580.439/639 Midterm Exam, 2014

Do all problems. 1 hour, closed book except for a 1-page help sheet. You can choose not to answer any two questions, but make that clear on your paper (i.e. which two). It's always unwise to skip the first or second part of a multi-part problem. All parts have equal value (14 points plus 2 for your name).

Problem 1 (One or two sentences is sufficient for each of these.)

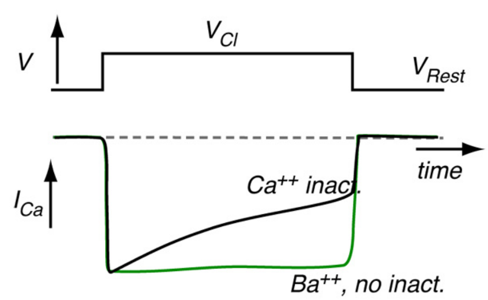
Part a) A transporter model moves one hydrogen ion (H^+) and one neutral molecule X into the cell in a coupled fashion. What term does the overall flux equation of a model of this system need to contain in order to properly model zero flux at equilibrium?

Part b) Consider a system in which a reaction like that below occurs

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} C$$

Give a condition that is sufficient to specify that *A, B,* and *C* are at equilibrium, or a definition of equilibrium for this system, and a second for steady state.

Problem 2



L-type calcium channels show Ca^{++}-dependent inactivation, but no voltage-dependent inactivation. In Ca inactivation, the I_{Ca} through the channel provides calcium ions that bind to the channel on the interior of the membrane, partially inactivating it. An example is provided in the figure at right. A depolarizing voltage clamp (V_{Cl}) is applied to a membrane containing Ca^{++} channels. When Ca^{++} is carrying the current (black trace), the response is a significant inward current that partially inactivates (decreases with time). As evidence, when Ba^{++} replaces Ca^{++} in the extracellular space, there is still a current (green trace) because Ba^{++} is permeable through Ca^{++} channels, but no inactivation because Ba^{++} doesn't bind to the inactivation system.

Part a) Write down the equations of an approximate model for this process containing the elements listed below. Note that this is a voltage clamp, so *V* is fixed as drawn above, and appears in the equations as a constant parameter, not a state variable.

1) Membrane depolarization opens activation gates in the Ca^{++} channels, admitting a Ca^{++} current.

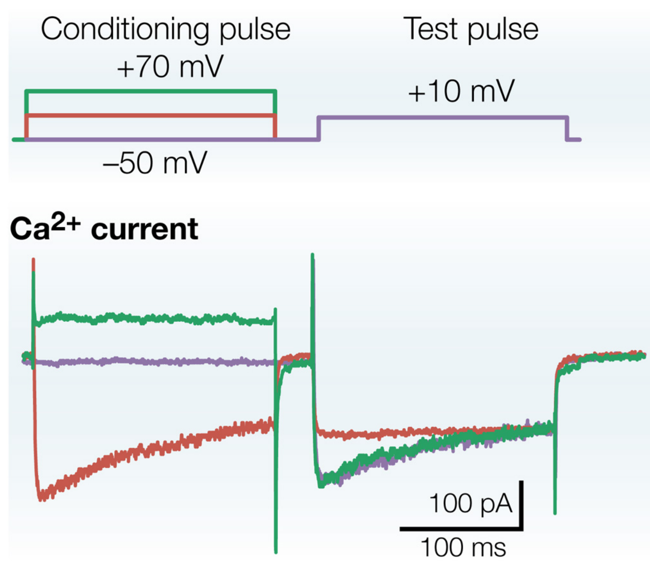
2) Ca^{++} accumulates in a certain volume *Vol* near the channels on the inside of the membrane. Ca^{++} escapes from this volume via diffusion at a rate $p \cdot Ca$.

3) The Ca^{++} binds to the channel according to the reaction $Ca + Ch \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CaCh$ where *Ch* is unbound channel and *CaCh* is bound channel. The channel in state *Ch* is non-inactivated whereas the channel in state *CaCh* is inactivated.

You will need three differential equations, one for each of three state variables.

Part b) When V_{Cl} is fixed at some interesting potential and the system of part a) comes to an equilibrium point, what are the values of the state variables at this point?

Part c) Consider the experiment in the figure at right, taken from Budde et al. *Nature Rev. Neurosci*. 3:873 (2002). A conditioning voltage clamp to one of three three voltages (-50 mV purple, +10 mV red, or +70 mV green) is followed by a test voltage clamp to +10 mV (which normally gives the largest I_{Ca}). Calcium inactivation is seen in the red trace during both the conditioning pulse (at V=+10 mV) where current declines with time, and during the test pulse where the current is fully inactivated at the beginning and shows no further decline. By contrast, the purple and green traces show no sign of inactivation during the conditioning pulse, but still show full inactivation during the test pulse. Answer the following questions:



1) Why is there no inactivation during conditioning in response to the green and purple traces? For each condition, tell which state variable from your model produces the effect, inactivation or no inactivation? (Hint, look at the signs and amplitudes of the currents in response to the conditioning).

2) Which state variable provides the memory of the conditioning from the first to the second pulse? Justify you answer (if you can; you may not be able to guess).

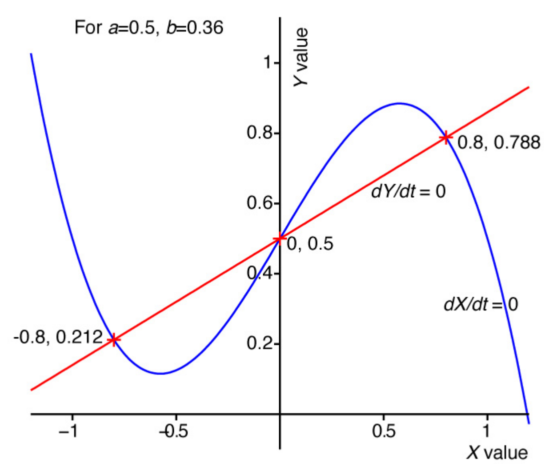
Problem 3

Consider the system with the phase plane drawn at right for a system with state variables X and Y (similar in shape to a MLE or HH phase plane with X playing the role of membrane voltage and Y playing the role of a HH gating variable). The phase plane shows the nullclines which are given by the equations:

$$Y_X = a - X(X-1)(X+1)$$

$$Y_Y = bX + a$$,

where Y_X is the nullcline for dX/dt = 0 and Y_Y is the nullcline for dY/dt = 0. The values of the parameters and the equilibrium points are marked on the graph. For this, assume a and b are as given on the plot.



Part a) Write a set of differential equations whose phase plane looks like the one above. There is not a unique way to do this for two (and more) reasons: (1) The phase plane is not sensitive to the sign of the r.h.s. of the differential equations; (2) One or both equations can be multiplied by a constant (like the “temperature” parameter discussed in class) without changing the phase plane. To eliminate the ambiguity, write the equations so that they contain a term in Y as below:

$$\frac{dX}{dt} = -Y + \cdots \quad \text{and} \quad \frac{dY}{dt} = -\phi Y + \cdots \quad ,$$

where $\phi > 0$.

Part b) So far, a system with three equilibrium points like the one drawn above always has always had a saddle node as the middle point (the one at $X=0$). Show that the middle equilibrium point in the system above is always a saddle for the constraints of part a), regardless of ϕ.

Part c) Often a system like this one has a low temperature limit cycle when ϕ is very small. Argue that the locations of the equilibrium points at X = -0.8 and +0.8 do not allow such a limit cycle. Although you haven’t proven it, you can easily show that both equilibrium points are stable for the parameters above, which is necessary for your argument.

Part d) Suppose the constraints of part a) are changed to reverse the sign of the r.h.s. of the equation for dX/dt.

$$\frac{dX}{dt} = +Y + \cdots \quad \text{and} \quad \frac{dY}{dt} = -\phi Y + \cdots$$

Show that the middle equilibrium point is now always stable.