580.439/639 Midterm Exam, 2010

Do all problems. Closed book except for one page.

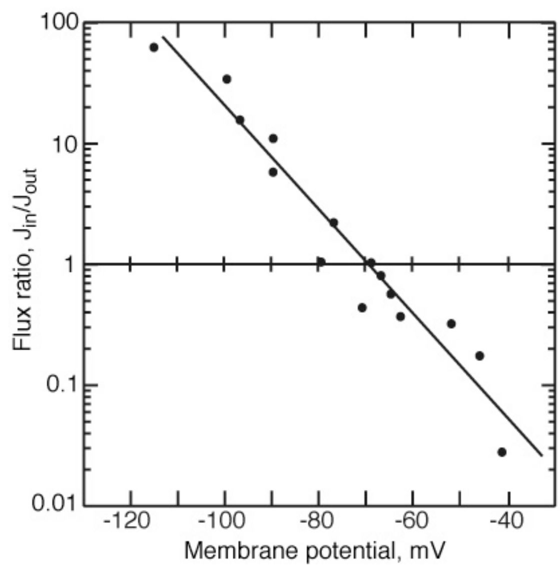
Problem 1

Part a) What does *independence* mean in ion flux models?

Part b) The Ussing flux ratio is a condition for independence of ion fluxes. It is usually written as follows:

$$\frac{J_{A\to B}}{J_{B\to A}} = \left(\frac{C_A}{C_B} e^{-zF(V_B - V_A)/RT} \right)^n$$

where J, C, z, F, V, R, and T have their usual meanings, A and B are the two sides of the membrane, and n is an exponent. If the ratio of unidirectional flux data (the l.h.s.) behaves as predicted by this equation with n=1, then the transport is consistent with independence. This was shown in a homework problem.



The plot at right shows data on the flux ratio of potassium ions in squid axon (from Hodgkin and Keynes, 1955). Is this flux consistent with independence? Compute an approximate value for n for these data. What is E_K for this experiment?

Note that you will have to define sides A and B to be inside or outside to make sense out of the data. Also remember that the absolute values of the fluxes are used on the l.h.s. of the flux equation.

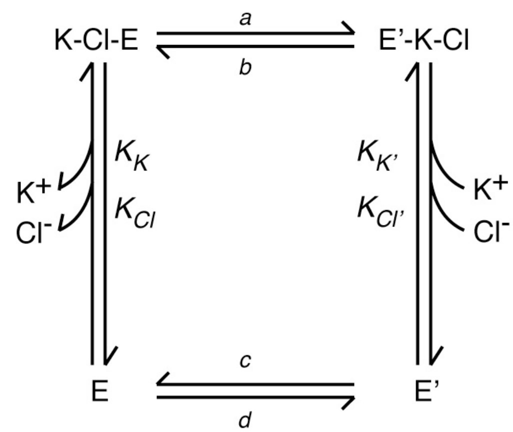
Part c) One interpretation of n above is that it is the number of ions that must move through a membrane together because of the structure of a transport protein. Discuss your value of n in terms of what is known about potassium channels. (This is a question about potassium channels, not flux ratios.)

Part d) (Extra credit, do this last) As a check on this result H&K measured the electrical conductance G_K of the membrane at membrane potentials near E_K (i.e. for ΔV-E_K small). Defining G_K = (net membrane K current)/(ΔV-E_K), show that

$$G_K \approx n \frac{F^2}{RT} J_{out}$$

for small (ΔV-E_K).

Problem 2



The potassium chloride cotransporter (KCC) transports a K^+ and a Cl^- ion together through the membrane (out of the cell) in a cycle like the one drawn at right. This system uses energy in the potassium gradient to lower the chloride concentration in the cell. If the inside of the cell is primed (at right in the diagram) and the outside of the cell is unprimed, then the normal forward direction of the transporter is a counter-clockwise rotation. Note that K^+ and Cl^- must be transported together. As was done in class, we assume that the reactions

$$K^+ + E \rightleftharpoons K^+E \quad \text{and} \quad Cl^- + E \rightleftharpoons Cl^-E$$

are at equilibrium on both sides of the membrane with the dissociation constants K_K, K_{Cl}, $K_{K'}$, and $K_{Cl'}$.

Part a) Consider the flux equation for a model of this system like the Laüger model for the Na-Ca cotransporter considered in class.

$$J_{KCl} = \frac{f(V, K_{out}, K_{in}, Cl_{out}, Cl_{in})}{g(V, K_{out}, K_{in}, Cl_{out}, Cl_{in})}$$

The numerator and denominator of these functions are constrained by thermodynamics and by the properties of chemical kinetics to take certain forms. Write an equation for *f*(..) showing the form it must take. You won't be able to show the full details of *f*(..) without actually working out the model above (don't do this), but show what must be present in this function and tell why.

Part b) Similarly, the denominator function *g*(..) must have a certain behavior at large concentrations, assuming that K_{in} and Cl_{in} increase together or K_{out} and Cl_{out} increase together. Show that behavior and explain why.

Part c) Suppose there is a charge z_E on the parts of the transporter molecule that moves through a fraction λ_E of the membrane potential when the transition $E \to E'$ or the opposite occur, i.e. on along of the horizontal arrows in the reaction diagram above. Draw a barrier diagram for the transitions and write equations for *a, b, c,* and *d*. If you need to define additional parameters, do so. Does this change your answer to part a)?

Problem 3

Consider a membrane with three channels (taken from an example in the Izhikevich book):

(1) Leak channel with G_L and E_L= -80 mV.

(2) Persistent (non-inactivating) sodium channel with G_{Na} and E_{Na}=20 mV. The activation gating is instantaneous, meaning $m = m_\infty(V) = 1/\left(1+e^{(V_1-V)/k_1}\right)$.

(3) An H channel. This is a channel with only an inactivation gate with variable h, G_H, and E_H = -43 mV. The gating of the inactivation variable h is controlled by

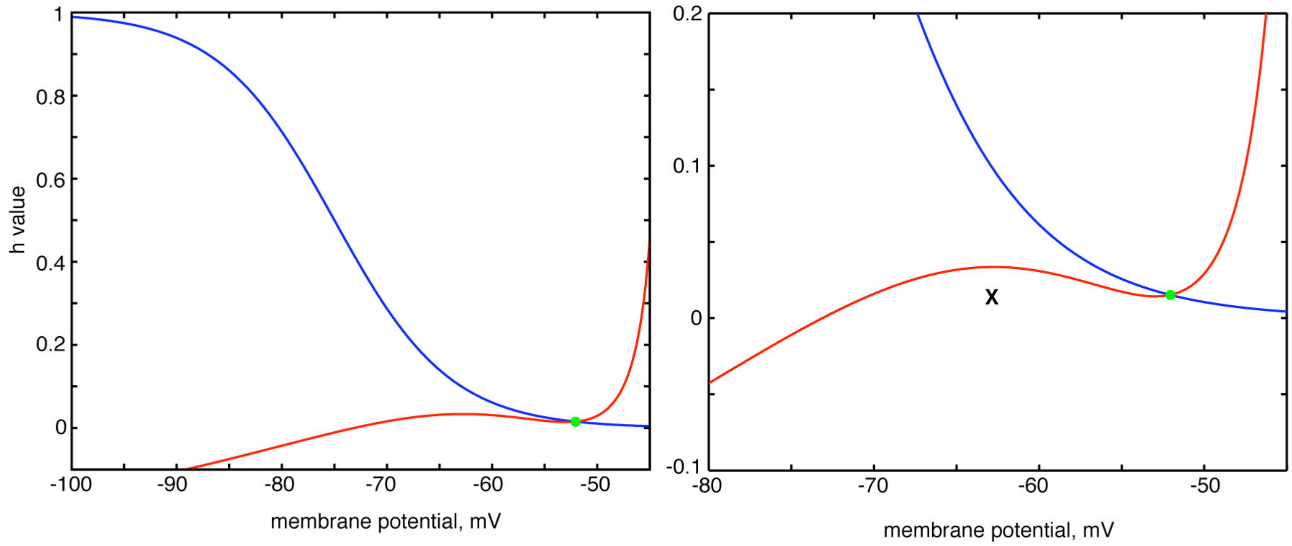
$$h_\infty(V) = 1\big/\left(1 + e^{(V_2 - V)/k_2}\right) \quad \text{and} \quad \tau_h = 100 + 1000 e^{-(V_3 - V)^2/\sigma^2}$$

Part a) Write the differential equations necessary to describe this system. Leave them in symbolic form, that is use $h_\infty(V)$, not the actual function for h_∞. Include an external current I in the model.

Part b) The nullclines of the system for I=0 are plotted on the next page. Label the nullclines (i.e. which is dV/dt=0 and which is dh/dt = 0?) and the equilibrium points and draw four arrows to indicate the direction of flows in the phase plane. This system has no limit cycle and the equilibrium point is stable. Assuming that $|dV/dt| >> |dh/dt|$, plot an approximate trajectory starting at the initial condition marked by "x" in the phase plane on the next page.

Part c) The nullclines of the same system for I=-1 are also shown on the next page. Now the equilibrium point is unstable Argue that there has to be a limit cycle for this system and draw an approximate trajectory for it, again assuming that $|dV/dt| >> |dh/dt|$.

Phase planes for problem 3b (same phase plane at two magnifications):



Phase planes for problem 3c (same phase plane at two magnifications):