

## 580.439/639 Final Solutions, 2009

### Problem 1

**Part a)** The operating principle is that the Nernst equation holds simultaneously for all permeant ions:

$$V = E_A = \frac{RT}{z_A F} \ln \frac{A_{out}}{A_{in}} = E_B = \frac{RT}{z_B F} \ln \frac{B_{out}}{B_{in}} = \dots E_N = \frac{RT}{z_N F} \ln \frac{N_{out}}{N_{in}}$$

meaning that concentration ratios  $(X_{out}/X_{in})^{1/z_x}$  should be the same for all ions. The non-permeant ions are not considered.

Subpart 1 – No equilibrium (compare Na and K)

Subpart 2 – No equilibrium (Cl has  $z_{Cl}=-1$ )

Subpart 3 – Equilibrium possible

Subpart 4 – Equilibrium possible

Subpart 5 – No equilibrium (Ca has  $z_{Ca}=2$ )

**Part b), Subpart 1)** A standard steady state of zero net flux through two or more mechanisms, active transport and calcium channel or other transporter, so that

$$I_{active}(Ca_{out}, Ca_{in}, V, \dots) + I_{passive}(Ca_{out}, Ca_{in}, V) = 0$$

If the active transport is the only way for calcium to move through the membrane (unlikely), then a steady state can be reached when the concentration of calcium is high enough inside the organelle that the free energy change required to pump calcium (due to concentration ratio and membrane potential) is larger than the energy available to the active transport.

**Subpart 2)** The increase in  $Ca_{out}$  will produce an increased flux into the organelle (or decreased flux out) through the passive and probably also the active mechanism, and the  $Ca_{in}$  inside the organelle will increase. In the second mechanism, because the pump is saturated, the increase in  $Ca_{out}$  will have no effect.

**Part c) Subpart 1)** The parts of the channel labeled *S1*, etc. are alpha helices originally drawn as transmembrane domains. *S3* and *S4* contain components of the gating paddle (part A of the figure), the positively charged part of the molecule that displaces in response to transmembrane voltage (which provides the energy for gating) and pulls the channel's gate open. *S5*, *S6*, and the pore domain between them form the ion conductive pore. The actual gate is the four *S6* helices that form a closed inverted teepee when the gate is closed and are pulled back to open the gate when the gating paddle moves in the membrane, presumably by force in the *S4-S5 linker*.

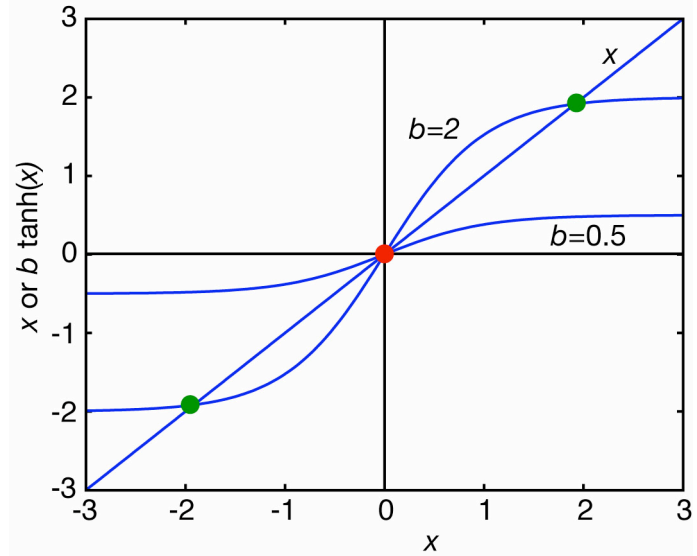
**Subpart 2)** The residues marked "O" can be attacked from the extracellular solution, implying that the paddle translocates through the membrane in the open channel condition, exposing them to the outside solution. This supports the reconstruction in part D of the figure from the paper by Jiang et al. The residues marked "H" can be attacked from the intracellular solution in the closed-gate condition (parts A and C of the figure), because they are located near the internal side of the

membrane. The residues marked “E” can be attacked from either solution. These data support the reconstruction of the gating paddle movement shown in parts C and D and also provide information about how far the paddle moves (far enough to expose the E residues but not the H residues).

## Problem 2

**Part a)** The equilibrium points are the roots of  $x = b \tanh(x)$ . There is always a root at  $x=0$  (red dot in the figure at right). There may be two additional ones (green dots) if  $b$  is large enough,  $b>1$ .

The critical value of  $b$  is 1, which is where the slope of  $b \tanh(x)$  at  $x=0$  is equal to 1. This follows from  $d(b \tanh x)/dx = b/\cosh^2(x) = b$  at  $x=0$ . Comparing the  $\tanh$  function with the line  $x$ , there are 3 equilibrium points for  $b>1$  and one point for  $b<1$ .



**Part b)** At  $x=0$ , the Jacobian is

$$J = \frac{d}{dx}[-x + b \tanh(x)] = -1 + \frac{b}{\cosh^2(x)} \quad \text{at } x=0 \quad J = -1 + b$$

The eigenvalue is 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, because trajectories are confined to the real line and therefore motion toward the equilibrium point must end at the equilibrium point.

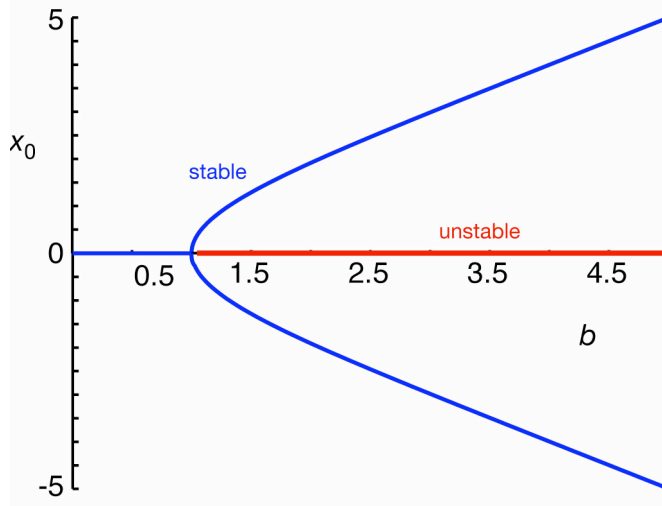
Support for this argument can be obtained by noting that for  $x$  large enough,  $\tanh(x) \approx 1$ , so that for large  $b$ ,  $x_0 \approx b$  and then

$$J = \frac{d}{dx}[-x + b \tanh(x)] = -1 + b[1 - \tanh^2(x)] \quad \text{at the equilibrium point} \quad J \approx -1 + b[1 - 1] = -1$$

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 by 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)** At any point on the line, there is a unique value of  $dx/dt$ , given by the differential equation. Oscillation, which requires back and forth motion along the line, is thus forbidden.

### Problem 3

**Part a)** Writing out  $\langle v^2 \rangle$  gives

$$\langle v^2 \rangle = \langle (\vec{w}^T \vec{u})^2 \rangle = \langle \vec{w}^T \vec{u} \cdot \vec{w}^T \vec{u} \rangle = \vec{w}^T \langle \vec{u} \vec{u}^T \rangle \vec{w} = \vec{w}^T \mathbf{C} \vec{w} ,$$

where  $\mathbf{C}$  is the correlation matrix of the input vector ensemble. If  $\vec{w}$  is the largest-eigenvalue eigenvector of  $\mathbf{C}$ , as discussed in class, then  $\vec{w}^T \mathbf{C} \vec{w} = \lambda_{\max}$  because the eigenvectors are orthonormal, so that  $\vec{w}^T \vec{w} = 1$ .

To show that  $\lambda_{\max}$  is the largest possible value of the quadratic form under the assumptions of this problem, suppose that  $\vec{w}$  is a vector other than the largest-eigenvalue eigenvector, say a sum of  $\vec{e}_{\max}$  and  $\vec{e}_1$ , some other eigenvector of  $\mathbf{C}$ , that is  $\vec{w} = \sqrt{1-\varepsilon^2} \vec{e}_{\max} + \varepsilon \vec{e}_1$ , for  $\varepsilon < 1$ . With this choice,  $\vec{w}^T \vec{w} = 1$  as required. Then using the orthonormality of the eigenvectors,

$$\langle v^2 \rangle = (1-\varepsilon^2) \lambda_{\max} + \varepsilon^2 \lambda_1$$

which has a maximum for  $\varepsilon=0$ , because  $\lambda_{\max} > \lambda_1$ .

**Part b)** The computation done by neuron 1 is not affected or changed by the presence of neuron 2, so the steady state value of neuron 1 will be the same regardless of neuron 2.

**Part c)** The computation done by neuron 2 is as follows.

$$v_2 = \bar{w}_2^T \bar{u} - b v_1 = \bar{w}_2^T \bar{u} - \bar{w}_2^T \bar{w}_1 v_1 = \bar{w}_2^T (\bar{u} - \bar{w}_1 v_1)$$

Neuron 2 thus behaves as if its inputs were the modified vectors  $\bar{u}^* = \bar{u} - \bar{w}_1 v_1$ . Applying Oja's rule, the correlation matrix in this case is  $\mathbf{C}_2 = \langle \bar{u}^* \bar{u}^{*T} \rangle$ , which is the correlation matrix of the input vectors after  $v_1 \bar{w}_1 = (\bar{w}_1^T \bar{u}) \bar{w}_1$  has been subtracted from each. If the input vectors are expressed as a sum of the eigenvectors of  $\mathbf{C}$  (the correlation matrix of the original ensemble  $\{\bar{u}\}$ ),

$$\bar{u} = \sum_{i=1}^n \alpha_i \bar{e}_i$$

then  $\bar{w}_1^T \bar{u} = \bar{e}_{\max}^T \bar{u} = \alpha_{\max}$  and therefore the modified input vectors of neuron 2 are

$$\bar{u}^* = \sum_{i=1}^n \alpha_i \bar{e}_i - \alpha_{\max} \bar{e}_{\max} = \sum_{\substack{i=1 \\ i \neq \max}}^n \alpha_i \bar{e}_i .$$

The modified inputs have their coefficients along  $\bar{e}_{\max}$  removed. The eigenvectors of  $\mathbf{C}_2$  are thus the same as those of  $\mathbf{C}$ , except that  $\bar{e}_{\max}$  is not present, so that  $\mathbf{C}_2$  has rank  $n-1$ . With Oja's rule, the weight vector  $\bar{w}_2$  will be set equal to the eigenvector of the largest remaining eigenvalue, which is the second largest eigenvector of  $\mathbf{C}$ . This process can be continued to find all the eigenvalues and eigenvectors of  $\mathbf{C}$ .

#### Problem 4

**Part a)** The dendritic tree parameters are

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

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  $G_{\infty}$  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

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

**Part b)** With the assumption about spines, the parameters of the secondary dendrites become

$$\lambda'_2 = \sqrt{\frac{a_2}{2(G_m + Ng_s)R_i}} \quad \text{and} \quad G'_{\infty 2} = \sqrt{\frac{2(G_m + Ng_s)}{R_i}} \pi a_2^{3/2}$$

The primes indicate parameters corrected for spines. This is a bit of a fudge because the units of  $G_m$  and  $Ng_s$  aren't really the same (conductance per area and conductance) unless corrected for area. A way to do that is to express the effect of spines as  $N$  spines in the area of the cylinder. This changes the effective conductance and capacitance as follows:

$$C'_m = \left( C_m + Nc_s \frac{2\pi a_2}{l_2} \right) \quad \text{and} \quad G'_m = \left( G_m + Ng_s \frac{2\pi a_2}{l_2} \right)$$

Then

$$\lambda'_2 = \sqrt{\frac{a_2}{2 \left( G_m + Ng_s \frac{2\pi a_2}{l_2} \right) R_i}} \quad \text{and} \quad G'_{\infty 2} = \sqrt{\frac{2 \left( G_m + Ng_s \frac{2\pi a_2}{l_2} \right)}{R_i}} \pi a_2^{3/2}$$

The properties of the other cylinders remain the same. The first condition for the equivalent cylinder still holds, because  $l_2/\lambda'_2$  is the same across the second-generation branches. Similarly, the termination condition still holds. However, preservation of  $G_\infty$  is now violated, even though the 3/2 power branching rule still holds. The  $G_\infty$ s have to match, as  $G_{\infty 1} = 2G'_{\infty 2} = 4G_{\infty 3}$  and this is no longer true because of the change of  $G_m$  in  $G_{\infty 2}$ .

The equivalent cylinder conditions could be restored at DC if the radius of the second cylinders were adjusted so that

$$\sqrt{G_m} a_1^{3/2} = 2 \sqrt{G_m + Ng_s \frac{2\pi a_2}{l_2}} a_2^{3/2} = 4 \sqrt{G_m} a_3^{3/2}$$

**Part c)** In actuality, the 3/2 power law condition includes  $q$ , the transform variable. That is, the condition is  $qG_{\infty 1} = 2qG_{\infty 2} = 4qG_{\infty 3}$ . Usually  $q$  is fixed throughout the dendrites, so can be ignored, as above.  $q$  includes the time constant of the membrane  $\tau_m = C_m/G_m$ , for example in the sinusoidal steady state,  $q = \sqrt{1 + j\Omega\tau_m}$ , where  $\Omega$  is real frequency, in radians/s. Thus, the actual equality that has to be maintained is

$$\sqrt{1 + j\Omega\tau_m} G_{\infty 1} = 2\sqrt{1 + j\Omega\tau'_m} G'_{\infty 2} = 4\sqrt{1 + j\Omega\tau_m} G_{\infty 3}$$

where  $\tau'_m = C'_m/G'_m$ . Clearly now the equality cannot be maintained by simply adjusting  $a_2$  because the adjustment needs to change with frequency. Of course, there is a possibility that  $g_s/c_s = G_m/C_m$  because the spines are made of the same material as the dendrite. In that case  $\tau'_m = \tau_m$  and the situation is the same as in part b).