

MCB137L/237L: Physical Biology of the Cell
Spring 2024
Homework 7
(Due 3/12/24 at 2:00pm)

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“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 Diffusion times

Make a log-log plot of the diffusion time (in seconds) as a function of length (in μm) using Python. Plot multiple lines considering the diffusion constants for ions and for a typical protein *inside a cell*. Finally, mark a few relevant biological sizes along the x-axis such as the size of an axon, a synaptic cleft, an *E. coli* cell, and a eukaryotic nucleus.

2 Bacterial foraging

Bacteria use swimming to seek out food. Imagine that the bacterium is in a region of low food concentration. For the bacterium to profit from swimming to a region with more food, it has to reach there before diffusion of food molecules makes the concentrations in the two regions the same. Here we find the smallest distance that a bacterium needs to swim so it can outrun diffusion.

(a) Make a plot in which you sketch the distance traveled by a bacterium swimming at a constant velocity v as a function of time t , and the distance over which a food molecule will diffuse in that same time. Indicate on the plot the smallest time and the smallest distance that the bacterium needs to swim to outrun diffusion. You don’t need to use Python here, just make the plot by hand and show the two curves schematically.

(b) Calculate these minimum times and distances for an *E. coli* swimming at a speed of $30 \mu\text{m/s}$. The diffusion constant of a typical food molecule is roughly $500 \mu\text{m}^2/\text{s}$.

(c) Estimate the number of ATP molecules the bacterium must consume (hydrolyze) per second in order to travel at this speed, assuming that all of the energy usage goes into overcoming fluid drag. The drag force felt by the bacterium is given by

$$F = 6\pi\eta Rv, \quad (1)$$

where R is the typical size of an *E. coli*, η is the viscosity (we can assume it's swimming in water) and v is the speed of the bacterium. The power necessary to move the bacterium at a speed v against this viscous drag is

$$P = Fv. \quad (2)$$

The amount of energy released from one ATP molecule is approximately $20 k_B T$. Note that the bacterial flagellar motor is actually powered by a proton gradient and this estimate focuses on the ATP equivalents associated with overcoming fluid drag.

3 The biological consequences of diffusion limited rates

In class, we introduced the diffusive speed limit as a fundamental constraint of biological reactions such as enzyme action. Here, we further explore the biological consequences of this speed limit. Specifically, we estimate the maximum rate of translation.

Learn about the complex of aminoacid-tRNA, EF-Tu, and GTP that binds to an active ribosome. For example, you can look at the section “Large Protein Movements Can Be Generated From Small Ones” on page 179 of Alberts *et al.* (5th edition), and their Figure 3-74, and section “Elongation Factors Drive Translation Forward and Improve its Accuracy” on page 377. Alternatively, you can look at Wikipedia or at a textbook of your choosing.

Let's work out the diffusion-limited rate with which the complex made out of aminoacid-tRNA, EF-Tu, and GTP arrive to an active ribosome. To make this possible, you will have to estimate the diffusion constant and size of this complex. You can use what you learned about these molecules from the sources suggested above or refer to BioNumbers. Compare your rate to the known translation rate. Of course, you will have to make some assumptions about c_o , the overall concentration of tRNA molecules in the cell. Find some typical concentrations by looking at Dong *et al.* (1996), which is provided on the course website. If you want to learn more about the consequences of this speed limit on bacterial growth, see the Klumpp *et al.* paper also provided on the website.

4 Analytical solution to the diffusion equation

In class, we derived the diffusion equation in 1D given by

$$\frac{\partial c(x, t)}{\partial t} = D \frac{\partial^2 c(x, t)}{\partial x^2}, \quad (3)$$

where $c(x, t)$ is concentration of molecules, and D is the diffusion constant. Further, in class we solved this equation numerically by integrating its chemical master equation for an initial condition corresponding to having N_0 molecules centered at $x = 0$.

(a) The analytical solution to the diffusion equation under the initial conditions described above is given by

$$c(x, t) = \frac{N_0}{\sqrt{4\pi Dt}} e^{-\frac{x^2}{4Dt}}. \quad (4)$$

Show that this is indeed a solution of the diffusion equation. To make this possible, plug in the proposed $c(x, t)$ above into the diffusion equation, do the derivatives on each side and show that, indeed, $\frac{\partial c(x, t)}{\partial t}$ is equal to $D \frac{\partial^2 c(x, t)}{\partial x^2}$.

Remember what you learned in calculus about the product of derivatives and the chain rule! Given a function $f(x, y)$, you can think of the partial derivative $\frac{\partial}{\partial x}$ as a measure of the derivative as we walk along the x -direction as shown in Figure 1. Operationally, taking a partial derivative is like taking a regular derivative: you just treat all other variables as constants. For example, let's define a function of x and y

$$f(x, y) = ax^2y^3. \quad (5)$$

Now, we take the partial derivative with respect to x

$$\frac{\partial f}{\partial x} = ay^3 \frac{\partial}{\partial x} (x^2). \quad (6)$$

Note that we just thought of ay^3 as constants and took them out of the derivative. As a result, we get

$$\frac{\partial f}{\partial x} = ay^3 2x. \quad (7)$$

Similarly,

$$\frac{\partial f}{\partial y} = ax^2 3y^2. \quad (8)$$

For more information on the partial derivative, please refer to “The Math Behind the Models: the Partial Derivative” on page 212 of PBoC.

(b) Now, let's plot this analytical solution. Specifically, plot the concentration profile (i.e., concentration vs. position) for 0.01 ms, 0.1 ms, 1 ms, 5 ms and 10 ms in a single figure. Note that we are not asking you to plot the $t = 0$ time point because Python won't necessarily know how to deal with the fact that, while the term $\frac{N_0}{\sqrt{4\pi Dt}}$ approaches infinity as $t \rightarrow 0$, the term $e^{-\frac{x^2}{4Dt}}$ approaches 0 for the same limit. Use a typical diffusion constant for a protein in the cell of $D = 10 \mu\text{m}^2/\text{s}$. You'll have to make reasonable choices for the model parameter N_0 . Think hard about the range of x -values over which to plot this distribution and the spacing of x -values in this range. You might note that your concentration peaks beyond N_0 ! This is because you're plotting $c(x, t)$, the concentration in an infinitesimal box of size dx . This means that the integral $\int_{-\infty}^{+\infty} c(x, t) dx = N_0$, indicating that the total amount of molecules is N_0 . We will discuss this subtlety in class.

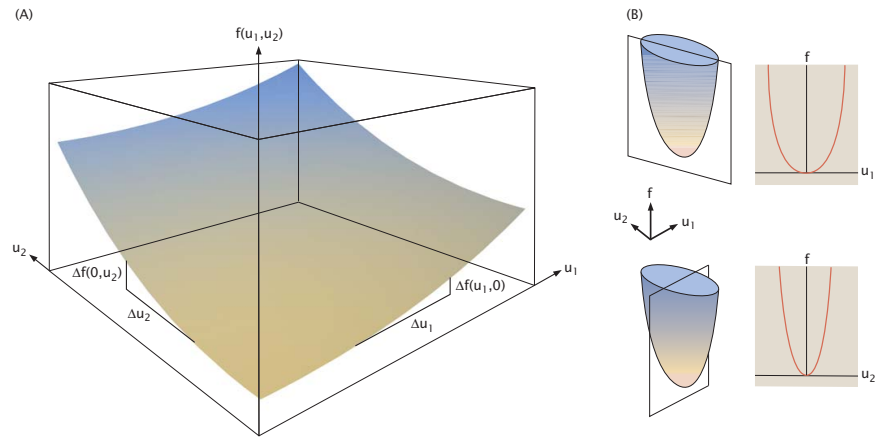


Figure 1: Illustration of the concept of a partial derivative. (A) The plot shows the function $f(u_1, u_2)$ which depends upon the variables u_1 and u_2 . If u_2 is held fixed, the surface is reduced to a curve and the partial derivative is nothing more than the ordinary derivative familiar from calculus, but on this particular curve. (B) Planar cuts through the function $f(u_1, u_2)$.

(c) Finally, we will check that our simulation makes sense by estimating the diffusion constant from the plots you've made. How long does it take for the distribution to spread to about $0.5 \mu\text{m}$? Is this consistent with the diffusion constant you used for your simulation? Note that we're not after an exact result for D , but instead are performing a sanity check to see whether our results make sense.