APh161: Physical Biology of the Cell
Homework 6
Due Date: Tuesday, March 1, 2005

"To do successful research, you don't need to know everything. You just need to know of one thing that isn't known." - Arthur Schawlow, quoted in "Lasers, Spectroscopy and New Ideas" edited by Yen and Levenson

Reading: Chaps. 10 and 12 of Howard.

1. Diffusion to Capture: The Hard Way

In class I gave an intuitive derivation of the problem of diffusion to capture without ever solving the diffusion equation. In this problem, I want you to work out the features of diffusion to capture with a perfect absorber using the full machinery of the diffusion equation.

(a) Recall that we wish to solve for the steady-state condition in which we prescribe a far-field concentration c_0 and assume that the absorber (a sphere of radius a) is a perfect absorber ($c(a) = 0$). Write the diffusion equation in spherical coordinates at steady-state (i.e. $\partial c/\partial t = 0$).

(b) Show that the resulting concentration profile is of the form

$$c(r) = A + \frac{B}{r}, \tag{1}$$

and use the conditions $c(a) = 0$ and $c(\infty) = c_0$ to determine the constants A and B.

(c) Compute the flux at the surface of the sphere and then use this to evaluate dn/dt and confirm the expression for the diffusive speed limit that I discussed in class.

(d) Recall Prof. Bob Austin's (Princeton Physics) quip that "physics isn't worth a damn unless you put in some numbers". Let's put in some numbers

and actually evaluate the diffusive speed limit for several cases of interest. In particular, let's work out the rate for actin monomers to be incorporated onto a growing actin filament and for oxygen arriving at hemoglobin. That is, make an estimate of the size and diffusion constant for G-actin and O_2 and compare the rates that you find with the k_{on} for the actin polymerization reaction and for the uptake of oxygen by hemoglobin. Of course, you will have to make some assumptions about c_0 - try the critical concentration for actin and for oxygen, maybe you can find some reasonable numbers on the web. The discussion on pgs. 308 and 309 of Howard give an interesting discussion of the diffusion-limited speed limit. Note that we are making a simplifying assumption by treating the growing filament and the hemoglobin as stationary.

2. Microtubule Dynamics.

There have been a number of models that have been set forth to examine the intriguing character of cytoskeletal dynamics. In this problem, I will walk you through one phenomenological model for steady-state microtubule dynamics that was introduced by Dogterom and Leibler in Phys. Rev. Lett. **70**, 1347 (1993) - the paper is on the course website. Note that there is a more interesting class of models that include GTP hydrolysis explicitly (see Phys. Rev. **E54**, 5538 (1996).) As an example of the type of data we are trying to come to terms with, see fig. 1 and fig. 6 of Fygenson *et al.*, Phys. Rev. **E50**, 1579 (1994). Fig. 1 shows a record of the length of a single microtubule as a function of time and reveals the series of "catastrophes" and "rescues" as the polymer changes its length.

(a) Deduce eqns. 1 and 2 of the Dogterom paper - in particular, note that they are thinking of a probability distribution $p_+(n,t)$ and $p_-(n,t)$ which gives the probability of finding a microtubule of length n that is growing $(+)$ or shrinking $(-)$. Write a master equation like we did in class for $p_+(n,t)$ and $p_-(n,t)$ by noting that there are 4 things that can happen to change the probability at each instant. Consider the $+$ case - (i) the $n-1$ polymer can grow and become an n polymer - characterized by a rate v_+, (ii) the n polymer can grow and become and $n+1$ polymer - also characterized by a rate v_+, (iii) the $n+$ polymer can switch from growing to shrinking with a rate f_{+-} and (iv) the $n-$ polymer can switch from shrinking to growing with

a rate f_{-+}. What I am arguing is that if you account for all four of these possibilities you will have the correct master equation. Use a Taylor expansion on stuff like $p_+(n-1,t) - p_+(n,t)$ to obtain the equations as written in the Dogterom paper.

(b) Solve these equations in the steady state (i.e. $\partial p_\pm(n,t)/\partial t = 0$) and show that the relevant parameter is

$$\sigma = \frac{v_+ f_{-+} - v_- f_{+-}}{v_+ v_-}. \tag{2}$$

Explain what all of this means. When I say "solve", what I mean is find all of the $p_\pm(n)$. What you have done is to find the distribution of lengths.

(c) Use fig. 1 from the Fygenson paper above to estimate the relevant parameters v_+, v_-, f_{+-}, f_{-+}, and then find the average length of the polymers which are *predicted* by this simple model. To find the average length you will need to sum over all lengths with their appropriate probability. The Fygenson data in their fig. 1 captures some key ideas - the slopes of the growth and decay regions tell you about the on and off rates, and the durations of the growth and decay periods tell you something about the parameters f_{+-} and f_{-+}. Note that by fitting the dynamical data, you are deducing/predicting something about the distribution of lengths.

3. ATP: A Feel for the Numbers.

a) (From Lehninger **Principles of Biochemistry**). A 68kg (150lb) adult requires a caloric intake of 2000kcal (8360 kJ) of food per day. The food is metabolized and the free energy is used to synthesize ATP, which then provides energy for the body's daily chemical and mechanical work. Assuming that the efficiency of conversion of food energy into ATP is 50%, calculate the weight of ATP used by a human in 24 hours. How many ATP molecules is this? Take this a bit further by making a crude estimate of the number of mitochondria in a human being and by assuming some reasonable number of ATP synthase molecules per mitochondrion. Use this to see whether the number of ATP synthesized each day is consistent with the rate at which the ATP synthase molecules can be producing it. (RP to class: this last bit is

very crude and I am not entirely confident that it will all work out.)

b) The Stokes drag formula (see Howard's book if you don't know about this) says that the drag force on a sphere under low Reynolds number conditions is given by $F_{drag} = -6\pi\eta a v$, where π is the ratio of the circumference of a circle to its diameter, η is the fluid's viscosity, a is the radius of the sphere and v is the particle's velocity. Consider a spherical bacterium! Taking our cue from *E. coli* which swims (by turning its flagellae) at a speed of about 20 $\mu m/sec$, figure out how many ATPs it must consume per second in order to travel at this speed, assuming that all of the energy usage goes into overcoming fluid drag. You will have to find a spherical representation of *E. coli*. Note that this problem is not quite right because the flagellar motor is powered by a proton gradient rather than ATP, but the main point is the same - you are trying to reconcile the energy budget of various cellular actions with the known liberation energy from ATP hydrolysis.

4. Equilibrium Constants.

Equilibrium constants are one of the key interpretive tools in molecular biology and biochemistry. In this problem, we revisit some of the conceptual foundations of equilibrium constants.

a) In class I swiftly derived the law of mass action on the basis of minimization of the Gibbs free energy. Repeat that derivation here making sure to attend to all details and explaining all of your steps and logic.

b) We begin by examining a kinetic interpretation of equilibrium constants and the associated question of whether or not the barrier which separates the two states of interest should play any role in the equilibrium constant (we already know the answer is no, but we will demonstrate it). Consider the simple reaction A + B $\rightleftharpoons$ C. In this case, we know that the equilibrium constant is given by

$$K = \frac{[C]}{[A][B]}. \tag{3}$$

However, we can also express this equilibrium constant in terms of the rate constants for the reaction. In particular, note that the reaction has a kinetic

equation

$$\frac{d[C]}{dt} = k_{on}[A][B] - k_{off}[C]. \tag{4}$$

At equilibrium, the left hand side of this reaction is zero and hence we have

$$K = \frac{k_{on}}{k_{off}} = \frac{[C]}{[A][B]}. \tag{5}$$

Sketch an energy landscape with two wells and a barrier between them. Call the free energy when A and B are separate E_1 and that when they are associated E_2. To make a transition from 1 to 2 requires going over a barrier of height E_b. Put all of this in your sketch. Transition state theory tells us that the rate of a reaction is of the form

$$\text{rate} = \nu_0 exp(-E/kT), \tag{6}$$

where E is the height of the barrier and ν_0 is an "attempt frequency". Compute the ratio k_{on}/k_{off} and show that the barrier height drops out of the problem (as it should).