MCB137L/237L: Physical Biology of the Cell
Spring 2020
Homework 6: Biological Dynamics
(Due 3/19/20 at 3:30pm)

Hernan G. Garcia

As a reminder, make sure to clarify your model parameters and simulation parameters in your homework submission, not just on your Python script. Also, please sure to attach all of your plots with proper axis labels and legends to your homework.

1 Solving Ligand-Receptor Multiple Ways

(A) In class, and then in the homework, 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 ligand-receptor binding problems. 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

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

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.

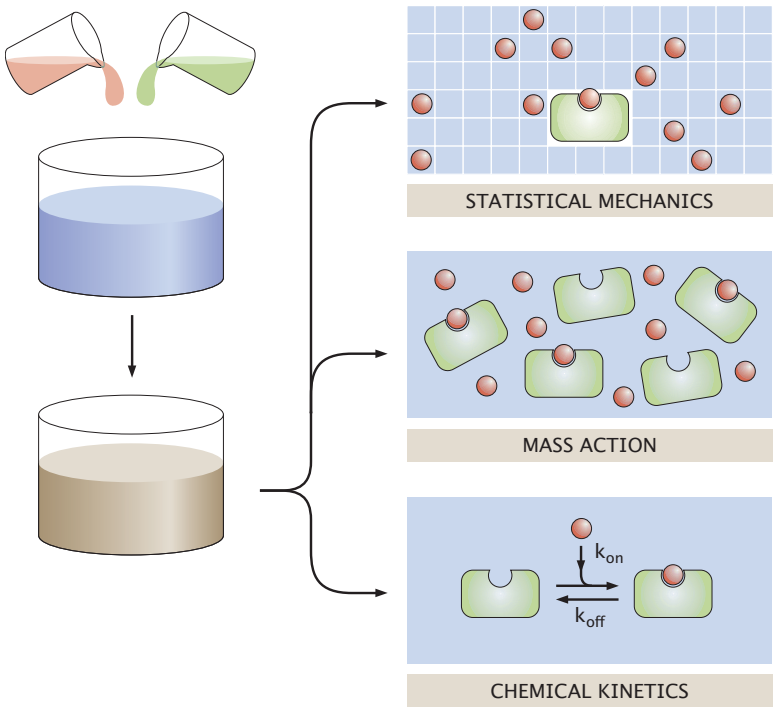

Figure 1: Three treatments of ligand-receptor binding.

2 Cytoskeletal polymerization

In this problem, we explore how the same master equation approach presented in class to describe the distribution of mRNA molecules can be used to understand how biological polymers such as actin or tubulin are assembled. Specifically, we think of a polymer that can incorporate or lose monomers at one end, as shown in Figure 2. The rate of incorporation is r and the rate with which monomers are lost is γ. Note that, unlike the mRNA case, the number of monomers that leave the filament in a time interval Δt is given by $\gamma\,\Delta t$ and is independent of the filament length.

(a) The master equation of the probability of a filament having length n at time t, $p(n,t)$, is given by

$$p(n,t+\Delta t) = p(n,t) + r\Delta t p(n-1,t) - r\Delta t p(n,t) - \gamma\Delta t p(n,t) + \gamma\Delta t p(n+1,t). \quad (3)$$

Justify why this is the master equation describing the length of a filament by carefully explaining the significance of each term in the master equation.

(b) Using Python, solve the master equation assuming $r = 1/\text{s}$ and $\gamma = 1.1/\text{s}$ and plot the resulting distribution for different time points. Assume that at time $t = 0$ there are no filaments by setting $p(n = 0, t = 0) = 1$ and $p(n > 0, t = 0) = 0$. Be careful about the boundary conditions! In particular, remember that you cannot have filaments with a negative number of monomers. Further, you cannot have Python calculate the probability of an arbitrarily long polymer. Hence, you will have to choose a maximum length of the polymer for your calculation. In doing so, make sure that the probability of having a filament of length n near

your chosen maximum polymer length is very close to zero.

(c) Plot the length distribution in steady state. To make sure you're in steady state, demonstrate that the distribution does not change as you extend the total simulation time.

(d) In class we solved the mRNA distribution of the constitutive promoter in steady state. Follow the same approach to now solve the steady-state distribution of filament lengths. To make this possible, explore the master equation for the specific cases of $n = 0$, $n = 1$, $n = 2$ in steady state and show that the distribution can be written as $p(n) = p(0)\left(\frac{r}{\gamma}\right)^n$, which is a geometric distribution.

(e) If you do the math, you can infer that $p(0) = 1 - r/\gamma$ (you don't need to show this). Now that you have the full distribution, plot it together with your simulation results to show that both approaches are consistent. If you want to compare your results to real data (and figure out more realistic values of r/γ, you can look at Figure 15.23 of PBoC2. Note that an actin monomer is about 2.4 nm in length.

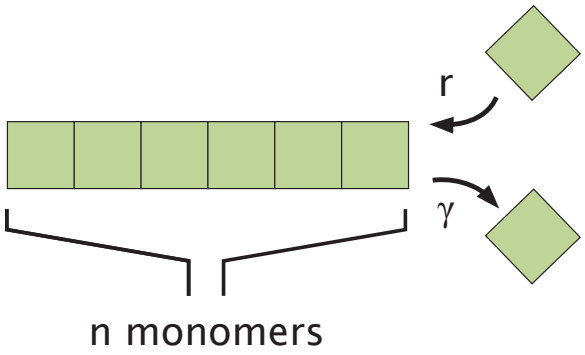

Figure 2: Simple model of filament polymerization. Monomers can only be added at one end of the filament.

3 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

$$m(t + \Delta t) = m(t) + r_m \Delta t - \gamma_m m(t) \Delta t. \tag{4}$$

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) The paper by Drocco *et al.* (available on the course website) uses a photoactivatable fluorescent protein to measure the lifetime of the Bicoid protein. Read the paper (available on the course website) and explain the technique in one paragraph. You might find it useful to draw a schematic plot such as shown in Figure 1f of the paper.

(E) 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.

4 Phase diagram for the logistic equation

In Homework 3, we solved the logistic equation numerically. This equation can describe the saturation of a bacterial culture by accounting for a limited food supply

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right), \tag{5}$$

where N is the number of cells, r is the growth rate, and is the carrying capacity or maximum population size. Note that this equation can also be written as

$$\frac{dN}{dt} = rN - \frac{rN^2}{K}. \tag{6}$$

Here, we can identify a "cell production" term and "cell destruction" term.

Like we did for the case of the constitutive promoter, plot a phase diagram where both production and destruction terms are plotted (either by hand or in Python). Use this plot to graphically show that there are two stable points at which the production and destruction are balanced out.

5 Random walks and biological polymers

Physicists know how to solve just a handful of problems. Fortunately, many dissimilar phenomena in physics and biology alike can be mapped onto such problems for which we know a solution. Here, we explore the mathematical connection between diffusion and the spatial arrangement of polymers such as DNA, actin, and microtubules.

(a) Read the introduction to Section 8.2 of PBoC ("Random Walk Models of Macromolecules View Them as Rigid Segments Connected by Hinges") to learn more about how polymers can be thought of as chains of connected rigid segments. Pay close attention to Figures 8.1 and 8.2. Here, the Kuhn length a is defined as the length of the segments. Look up the Kuhn length for DNA, actin, and microtubules in order to get a feeling for these polymers. Note that you might find reference to the persistence length $\xi_p = a/2$ instead of the Kuhn length.

(b) Now, think of a polymer chain of N segments in 1D. As shown in Figure 8.3 of PBoC each segment can either be pointing to the right of to the left. Given n_R and n_L segments pointing to the right and left, respectively, the position of the end of the chain is given by $L = (n_R - n_L)\, a$. Map this problem onto the diffusion problem we solved in class where we calculated the $\langle x \rangle$ and $\langle x^2 \rangle$ of a random walker that start at the origin shown in Figure 3. To make this possible, note that each segment can be randomly pointing to the left or right. In particular, calculate $\langle n_R - n_L \rangle$ and $\langle (n_R - n_L)^2 \rangle$ and show that the size of the polymer is given by

$$\text{size} \approx \sqrt{\langle L^2 \rangle} = a\sqrt{N} \tag{7}$$

by repeating graphical the derivation we did in class.

(c) Think of the size of the polymer you derived in (b) as the linear dimension of the blob the polymer will make on a surface such as shown in the figures below. Use the derived formula to estimate the genome length (in μm and bp) of the bacteriophage T2 shown in Figure 1.16 of PBoC and of the *E. coli* in Figure 8.5 of PBoC. How well did your estimate do?

All relevant figures from PBoC can also be found in Figures 4 and 5 below.

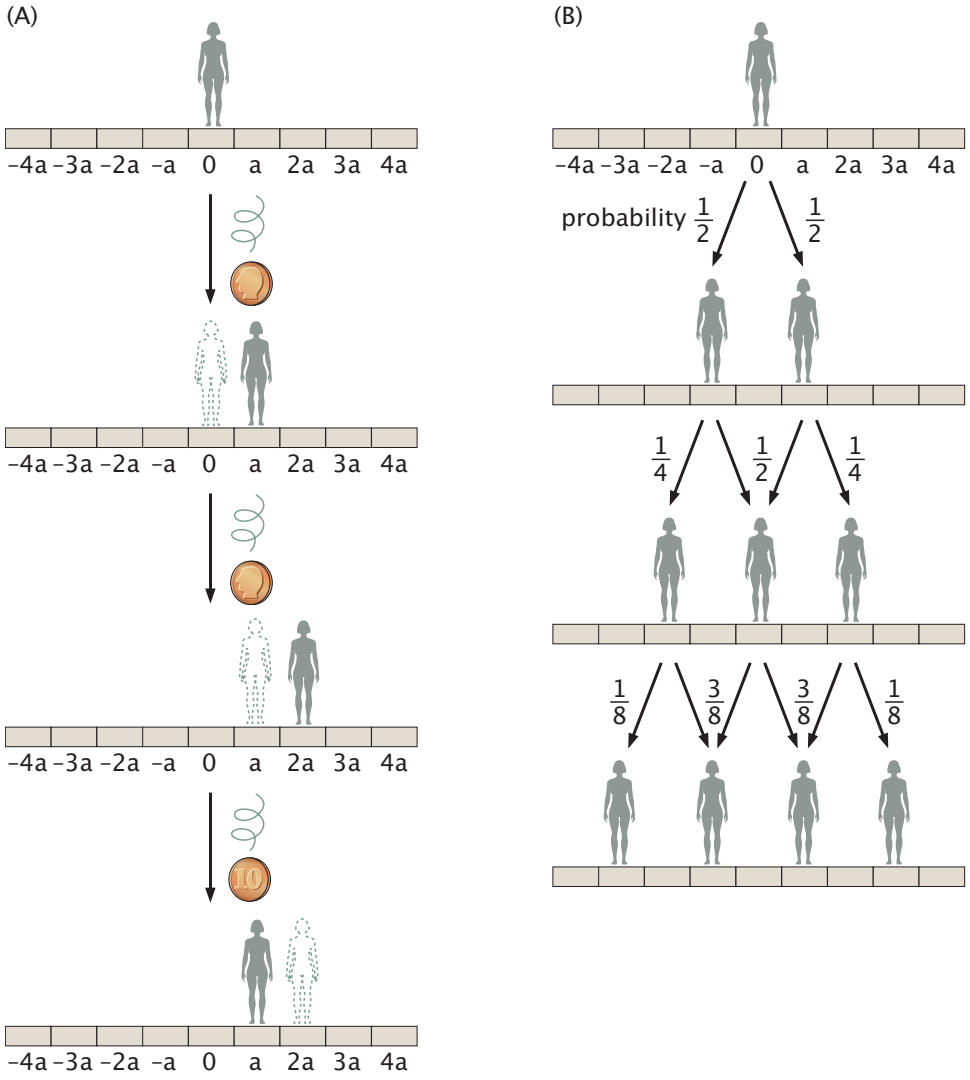

Figure 3: Coin flips and diffusion. (A) Stochastic "simulation" of a coin flipping process with the random walker stepping to the right when a heads is flipped and stepping to the left when a tails is flipped. (B) Scheme for calculating the probability of each and every possible outcome after a total of N steps.

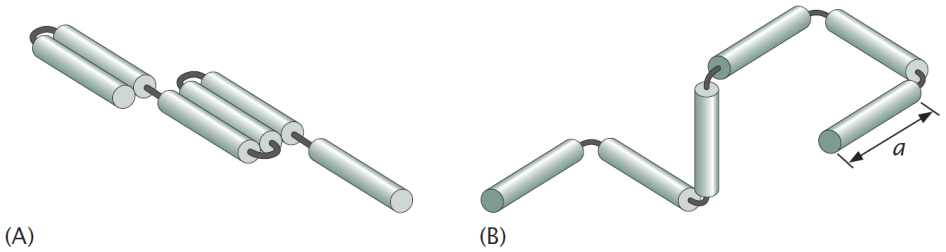

Figure 8.1: Random walk model of a polymer. Schematic representation of (A) a one-dimensional random walk and (B) a three-dimensional random walk as an arrangement of linked segments of length *a*.

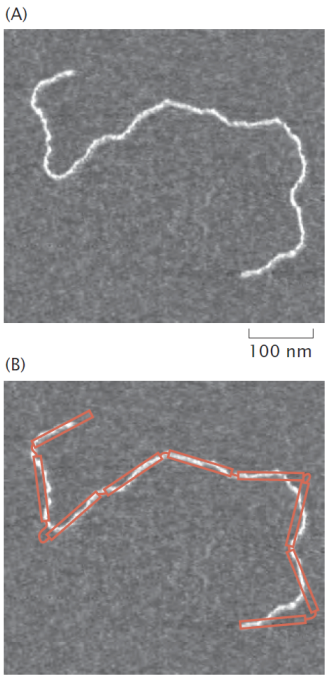

Figure 8.2: DNA as a random walk. (A) Structure of DNA on a surface as seen experimentally using atomic-force microscopy. (B) Representation of the DNA on a surface as a random walk. (Adapted from P. A. Wiggins et al., *Nat. Nanotech.* 1:37, 2006.)

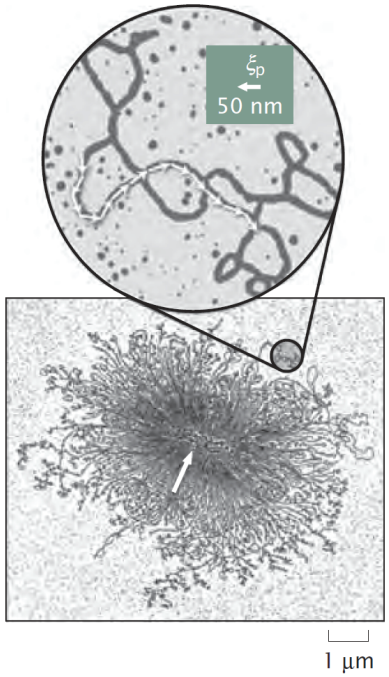

Figure 8.5: Illustration of the spatial extent of a bacterial genome that has escaped the bacterial cell. The expanded region in the figure shows a small segment of the DNA and has a series of arrows on the DNA, each of which has a length equal to the persistence length in order to give a sense of the scale over which the DNA is stiff. (Adapted from an original by Ruth Kavenoff.)

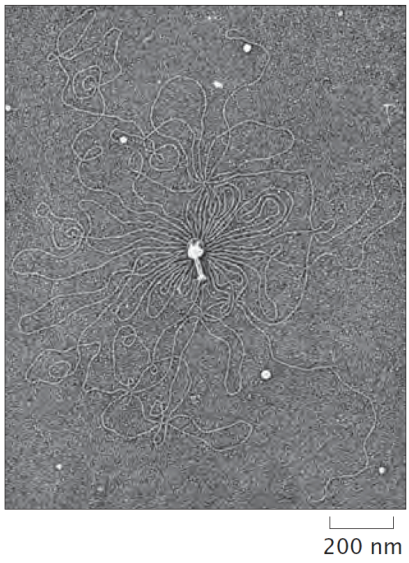

Figure 1.16: Electron microscopy image of a bacteriophage genome that has escaped its capsid. Simple arguments from polymer physics can be used to estimate the genomic size of the DNA by examining the physical size of the randomly spread DNA. We will perform these kinds of calculations in Chapter 8. (Adapted from G. Stent, Molecular Biology of Bacterial Viruses. W. H. Freeman, 1963.)

Figure 4: Figures 8.1, 8.2, 8.5 and 1.16 from PBoC.

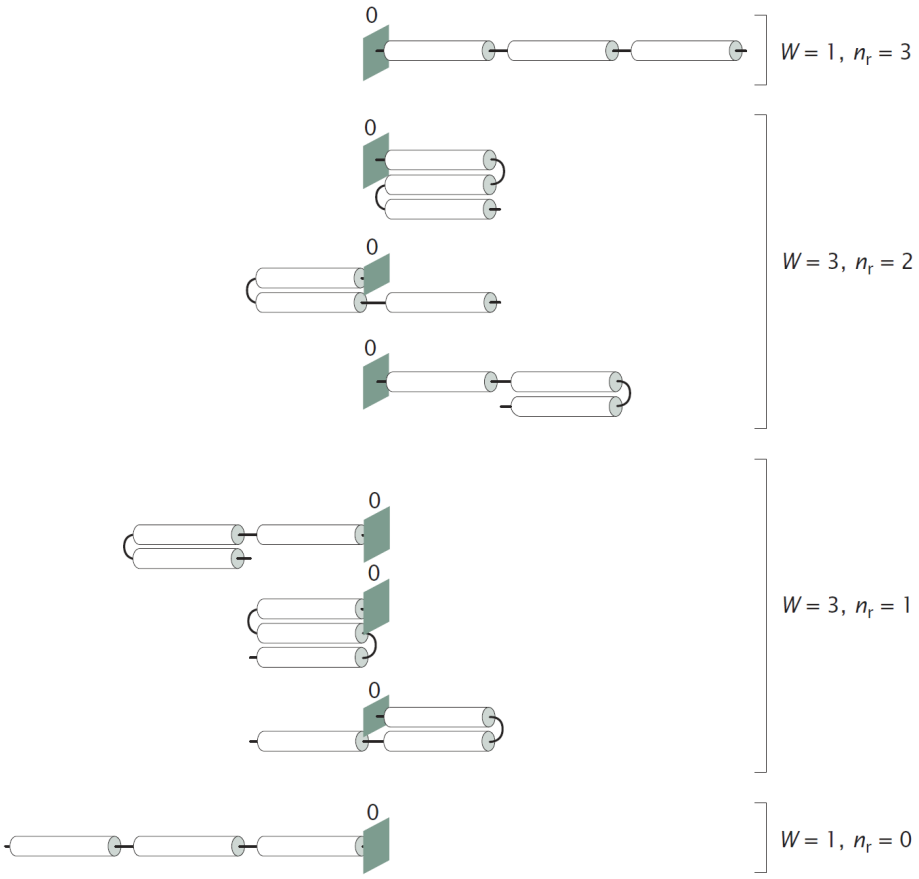

Figure 8.3: Random walk configurations. The schematic shows all of the allowed conformations of a polymer made up of three segments ($2^3 = 8$ conformations) and their corresponding degeneracies.

Figure 5: Figure 8.3 from PBoC.