580.439/639 Final Exam Solutions, 2012

Problem 1

Part a) At equilibrium there must be no change in free energy of the consituents involved in the active transport. For this system

$$RT\ln(X_i) + zFV_i + H = RT\ln(X_e) \quad ,$$

so

$$\frac{X_i}{X_e} = e^{-(zFV+H)/RT} \quad .$$

Part b) Active transport to go to zero at pump-equilibrium, so there has to be a term in P like the following

$$P(X_i, X_e, V) = f\left(X_i - X_e e^{-(zFV+H)/RT}\right) \quad ,$$

where f is some function of X_i, X_e, and V. It may contain saturation terms and others determined by the details of the transport process.

Part c) The transport of X has two components, the current through the channel G_X and the current through the pump. Putting everything in units of moles/s

$$U_i \frac{dX_i}{dt} = -\frac{S\bar{G}_X}{zF} m(V - E_X) - S \cdot P(X_i, X_e, V)$$
$$\frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau_m(V)} \quad .$$

The second equation is necessary to compute m. In a full model, additional equations would be required for membrane potential and the other ions in the system. The signs are negative because the positive direction for both the flux of X through the ion channel and the pumping of X is outward.

Part d) At steady state the time derivatives are zero, so if $V=V_{SS}$ as stated in the problem, then

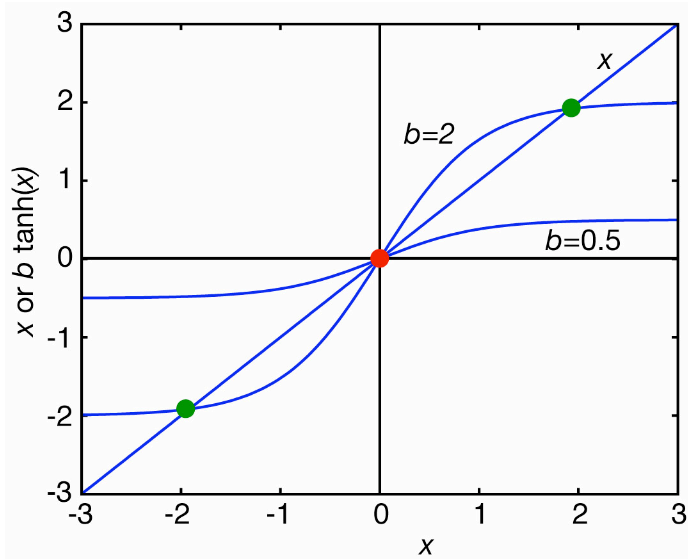
$$\frac{\bar{G}_X}{F} m_\infty(V_{SS})(V_{SS} - E_X) = -P(X_i, X_e, V_{SS}) \quad .$$
$$m = m_\infty(V_{SS})$$

This is an implicit solution for X_i which is the only undetermined variable in the equation.

The part of this question about whether this is an equilibrium is poorly stated, sorry. The difficulty is equilibrium of what? X is at equilibrium if $V_{SS}=RT/zF\ log(X_e/X_i) = E_X$, by the strict definition of equilibrium. From part b), the <u>pump</u> is at equilibrium when $V_{SS} = E_X - H/zF$. Thus, there is an overall equilibrium only if $H=0$.

Problem 2

Part a) The equilibrium points are the roots of $x = b\tanh(x)$. There is always a root at x=0. There may be two additional ones if b is large enough. As shown in the figure, for b>1, there are three roots, where x = b tanh(x). The critical value of b is 1, where the slope of b tanh(x) at x=0 is 1. This follows from d(b tanh$x$)/dx = $b/\cosh^2(x)$. A sketch of this plot was a sufficient answer.



Part b) At zero the Jacobian is

$$\frac{\partial}{\partial x}[-x + b\tanh(x)] = -1 + \frac{b}{\cosh^2(x)} \qquad \text{at } x = 0 \qquad \frac{\partial[\ ]}{\partial \mathrm{x}} = -1 + b$$

The eigenvalue is just equal to the Jacobian in this one-dimensional system, so the equilibrium point at zero is stable for b<1 and unstable for b>1.

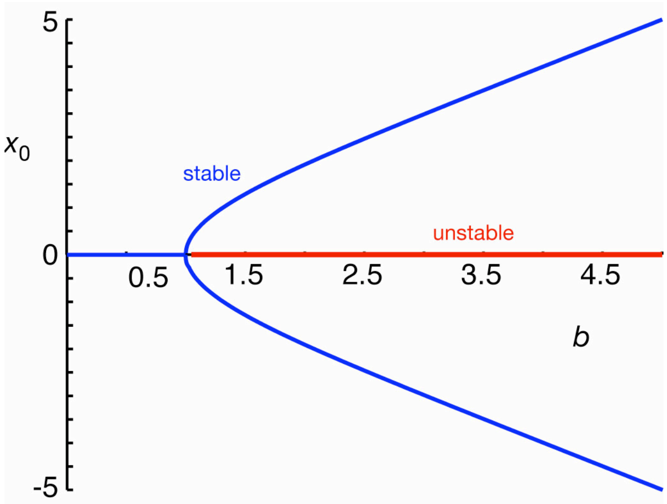
For the other equilibrium points the stability can be argued intuitively by looking at the rhs of the differential equation for small deviations from the equilibrium point. For the positive equilibrium point x_0, for example, at $x_0+\Delta x$, the rhs of the differential equation is negative, because the function x is larger than the function b tanh(x) (from the graph above). Thus x will be driven back to the equilibrium point. The opposite argument applies for $x_0-\Delta x$ and a similar argument can be made for the negative equilibrium point. These arguments are convincing in the case of a first order system, since trajectories are confined to the real line and therefore motion toward the equilibrium point must end at the equilibrium point.

Support for this argument can be obtained by noting that for x large enough, tanh(x) ≈ 1, so that for large b, $x_0 \approx b$ and then

$$\frac{\partial}{\partial x}[-x + b\tanh(x)] = -1 + b\left[1 - \tanh^2(\mathrm{x})\right] \qquad \text{at the equilibrium point} \qquad \frac{\partial[\ ]}{\partial \mathrm{x}} = -1 + b[1-1] = -1$$

so the equilibrium point is stable.

The bifurcation diagram must show only one stable equilibrium point at x=0 for b<1. for b>1, there are three equilibrium points, two stable and one unstable (at zero). Thus the diagram looks like the plot below. For b>1 the plot can be constructed with the trick of recasting the condition for the equilibrium point as b=x/tanh(x) and computing b as a function of x. Again, an approximate sketch would be sufficient. The condition b large at which $x_0 \approx b$ can be seen in the diagram as the straight-line regions.



Part c) Solutions can only move along the real line. Because the direction of movement at any point is a unique function of that value, oscillations are not possible.

Problem 3

Part a) The dendritic tree parameters are

$$\tau_m = \frac{C_m}{G_m} \qquad \lambda_k = \sqrt{\frac{a_k}{2G_m R_i}} \qquad \text{and} \qquad G_{\infty k} = \sqrt{\frac{2G_m}{R_i}}\,\pi\, a_k^{3/2} \qquad (*)$$

where k is the branching generation. The first condition of the equivalent cylinder theorem is satisfied, since all branches of each generation have the same length and radius. In order for G_∞ to be preserved at each branch point, the 3/2 power rule is sufficient:

$$a_1^{3/2} = 2\,a_2^{3/2} = 4\,a_3^{3/2}$$

The equivalent-termination rule is also satisfied, since $Y_{\text{load}} = 0$ at the tips of all dendrites.

The properties of the equivalent cylinder are

$$\tau_m = \frac{C_m}{G_m} \quad L = l_1/\lambda_1 + l_2/\lambda_2 + l_3/\lambda_3 \qquad \text{and} \qquad G_\infty = G_{\infty 1} = \sqrt{\frac{2G_m}{R_i}}\,\pi\, a_1^{3/2}$$

Part b) The definitions of voltage gain and transfer impedance are as follows:

$$A(x,y) = \frac{V_y}{V_x} \qquad K_{xy} = \frac{V_y}{I_{x\,ext}} \qquad K_{xx} = \frac{V_x}{I_{x\,ext}} \quad .$$

From these definitions, it follows that

$$A(x,y) = \frac{K_{xy} I_{x\,ext}}{V_x} = \frac{K_{xy} I_{x\,ext}}{K_{xx} I_{x\,ext}} = \frac{K_{xy}}{K_{xx}} \quad \text{and} \quad A(y,x) = \frac{K_{yx}}{K_{yy}} \ .$$

Because K_{xy}=K_{yx}, shown in class, $A(x,y) = A(y,x)\frac{K_{yy}}{K_{xx}}$, as requested.

Part c) x and y are the points in the original dendritic tree, as in the problem statement. z is the point in the equivalent cylinder that corresponds to y, in that it is the same electrotonic distance from the soma, as in part 3 of the equivalent cylinder theorem. From the first part of the equivalent cylinder theorem $K_{xy} = K_{xz}$. From the properties of transfer impedance $K_{yx} = K_{xy}$ and $K_{xz} = K_{zx}$, so that $K_{yx} = K_{zx}$. This means that a current injected at y will produce the same potential at x as if the current were injected at z in the equivalent cylinder.

Problem 4

Part a) This problem is exactly the same as a homework problem where the method was applied to the delayed-rectifier potassium channel. A fuller development of the linearization can be found in Mauro et al., *J. Gen. Physiol.* 55:497 (1970). Essentially the problem is to linearize the following equations around the resting potential V_R, assumed to be an equilibrium point

$$\frac{dV}{dt} = \frac{1}{C}\left[I_{ext} - g_L(V - E_L) - \overline{g}_{Na} m^3 h_\infty (V - E_{Na}) \right]$$
$$\frac{dm}{dt} = \alpha_m (1-m) - \beta_m m \qquad (4.1)$$

To simplify the problem, it is assumed that changes in h are slow, so that the approximation h=$h_\infty(V_R)$ is made, i.e. h is fixed at its steady-state value at the resting potential. This assumption eliminates the third differential equation in Eqn. 4.1. Linearization can proceed by replacing each variable by a constant plus a small-signal deviation (as in the homework problem solutions) or by computing the Jacobian of the r.h.s. in the first two parts of Eqn. 4.1. In either case, the result is below, in terms of linearization variables v, i_{ext}, and μ. i_{ext} is not a state variable and is usually not included in linearizations. However it can be treated in the same way as a state variable and is needed here in order to connect the membrane model to the rest of the cell.

$$\frac{dv}{dt} \approx \frac{1}{C}\left\{ i_{ext} - \left[\overline{g}_L + \overline{g}_{Na} m_\infty^3(V_R) h_\infty(V_R)\right] v - 3\overline{g}_{Na}\, m_\infty^2(V_R) h_\infty(V_R)\left(V_R - E_{Na}\right)\mu \right\}$$
$$\frac{d\mu}{dt} \approx \left[k_{\alpha m}\left(1 - m_\infty(V_R)\right) - k_{\beta m} m_\infty(V_R)\right] v - \left[\alpha_m(V_R) + \beta_m(V_R)\right]\mu \qquad (4.2)$$

where $k_{\alpha m}$ and $k_{\beta m}$ are the slopes $d\alpha_m/dV$ and $d\beta_m/dV$ evaluated at V_R.

Part b) Laplace transforming Eqn. 4.2 from 0 initial conditions and rearranging gives:

$$\mathbf{i_{ext}}(s) = \left[sC + \overline{g}_L + \overline{g}_{Na} m_\infty^3(V_R) h_\infty(V_R)\right]\mathbf{v}(s) + 3\overline{g}_{Na}\, m_\infty^2(V_R) h_\infty(V_R)(V_R - E_{Na})\boldsymbol{\mu}(s)$$

$$0 = \left[k_{\alpha m}(1 - m_\infty(V_R)) - k_{\beta m} m_\infty(V_R)\right]\mathbf{v}(s) - \left[s + \alpha_m(V_R) + \beta_m(V_R)\right]\boldsymbol{\mu}(s) \tag{4.3}$$

where the boldface indicates Laplace transformed variables. Eliminating $\boldsymbol{\mu}(s)$ between equations gives

$$\mathbf{i_{ext}}(s) = \left\{ \begin{aligned} & sC + \overline{g}_L + \overline{g}_{Na} m_\infty^3(V_R) h_\infty(V_R) + \\ & \qquad \frac{3\overline{g}_{Na} m_\infty^2(V_R) h_\infty(V_R)(V_R - E_{Na})\left[k_{\alpha m}(1 - m_\infty(V_R)) - k_{\beta m}\, m_\infty(V_R)\right]}{s + \alpha_m(V_R) + \beta_m(V_R)} \end{aligned} \right\}\mathbf{v}(s) \tag{4.4}$$

The current-voltage relationship of the circuit in Fig. 1 of the problem can be written as:

$$I = I_C + I_{R_1} + I_{L\,R_0}$$

$$\mathbf{I}(s) = \left\{ sC + \frac{1}{R_1} + \frac{1}{sL + R_0} \right\}\mathbf{V}(s) \tag{4.5}$$

Matching terms in Eqns. 4.4 and 4.5 gives the result that the capacitor is C in either case and the resistors and inductors are related as follows:

$$\frac{1}{R_1} = \overline{g}_L + \overline{g}_{Na}\, m_\infty^3(V_R)\, h_\infty(V_R)$$

$$L = \frac{1}{3\overline{g}_{Na}\, m_\infty^2(V_R) h_\infty(V_R)(V_R - E_{Na})\left[k_{\alpha m}(1 - m_\infty(V_R)) - k_{\beta m} m_\infty(V_R)\right]} \tag{4.6}$$

$$R_0 = (\alpha_m(V_R) + \beta_m(V_R))\, L$$

Part c) You have also seen this problem before, in a homework on cable theory. The general form of the cable equation is

$$\frac{1}{r_i + r_e}\frac{\partial^2 V}{\partial x^2} = I_m(x,t,V) = \text{membrane current / unit length of cylinder} \tag{4.9}$$

For this problem, we assume that the membrane current I_m is flowing through the circuit provided by the linearized membrane conductance derived above. In Fourier transformed form:

$$\mathbf{I_m} = \mathbf{V}\,\mathbf{Y_m} = \mathbf{V}\left[j\omega C + \frac{1}{R_1} + \frac{1}{j\omega L + R_0} \right] 2\pi a \tag{4.10}$$

where boldface again indicates transformed variables. The factor of $2\pi a$ is necessary to convert the membrane conductances from conductance per unit area of membrane (S/cm^2, etc.) to conductance per unit length of membrane cylinder (S/cm, etc.). The conductances were derived above in area units, but conductance/length of cylinder is appropriate for the cable equation.

Fourier transforming Eqn. 4.9, ignoring r_e and using Eqn. 4.10 gives the linear cable equation for this situation (now an ordinary differential equation):

$$\frac{d^2\mathbf{V}}{dx^2} = \mathbf{I_m}(x,t,V) = 2\pi a r_i \left[j\omega C + \frac{1}{R_1} + \frac{1}{j\omega L + R_0} \right] \mathbf{V} = \boldsymbol{\gamma}^2(j\omega)\,\mathbf{V} \tag{4.11}$$

where $\boldsymbol{\gamma}(j\omega)$ is a generalized length constant, written as a function of $j\omega$ to emphasize that it is a complex function of frequency.

Part d) Assuming a semi-infinite cylinder with a current injected at the closed end gives the following boundary conditions:

$$-\frac{1}{r_i}\frac{d\mathbf{V}}{dx}\bigg|_{x=0} = \mathbf{F}\left[I_0 e^{j\omega_0 t}\right] = 2\pi I_0\,\delta(\omega - \omega_0) \quad \text{and} \quad V(x,t) < \infty \text{ as } x \to \infty \tag{4.12}$$

where $\mathbf{F}[\cdot]$ means the Fourier transform of the function in the brackets. As usual, one boundary condition is a regularity condition. The solution to the differential equation 4.11 is

$$\mathbf{V}(x,j\omega) = \mathbf{A}(j\omega)e^{\gamma x} + \mathbf{B}(j\omega)e^{-\gamma x} \tag{4.13}$$

$\boldsymbol{\gamma}^2$ is complex, so there are two possible values of $\boldsymbol{\gamma}$, one with a positive real part and a second with a negative real part. Chose the positive-real root; as was shown in class, choosing the other root gives the same ultimate answer. The regularity condition in Eqn. 4.12 then implies that $\mathbf{A}(j\omega)=0$. Applying the boundary condition in Eqn. 4.12 allows the solution to be written:

$$-\frac{1}{r_i}\frac{d\mathbf{V}}{dx}\bigg|_{x=0} = \frac{\boldsymbol{\gamma}}{r_i}\mathbf{B}(j\omega) = 2\pi I_0\,\delta(\omega - \omega_0) \quad \text{so that} \quad \mathbf{V}(x,j\omega) = \frac{2\pi I_0 r_i}{\boldsymbol{\gamma}}\delta(\omega - \omega_0)e^{-\gamma x} \tag{4.14}$$

Equation 4.14 is the Fourier transform of the membrane potential in the cylinder. Because of the delta function, this transform is easy to invert:

$$\begin{aligned} V(x,t) &= \frac{1}{2\pi}\int_{-\infty}^{\infty} \frac{2\pi I_0 r_i}{\gamma(j\omega)}\delta(\omega - \omega_0)e^{-\gamma x}\, e^{j\omega t}\, d\omega \\ &= \frac{I_0 r_i}{\gamma(j\omega_0)} e^{-\gamma x}\, e^{j\omega_0 t} \\ &= \left|\frac{I_0 r_i}{\gamma}\right| e^{-\mathrm{Re}[\gamma]x}\, e^{j\omega_0 t + \theta} \quad \text{where} \quad \theta = \angle\left[\frac{1}{\gamma}\right] - \mathrm{Im}[\gamma]x \end{aligned} \tag{4.15}$$

where $\angle[1/\boldsymbol{\gamma}]$ is the negative of the phase of $\boldsymbol{\gamma}$.