MCB137L/237L: Physical Biology of the Cell
Spring 2022
Homework 6: Biological Dynamics
(Due 3/10/22 at 11:00am)

Hernan G. Garcia

"Mathematics, rightly viewed, possesses not only truth, but supreme beauty cold and austere, like that of sculpture, without appeal to any part of our weaker nature, without the gorgeous trappings of painting or music, yet sublimely pure, and capable of a stern perfection such as only the greatest art can show. The true spirit of delight, the exaltation, the sense of being more than Man, which is the touchstone of the highest excellence, is to be found in mathematics as surely as in poetry." - Bertrand Russel in *Study of Mathematics*

1. Solving Ligand-Receptor Multiple Ways

In class we solved for the dynamics of mRNA production and degradation using the dynamics protocol. In this problem, we are going to use that analysis as a jumping off point for thinking about one of the most ubiquitous problems in biology: ligand-receptor binding. This ligand-receptor binding problem is a paradigm for a broad swath of biological processes ranging from neuroscience, to physiology, to gene regulation.

(a) Imagine a situation in which we have a receptor fixed at some point in space as shown in the top right panel of Figure 1. Write a rate equation for the concentration of ligand-receptor pairs in terms of the concentration of ligands and receptors. Now, assume steady state and, given that equation, derive an expression for the dissociation constant

$$K_d = \frac{[L][R]}{[LR]} \tag{1}$$

in terms of the on and off rates. Make sure you explain the dimensions of your on and off rates and hence, the dimensions of K_d.

(b) A second route to considering ligand-receptor interactions is to think of binding probabilistically with the probability that the receptor is occupied given by

$$p_{bound} = \frac{[LR]}{[R] + [LR]}. \tag{2}$$

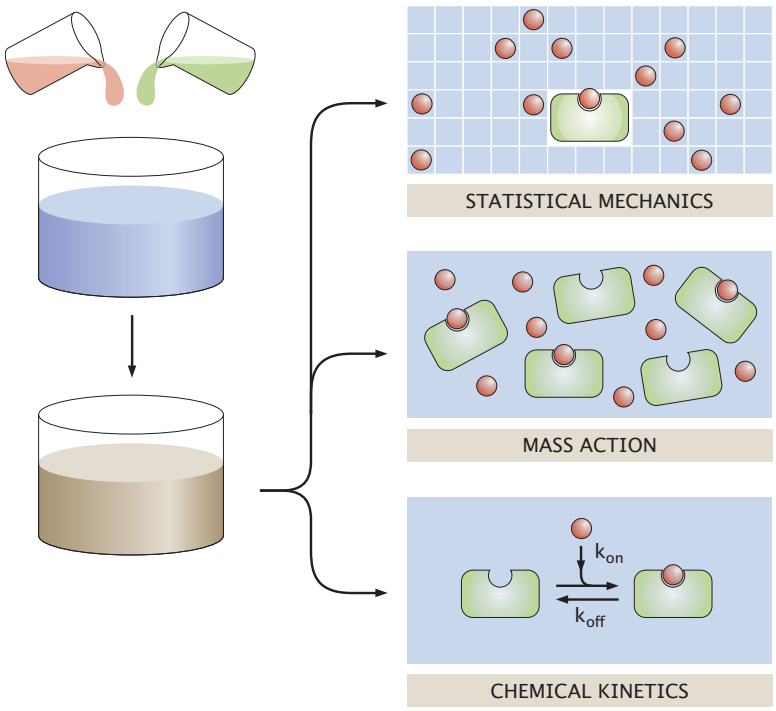

Figure 1: Three treatments of ligand-receptor binding.

Given the definition of the dissociation constant introduced in the previous part of the problem, find a simple expression for $p_{bound}([L])$ that is only a function of the concentration of ligand. (NOTE: for now, we are ignoring the subtlety that the amount of total ligand and free ligand are not actually the same, though in the case considered here with a single receptor we have somewhat finessed that point.) Make a plot of $p_{bound}([L])$ as a function of $[L]$ and comment on where K_d belongs on the axes. Later on in the course, we will solve this problem in yet another way, by using statistical mechanics.

2. Protein-mRNA Ratio

In this problem we go beyond the calculation on mRNA production we did in class, and think about how transcription and translation shape the protein-to-mRNA ratio inside cells.

(a) In class, we described the temporal evolution of the number of mRNA molecules using the equation

$$m(t + \Delta t) = m(t) + r_m \Delta t - \gamma_m m(t) \Delta t. \tag{3}$$

Here, $m(t)$ is the number of mRNA at time t, r_m is the rate of mRNA production, and γ_m is the mRNA decay rate. Write the corresponding equation for the number of protein molecules given a rate of protein production *per mRNA* of r_p and a protein decay rate γ_p. Make sure to incorporate the fact that the number of mRNA molecules present will determine how many proteins are produced in a time interval Δt.

(b) Calculate the ratio of protein to mRNA in steady state, p_{SS}/m_{SS} and show that it is given by r_p/γ_p. Find typical values for the various model parameters in *E. coli* and estimate the ratio of proteins to mRNA molecules. How do your numbers compare to those measured in Figure 3C of Taniguchi *et al.*, which is provided on the course website?

We can also obtain this protein-mRNA ratio in the context of fruit flies.

(c) Using flies with different dosages of Bicoid-GFP, Petkova *et al.* measured the relation between the number of *bicoid* mRNA molecules deposited by the mother, and the resulting number of Bicoid proteins. Read their paper (available on the course website) and write a short paragraph about how their Figure 3 is generated.

(d) Assuming that Bicoid-GFP is in steady state, use what you learned about r_p and γ_p for the Bicoid protein in order to calculate its protein-mRNA ratio r_p/γ_p. To get values for the protein degradation rate γ_p, you might want to refer back to the Drocco *et al.* paper you read for Homework 5.

3. Breaking the 2nd Law and Rectifying Thermal Noise

In a great *Physics Today* article (provided on the course website), Chris Jarzynski and colleagues state that "A liter of ordinary air weighs less than half a US penny, but it contains enough thermal energy to toss a 7-kg bowling ball more than 3 m off the ground. A gadget able to harvest that abundant energy by converting the erratic movement of colliding molecules into directed motion could be very useful indeed."

Check his assertion about the weight of the air in the room and the energy within it. Remember the meaning of k_BT as the energy scale of the particles in our system.

4. What Living Organisms Must Fight

In class we talked about how systems will tend towards the state of maximum entropy. In this problem, you are going to flesh out the details of the calculations leading to the graphs we showed in class and will provide your own graphs.

(a) Equilibrium with respect to mass transport. Consider a system partitioned equally into two parts, each of which contains Ω lattice sites. We want to write the total entropy as $S_{tot}(L) = S_L(L) + S_R(L_{tot} - L)$. Show that these contributions to the entropy can be written as

$$S_L(L) = k_B \log \frac{\Omega^L}{L!} \tag{4}$$

for the left side and

$$S_R(L_{tot} - L) = k_B \log \frac{\Omega^{L_{tot}-L}}{(L_{tot} - L)!} \tag{5}$$

for the right side. Using the Stirling approximation, derive the expression

$$S_{tot}(L) = -k_B L_{tot} \left[\frac{L}{L_{tot}} \ln \frac{L}{L_{tot}} + \left(1 - \frac{L}{L_{tot}}\right) \ln \left(1 - \frac{L}{L_{tot}}\right) - \left(\ln \frac{L_{tot}}{\Omega} - 1\right) \right] \tag{6}$$

for the total entropy. Plot the entropy of the left part, the right part and the total entropy as a function of the number of ligands in the left side of the container which can run from $L = 0$ to $L = L_{tot}$. To make this plot, you will need to assume a certain number of lattice sites. Imagine a container with $\Omega = 10^9$ lattice sites. If each such lattice site has a volume of 1 nm^3, then the total volume of each side is 1 μm^3.

(b) We next consider the case in which the partition between the two sides is mobile. In this case, we are interested in how the entropy on the left side and the right side play against each other, conspiring to give a total entropy of the form

$$S_{tot}(x) = S_L(x) + S_R(x), \tag{7}$$

where x is the label used to characterize the position of the interface. As usual, the entropy is given by the Boltzmann formula which in this case takes the form

$$S_L(x) = k_B \log W_L(x) \tag{8}$$

and

$$S_R(x) = k_B \log W_R(x). \tag{9}$$

To make progress, we now need to reckon the number of states as a function of the position x of the partition. When the partition is at the midpoint, each of the subcompartments has a volume V. The volume swept out by the motion of the partition by a distance x is xA, where A is the cross-sectional area of that partition. As a result, show that the number of states added or subtracted due to the motion of the partition is xA/v, leading to the results

$$W_L(x) = \frac{(\frac{V+xA}{v})^{L_L}}{L_L!}, \tag{10}$$

and

$$W_R(x) = \frac{(\frac{V-xA}{v})^{L_R}}{L_R!}. \tag{11}$$

Use these results to show that

$$S_{tot}(x) = k_B L_L \log \frac{V + xA}{v} - k_B \log L_L! + k_B \log \frac{V - xA}{v} - k_B \log L_R!, \tag{12}$$

and make a plot of the resulting entropy of the two sides and the total entropy as a function of the position of the partition x.