APh161: Physical Biology of the Cell
Homework 6
Due Date: Wednesday, February 27, 2013

"I may add that as we daily see men arriving at opposite conclusions from the same premises it seems to me doubtful policy to speak too positively on any complex subject however much a man may feel convinced of the truth of his own conclusions." - Charles Darwin in a letter to E. Haeckel

Useful reading can be found in chap. 5 for thinking about hydrophobicity and in chap. 19 for thinking about genetic circuits.

1'. Redo: Estimate of integration time: Berg-Purcell problem.

In class I gave a long discussion of the idea that receptors use occupancy measurements as a way to figure out what the external concentration is. We argued that there is a measurement error and the longer the system makes the measurement, the smaller that error. In this problem, we are going to come at this problem from a different angle than I did in class, but arriving at effectively the same result. I am assigning this problem because one of the things I want you to leave this class with is an appreciation of the physical limits to biological detection.

(a) Imagine a receptor with a length scale a (i.e. molecular dimensions a). If the concentration in the neighborhood of the receptor is c, how many molecules are there in a region with characteristic size a? Given this result, what is $\delta N/N$? This is the error in making a single measurement.

(b) The next idea is that we can improve the measurement by repeating it again and again during a total integration time. The argument made by Bialek in his excellent book "Biophysics" is that we need to wait a time given by the diffusion time before making the next measurement. What I mean by this is that there is some characteristic time scale for particles to diffuse out of the region of size a. What is this time scale?

(c) Now what we want to do is to compute the precision of our measurement

by using

$$\frac{\Delta p}{p} = \frac{1}{\sqrt{\text{number of measurements}}} \frac{\delta N}{N}, \tag{1}$$

where the quantity $\delta N/N$ is the uncertainty in one measurement, and $\frac{\Delta p}{p}$ is defined as in class. Now figure out how many measurements are made in time T by figuring out how many diffusion times τ_D there are in this period and get a formula for $\frac{\Delta p}{p}$ and estimate the numerical value for the integration time.

1. Genetic Switch Design 2.

In class we worked out the dynamics of a genetic switch using a model of auto-activation. I also showed you schematically how a switch might work with two genes that each code for a repressor that represses the other gene. This is the subject of section 19.3.5 of PBoC2. We considered repressor binding in which the Hill coefficient $n = 2$. In this problem, you will work out this model in more depth for several different choices of the Hill coefficient.

(a) Begin by deriving the probability of repressor binding assuming that the repressor can only bind as a dimer and show that p_{bound} is of the Hill form. Then derive the differential equations for the protein concentrations like I did in class and write everything in dimensionless form in terms of the two dimensionless protein concentrations, u and v. Next, show that in steady state (as we did in class) that

$$u = \frac{\alpha(1+u^2)^2}{(1+u^2)^2 + \alpha^2}. \tag{2}$$

Now plot the two sides of the equation and examine their intersection for three choices of $\alpha = 1, 2, 3$. Explain the significance of your graphical result with respect to the number of solutions. Basically, you are telling the same story I told in class using phase portraits, but rather than solving the problem analytically you are solving it graphically. In addition, make vector field plots that show the fixed points for these same different values of α and use these plots as a second way of explaining the dynamics.

(b) Repeat the derivation given in class but now for the case where the Hill coefficient is $n = 1$ and show that there is only one solution (i.e. there is no

switching behavior). Make sure to discuss, comment and observe. I want to hear you reason about this problem, not just show the one particular result that is asked of you.

2. Multiplicities and entropy.

Do problem 5.5 of PBoC2. My reason for assigning this problem is that I want you to develop intuition for the way that entropy is computed in preparation for the following problem on hydrophobicity.

3. Hydrophobicity and statistical mechanics.

In class I gave a quick impression of the hydrophobic effect as an idea that is invoked often with great explanatory power. In this problem, you will estimate the magnitude of the interfacial energy that is assigned to having certain chemical groups in contact with water. This will give us an idea of how much free energy is gained when different molecules come into contact and sequester these hydrophobic structural elements. The essential argument is that the water molecules that surround the hydrophobic region of a molecule are deprived of some of their entropy because they can adopt fewer hydrogen bonding configurations. In particular, the water molecules are thought to form cages known as clathrate structures such as are shown in the accompanying figure.

(a) Estimate the entropy lost for each water molecule by appealing to the schematic of the tetrahedron shown in the figure. The basic idea is that if we think of the O of the water molecule as being situated at the center of the tetrahedron then the two H atoms can be associated with any two adjacent vertices (or, there are a total of six configurations). However, when in the presence of the hydrophobic molecule, one of the faces of the tetrahedron can be thought of as facing that hydrophobic molecule and hence all configurations (three of the edges) facing that molecule are unavailable for hydrogen bonding. How many configurations are available now? Compute the entropy change of a single water molecule as a result of this configurational inhibition.

(b) Next, we need to estimate how many water molecules neighbor a given hydrophobic molecule. Consider the case of methane and ethane and estimate the radius of sphere that represents the hydrophobic surface area they

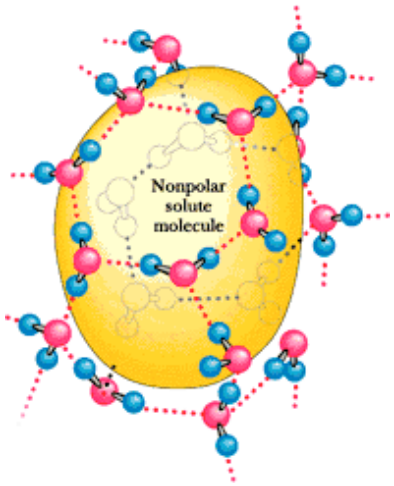

Figure 1: Schematic of the clathrate structure adopted by water molecules surrounding a hydrophobic molecule.

present. Next, estimate how many water molecules neighbor these molecules and hence the total free energy difference because of the lost entropy. Convert your result into an interfacial energy and use units both of J/m^2 and cal/mol $\AA^2$. Compare the result to the rule of thumb I quoted in class which is 25 cal/mol $\AA^2$.

(c) Since we have said that hydrocarbons are hydrophobic, go back and examine the 20 amino acids and decide which residues are hydrophobic. Further, estimate the free energy cost for several of these residues (you choose which ones) when they are not properly sequestered from water. Report your energies in units of kT.

NOTE: this problem provides a highly idealized toy model of hydrophobicity. The hydrophobic effect is much more subtle than I have made it sound.

4. Mathematics of curvature

Do problem 11.3 of PBoC2.

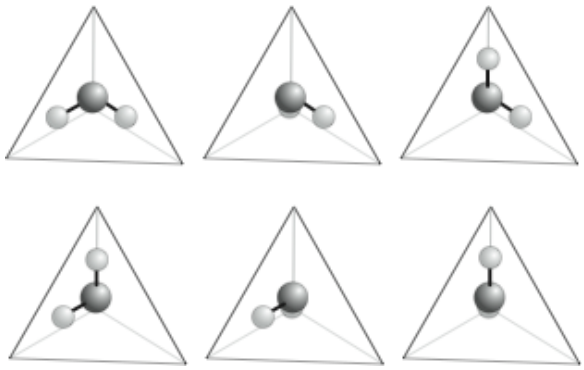

Figure 2: Schematic of the arrangements available to a water molecule when in a complete network of other water molecules.