580.439/639 Final Exam

Answer all questions. Closed book except for two pieces of paper. Point values are indicated, for a total of 100.

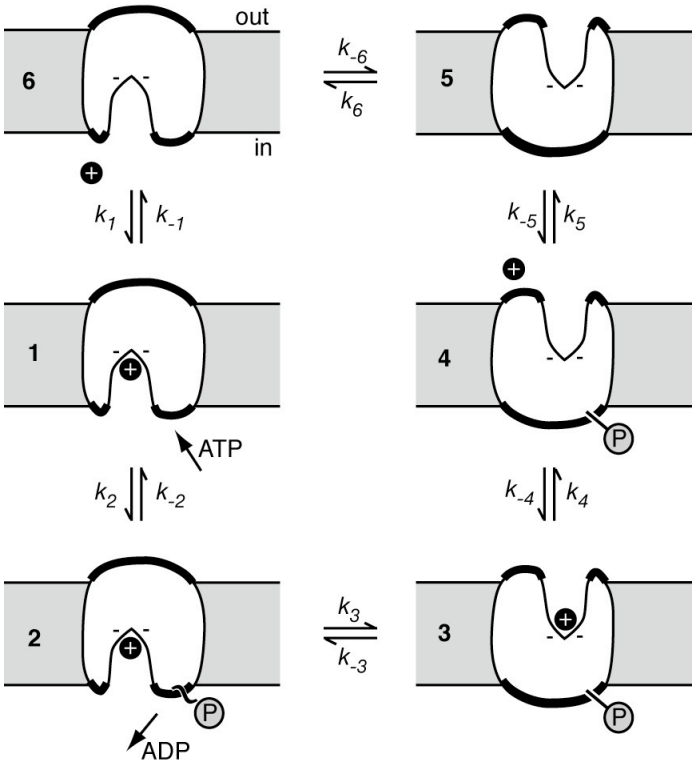
Problem 1

Calcium is released from a cell's internal compartment (like the ER or SR) into the cytoplasm.

Part a) (5 points) Does the membrane potential change directly as a result of that Ca current (i.e. as a direct result of the charge carried by the Ca current)?

Part b) (5 points) Explain how the membrane potential could change due to the calcium release

Problem 2



This problem concerns an imaginary active-transport enzyme E for a cation L^+ which is translated from the intracellular to extracellular space with the hydrolysis of an ATP molecule to provide energy. Based on real ATP-ase pumps, the cyclical sequence of steps is schematized at right. The cycle is assumed to be a sequence of 6 steps, numbered **1** through **6**. At the start of the cycle (state **6**) E has a deep vestibule on its intracellular side. In step **6→1**, an L^+ binds in the vestibule. In step **1→2**, an ATP molecule is hydrolyzed leaving a phosphate group bound to the intracellular surface of E with a high energy bond (~). The energy given up by the ATP molecule in this reaction is transferred to E via this bond. In step **2→3**, E changes conformation, closing its inner vestibule and opening an outer vestibule, In the process L^+ and some charges attached to the protein translate partially through the membrane. The energy in the P-bond is transferred to the protein and to L in this process. In step **3→4,** L leaves the vestibule of E for the extracellular solution. In step **4→5**, the phosphate group leaves E. Finally in step **5→6** E returns to its original conformation with

the vestibule facing the intracellular solution. The process is cyclical, meaning that E is in the same state at the end as at the beginning.

The rate constants for each step are given on the diagram, so k_1 is the forward rate constant for step **6→1**, k_{-1} is the reverse rate constant for the same step, and so on.

Part a) (7 points) Which of the rate constants are likely to be voltage dependent and what is the associated gating charge? Assume the membrane potential V is measured between the inner face of E and its outer face (i.e. between the two heavy lines in the sketches). Assume that L^+ has a valence z_L and that there is a charge z_E associated with the conformational change in moving the vestibule from outside to inside. You will have to define some additional constants. Explain clearly what they are.

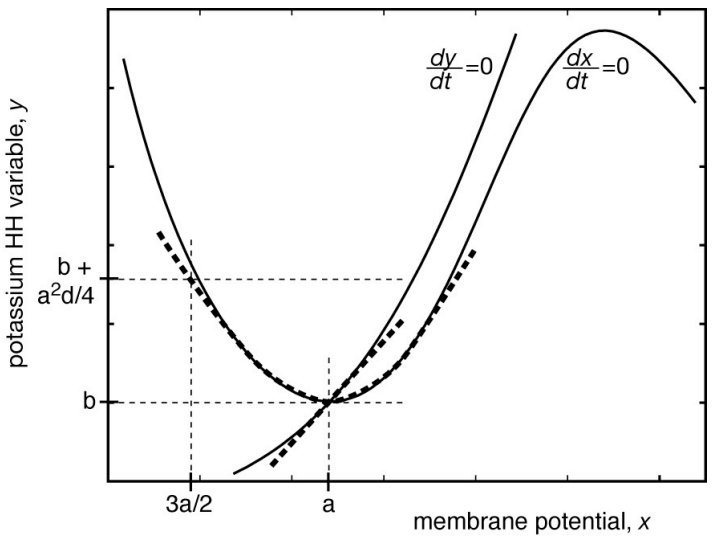
Part b) (7 points) Write down the net reaction for one cycle of the transport process, differentiating between ions in solution 1 and solution 2, etc. By "net" is meant don't include elements that do not change in a cycle. Write an equation for the net molar free energy change $\Delta\mu$ through one cycle of transport.

Part c) (7 points) What is the condition, in terms of the free energies of part b), for the transport to proceed in the forward direction (L goes from side 1 to side 2)? In practice, some energy is lost in each cycle to heat, so the condition should be an inequality.

Part d) (10 points) Consider states **1**, **2**, **3**, and **4**. Draw an energy diagram (free energy on the ordinate, state on the abscissa) that shows the relationships of the free energies of E and L^+. Only show the energy wells, the peaks are not relevant here. Do not include the free energies of ATP and ADP, except to the extent that those are transferred to E and L^+. Be sure to show how the energies in your diagram relate to the free energies considered in part b), i.e. $\Delta\mu_{ATP}$ the energy of hydrolysis of ATP ($\mu_{ADP} + \mu_P - \mu_{ATP}$) and $\Delta\mu_L$ ($\mu_{L2} - \mu_{L1}$), bearing in mind the energy loss mentioned in part c).

Problem 3 (taken from Izhikevich, 2007, p. 154)

For models like the Morris-Lecar equations, the phase plane near the resting potential often looks like the example at right. The $\dot{x} = 0$ nullcline can be approximated by a parabola centered on the equilibrium point (a,b) and the $\dot{y} = 0$ nullcline by a straight line. The approximations are shown by dashed lines.



An idea of the properties of the system near the equilibrium point can be obtained using a system that gives the approximate nullclines. For example, threshold behavior should be apparent in this system.

Part a) (8 points) Write equations for the approximate nullclines as drawn in the figure above, i.e. a parabola for $\dot{x} = 0$ and a straight line for $\dot{y} = 0$. The slope of the line is c. From these, write differential equations, i.e. $dx/dt = X(x,y)$ and $dy/dt = Y(x,y)$ that have these nullclines. There are, of course, many possible answers for the differential equations; for your own benefit in the rest of this problem make these as simple as possible. Add an input current I (which is zero in the plot above) to the appropriate equation. For this and following parts, assume that c and d are positive (>0).

Part b) (6 points) Show that the following system has the same nullclines as the (x,y) system in the figure above, after a suitable change of variables. To show this, it will be easiest to take your differential equation from part a) and do a change of variables to get the following.

$$\begin{aligned} \frac{dv}{dt} &= I + v^2 - u \\ \frac{du}{dt} &= \frac{c}{\sqrt{d}} v - u \end{aligned} \qquad (*)$$

Part c) (6 points) Under what conditions is the equilibrium point of the system in (*) stable? Define the stability of the equilibrium point for all values of $c/d^{1/2}$. It is unwise to try to solve this part with Lyapunov.

Problem 4

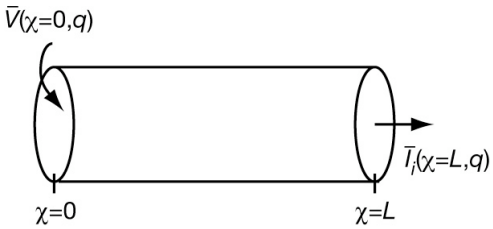
Consider the following problem for a linear dendritic cable of electrotonic length L with parameters G_∞ and τ_m. As was shown in class, the cable equation takes the following form after being transformed, for example by a Laplace transform from initial conditions or in D.C. steady state:

$$\frac{\partial^2 \bar{V}}{\partial \chi^2} = q^2 \bar{V} \ .$$

$\bar{V}(\chi, q)$ is the transformed membrane potential and q is the transform variable, 1 for D.C. steady state or $\sqrt{1+s}$ for the Laplace-transformed case. The homogeneous solution of this equation is

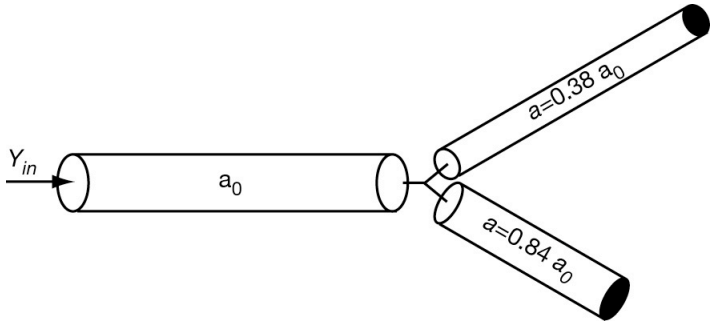
$$\bar{V}(\chi, q) = A(q) e^{q\chi} + B(q) e^{-q\chi}$$

Part a) (10 points) Suppose the finite cable has the boundary conditions shown in the figure at right, a voltage clamp at χ=0 and a current clamp (fixed current) at χ=L. Write equations for $\bar{V}(\chi,q)$ and $\bar{I}_i(\chi,q)$, the membrane potential and axial current in the cylinder; that is, solve for A and B for these boundary conditions and write the equations for the membrane potential and axial current in the cylinder.



Part b) (10 points) Suppose that the cable in the figure above is terminated by an open circuit, i.e. no current flows out the end of the cable at χ=L. Given this condition, compute the input admittance $\bar{Y}_{in} = \bar{I}_i(\chi = 0,q)/\bar{V}(\chi = 0,q)$ of the finite cable for this special case. Use the equations derived in part a).

Part c) (7 points) Consider the branched dendritic tree sketched below. All three cylinders have electrotonic length L and the radii indicated. The boundary condition at the right-hand end of the two daughter cylinders is zero-current as in part b). What is the input admittance Y_{in} of this tree? There is an easy way and a hard way to do this. The easy way involves your result in part b). (Hint: why is there so much attention paid to the radii of the cylinders?)



Problem 5

Part a) (6 points) Describe three ways in which dendritic trees are non-linear, i.e. ways in which summation of inputs in dendrites departs from the predictions of linear cable theory with inputs applied by current injection.

Part b) (5 points) Real neurons have thousands of synaptic inputs, all of which are active at some moderate rate in vivo. What should be the effect of the activation of postsynaptic channels in this way on the electrotonic parameters of a cable (e.g. electrotonic length, input admittance, time constant, and voltage gain from a synaptic site to the soma)? Assume, for simplicity that some fraction of the channels are active at all times, so that the effect of the synaptic activity can be considered to be a steady moderate synaptic input. Detailed analysis of these issues is not necessary, but some equations are necessary.

Part c) (5 points) In one paper, the authors reported that when they injected DC currents into the dendritic tree of a cell, the amplitude of the depolarization of the soma decreased approximately exponentially with the distance of the site of current injection from the soma. In a different paper, the authors report that the size of EPSPs evoked in the soma, by activation of dendritic synapses at different distances from the soma, is roughly constant, independent of the distance of the synapse from the soma. Explain how these two apparently contradictory results could be obtained in the same cells. Again, detailed analysis of these issues is not necessary, but some equations are helpful.