar{g}_{Ca1} = 0.21$ $\bar{g}_{Ca2} = 0.047$	E_{Ca} *	$K_{aCa1} = 50$ $K_{bCa1} = 16$	$V_{aCa1} = -11$ $V_{bCa1} = -50$	$S_{aCa1} = -7$ $S_{bCa1} = 8$	

			$K_{aCa2} = 10$	$V_{aCa2} = 22$	$S_{aCa1} = -7$	
Inward Rectifier	$\overline{g}_h = 0.037$	$E_h = -10$	$C_r = 0.33$	$V_r = -70$ $V_{kr} = -110$	$S_r = 7$ $S_{kr} = -13$	
Fast Na^+	$\overline{g}_{Na} = 2300$	$E_{Na} = 50$	$K_m = 10000$ $K_h = 500$	$V_{am} = -6$ $V_{bm} = -34$ $V_{ah} = -39$ $V_{bh} = -40$	$S_{am} = -20$ $S_{bm} = -13$ $S_{ah} = -8$ $S_{bh} = -5$	$c_{am} = 0.11$ mV^{-1} $c_{bm} = 15$ $c_{ah} = 0.08$
Leak	$\overline{g}_l = 0.1$	$E_l = -50$				$C_m = 1.7$ nF

Notes on Parameters

The currents are the ionic currents moving through the membrane of a lateral pyloric (LP) cell of the stomatogastric ganglion (STG) of the rock crab, *Cancer Borealis*. Maximum Conductances, reciprocals of resistances, reflect the 'ease' of flow for ions through membrane passages. Reversal Potential (also known as the Nernst Potential) is the membrane voltage where no particles flow in either direction. It is named as such because it indicates the point where current flow will switch directions. Rate constants indicate the particular current's pace of relaxation or activation given stimulus. Half-Maximal Potential is the potential where $a_\infty(V)=½$. Step Width is, according to the paper, "the range of potentials centered at V_a over which $a_\infty(V)$ varies from ~0 to ~1". The other parameters are specific to each current. For example, the Ca-activated outward current relies on concentration of Ca, and thus initial concentration is given as a parameter.

State Variables

The system incorporates 7 currents determining membrane potential. Each current is different, but they are largely described by 3 standard equations: standard current, standard rate, and standard voltage dependence. Important to note is that in each current, activation depends on voltage dependence (which of course depends on voltage); inactivation is similar.

Important to note is the relationship between the outward-activated Ca^{2+} current and the Ca^{2+} current; the outward current depends on the inner current, and both depend on the Calcium ion concentration. This is effectively three coupled differential equations within the larger system. Also, note that the transient A-like current includes a weighting factor that weighs the

contribution of its two inactivation processes, such that the slower term is favored at low voltages, and the faster term at depolarized voltages. This represents an extra equation (and thus calculation). These two are the most complicated of the currents; the rest follow the standard patterns and will be easy to recreate simply by changing parameters and adding/removing standard equations.

Table 2: Current Descriptions

Delayed Rectifier	An outward current with a long voltage-dependent delay and no inactivation. It acts in the cell as a rectifier acts in a circuit.
Ca^{2+} outward-activated	This current is relatively complex. It relies on calcium concentration for its activation and inactivation factors, which in turn is affected by the inward calcium current.
Transient A-like	The current has two inactivation factors, and a weighting factor to determine which controls it; the slower term is favored at low voltages, and the faster term at depolarized voltages.
Ca^{2+}	There are two components displaced in voltage from one another controlling the current. The first has an inactivation factor, and the second does not. They are summed to determine overall impact. This affects the amount of Calcium in the cell.
Inwardly Rectifying, or Hyperpolarization Activated	This slow current is activated at voltages more hyperpolarized than the resting potential. There is no inactivation observed, or included in the model. Instead, it's relaxation rate cause it to diminish as the cell grows less polarized.
Fast Na^{+}	The current is generated far from the cell body, and thus not measurable in biological experiments. The activation is much faster than any other current, and in the model is instantaneous. The parameters were set so as to observe firing action potentials. The voltage dependencies are in Hodgkin-Huxley form.
Leak	The linear component of the steady-state current-voltage (I-V) curve. This lacks an activation or inactivation, as it is linear. Maximum capacitance was measured by the input conductance of the LP neurons in the region of the I-V curve with lowest conductance.

<u>Calculating Results</u>

The paper builds each current and creates time plots of the membrane potential **for the particular current** and compares to biological data, if it exists (the recreation of these will be intermediate goals, as is described in the timeline below). If it does not, the paper simply incorporates it into similar graphs for the overall model and compares to overall data. We intend to recreate each of these graphs, if feasible. Our model can be compared to the graphs containing biological data in the paper.

The paper finds some parameters by adjusting their values so that currents line up with biological data. This could provide an interesting opportunity to construct Manipulate functions in Mathematica, in order to see what values give the best fits. In particular, eigenvalues could be calculated and inspected similarly to Problem One at the end of Chapter 7.

Bifurcation diagrams describing the calcium concentration's effect on both the two calcium currents and the overall model will be a valuable observation. It may be possible that calcium concentration can be suppressed so we can identify the relationship between the two currents. This would be an opportunity for extension.

Model Calculations: Ordering

The most complex ion streams, the two calcium streams, are coupled together and with the concentration of calcium. Calcium concentration should be calculated first, followed by the voltage dependencies and current of the inward calcium current. These can then be used to find the outward-activated calcium current. The calcium concentration is updated by the inward calcium current, so concentration must be calculated first at each step.

Next should follow the remaining currents, which can occur in tandem since they are not directly coupled. Finally, the currents are summed to determine membrane capacity, the final step. This should all be updated over a period of time in order to recreate graphs of the full neuron potential. Individual currents can be looked at by setting other current's maximum capacities to zero, thus allowing a membrane capacity to be calculated based solely on the particular current.

Since the membrane potential equation simply sums individual currents, it is trivial to add or remove currents. This provides an avenue for expansion, as is noted in the paper's Discussion section.

Tentative Schedule (**goals bolded**)

- 3/21: **Create the Delayed Rectifier current in Mathematica**; test for different voltages; determine optimal way to organize parameters
- 3/26: **Finish Calcium currents**; test their complex coupling; combine with Delayed Rectifier to begin completing the model
- 3/28: Work towards finishing all currents; continue testing different voltages; work on model description
- 4/2: same as above; have model description complete
- 4/4: **Try to have full model working by today**; if so, begin attempting to validate with data in paper; if not, finish model
- 4/9: **Have at least one graph recreated from paper**; ensure notebooks are up to par; work towards completion of third benchmark
- 4/11: **Finish recreating graphs from model**; finish validation of model; outline paper, results
- 4/16: Feel confident in model and its operation; begin testing extensions; **benchmark 3 due**
- 4/18: attempt to have at least one solid extension item completed; continue drafting paper
- 4/23: **draft full paper**; attempt a presentation
- 4/25: put finishing touches on paper; **Present**
- 4/29: **Term Paper Due**