APh161: Physical Biology of the Cell
Homework 7
Due Date: Tuesday, March 7, 2006

"The good steel must pass through the fire." - Charles Dickens

NOTE: The first three problems must be submitted by email to Rob (and both TAs) - no hard copies accepted.

1. An Argument.

This course has been built around the idea of "physical biology" as the basis of a new era of investigating biological problems using the tools of physics. (a) In less than one paragraph, make the argument that "physical biology" is just a fad and explain why it will not represent a permanent transformation of the way we do biology. (b) In less than one paragraph, make the argument that "physical biology" is transforming the way we view biology and why it is here to stay.

The whole point of this problem is to get you to think critically about the entire concept of this course. By making the argument from both sides, you will have a chance to see both the positive and negative facets of insisting upon a physical approach to biological problems. Also, I think it is very important for you to be aware of the role of fads in science. Just because there is a string of papers in *Science* or *Nature* does not mean that the topic of those papers will ultimately have scientific staying power. You need to be careful judges of what has merit and what does not. My own favorite metric of whether or not a particular topic seems to me to be really timely or important is this: would I want to talk about it in class.

2. The Top Five.

Identify and explain the five most important things you learned in this course. Be thoughtful and justify your arguments. I am not asking for you to regurgitate material from the class. Figure this out for yourself. Give roughly a paragraph to explain each of your choices. In particular, make sure that each entry is described in detail with a discussion of why the topic meant something to you and how it fits into your picture of biology.

3. Physical Biology of the Cell: Your Turn.

Imagine yourself teaching a course entitled "Physical Biology of the Cell" which is aimed at arguing for a study of the living world using any and all tools available (i.e. conventional tools of molecular biology, biochemistry, mathematics, statistical mechanics, elasticity theory, statistics, etc.). In particular, I am asking you to reject the way that departments in universities are organized and just think about the questions of interest - how cells and the machines within them work. Your job in this problem is to write a course outline for such a course - organize it lecture by lecture and imagine that you have 20 lectures. Give a one sentence justification for the choice of topic in each lecture. Try to think out of the box - don't necessarily organize things the way that I did - put forth a real attempt at originality.

4. Load Dependence of Motors.

(a) In class, I worked out the velocity of a one-state motor for a model in which the load dependence all appears in $k_-(F)$. In this problem, I want you to derive the velocity and randomness for a model in which all of the force dependence is buried in $k_+(F)$. Make sure you explain the whole story - derive everything, explain the logic, discuss the meaning of your results and make plots like I did in class both for $k_+(F)$ and for $v(F)$. That is, discuss the nature of the model, derive the relevant rate equation and reproduce the derivation of the driven diffusion equation. Then, show how the driven diffusion equation can be solved and see if you can find choices of v and D (and hence $k_+(F)$ and $k_-(F)$) that best describe the motion of kinesin - use the same data used by Fisher and Kolomeisky (there paper is posted with the homework). As I mentioned in class, Fisher and Kolomeisky find that even the two-state model is not sufficient to fit kinesin data so we should not be too surprised if the fit doesn't work out too well.

(b) In class I used simple equilibrium arguments to derive the Michaelis-Menten equation for the rate of an enzyme reaction as a function of the substrate concentration. In this part of the problem, we will use rate equation in steady-state to derive this same result. Write a rate equation for the concentration $[ES]$ in terms of the rate constants k_1, k_{-1} and k_p that we used in class. Note that this rate equation should have three terms. Next,

set this rate equal to zero (i.e. steady state) and replace the concentration of enzyme $[E]$ with $([E_{tot}] - [ES])$. Solve the resulting equation for $[ES]$ and then use $v = k_p[ES]$ and $v_{max} = k_p[E_{tot}]$ to write the Michaelis-Menten equation. Make sure to relate the constants in your rate formulation to the formulation I gave in class. For kicks, work out how much change in substrate concentration needed to increase the reaction rate from $0.1v_{max}$ to $0.9v_{max}$. Take a look at the data from the Block group on kinesin that I showed in class and see how well you can fit the ATP dependence of the velocity using the Michaelis-Menten fit you have derived. The data you will need is posted with this homework.

(c) In class I have repeatedly shown single molecule experiments in which motor molecules are attached to polystyrene beads which are used to monitor the motion of the motor. In this part of the problem I want you to estimate the force acting on such a motor as a result of the Stokes drag on the bead. Use a characteristic speed for a motor like kinesin and work out the drag force resulting from an attachment to a one micron bead. Comment on the magnitude of this drag force relative to the stall force of such motors.

5. Solution to the Diffusion Equation for a Point Source.

(a) In class I sketched the solution of the diffusion equation by Fourier transformation. In this problem, I want you to repeat that derivation showing every detail to show that

$$c(x,t) = \frac{c_0}{\sqrt{4\pi Dt}} e^{-x^2/4Dt}. \tag{1}$$

Use the Fourier transform convention

$$\tilde{c}(k,t) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} e^{ikx} c(x,t) dx. \tag{2}$$

Make sure you show all of your details. This includes demonstrating how you Fourier transform the diffusion equation (and in particular, how you Fourier transform derivatives). Once you have the Fourier transformed equation, you will need an initial condition - take $c(x,0) = c_0\delta(x)$.

(b) Formally derive the relation $\langle x^2 \rangle = 2Dt$ by computing the average explicitly using the solution from part (a). Then, make a plot of the relation

between distance diffused and the time it takes using a log-log plot. Make plots for several choices of D - in one case use the typical diffusion coefficient for an ion species like K^+ or Na^+, in the second case, use a typical diffusion coefficient for a protein - justify your choice of diffusion coefficient by using the Stokes relation $D = k_B T/6\pi\eta a$.

(c) Now imagine that you have spiked a one-dimensional "cell" (which is infinitely long!!) with a pipette that inserts GFP with a concentration c_0 between $-a$ and a. Find the concentration everywhere at all times by integrating over the solution worked out in part (a) of this problem. Make sure you explain why this is the right thing to do using the linearity of the diffusion equation. Plot the solution for various times and show how the profile evolves over time. Also, explain why I claim the cell is infinitely long given our mathematical approach to the problem.