# BE/APh161: Physical Biology of the Cell
# Homework 3
# Due Date: Wednesday, February 6, 2013

"The quality of a person's life is in direct proportion to their commitment to excellence, regardless of their chosen field of endeavor." - Vince Lombardi

Helpful reading - for problem 1, chap. 13 of PBOC is useful. For problem 2, chaps. 6 and 7 provide the relevant background material. Note that in problem 1, when you actually sit down and try this, you should first attempt it with the book closed and really think hard about each detail on your own.

**1. Diffusive speed limits: It's not just a good idea, it's the law**

In order for a chemical reaction to take place, the reactants must be at the same place at the same time. A very interesting calculation explores the way in which diffusion can control the on rate for reactions. Imagine some reaction in which $A$ and $B$ come together to form the complex $AB$. To simplify the problem, we are going to imagine $B$ as a sphere of radius $a$ that is fixed at the origin of our coordinate system. Further, we are going to imagine that very far away the concentration of $A$ is held at $c_0$. What I really mean by this is that $lim_{r\to\infty} c(r) = c_0$, where $c(r)$ is the concentration of reactant $A$ as a function of distance from the origin. Our goal is to compute the so-called "diffusion-limited on rate" for the reaction. We begin by working out the steady-state solution to the diffusion equation with the boundary condition that $c(a) = 0$, which corresponds to the physical statement that the sphere is a "perfect absorber". What this really means is that every time a molecule of $A$ arrives at the sphere, the reaction occurs. (Note that this tells us that the diffusion-limited on rate is the fastest that a reaction could occur. It could be true that after the molecule arrives, it has to wait for some favorable orientation to occur, for example, which would make the rate of the reaction even slower).

(a) Solve the diffusion equation in steady state and find the concentration profile $c(r)$ as a function of $c_0$ and $a$.

(b) Use that result to compute the diffusive flux $J(a)$ at the surface of the

sphere.

(c) Use the result of part (b) to write an equation for $dn/dt$, the rate at which $A$ molecules arrive at the sphere and thus the rate of production of $AB$. The function $n(t)$ simply tells me how many molecules have arrived at the "perfect absorber" during the time between $t = 0$ and the time $t$.

(d) Now, use the result of part (c) to write an equation of the form

$$\frac{dn}{dt} = k_{on} c_0, \tag{1}$$

and hence write an expression for $k_{on}$. This is the so-called Smoluchowski rate.

(e) Find a numerical value for this diffusion limited on rate, $k_{on}$. Justify the units it has and provide an actual numerical value by estimating the relevant parameters that determine $k_{on}$.

**2. Binding Problems**

In class, I have used two different schemes for writing the states and weights and associated probability for binding. The first version we worked out used the canonical ensemble and explicitly accounted for the $L$ ligands that are jiggling around in the vicinity of the receptor. In the second version of the problem, we used the so-called grand canonical distribution which suppresses all explicit reference to the reservoir of ligands. In this problem, we are going to quickly work through some examples of binding problems that will give you practice in doing both distributions.

(a) Simple Binding. Consider the case of a receptor that can bind only one ligand. Show the states and weights for this problem using both the canonical and grand canonical distributions and use them to get the probability that the receptor is occupied as a function of the concentration of ligand. Make sure to explain your intermediate steps. I basically did this in class and it is not here to annoy you or bludgeon you with repetition. The point is for you to think through all of the details and to explain them.

(b) Binding to a heterodimer. Consider a receptor with two binding pockets that can each bind a ligand separately. Again, using the canonical and grand canonical distributions, work out the average number of bound ligands as a function of the ligand concentration. NOTE: include cooperative binding by assuming that when both ligands are bound simultaneously, there is an additional "interaction" energy $\epsilon$. What happens to your formula when the binding energies for the two sites are identical (i.e. a homodimer) and the interaction energy is 0? Specifically, how does the resulting binding formula compare to that for simple binding?

**3. Chemotaxis and Receptor Binding: Part 2**

In class, I noted that chemoreceptors come in groups. Consider the case in which a cluster of $N$ chemoreceptors works as a "team" in which either all are active or all are inactive simultaneously, with no middle ground in which some fraction are active and the rest are inactive.

(a) Using the grand canonical distribution, illustrate the states and weights for the situation in which $N$ chemoreceptors are assembled into a group that is either all active or all inactive. Compute the probability that the chemoreceptors are active as a function of the concentration of ligands.

(b) In my opinion, one of the most important insights to come out of this kind of analysis is the idea that all of the data for different mutants can be "collapsed" onto a single master curve. Read the paper by Keymer *et al.* and explain how they obtained the data collapse they show in Figure 5. Specifically, rewrite your expression from part (a) of this problem in the form

$$p_{active} = \frac{1}{1 + e^{-\beta F}}. \tag{2}$$

What is the specific functional form of $F$ that you get when you rewrite your activity curve in this way and explain how this relates to the data collapse revealed in their Fig. 5b.