MCB137L/237L: Physical Biology of the Cell
Spring 2022
Homework 7
(Due 3/17/22 at 11:00am)

Hernan G. Garcia

"The quantum physicist Richard Feynman once gave a lecture on color vision in Caltech's Beckman Auditorium. He explained the molecular events that take place in the human eye and brain to show us red, yellow, green, indigo, and blue. This chain of reactions was one of the early discoveries of molecular biology, and fascinated Feynman. 'Yeah,' someone in the audience said, 'but what is really happening in the mind when you see the color red?' And Feynman replied, 'We scientists have a way of dealing with such problems. We ignore them, temporarily.' " - Jonathan Weiner in *Time, Love, Memory.*

1. Phase diagram for the logistic equation

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

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

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

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

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.

2. Waiting time distributions.

One of the big messages of the course is the deep insights that come from a probabilistic assessment of biological systems. Our slogan might be: mechanistic information is hidden in the probability distributions. The binding problems that we worked out for ligands and

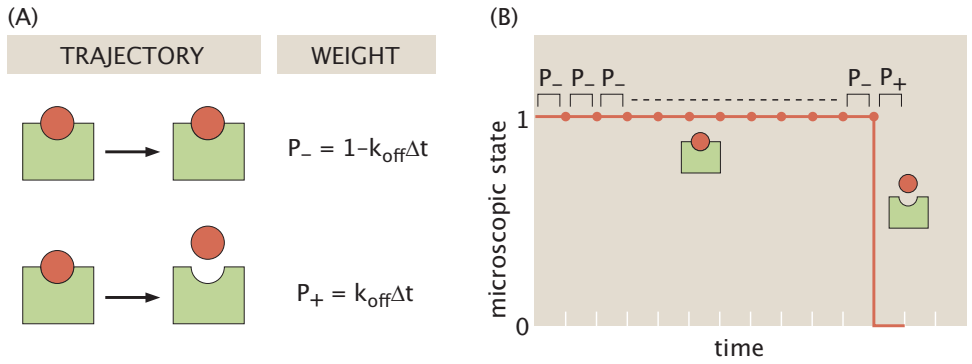

Figure 1: Computing the waiting time distribution. (A) The possible microscopic trajectories that can occur during a time step Δt. (B) Schematic of the states during all the time steps leading up to the ligand falling off of the receptor.

receptors 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. Thinking about waiting time distributions is critical to the way we will think in turn about kinetic proofreading as laid out in the recorded vignettes and is the subject of the second problem on this homework.

(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 1, 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

$$lim_{n\to\infty}(1 - x/n)^n = e^{-x} \tag{3}$$

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

$$p(T)\Delta t = k_{off}e^{-k_{off}T}\Delta t. \tag{4}$$

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

$$\langle t \rangle = \int_0^\infty tp(t)dt. \tag{5}$$

EXTRA CREDIT: (b) When we think 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 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 $t_1 + t_2 = T$. Make a plot of this kind of distribution and comment on what it means.

3. Leaky Membranes: The Cost of Defying Diffusion

As we saw in class, some ionic species are at a higher concentration inside the cell than outside the cell. As a result of this concentration gradient, there will be a flux of ions leaving the cell given by the concentration difference and the permeability which can be written as

$$\text{flux} = P(c_{in} - c_{out}) \tag{6}$$

where P is the permeability as illustrated in Figure 2.

(A) Calculate the number of ions of a species such as K^+ that leave the cell per second due to the permeability of the membrane. Essentially, this tells us about the leakiness of the cell membrane to ions which will over time lead to a complete dissipation of the gradient. You might find it useful to read up on permeability in Section 11.1.3 of PBoC2.

(B) Using ideas worked out in class about the protonmotive force, make an estimate of the power in ATP/s or k_BT/s that it costs to maintain the concentration gradient against the perpetual leakiness of the membrane. Make sure you spell out the quantitative details of how you make this estimate.

(b) How does the energy necessary to maintain the K^+ gradient compare to that required to build a bacterial cell?

4. Protein Sequences: The Frances Arnold Estimate Problem

In a 2001 Bioengineering seminar at Caltech, Professor Frances Arnold made a startling remark that it is the aim of the present problem to examine. The basic point is to try and generate some intuition for the **HUGE**, **ASTRONOMICAL** number of ways of choosing amino acid sequences. To drive home the point, she noted that if we consider a protein with 300 amino acids, there will be a huge number of different possible sequences.

(a) How many different sequences are there for a 300 amino acid protein?

But that wasn't the provocative remark. The provocative remark was that if we took only one molecule of each of these different possible proteins, it would take a volume equal to five of our universes to contain all of these different *distinct* molecules.

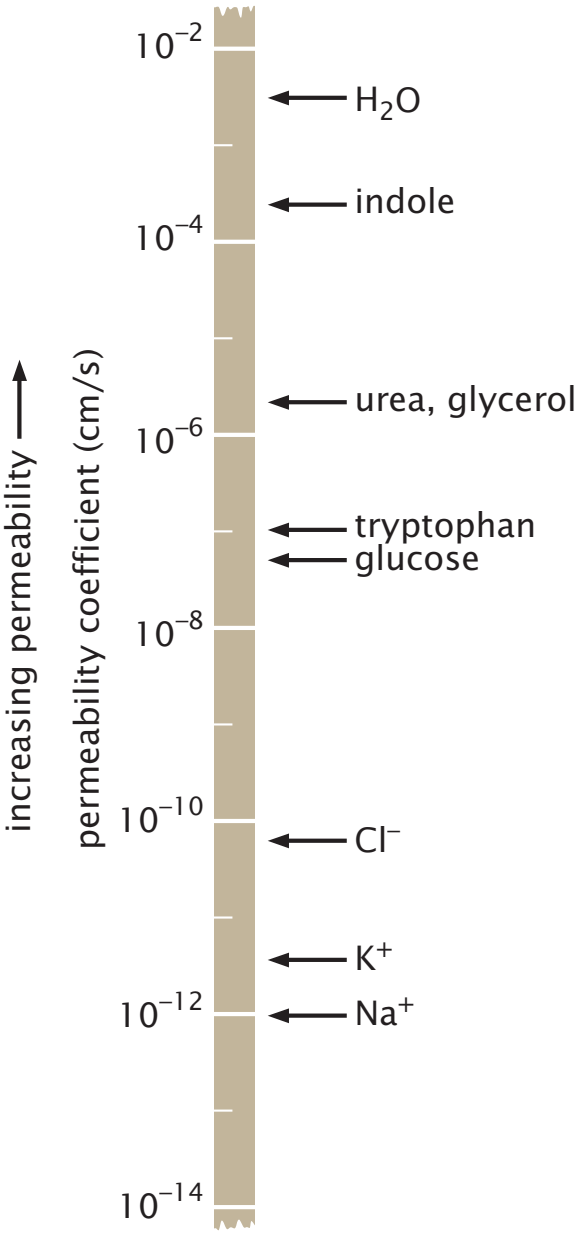

Figure 2: Permeability of various ions and molecules across membranes.

(b) Estimate the size of a protein with 300 amino acids. Justify your result, but remember it is an estimate. Next, find an estimate of the size of the universe and figure out whether Frances was guilty of hyperbole or if her statement was on the money.

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.

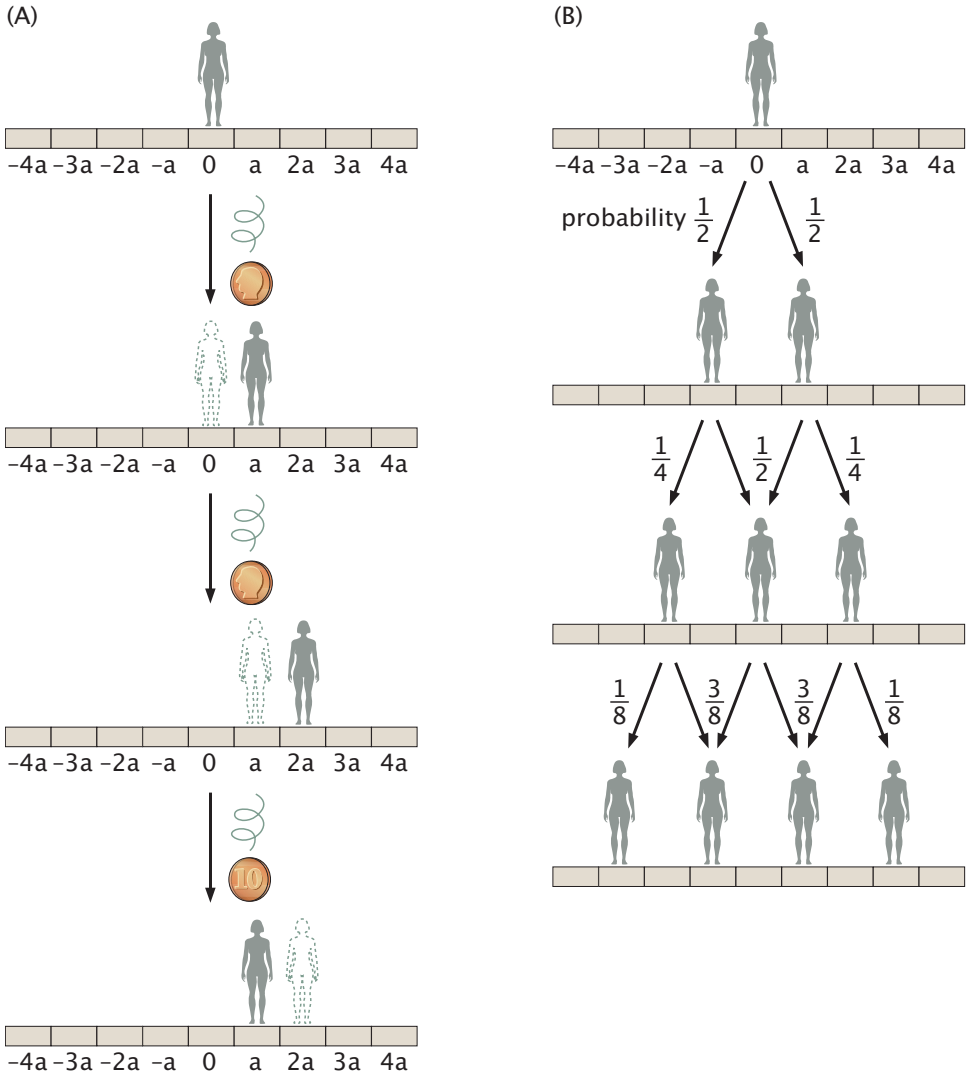

Figure 3: Coin flips and diffusion. (A) Stochastic "simulation" of a coin flipping process with the random walker stepping to the right when a heads is flipped and stepping to the left when a tails is flipped. (B) Scheme for calculating the probability of each and every possible outcome after a total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

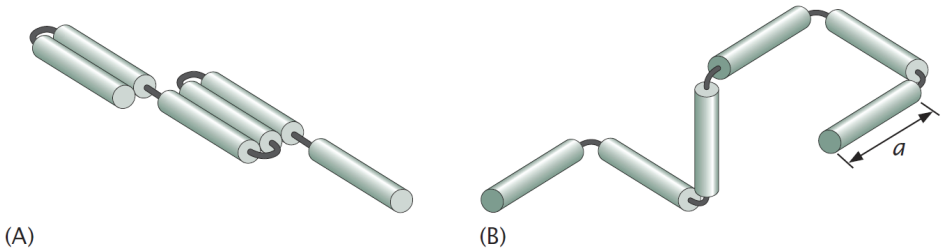

Figure 8.1: Random walk model of a polymer. Schematic representation of (A) a one-dimensional random walk and (B) a three-dimensional random walk as an arrangement of linked segments of length *a*.

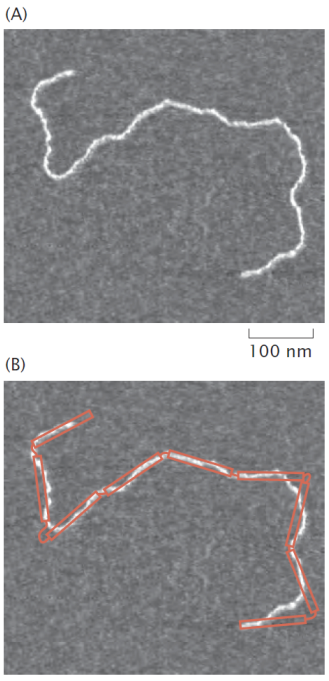

Figure 8.2: DNA as a random walk. (A) Structure of DNA on a surface as seen experimentally using atomic-force microscopy. (B) Representation of the DNA on a surface as a random walk. (Adapted from P. A. Wiggins et al., *Nat. Nanotech.* 1:37, 2006.)

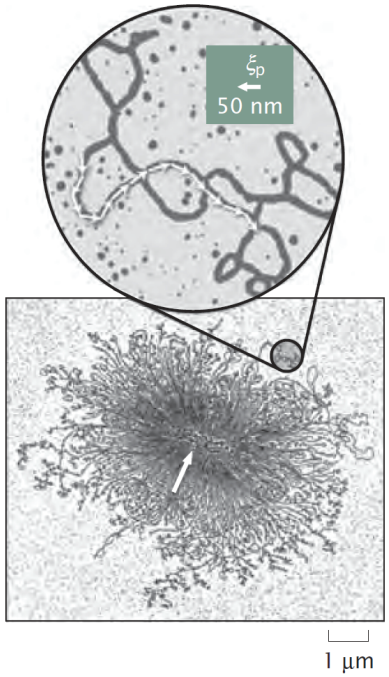

Figure 8.5: Illustration of the spatial extent of a bacterial genome that has escaped the bacterial cell. The expanded region in the figure shows a small segment of the DNA and has a series of arrows on the DNA, each of which has a length equal to the persistence length in order to give a sense of the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

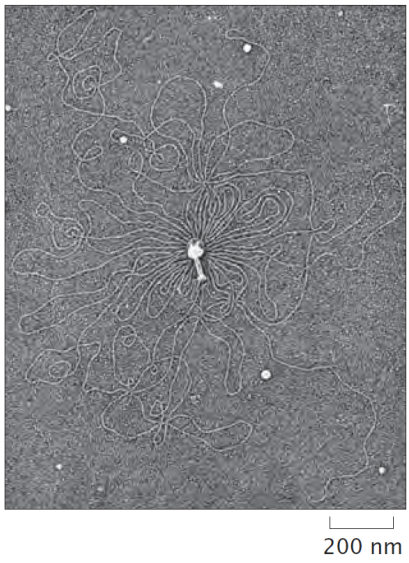

Figure 1.16: Electron microscopy image of a bacteriophage genome that has escaped its capsid. Simple arguments from polymer physics can be used to estimate the genomic size of the DNA by examining the physical size of the randomly spread DNA. We will perform these kinds of calculations in Chapter 8. (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.

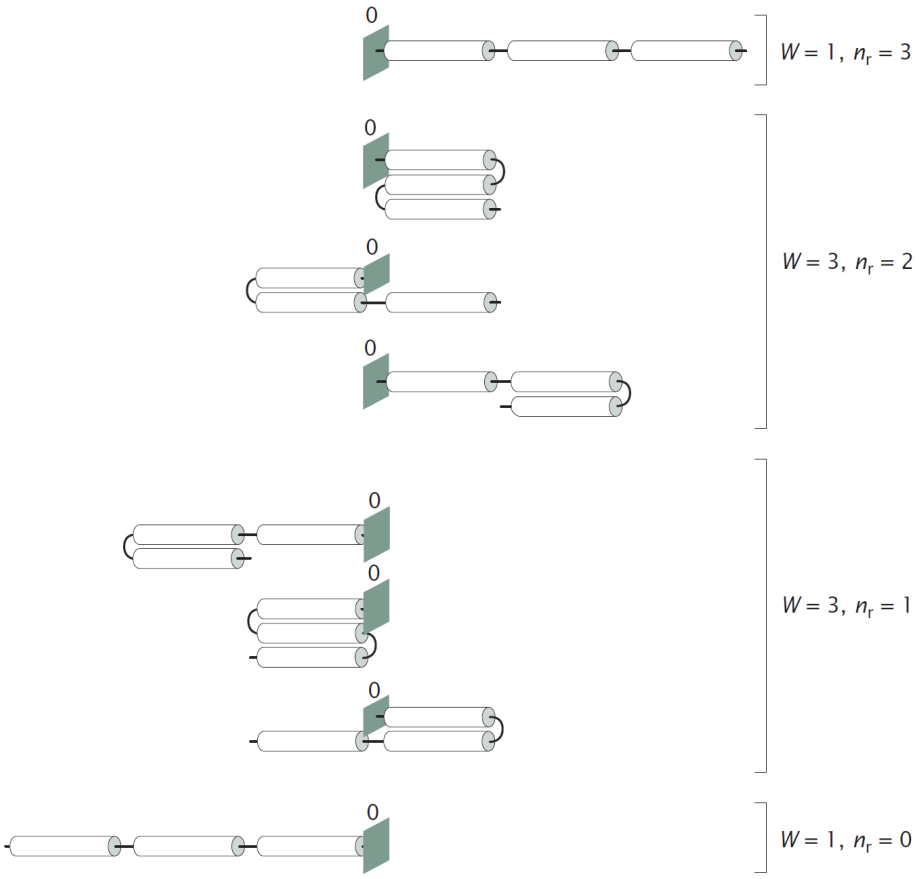

Figure 8.3: Random walk configurations. The schematic shows all of the allowed conformations of a polymer made up of three segments ($2^3 = 8$ conformations) and their corresponding degeneracies.

Figure 5: Figure 8.3 from PBoC.