BE/APh161: Physical Biology of the Cell
Homework 4
Due Date: Wednesday, February 1, 2017

"You can't depend on your eyes when your imagination is out of focus." - Mark Twain

1. Statistical Physics of Ligand-receptor binding

Here we will consider three different ways of working out the probability of ligand-receptor binding based upon ideas already discussed in class. In particular, this problem gives you a chance to practice with the "statistical mechanics protocol" developed in lecture.

(a) Consider the ligand-receptor binding reaction characterized by the kinetic scheme

$$\mathrm{L} + \mathrm{R} \rightleftharpoons \mathrm{LR}. \tag{1}$$

This reaction is described by a dissociation constant given by the law of mass action as

$$K_d = \frac{[\mathrm{L}][\mathrm{R}]}{[\mathrm{LR}]}. \tag{2}$$

Given that p_{bound} is given by

$$p_{bound} = \frac{[\mathrm{LR}]}{[\mathrm{R}] + [\mathrm{LR}]}, \tag{3}$$

write an expression for p_{bound} that just depends upon $[L]$ and K_d. The result is the so-called Langmuir binding isotherm, also sometimes known as a Hill function with Hill coefficient = 1. Make a plot of p_{bound} as a function of $[L]$ and give a simple interpretation of K_d.

(b) This part of the problem is the main goal of our work, namely, to use the method of states and weights to work out the probability of different microstates. Consider the states shown in figure 1 and explain the choices made for energies, multiplicities and weights and then use these weights to compute the probability that the receptor is bound. Then, reconcile your

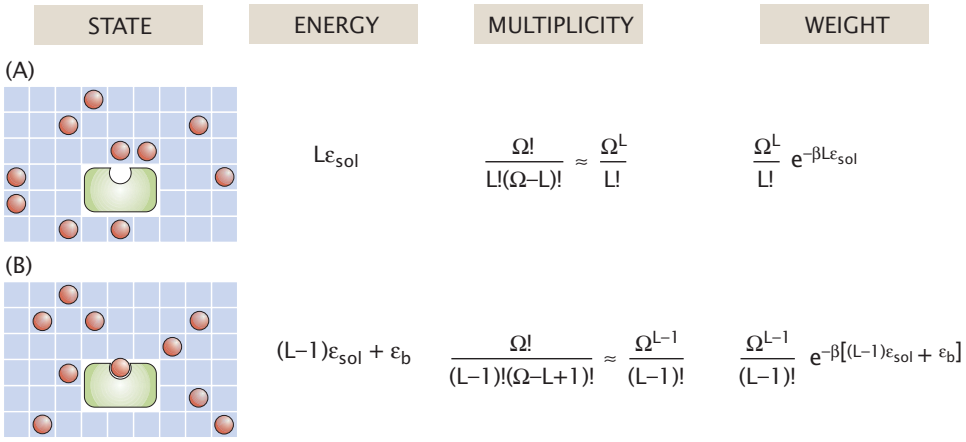

Figure 1: States and weights for receptor-ligand binding.

expression from part (a) with this result by using the fact that v is the volume per lattice site in the lattice model. Find an explicit expression for K_d in terms of the microscopic parameters.

(c) We are interested in the quantities $p_{bound}([L], t)$ and $p_{unbound}([L], t)$. I claim that we can write the equation for $p_{unbound}([L], t)$ as

$$\frac{dp_{unbound}([L], t)}{dt} = -k_{on}[L]p_{unbound} + k_{off}p_{bound}. \tag{4}$$

Explain why this makes sense. Using the constraint that $p_{bound}([L], t) + p_{unbound}([L], t) = 1$ (why is that true?), eliminate p_{bound} from the differential equation and obtain an equation strictly involving $p_{unbound}$. Find the analytic solution to that problem and determine the long time limit for p_{bound} and demonstrate that it can be written in the same form considered in class, namely,

$$p_{bound}([L]) = \frac{[L]/K_d}{1 + [L]/K_d}. \tag{5}$$

Given this result, how does K_d depend upon k_{on} and k_{off}?

(d) In light of the problem we did last week on the diffusion-limited on rate, now make a log-log plot of k_{off} as a function of K_D.

2. Waiting time distributions.

The binding problem that we worked out above can be thought of as giving rise to a time series that looks like a so-called telegraph signal, going back and forth between 0 and 1. Because the time of switching between bound and unbound is very fast compared to the time spent in those two states, the occupancy of the receptor is either 0 or 1.

(a) In light of this, it is interesting to explore the distribution of waiting times that we spend in the unoccupied or occupied state. To that end, we can use the interpretation of rates as follows. Consider that the receptor is currently occupied and we start a stopwatch to measure how long until a ligand hops off of it. In each instant Δt, as shown in Figure 2, there is a probability $p_+ = k_{off}\Delta t$ of hopping off of the receptor. The goal of our calculation is to work out the probability that the ligand will fall off after a time $T = n\Delta t$, where n is the number of time steps we have to wait until the ligand falls off. To do so, we imitate the figure by noting that to fall off at time T this means that the ligand will have to have *not* fallen off during all the previous steps. Since we have discretized time into slices of length Δt, show how to write the probability as a product of n independent probabilities. Use the insight that

$$lim_{n\to\infty}(1 - x/n)^n = e^{-x} \tag{6}$$

to show that the probability that the ligand falls off between time T and $T + \Delta t$ is given by

$$p(T)\Delta t = k_{off}e^{-k_{off}T}\Delta t. \tag{7}$$

Show that this probability distribution is properly normalized and then compute the average waiting time

$$\langle t \rangle = \int_0^\infty tp(t)dt. \tag{8}$$

(b) Later in the term when we talk about molecular motors, we will be interested in molecules that transition between more than two states, but have exponential waiting times in each of those states. Consider the case of a molecular motor that has two steps, each with a waiting time distribution that is exponential like you worked out in the first part of the problem. Using that, work out an expression for the waiting time distribution for the *composite* process made up of those two steps. That is, once again find $p(T)$ given

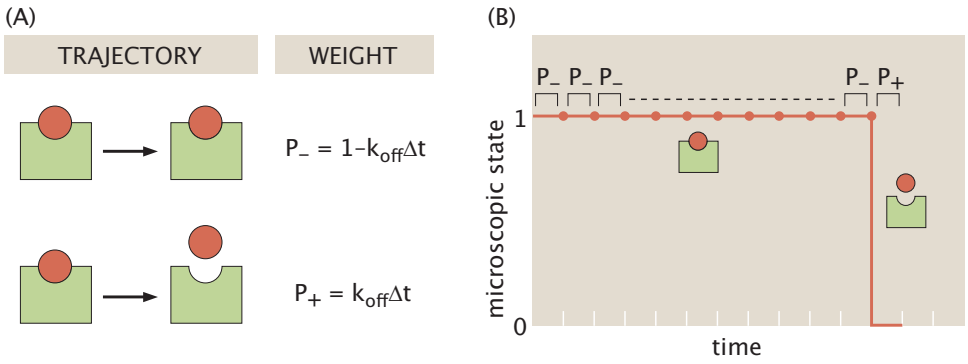

Figure 2: Computing the waiting time distribution. (A) The possible microscopic trajectories that can occur during a time step Δt. (B) Schematic of the states during all the time steps leading up to the ligand falling off of the receptor.

that both t_1 and t_2 are exponentially distributed, where t_1 is the waiting time for the first step and t_2 is the waiting time for the second step. The key point in formulating your thinking is that you must respect the constraint that $t_1 + t_2 = T$.

3. Transcriptional Activation.

Consider the process of activation of transcription. We are going to think about a bacterial promoter. The states and weights for this promoter are shown in Figure 19.9 of PBOC2. Explain the states and weights for each state and also comment on the rate of transcription that you expect from each of those states. Work out the fold-change and plot it as a function of the number of activators, essentially reproducing Figures 19.12 and 19.29A. Make sure you explain what all the parameter choices you made were and give some justification, even if it is something as simple as "a few H bonds gives an energy of $\approx 5\ k_B T$".