580.439/639 Midterm Solutions, 2009

Problem 1

Part a) The change in free energy when the transporter goes forward by 1 mole (KCl out) is as follows:

$$
\begin{aligned}
\Delta\mu &= \mu_{outK} - \mu_{inK} + \mu_{outCl} - \mu_{inCl} \\
&= RT\ln K_{out} + FV_{out} - RT\ln K_{in} - FV_{in} + RT\ln Cl_{out} - FV_{out} - RT\ln Cl_{in} + FV_{in} \\
&= RT\ln\frac{K_{out}}{K_{in}} + RT\ln\frac{Cl_{out}}{Cl_{in}} = RT\ln\frac{K_{out}Cl_{out}}{K_{in}Cl_{in}}
\end{aligned}
$$

Because the transporter is electroneutral (equal + and – charge transport), the membrane potential doesn't affect the free energy change or the transport. For the parameters given in the problem,

$$\Delta\mu = RT\ln\frac{5\cdot 125}{120\cdot 12.5} < 0 \tag{1}$$

The free energy change is negative, so the transporter will move KCl out of the cell.

Part b) At the steady state, there should be no flux which is achieved if $\Delta\mu=0$ or $K_{out}Cl_{out}/K_{in}Cl_{in} = 1$. If x moles of KCl is transported,

$$\frac{K_{out}Cl_{out}}{(K_{in}-x)(Cl_{in}-x)} = 1 \quad \text{so that} \quad 5\cdot 125 = 120\cdot 12.5 - (120+12.5)x + x^2 \tag{2}$$

The solutions are x = 6.97 and 125.5. The second one results in negative concentrations, so clearly the appropriate solution is x=7 and K_{in} = 113 mM, Cl_{in} = 5.5 mM.

Part c) The K^+ channel allows a net flux of charge (K^+); because of the concentration gradient of K^+ this will be out of the cell, creating a negative membrane potential. The K^+ flux will stop when K^+ comes to equilibrium at $V = E_K$ but, as discussed in the problem statement, this will not transfer enough K^+ to change the concentration inside the cell. Thus the steady state of part b) will not be disturbed. At steady state, K^+ is at equilibrium and $V=E_K$= -81 mV.

Part d) The hint suggests looking at the steady state from parts b) and c). In that steady state, both K^+ and Cl^- are in equilibrium because (from Eqn. 2)

$$\frac{K_{out}Cl_{out}}{K_{in}Cl_{in}} = 1 \quad \Rightarrow \quad \frac{K_{out}}{K_{in}} = \frac{Cl_{in}}{Cl_{out}} \quad \Rightarrow \quad E_K = E_{Cl}$$

Thus one solution to this part is for all the ions to be at equilibrium and for all the fluxes to be zero.

A more long winded argument is to write the steady-state conditions for the three fluxes.

$$J_K + J_{KCl} = 0$$
$$J_{Cl} + J_{KCl} = 0$$
$$J_K = J_{Cl}$$

where J_K is the flux (moles/(s m^2), positive outward) through the K^+ channel, J_{Cl} is the flux through the Cl^- channel, and J_{KCl} is the flux through the transporter. The first equation guarantees no net transport of K^+, the second guarantees no net transport of Cl^-, and the third guarantees no net transfer of charge. J_{KCL} is not involved in the third equation because the transporter does not move charge. An equation for electroneutrality is not needed because it is redundant.

These equations are redundant, so don't lead to a solution. However, consider the following argument. Suppose $J_{KCL} > 0$, i.e. an outward flux through the transporter. As argued in Eqns. 1 and 2 this requires that $(K_{out}Cl_{out})/(K_{in}Cl_{in}) < 1$ so that

$$\frac{K_{out}}{K_{in}} < \frac{Cl_{in}}{Cl_{out}} \qquad \Rightarrow \qquad E_K < E_{Cl}$$

The membrane potential must be halfway between E_K and E_{Cl}, according to the GHK or a similar equation. As a result there must be a net *outward* flux of both K^+ and Cl^-. That is, KCl will move out of the cell through both transport mechanisms. A similar conclusion holds if $J_{KCl} < 0$, i.e. a net inward flux, in this case KCl will move inward through the ion channels as well. Neither of these cases is a steady state.

The only situation in which there is a steady state is if J_{KCl}=0 in which case

$$\frac{K_{out}Cl_{out}}{K_{in}Cl_{in}} = 1 \qquad \Rightarrow \qquad \frac{K_{out}}{K_{in}} = \frac{Cl_{in}}{Cl_{out}} \qquad \Rightarrow \qquad E_K = E_{Cl}$$

and all ions are in equilibrium with $V=E_K=E_{Cl}$.

Part e) This case is more involved. Now the steady-state equations are

$$J_{KCl} = 0$$
$$J_{Na} = 0$$
$$J_K + J_{KCl} = 0$$

The first guarantees no net transport of Cl^-, the second no net transport of Na^+, and the third no net transport of K^+, actually it could be written $J_K = 0$, given the first equation. Another equation could be added for charge, but it is redundant with the above. These equations require the following ion concentrations

$$\frac{K_{out}Cl_{out}}{K_{in}Cl_{in}} = 1$$
$$V = E_{Na} = \frac{RT}{F}\ln\frac{Na_{out}}{Na_{in}}$$
$$V = E_K = \frac{RT}{F}\ln\frac{K_{out}}{K_{in}}$$

The first is the condition from parts a) and b). The second makes J_{Na} = 0 (equilibrium) and the third makes J_K = 0 (equilibrium), as required by the third equation above if J_{KCl}=0. Equating membrane potentials in the second and third equations, rearranging, and adding an equation for electroneutrality gives

$$K_{in} - \frac{K_{out}}{Na_{out}}Na_{in} = 0$$
$$K_{in}Cl_{in} = K_{out}Cl_{out}$$
$$K_{in} + Na_{in} - Cl_{in} = N_{in}$$

The extracellular concentrations are fixed, so these equations are three equations in three unknowns. Eliminating Cl^- between the second and third equations and substituting for the extracellular concentrations gives

$$K_{in} - \frac{5}{120}Na_{in} = 0$$
$$K_{in} - \frac{5\cdot 125}{K_{in}} + Na_{in} = 117.5 \qquad \Rightarrow \qquad K_{in}^2 + (Na_{in} - 117.5)K_{in} - 5\cdot 125 = 0$$

Eliminating Na_{in}

$$K_{in}^2 + \left(24K_{in} - 117.5\right)\cdot K_{in} - 625 = 0 \qquad \Rightarrow \qquad 25K_{in}^2 - 117.5K_{in} - 625 = 0$$

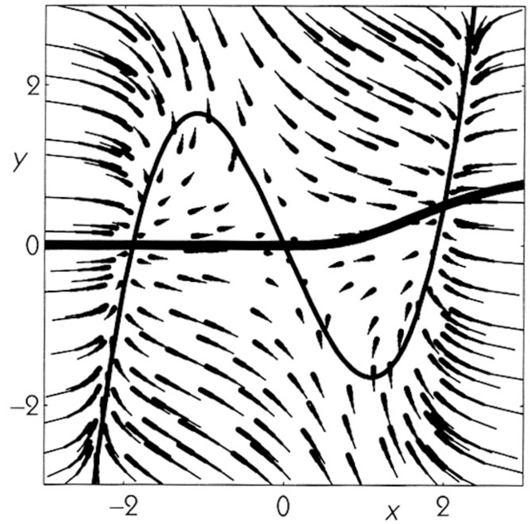
The meaningful solution is K_{in} = 7.9 mM, Na_{in} = 189 mM, and Cl_{in} = 79.4 mM. Additional transport mechanisms, like a NaK-ATPase are needed to give a more physiological answer.

Problem 2

Part a) *V* and *w* are corresponding state variables in the FN and ML systems. As for the r.h.s. of the *V* equation, 1 is the injected current, the term in brackets [v^3 . . .] represents the calcium and leakage currents, and the *w* term is the potassium current. Although the latter does not multiply *V* as it should, it acts to restore *V* to the resting state because of its negative sign. In the r.h.s. of the *w* equation, *bV* is the w_∞ function. *w* is activated by depolarization of *V*.

Part b) *y* has exactly the form of a HH equation with *y* corresponding to *w* and $x^3/(8+x^3)$ being the y_∞ function. Then *x* is membrane potential and the polynomial in *x* represents the calcium and leak currents. The current gated by *y* is represented in simplified form by the term *y*. Note that the sign of this is reversed for a K^+ current, see part e).

Part c) The phase plane with isoclines and arrows is shown at right (copied from Kaplan and Glass, p. 398). Note that the *dV/dt* isocline is inverted from what the ML equations give. This is because of the sign inversion of the *w* term in the *dV/dt* equation.



Part d) The equilibrium points are at

$-(18/5)^{1/2}, 0$ $\quad$ $0, 0$ $\quad$ $2, ½$

Part e) The Jacobian **J** is given by the usual differentiation. For x>0

$$\mathbf{J} = \begin{bmatrix} -\frac{15x^2}{8} + \frac{9}{4} & 1 \\ \frac{24x^2}{(8+x^3)^2} & -1 \end{bmatrix}$$

and for x<0

$$\mathbf{J} = \begin{bmatrix} -\frac{15x^2}{8} + \frac{9}{4} & 1 \\ 0 & -1 \end{bmatrix}$$

Note that there is no discontinuity in the Jacobian at 0.

The easiest one to calculate is for $[x,y] = [0, 0]$, for which the eigenvalues are 9/4 and -1, making it a saddle node. For the left-hand equilibrium point, the eigenvalues are -18/4 and -1 so this is a stable node. At the right-hand equilibrium point, the eigenvalues are $-25/8 \pm [(25/8)^2 - 39/4]^{1/2}$ which are also both negative real, so this point is also a stable node.

Part f) The sign inversion suggests that this +*y* term represents the gating variable of a depolarizing channel, like a persistent-sodium channel.