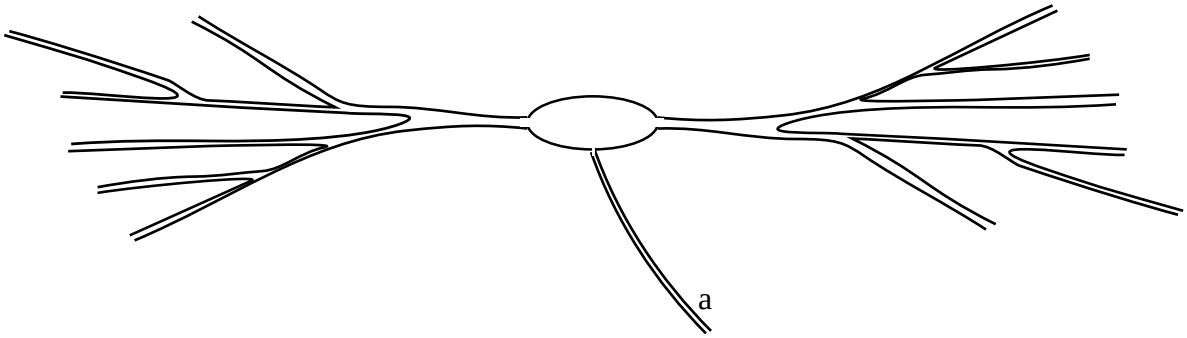
580.439 Final Exam, 1998

Three hours, closed book except for two sheets of paper. Do all problems. Each problem is worth 25 points. Problem 3e is optional and can be done for extra credit.

Problem 1

Part a: Give a definition of equilibrium and of steady state and give an example of each, including an equation or two.

Part b: Write the equations necessary to model action potential propagation in a myelinated axon. If you are building a model of the myelinated action potential for your second project, then write the equations to model a cell like the one drawn below, with a soma and an axon containing active channels and two dendritic trees that can be assumed to be passive. The dendrites receive different inputs. In either case, define the variables you are using and state your assumptions.



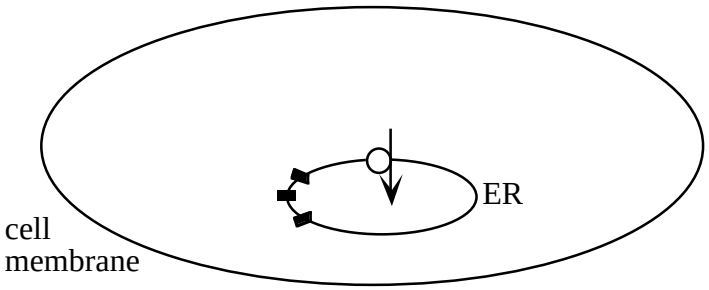
Part c: In Project 1, you studied the Morris-Lecar equations, which model a patch of membrane with a calcium channel, a potassium channel, and a leakage channel. As part of the phase-plane analysis, you showed that injecting an external current into the model moved one of its isoclines in the phase plane and changed the equilibrium point of the model. At zero or low current, the model was stable at its rest potential. As the current increased, the model underwent a Hopf bifurcation and began firing a steady train of action potentials.

Suppose that instead of injecting a steady current, a second leakage channel, which admits only sodium ions, is added to the model. The conductance of this channel is then increased from zero to inject a current into the model. This models a modulatory effect on the cell due to some slow-acting non-ionotropic receptor. Are the effects of a changing a leakage channel conductance the same as the effects of injecting a steady current? Answer this for two aspects of the phase plane: 1) the isoclines and equilibrium points and 2) the stability of the system near its equilibrium point. Just give an answer (yes or no) and tell why, don't work out the details. In case you've forgotten the Morris-Lecar equations, they are as follows:

$$C\frac{dV}{dt} = I_{ext} - \overline{G}_{Ca}\, m_\infty(V)\,(V - E_{Ca}) - \overline{G}_K\, w\,(V - E_K) - \overline{G}_L\,(V - E_L)$$

$$\frac{dw}{dt} = \phi\frac{w_\infty(V) - w}{\tau_w(V)}$$

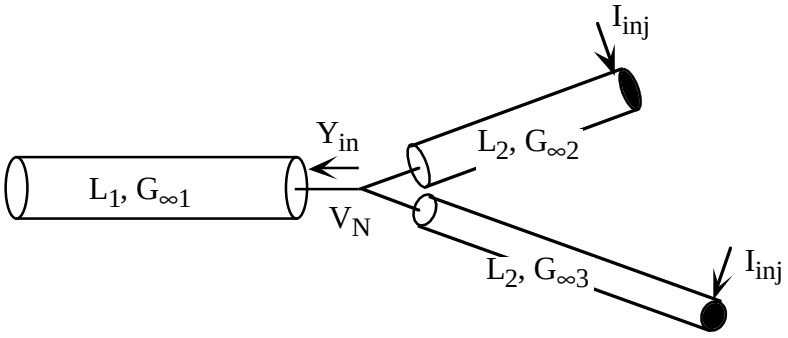
Part d: Consider the cell sketched at right. The cell contains a calcium accumulating endoplasmic reticulum compartment (ER). Calcium is accumulated by active transport with ATP providing the energy. Assume first that the ER membrane contains no transporters or ion channels other than the calcium pump. In the steady state, what determines the relative calcium concentration in the ER and in the cell cytoplasm (you've seen this question before)? Will there be a membrane potential across the ER membrane? If so, why? Does the number of pump molecules in the ER membrane affect the steady-state calcium concentration and why?



Now assume that there are also calcium channels (the little black rectangles) that provide a steady leak of calcium consistent with the GHK equation. What determines the steady-state calcium concentrations now (you won't be able to give a precise answer to this without a detailed model for the transporter, so just describe the general conditions for a steady state here)? Will there still be a potential difference across the ER membrane? Will the number of pump molecules in the ER membrane affect the steady state concentration and why?

Problem 2

Consider the branched structure shown in the figure at right. A current I_{inj} is injected into one or the other of the two branches at the end of the tree, as shown. Assume that the ends of the dendrites (black circles) are closed, i.e. that no axial current flows out of the dendrites at their right end. The electrotonic lengths and G_∞ values are shown for each of the cylinders. Note that the branches have the same electrotonic lengths (L_2), although not the same G_∞s. Assume that the membrane is passive in this system.



Part a: What can you conclude about the relationship between the physical lengths and radii of the two child branches from the information above? (Hint, they are not equal)

Part b: What additional relationship among the lengths and radii of the cylinders would be necessary to satisfy the conditions of the equivalent cylinder theorem?

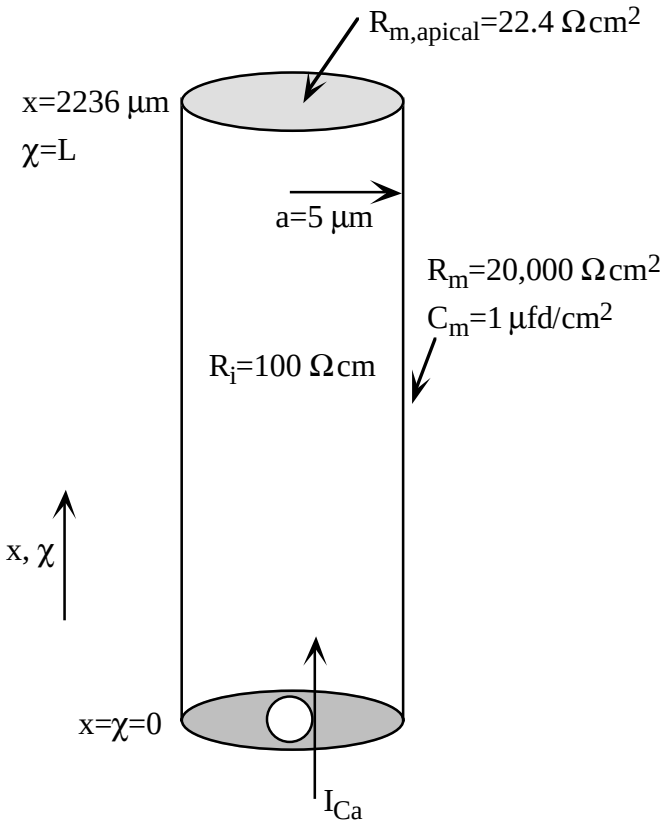
Part c: Show that the potential at the branchpoint V_N is the same regardless of which branch the current I_{inj} is injected into (this can be messy; to cut down on the mess, you should be able to get the answer without working out Y_{in} explicitly). Note: you can't do this by invoking the equivalent cylinder theorem, which has not been assumed to hold here.

Part d: Are the potentials in the child branches the same? That is, is the potential in branch 2 with current injected into branch 2 the same as the potential in branch 3 with current injected in branch 3? (A yes or no plus a brief proof is sufficient; working out the actual potentials is not necessary and is very messy. As a hint, consider the input impedances seen at the two current injection sites.)

Problem 3

Consider the cell sketched at right below. The cell is part of an epithelium which transports ions. At its basal end, the cell transports calcium ions into its cytoplasm, generating a calcium current I_{Ca} (the pumps move calcium only with no countertransport). There is no other ionic current or transport through the basal membrane. The cell's membrane is entirely passive, except for the calcium pumps. The passive cable parameters for the membrane are given in the figure. Note that R_m is different for the lateral membrane of the cylinder and the apical terminal membrane.

Part a: Calculate the length constant, electrotonic length, and G_∞ for the cell and calculate the termination conductance offered by the apical end of the cell.



Part b: Compute the membrane potential of the cell along its length (in the *x* direction), <u>in the D.C. steady state</u> using cable theory. Express the answer in terms of I_{Ca}. Assume that potential varies only with *x*, not with radius or angular position in the cylinder. (Hint: considerable simplification of this function results from the fact that the conductance of the end of the cylinder bears a simple relationship to G_∞).

Part c: In the last lecture, a cable equation for calcium transport was derived based on 1) diffusion of calcium down the cylinder; 2) rapid buffering of calcium at each point; and 3) pumping of calcium through the cylinder wall. To remind you, the elements of the derivation are given in the appendix, yielding the calcium cable equation, Eqn. 7.

Equation 7 is in dimensional form and is identical in form to the linear cable equation. Factors analagous to λ, the length constant, τ_m, the membrane time constant, and G_∞, the input conductance, can be derived for the calcium cable equation. Derive them.

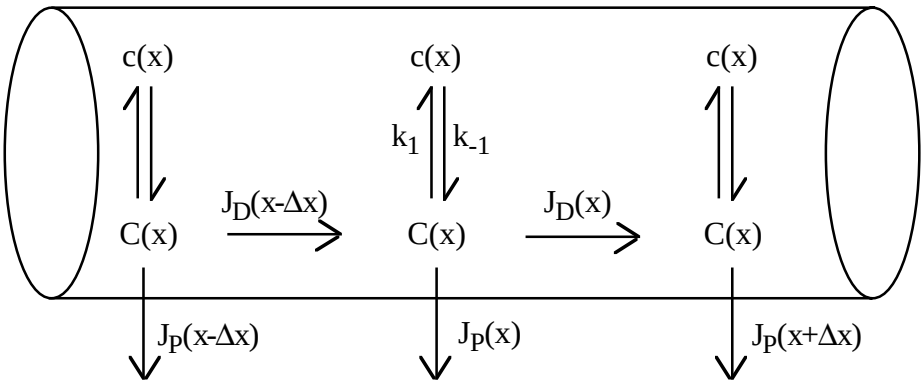
Part d: Assuming that Eqn. 7 applies to the epithelial cell considered above, compute the calcium concentration in the cell, as a function of *x*, <u>in the D.C. steady state</u>. (Hint: it will be helpful

to consider the fact that $\sqrt{D/P} = 5\,\mu m$ in doing this problem; that is, explain why you can assume the cell is an infinitely long cylinder w.r.t. calcium diffusion).

Part e (OPTIONAL): The cable equations used in parts a and b are, in fact inconsistent. The cable equation for voltage ignores an important feature assumed in the cable equation for calcium (the calcium pumps in the lateral wall) and the cable equation for calcium ignores an important feature of calcium flux (the fact that calcium flux is driven by both electrical potential gradients and concentration gradients). Write modified versions of the two cable equations to reconcile them for this problem. This will require diving into the derivations of both equations. (Hint: assume the calcium pumps can be modeled as membrane current sources and consider the Nernst-Planck equation).

Appendix: derivation of the calcium cable equation

Consider the situation diagrammed below. $C(x)$ is the concentration of free calcium and $c(x)$ is the concentration of calcium bound to buffer (as moles/cm of cylinder), J_D is the flux of calcium down the cylinder due to diffusion (moles/s), and J_P is the rate of pumping of calcium through the cylinder membrane (moles/s·cm).



Buffering: assume that calcium is <u>at equilibrium</u> with <u>an excess of buffer</u> at each point in the cylinder, that is the reaction:

$$B + C \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} c \qquad (1)$$

is at equilibrium, where $B(x)$ is the concentration of free buffer. Using the fact that the total buffer concentration $B(x)+c(x) = B_0$ is fixed, the equilibrium concentrations are

$$\frac{B(x)\,C(x)}{c(x)} = \frac{(B_0 - c(x))\,C(x)}{c(x)} = \frac{k_{-1}}{k_1} = K_D \quad \Rightarrow \quad c(x) \approx \frac{B_0}{K_D} C(x) \qquad (2)$$

where the last equation follows from the assumption of excess buffer, $B_0 >> c(x)$.

Calcium flux: from the fact that the net calcium flux into an Δx long element of cylinder must equal the rate of change of calcium within the element:

$$\frac{d[C+c]}{dt}\Delta x = \left\{\begin{array}{l}\text{rate of change}\\ \text{of total calcium}\\ \text{content in a } \Delta x\\ \text{long piece of}\\ \text{cylinder at } x\end{array}\right\} = J_D(x-\Delta x) - J_D(x) - J_P(x)\Delta x \qquad (3)$$

Combining Eqns. 2 and 3 and taking the limit as Δx goes to 0:

$$\left(1+\frac{B_0}{K_D}\right)\frac{\partial C}{\partial t} = \frac{J_D(x-\Delta x) - J_D(x)}{\Delta x} - J_P = -\frac{\partial J_D}{\partial x} - J_P \qquad (4)$$

Calcium pumping: a simple model in which the pump rate is proportional to calcium concentration gives

$$J_P(x) = P\,C(x) \qquad (5)$$

Diffusion of calcium: Fick's law gives

$$J_D = -D\frac{\partial C}{\partial x} \qquad (6)$$

Note the assumption that diffusion is driven only by the gradient of free calcium. The gradient of calcium bound to buffer is ignored under the assumption that diffusion of buffer is very slow compared to diffusion of free calcium.

Calcium cable equation: Combining Eqns. 4, 5, and 6 gives:

$$D\frac{\partial^2 C}{\partial x^2} = \left(1+\frac{B_0}{K_D}\right)\frac{\partial C}{\partial t} + P\,C \qquad (7)$$