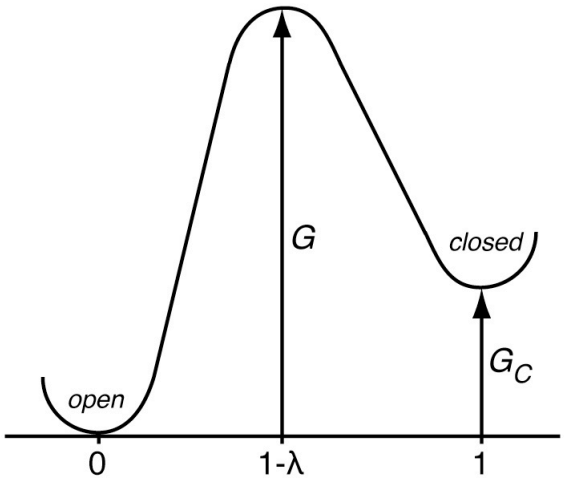
580.439/639 Homework #3

Due September 29, 2014

Problem 1

Rate theory can be used to construct a model of gating in the squid giant axon potassium channel. Suppose that the channel consists of four subunits that each can exist in either the open or closed state. The channel is open when all four subunits are open. Their relative free energies (when membrane potential is zero) and the activation energy barrier between them are shown at right below. Note that the open state is energetically favored over the closed state when membrane potential is zero (as drawn). This corresponds to the actual channel, which is open when the membrane is depolarized to 0 mV.

Let n be the fraction of subunits that are open and (1-n) be the fraction that are closed. n is then roughly the same as the Hodgkin-Huxley n parameter. The membrane potential affects n because opening or closing the channel involves translating a *gating charge* z_G through the membrane. Assume that closing a subunit is equivalent to transfer of an ion with charge z_G through the membrane from 0 to 1 in the diagram at right; with this assumption, the model is exactly analogous to permeation of a single-barrier channel by an ion with charge z_G. (1-λ) is the fraction of the membrane potential through which the gating charge has been carried when the transition from open to closed passes over the peak of the energy profile.



a) Assuming that the gating charge is near the outside of the membrane when a subunit is open and is near the inside of the membrane when the subunit is closed, which polarity (+ or -) of gating charge is necessary to produce the qualitative voltage dependence observed in the squid giant axon potassium channel?

b) Show that the following differential equation can be written for n, using the model above.

$$\frac{dn}{dt} = \alpha\, e^{\lambda z_G v}\left[1 - n\left(1 + e^{-z_G(v+v_h)}\right)\right]$$

where α and v_h are constants and v is membrane potential V in dimensionless form, as $v = FV/RT$. Give expressions for α and v_h in terms of the parameters of the model.

c) Write expressions for the HH parameters $n_\infty(V)$ and $\tau_n(V)$ in terms of the rate theory model expressed in the differential equation above.

d) Find values of z_G, v_h, λ, and α that provide a good fit of the equations for $n_\infty(V)$ and $\tau_n(V)$, derived in c) above, to the empirical model provided by Hodgkin and Huxley, summarized by the equations below.

$$n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n} \quad \text{and} \quad \tau_n = \frac{1}{\alpha_n + \beta_n}$$

where (voltages in mV):

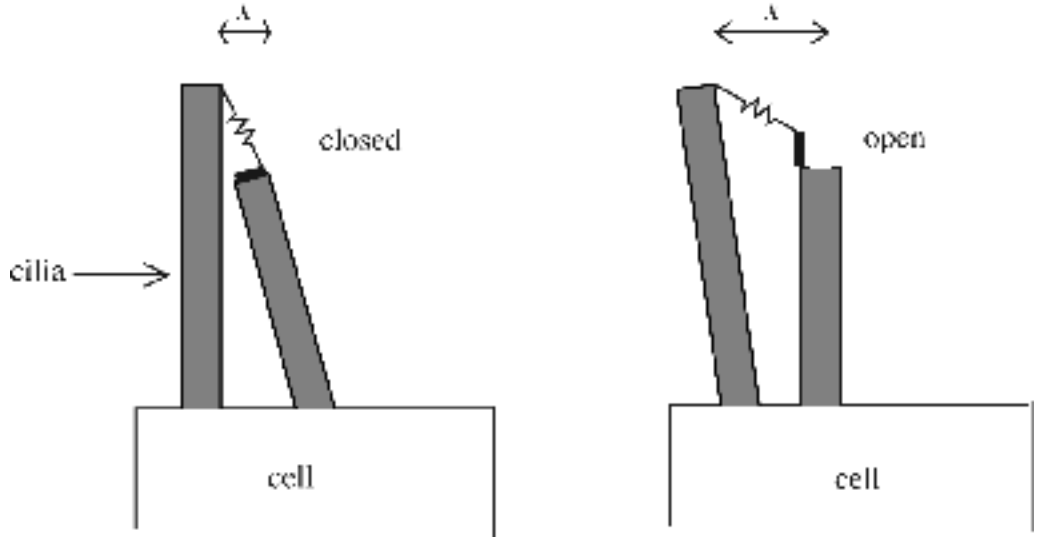
$$\alpha_n = \frac{0.01(V+60)}{1-\exp\left[\frac{-V-60}{10}\right]} \quad \text{and} \quad \beta_n = 0.125\exp\left[\frac{-V-70}{80}\right]$$

Note that you will be able to obtain only an approximate fit. There is no one correct answer to this problem, but you should describe what criterion or method you use to do the fit.

e) On p. 58, Hille or p. 163 Johnston and Wu, a value of 4.5 for the gating charge z_G is given. How does this compare with your value in part d)? If the values are different, why are they different? What if the gating charge doesn't move all the way through the membrane?

Problem 2

The transduction channel in vertebrate hair cells is hypothesized to operate as sketched below. The channel (▬) is at the tip of a cilium; its gate is attached by a spring (—∿∿—) to an adjacent cilium so that when the cilia are spread apart, the spring pulls on the gate in such a direction as to open it. That is, the probability of a channel being open (conducting) is increased by the force exerted on the channel's gate by the spring.



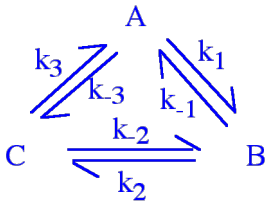
Construct a transduction model for this cell based on the sketch above. Use a single-barrier rate theory model in which the two states are channel-closed and channel-open and the barrier is the amount of energy the channel gate needs in order to change conformations from closed to open or vice-versa. Assume that the presence of the spring modifies the energy barrier profile according to the potential energy in the spring, which is a function of the spread x of the cilia and the state (open or closed) of the gate. That is, the spring has a potential energy $s \cdot d(x)^2$, where s is the spring constant and $d(x)$ is the extension of the spring at cilia spread x; this energy should be added to the barrier model's potential energy wells and peak, in a way analogous to the way that membrane potential modifies the energy barrier of an ion channel. Ignore membrane potential in this model.

a) Derive an equation for the probability that the channel is open expressed in terms of the energy barrier, the mechanical properties of the spring, and the separation x of the cilia. Assume for this part that the system is in a steady-state. This problem is intentionally vague and you will have to make some additional assumptions. A good assumption to make is that the change in length of the spring when the channel opens is very small compared to the length of the spring (i.e. the spacing x is exaggerated in the figure above).

b) Suppose that the cilia have been held at separation x_0 and are suddenly displaced to separation x_1, where x_1 is larger than x_0. From the results of part a), you should conclude that additional

channels will open. What is the initial rate of opening of channels, i.e. d(number of open channels)/dt at time 0^+, just after the ciliary movement?

Problem 3



An important rule for kinetic models is that the product of the rate constants going clockwise around any loop must equal the product of the rate constants going counter-clockwise, in the absence of energy sources or transfers of material into or out of the loop. Thus for the 3-state model at right, $k_1 k_2 k_3 = k_{-1} k_{-2} k_{-3}$. This rule is called *microscopic reversibility*.

a) Draw an energy barrier model for the example system and show from that diagram that microscopic reversibility must hold. In doing this, IGNORE THE EFFECTS OF ELECTRICAL POTENTIALS. This assumption doesn't change the conclusion, it just makes it simpler.

b) Another way to prove microscopic reversibility is to demand that, at equilibrium, there should be zero net flux through the system (*principle of detailed balance*). Write equations for the three fluxes in this system and show that if the three net fluxes are zero at equilibrium, then microscopic reversibility must hold.

c) Consider whether a steady-state of flux could occur in such a system. That is, could there be a non-zero net flux around the system in either the clockwise or counterclockwise direction in steady state? Apply the usual steady-state condition to the fluxes in the model and argue that microscopic reversibility implies that there cannot be such a flux. Of course, the system cannot be at equilibrium for this steady state to occur.

d) Suppose state B is on one side of the membrane, at a potential V relative to states A and C which are on the other side of the membrane at 0 potential; the reaction species have a fixed charge z which is the same in states A, B, and C. Argue that microscopic reversibility still holds.