580.439/639 Midterm Exam Solutions, 2005

Problem 1:

Part a) The equilibrium potentials are given in the table below, calculated from the Nernst equation. The directions of active transport are also given. These are the opposite direction of the passive current flows. The potential of endolymph is assumed to be +90 mV w.r.t. perilymph.

$$E_i = \frac{RT}{z_i F}\ln\frac{C_{out}}{C_{in}} \qquad C_{out} = \text{conc. in perilymph;}\ \ C_{in} = \text{conc. in endolymph.}$$

Ion	perilymph	endolymph	E_i	AT direction
Na^+	145 mM	2 mM	111 mV	out of endo
K^+	5	157	-90	into endo
Ca^{++}	1	0.02	51	into endo
Cl^-	120	132	2.5	out of endo
HCO_3^-	20	31	11	out of endo
urea	5	5	--	equilibrium

Part b) The electrochemical gradient for sodium must exceed that for potassium plus twice that of chloride, so that the net change in electrochemical potential is negative each time a transport step is taken. Assuming the transport goes directly from perilymph to endolymph,

$$\sum_{i=Na,K,2Cl} \mu_{i,endo} - \mu_{i,peri} \le 0,$$

$$\sum_{i=Na,K,2Cl} RT\ln\frac{C_{i,endo}}{C_{i,peri}} + z_i F(V_{endo} - V_{peri}) \le 0,$$

$$26\ln\frac{2}{145} + 26\ln\frac{157}{5} + 2\cdot 26\ln\frac{132}{120} + (1+1-2)\cdot 90 = -16.8 \text{ mV}.$$

The equation has been divided by F at the third line above. So this transporter could move K^+ and Cl^- into the endolymph at the cost of moving Na^+ into the endolymph. Clearly a Na^+ transport out of the endolymph and a Cl^- transport out of the endolymph would also be needed.

If the transporter were electrogenic (1 positive charge is moved for each transport cycle) then the last line of the calculation above would be

$$26\ln\frac{2}{145} + 26\ln\frac{157}{5} + 26\ln\frac{132}{120} + (1+1-1)\cdot 90 = +70.7 \text{ mV}.$$

In this case, the transporter can't run in the forward direction. The reason, of course, is the large positive potential in the endolymph, which doesn't affect the neutral transporter in the first calculation.

Part c) For equilibrium to hold as in the problem statement,

$$\mu_{X,peri} = \mu_{X,IS} \quad \text{and} \quad \mu_{X,IS} = \mu_{X,endo} \quad \text{so that} \quad \mu_{X,peri} = \mu_{X,IS} = \mu_{X,endo}.$$

However, X is not at equilibrium between endolymph and perilymph from the problem statement. A longer-winded proof can be given by writing out the Nernst equations, but it reduces to the statement above.

Part d) The potential V must be such that K^+ is at least at equilibrium across the apical membrane (between the cell interior and the endolymph); actually it will have to be slightly more positive to push K^+ into the endolymph. Apply Nernst at the apical membrane of the cells:

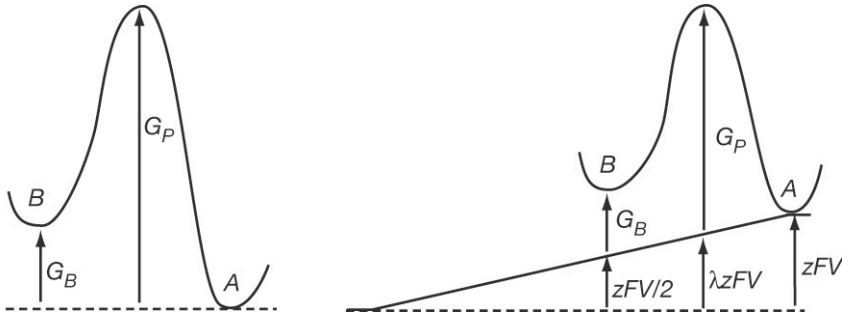
$$V - 90 = \frac{RT}{F} \ln \frac{K_{endo}}{K_{inside\ cell}} = 26 \ln \frac{157}{150} = 1.2 \text{ mV}.$$

So the potential in the cell interior would have to be over +91 mV! This remarkable positive membrane potential appears to hold experimentally.

Problem 2

Part a) The binding of Ca^{++} to the channel will not be affected by transmembrane potential in the left model, because the Ca^{++} does not have to move through any fraction of the membrane potential. In the right-hand model, the Ca^{++} translates through about half the membrane potential, so depolarization of the membrane will increase the driving force pushing Ca^{++} onto the channel.

Part b) The barrier models are below:



The left model is for the channel with its Ca^{++} site on the interior surface of the membrane. A is unbound and B is bound Ca^{++}. This is a simple $A \rightleftharpoons B$ transition unaffected by membrane potential. The model at right shows the membrane potential V

added to the same barriers. Half the membrane potential affects the energy level of the *B* ground state and a fraction λ affects the peak energy.

Part c) Using the usual kinetic model for a single barrier between states *A* and *B* with forward and reverse rate constants k_1 and k_{-1},

$$\frac{dB}{dt} = k_1 \cdot Ca \cdot A - k_{-1}B = k_1 \cdot Ca - (k_1 \cdot Ca + k_{-1})B \quad \text{using the fact that } A = 1 - B.$$

In the equation above, *A* and *B* are the fraction of channel in the *A* and *B* states. The rate constants are given by

$$k_1 = \alpha e^{-G_P/RT} \quad \text{and} \quad k_{-1} = \beta e^{-(G_P - G_B)/RT}$$

for the model wiMacintosh cubethout membrane potential and by

$$k_1 = \alpha e^{-(G_P + \lambda zFV - zFV)/RT} = \alpha e^{-(G_P - (1-\lambda)zFV)/RT} \quad \text{and}$$

$$k_{-1} = \beta e^{-(G_P - G_B + \lambda zFV - zFV/2)/RT} = \beta e^{-(G_P - G_B + (\lambda - 0.5)zFV)/RT}$$

for the model with membrane potential. In steady-state, dB/dt=0 so that B(SS) = $k_1Ca/(k_1Ca+k_{-1})$. Substituting the rate constants, the model without membrane potential gives

$$B = \frac{1}{1 + \frac{1}{Ca} e^{-G_B/RT}}$$

and with membrane potential

$$B = \frac{1}{1 + \frac{1}{Ca} \exp\left[\left(G_B - zFV/2\right)/RT\right]}.$$

Problem 3

Part a) The equilibrium points are the intersections of the nullclines for this system. The nullclines are as follows:

$$\frac{du}{dt} = 0 \quad \Rightarrow \quad v_u = -\frac{1 - (b+1)u}{au^2} \quad \text{and} \quad \frac{dv}{dt} = 0 \quad \Rightarrow \quad v_v = \frac{b}{au}.$$

At the equilibrium points

$$
\begin{aligned}
v_u &= v_v, \\
-\frac{1-(b+1)u}{au^2} &= \frac{b}{au}, \\
-1+(b+1)u = bu \quad &\Rightarrow \quad u_{eq.pt.} = 1 \quad \text{and} \quad v_{eq.pt.} = b/a.
\end{aligned}
$$

The equation for the equilibrium point turns out to be linear, so there is only one equilibrium point.

Part b) The Jacobian for this system is found in the usual way.

$$
J = \left[\begin{array}{cc} \dfrac{\partial F_u}{\partial u} & \dfrac{\partial F_u}{\partial v} \\ \dfrac{\partial F_v}{\partial u} & \dfrac{\partial F_v}{\partial v} \end{array}\right]_{\text{eq.pt.}} = \left[\begin{array}{cc} -(b+1)+2auv & au^2 \\ b-2auv & -au^2 \end{array}\right]_{\text{eq.pt.}} = \left[\begin{array}{cc} b-1 & a \\ -b & -a \end{array}\right].
$$

The eigenvalues of the Jacobian are given by solving the usual characteristic equation.

$$
\begin{aligned}
\det\left[\lambda \mathbf{I} - \mathbf{J}\right] &= 0, \\
(\lambda - b + 1)(\lambda + a) + ab &= 0, \\
\lambda^2 + (a - b + 1)\lambda + a &= 0.
\end{aligned}
$$

The quadratic equation has the following roots

$$
\lambda = \frac{b-a-1}{2} \pm \frac{\sqrt{(b-a-1)^2 - 4a}}{2} \quad \text{or} \quad \lambda = \frac{b-a-1}{2}\left[1 \pm \sqrt{1 - \frac{4a}{(b-a-1)^2}}\right] \qquad (*)
$$

Part c) The eigenvalues are complex if the value under the radical in the eigenvalue equation above is negative, so

$$
\frac{4a}{(b-a-1)^2} > 1 \quad \text{or} \quad a^2 - 2ab - 2a + 1 - 2b + b^2 < 0 \qquad (**)
$$

where the quadratic equations follow from the first equation with some algebra. Note that the quadratic equation is symmetric in a and b. To find the boundary between real and complex eigenvalues, the quadratic can be set to 0 and solved. The solution can be found by writing it as a quadratic in terms of either variable and applying the quadratic formula, giving

$$
a^2 - 2(b+1)a + (b-1)^2 = 0 \quad \Rightarrow \quad a = (b+1) \pm 2\sqrt{b},
$$

or

$$
b^2 - 2(a+1)b + (a-1)^2 = 0 \quad \Rightarrow \quad b = (a+1) \pm 2\sqrt{a}.
$$

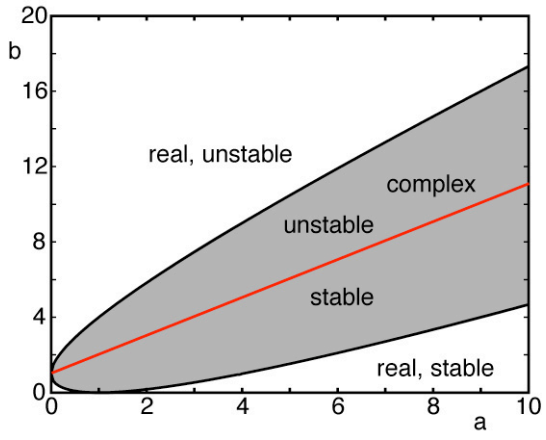
The regions of the (a,b) plane are sketched below from these solutions. The inequality in Eqn. (**) is satisfied in the shaded region, where the eigenvalues are complex. Note that

Eqn. (**) has a zero denominator when $b = a+1$. However, looking back at Eqn. (*) shows that λ is well-behaved and imaginary at that value, which is on the red line.

If the eigenvalues are complex, then from Eqn. (*), the real part of λ is negative (stable) for

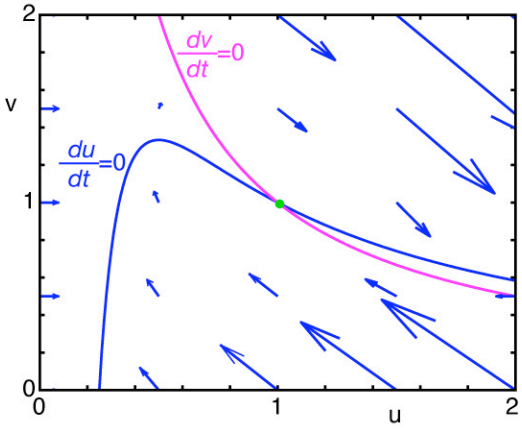
$$b - a - 1 < 0 \quad \text{so} \quad b < a + 1 \qquad (***)$$

that is, in the region below the red line in the sketch.



Part d) If the value under the radical in Eqn. (*) is positive (real eigenvalues), it has to be smaller than 1, because both $4a$ and $(b\text{-}a\text{-}1)^2$ are positive. Thus the value $1 \pm \sqrt{\cdot}$ in Eqn. (*) is always positive and the eigenvalues have the sign of $(b\text{-}a\text{-}1)/2$. Thus the condition for stable real eigenvalues is that they be outside the shaded area in the figure and below the red line, Eqn. (***).

For the same reason, saddle nodes are not possible in this system.



Part e) A phase plane is plotted at right using a=3, b=3, within the stable spiral region. The structure of the plane doesn't change much with parameters, although the quiver plots do. The equilibrium point at u=1, v=b/a is shown by the green dot. Poincare-Bendixson cannot be applied because an appropriate boundary on the r.h.s. of the plot does not exist. However, if a limit cycle exists, it must circle the equilibrium point and be within the 1st quadrant, shown in the plot. That is, the limit cycle cannot cross the v or u axes because flow near them is only in one direction, as plotted. So, without more information, a limit cycle might exist, but cannot be proven.