580.439 Final Exam Solutions, 1998

Problem 1

Part a: Equilibrium means that the thermodynamic potential of a constituent is the same everywhere in a system. An example is the Nernst potential. If the potential across a membrane equals an ion's Nernst potential, then that ion is at equilibrium across the membrane ($V = RT/zF \ln C_{out}/C_{in}$).

Steady state means that all variables are constant in time. The concentrations of ions inside a resting cell, for example, are constant in time. This occurs because the sum of all active and passive transports through the membrane are zero for each ion.

Part b: At the nodes, there must be an equation for balance of current through the membrane capacitance, the ion channels present in the node, and the currents flowing into the nodes from the adjacent internodes. For example

$$C\frac{dV}{dt} = - \sum_{\substack{\text{all ion} \\ \text{channels}}} G_i(V,t)(V - E_i) + I_{\text{left cable}} + I_{\text{right cable}}$$

where $I_{left\ cable}$ and $I_{right\ cable}$ are the boundary condition currents for the cable equation at the adjacent internodes (see below).

In addition, at the nodes, the ion channel conductances G_i must be modeled by appropriate Hodgkin-Huxley equations.

For the internodes, there is a cable equation whose boundary conditions are the currents flowing from the internodes into the nodes ($I_{left\ cable}$ and $I_{right\ cable}$ above).

$$\frac{\partial^2 V}{\partial \chi^2} = \frac{\partial V}{\partial t} + V$$

$$-G_\infty \frac{\partial V}{\partial \chi}\bigg|_{\chi=0} = -I_{\text{right cable}} \quad \text{and} \quad -G_\infty \frac{\partial V}{\partial \chi}\bigg|_{\chi=L} = I_{\text{left cable}}$$

with whatever time boundary condition is appropriate (say all voltages are 0 at time 0). There will be one such equation for each node and internode in the problem. At the ends of the axon there will be some appropriate boundary condition. For example, at the left end, $I_{left\ cable}$ would be a current injected into the first node to initiate the action potential. At the right end, the cable might just end with a node to model an axon terminal.

The equations are similar for the cell in the problem. For example, we could assume that the dendrites can be reduced to equivalent cylinders; they would then be modeled by the cable equation with zero current boundary conditions at their distal ends

and with the current into the soma at the other end. The soma could be modeled as a single membrane patch with a capacitance and ion channels. Again the current injected into the soma would be the sum of the boundary-condition currents for the dendrites. The axon would be modeled as a sequence of membrane patches containing a capacitance and ion channels, coupled by resistors.

Part c: The isoclines are given by:

$$W_{Viso}(V) = \frac{I_{ext} - \overline{G}_{Ca}\, m_\infty(V)(V - E_{Ca}) - \overline{G}_L(V - E_L) - \overline{G}_{LNa}(V - E_{Na})}{\overline{G}_K(V - E_K)}$$

$$W_{Wiso}(V) = w_\infty(V)$$

where the term $\overline{G}_{LNa}(V - E_{Na})$ is the added sodium leak channel. Clearly there is no difference between the isoclines with a particular value of I_{ext} and the isoclines with an equal value of $\overline{G}_{LNa}(V - E_{Na})$ in the D.C. steady state. Notice that $\overline{G}_{LNa}(V - E_{Na})$ is negative, because $V < E_{Na}$, so activating this sodium leak channel has the same effect as injecting a positive current I_{ext}. Thus any equilibrium point and isocline which can be achieved by injecting a current can be achieved by adjusting the sodium leak (up to the sodium equilibrium potential).

However, the eigenvalues at a given equilibrium point will not necessarily be the same because the leak term enters the Jacobian whereas the external current does not. To see this, consider the $\partial F_V / \partial V$ term in the Jacobian. I_{ext} has no effect on this term, whereas the sodium leak adds $-\overline{G}_{LNa} / C$ to this term. The other terms in the Jacobian are not changed. Nevertheless, at a given equlibrium point, the eigenvalues will, in general, be different.

Part d: With only the transporter in the ER membrane, there will be a membrane potential, positive inside the ER, because of the charge carried by calcium into the ER. The steady state concentration difference will be given by the concentration and potential difference necessary to stop the pump, which occurs when the free energy gained by the pump by hydrolyzing ATP equals the free energy difference of calcium inside relative to outside the ER. It doesn't matter how many pump molecules there are. (Note that this is a totally unrealistic situation because in the absence of any leak, the membrane potential across the ER membrane will rapidly build up to a high enough value to stop the pump.)

In the presence of a leak, there will still be a potential difference, positive inside the ER, again due to the charge carried by calcium into the ER. The steady state occurs when the flux of calcium through the leak channels equals the active flux of calcium due to the transporter. In this case the number of transporter molecules matters because the more molecules there are, the larger the calcium flux, at a given electrochemical gradient.

Problem 2

Part a: Because the electrotonic lengths are the same,

$$L_2 = \frac{l_2}{\lambda_2} = \frac{l_2}{\sqrt{\frac{R_m}{2R_i}} a_2} \quad \text{and} \quad L_2 = \frac{l_3}{\lambda_3} = \frac{l_3}{\sqrt{\frac{R_m}{2R_i}} a_3}$$

so

$$\frac{l_2}{C\sqrt{a_2}} = L_2 = \frac{l_3}{C\sqrt{a_3}} \quad \text{or} \quad \frac{l_2}{\sqrt{a_2}} = \frac{l_3}{\sqrt{a_3}}$$

where $C = \sqrt{R_m/2R_i}$.

Part b: The requirements of the equivalent cylinder theorem are met except for the requirement $G_{\infty 1} = G_{\infty 2} + G_{\infty 3}$, which means that

$$a_1^{3/2} = a_2^{3/2} + a_3^{3/2}$$

Part c: The potential V_N can be computed using the transfer impedance rule across the cable of the branch into which the current was injected:

$$V_N = I_{inj} K_{IN} = \frac{I_{inj}}{\left(0 + Y_{in} + Y_{other}\right)\cosh qL_2 + \left(\frac{0 \cdot (Y_{in} + Y_{other})}{G_\infty q} + G_\infty q\right)\sinh qL_2}$$

where the load admittance at the right-hand end of the branch is 0 (closed-end boundary condition) and the load admittance at the branch point is $Y_{in}+Y_{other}$. Y_{in} is the input admittance of the parent branch and Y_{other} is the input admittance of the other branch (i.e. the one into which current is <u>not</u> injected). Because of the closed-end boundary condition,

$$Y_{other} = G_{\infty other} q \tanh qL_2$$

Combining these equations,

$$V_N = \frac{I_{inj}}{\left(Y_{in} + G_{\infty other} q \tanh qL_2\right)\cosh qL_2 + G_\infty q \sinh qL_2}$$

$$= \frac{I_{inj}}{Y_{in}\cosh qL_2 + G_{\infty other} q \sinh qL_2 + G_\infty q \sinh qL_2}$$

$$= \frac{I_{inj}}{Y_{in}\cosh qL_2 + (G_{\infty other} q + G_\infty q)\sinh qL_2}$$

where use has been made of the fact that $\tanh x = \sinh x / \cosh x$. The last equation above is the same regardless of which branch the current is injected into. Thus, V_N is the same in the two cases.

Note that this is one of the conclusions of the equivalent cylinder theorem, but is true in the absence of one of the assumptions of that theorem. This is a special case, which is only true with the currents at the ends of the child cylinders.

Part d: The easiest way to see that the potentials in the child branches are not the same is to consider the potential at the injection site, which is $I_{inj} K_{II}$ where K_{II} is the input impedance at that point. The input admittance is given by the second of the three rules developed in class:

$$1/K_{II} = Y_{II} = G_\infty q \frac{(Y_{in} + Y_{other})/G_\infty q + \tanh qL_2}{1 + \tanh qL_2 \, (Y_{in} + Y_{other})/G_\infty q}$$

Where the symbols are defined as in part c. Replacing Y_{other} with its value and rearranging

$$Y_{II} = G_\infty q \frac{(Y_{in} + G_{\infty other} q \tanh qL_2)/G_\infty q + \tanh qL_2}{1 + \tanh qL_2 \, (Y_{in} + G_{\infty other} q \tanh qL_2)/G_\infty q}$$

$$= \frac{Y_{in} + G_{\infty other} q \tanh qL_2 + G_\infty q \tanh qL_2}{1 + \tanh qL_2 \, (Y_{in} + G_{\infty other} q \tanh qL_2)/G_\infty q}$$

$$= \frac{Y_{in} + (G_{\infty other} q + G_\infty q) \tanh qL_2}{1 + \tanh qL_2 \, (Y_{in} + G_{\infty other} q \tanh qL_2)/G_\infty q}$$

Consider the last equation above. The numerator is the same regardless of which branch the current is injected into. However, the second term in the denominator is different if the G_∞s of the two child branches are different. Thus the input impedances of the two current injection points are different.

Because the input impedances are different, the potential at the point of current injection is also different and so the potential everywhere in the child cylinders will be different. Inspection of the equations above shows that the cylinder with the larger G_∞ value will have the smaller potential.

Problem 3

Part a: Using the usual definitions and the parameters in the problem:

$$\lambda = \sqrt{\frac{R_m \, a}{2 \, R_i}} = \sqrt{\frac{2x10^4 \, \Omega cm^2 \cdot 5x10^{-4} cm}{2 \cdot 10^2 \, \Omega cm}} = 0.2236 \text{ cm} = 2236 \text{ μm}$$

$$L = \frac{\text{length}}{\lambda} = 1$$

$$G_\infty = \sqrt{\frac{2}{R_m R_i}} \pi a^{3/2} = \sqrt{\frac{2}{2x10^4 \, \Omega cm^2 \cdot 10^2 \, \Omega cm}} \, \pi \left(5x10^{-4} cm\right)^{3/2} = 0.035 \text{ μS}$$

$$G_{\text{apical end}} = \frac{\pi a^2}{R_{m,\text{apical}}} = \frac{\pi \left(5x10^{-4} cm\right)^2}{22.4 \, \Omega cm^2} = 0.035 \text{ μS}$$

Note that $G_{\text{apical end}} = G_\infty$.

Part b: This problem can be done in several ways. Below is the most direct. The cable equation and boundary conditions for the D.C. steady state $(\partial V/\partial t = 0)$ is

$$\frac{d^2 V}{d\chi^2} = V$$

$$-G_\infty \frac{dV}{d\chi}\bigg|_{\chi=0} = I_{Ca} \quad \text{and} \quad -G_\infty \frac{dV}{d\chi}\bigg|_{\chi=L} = G_{end} \, V|_{\chi=L} = G_\infty \, V|_{\chi=L}$$

where G_{end} is the conductance of the apical end of the cell, equal to G_∞. The solution to the cable equation is

$$V(\chi) = A \sinh \chi + B \cosh \chi$$

$$I_i(\chi) = -G_\infty \left[A \cosh \chi + B \sinh \chi\right]$$

At χ=0:

$$I_i(0) = -G_\infty A = I_{Ca} \quad \Rightarrow \quad A = -\frac{I_{Ca}}{G_\infty}$$

and at χ=L:

$$I_i(L) = G_\infty V(L)$$

$$-G_\infty\left[-\frac{I_{Ca}}{G_\infty}\cosh L + B\sinh L\right] = G_\infty\left[-\frac{I_{Ca}}{G_\infty}\sinh L + B\cosh L\right]$$

$$B = \frac{I_{Ca}[\sinh L + \cosh L]}{G_\infty[\sinh L + \cosh L]} = \frac{I_{Ca}}{G_\infty}$$

so that

$$V(\chi) = \frac{I_{Ca}}{G_\infty}[\cosh\chi - \sinh\chi] = \frac{I_{Ca}}{G_\infty}e^{-\chi}$$

This same result could have been gotten by arguing simply that, because the apical terminal admittance is equal to G_∞, the cylinder behaves like a semi-infinite one, so the membrane potential is equal to $V(0)e^{-\chi}$, $V(0)=I_{Ca}/G_{in}$, and $G_{in}=G_\infty$.

Part c: Beginning with Eqn. 7 of the appendix

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

Proceeding in the same way as for the linear cable equation, divide through by P

$$\frac{D}{P}\frac{\partial^2 C}{\partial x^2} = \frac{(1+B_0/K_D)}{P}\frac{\partial C}{\partial t} + C$$

Now, as for the electrical cable equation, the length and time constants are

$$\lambda_{Ca} = \sqrt{D/P} \quad \text{and} \quad \tau_m = \frac{1+B_0/K_D}{P}$$

Note that these have the correct units, of distance and time.

$$\sqrt{\frac{D \quad cm^2/s}{P \quad /s}} = \lambda_{Ca} \quad cm \quad \text{and} \quad \frac{1+\dfrac{B_0}{K_D}\dfrac{mole/cm}{mole/cm}}{P \quad /s} = \tau_{Ca} \quad s$$

The equivalent of G_∞ can be gotten by analogy with the electrical cable equation where $G_\infty=1/r_i\lambda$ by considering what the equivalent of $1/r_i\lambda$ should be. r_i is the ratio between the membane potential gradient ($-\partial V/\partial x$, ignoring V_e) and axial current. The equivalent in the calcium cable equation is $1/D$, the ratio beteen the gradient of calcium concentration and calcium flux (Eqn. 6 in the appendix). Thus the calcium equivalent of G_∞ is

$$G_{\infty Ca} = \frac{D}{\sqrt{D/P}} = \sqrt{DP}$$

This can also be derived from the results in part d below as the ratio between the calcium flux injected into the basal membrane of the cell $I_{Ca}/2F$ and $C(0)$.

Note that alternate definitions of $G_{\infty Ca}$ can be written, depending on what is assumed to be the analog of electrical current flow in the calcium system. Above it was assumed that calcium flux J_D is the appropriate analog, but electrical current $2FJ_D$ could also be used, giving a slightly different $G_{\infty Ca}$ value.

Part d: Assuming the D.C. steady state, the calcium equation becomes

$$\frac{D}{P}\frac{d^2 C}{dx^2} = C \qquad (*)$$

The boundary condition at $x=0$ is that the flux of calcium down the cylinder (J_D in Eqn. 6 of the appendix) is equal to the calcium carried into the cell by I_{Ca}. Thus

$$J_D(0) = -D\frac{dC}{dx}\bigg|_{x=0} = \frac{I_{Ca}}{2F} \qquad (**)$$

where F is the Faraday, to convert I_{Ca} from electrical (amps) to chemical (moles/s) units. This provides one boundary condition. The second boundary condition could be some condition on calcium flux at the apical end of the cell. However, the form of Eqn $(*)$ above is the same as the electrical cable equation before the spatial variable is non-dimensionalized. The calcium space constant is $\sqrt{D/P}$ and this distance is a measure of how far disturbances of calcium will spread. Given that $\sqrt{D/P}=5$ µm, it is safe to conclude that calcium will not spread far from the base of the cell, since the length of the cell is much larger, 2236 µm. In other words, it is safe to assume that the cell is semi-infinite in length, so the second boundary condition is that C is finite as $x \to \infty$, a regularity condition.

The solution to the calcium cable equation is

$$C(x) = Ae^{-x/\sqrt{D/P}} + Be^{x/\sqrt{D/P}}$$

The regularity condition requires that $B=0$ and the boundary condition at $x=0$ (Eqn. $(**)$) gives

$$-D\frac{dC}{dx}\bigg|_{x=0} = \frac{DA}{\sqrt{D/P}}e^{-0/\sqrt{D/P}} = \frac{I_{Ca}}{2F} \qquad \Rightarrow \qquad A = \frac{I_{Ca}}{2F\sqrt{DP}}$$

so that the calcium concentration is

$$C(x) = \frac{I_{Ca}}{2F\sqrt{DP}} e^{-x/\sqrt{D/P}}$$

Note, if you made a different assumption about the second boundary condition, such as calcium flux at the apical pole equals zero, then you would have gotten a more complex equation, which would reduce to the equation above, given that the length of the cylinder is large compared to $\sqrt{DP}$.

Part e: For the electrical cable theory, begin with the non-linear cable equation:

$$\frac{1}{r_i}\frac{\partial^2 V}{\partial x^2} = c_m\frac{\partial V}{\partial t} + I_m(x,t,V)$$

where I_m is the ionic membrane current/length and the external resistance r_e has been ignored. In deriving the cable equation used in part b above, it was assumed that $I_m = g_m V$, the usual assumption in the linear cable theory. However, in this case, there is an additional current due to calcium pumps in the lateral membrane, so that

$$I_m(x) = g_m V(x) + I_{CaP}(x)$$

$$= g_m V(x) + 2FPC(x)$$

where 2FPC is the model for calcium pump current from the derivation of the calcium cable equation (Eqn. 5). The electrical cable equation now becomes

$$\frac{1}{r_i}\frac{\partial^2 V}{\partial x^2} = c_m\frac{\partial V}{\partial t} + g_m V + 2FPC$$

or, in non-dimensional terms

$$\frac{\partial^2 V}{\partial \chi^2} = \frac{\partial V}{\partial T} + V + \frac{2FP}{g_m}C$$

The calcium equation must be modified to include the effects of the potential gradient in the cylinder on the calcium flux. The relevant equation is Eqn. 6 in the appendix, which contains only a diffusion term. The Nernst-Planck equation for calcium is

$$J_D = -u_{Ca}RT\frac{dC}{dx} - u_{Ca}z_{Ca}FC\frac{dV}{dx}$$

The first term on the right is the same as Eqn. 6 of the appendix, since $D = u_i RT$. The second term is flux due to the electrical potential gradient. Note that membrane potential V has been equated to intracellular potential V_i here, ignoring V_e as usual. Combining this equation with Eqns. 4 and 5 in the appendix gives

$$D\frac{\partial^2 C}{\partial x^2} + D\frac{z_{Ca}F}{RT}\frac{\partial}{\partial x}\left(C\frac{\partial V}{\partial x}\right) = \left(1 + \frac{B_0}{K_D}\right)\frac{\partial C}{\partial t} + PC$$

where the second term on the left hand side is the effect of electrical potential gradient on the calcium flux.