MCB137L/237L: Physical Biology of the Cell
Spring 2025
Homework 9:
(Due 4/1/25 at 2:00pm)

Hernan G. Garcia

"Biology is catching up" - PAM Dirac

1 Diffusion times

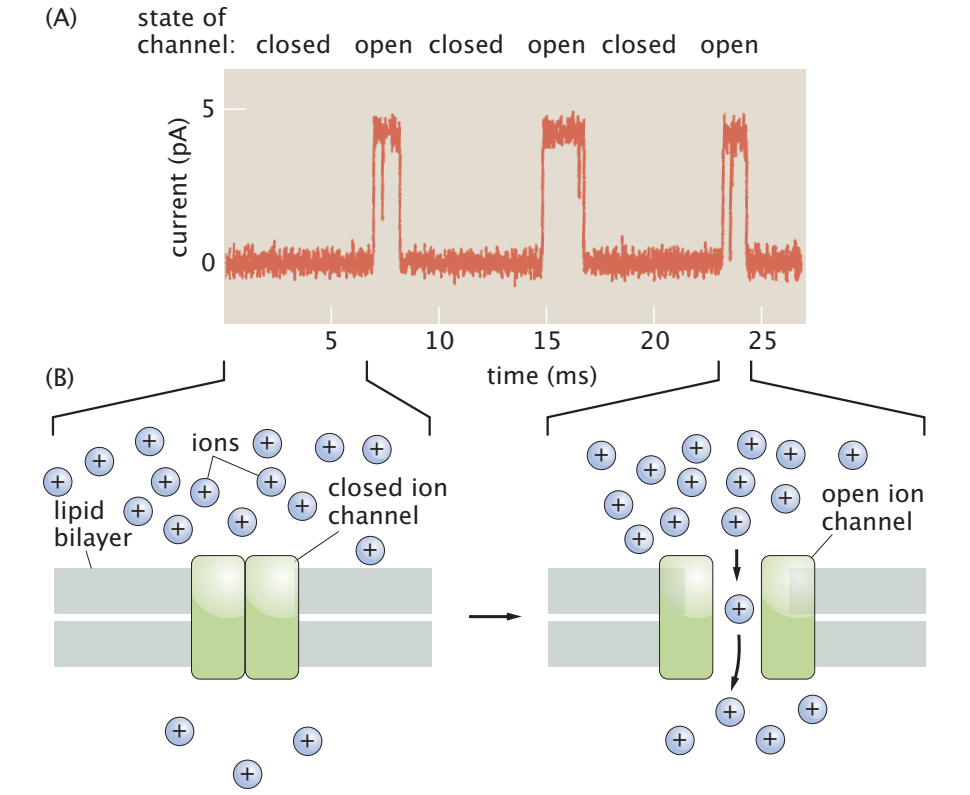
Make a log-log plot of the diffusion time (in seconds) as a function of length (in μm) using Python. Plot multiple lines considering the diffusion constants for ions and for a typical protein *inside a cell*. Finally, mark a few relevant biological sizes along the x-axis such as the size of an axon,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

2 Ion channel currents

Figure 1A shows a single-channel recording of the current passing through a voltage-gated sodium channel. The data reveal that the channel transitions between open and closed states as shown in Figure 1B. When in the open state, Na^+ ions can flow from one side of the membrane to the other, resulting in a current across the membrane.

Given that ions have a typical diffusion constant of 1000 $\mu m^2/s$, given the difference between the sodium intracellular and extracellular concentrations shown in Figure 1C, and using a rough guess for the radius of an ion channel, estimate the current that flows through the ion channel when in the open state.

Recall that the charge of one monovalent ion is 1.6×10^{-19} C (Coulomb), and that 1 A = 1 C/s (Ampere = Coulomb/second). Compare your estimate to the current measured in Figure 1A.



(C)

$D_{small\ ions}$ = 1000 μm²/s

ion species	intracellular concentration (mM)	extracellular concentration (mM)
K^+	155	4
Na^+	12	145
Ca^{2+}	10^{-4}	1.5
Cl^-	4	120

Figure 1: Electrical current flowing through an ion channel. (A) Current flowing through a single voltage-gated sodium channel. (B) The channel recording reveals transitions through an open and a closed state. (C) The concentration gradient of Na^+ ions across the membrane can be used to estimate the current when the channel is open. (A, adapted from B. U. Keller et al., *J. Gen. Physiol.* 88:1, 1986; B, adapted from B. Hille, Ion Channels of Excitable Membranes. Sinauer Associates, 2001)

3 Diffusion on a microtubule

Read the great paper by Helenius *et al.* (provided on the course website) dissecting the mechanism of microtubule depolymerization by the kinesin MCAK. Here, they show how the MCAK molecular motor diffuses along the microtubule towards both ends, triggering the depolymerization of a few tubulin dimers before falling off the microtubule.

(**a**) In their Figure 2b, they show the mean squared displacement of MCAK $\langle x^2 \rangle$ as a function of time t. Remember that, using dimensional analysis, we concluded that $\langle x^2 \rangle = Dt$, where D is the diffusion constant (there's a difference of a factor of two between our expression

and the one used by Helenius *et al.*, but we can ignore that for now). Fit the data in the figure (provided on the course website) "by eye" in order to determine the value of D. To make this possible, plot the expected relation between $\langle x^2 \rangle$ and t for different values of D and decide which value of D better recapitulates the data.

(**a, EXTRA CREDIT**) Write a chi^2 minimization program to determine the diffusion constant. Make sure to plot the chi^2 as a function of D.

(**b**) In their Figure 3, they argue that a diffusive mechanism can be faster than one of directed motion on short length scales. Explain how this assertion is supported by the plot shown in their Figure 3b, and reproduce the plot in Python.

4 Analytical solution to the diffusion equation

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

$$\frac{\partial c(x,t)}{\partial t} = D\frac{\partial^2 c(x,t)}{\partial x^2}, \tag{1}$$

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 inital conditions described above is given by

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

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 2. 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

$$f(x,y) = ax^2y^3. \tag{3}$$

Now, we take the partial derivative with respect to x

$$\frac{\partial f}{\partial x} = ay^3 \frac{\partial}{\partial x}\left(x^2\right). \tag{4}$$

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

$$\frac{\partial f}{\partial x} = ay^3 2x. \tag{5}$$

Similarly,

$$\frac{\partial f}{\partial y} = ax^2 3y^2. \tag{6}$$

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

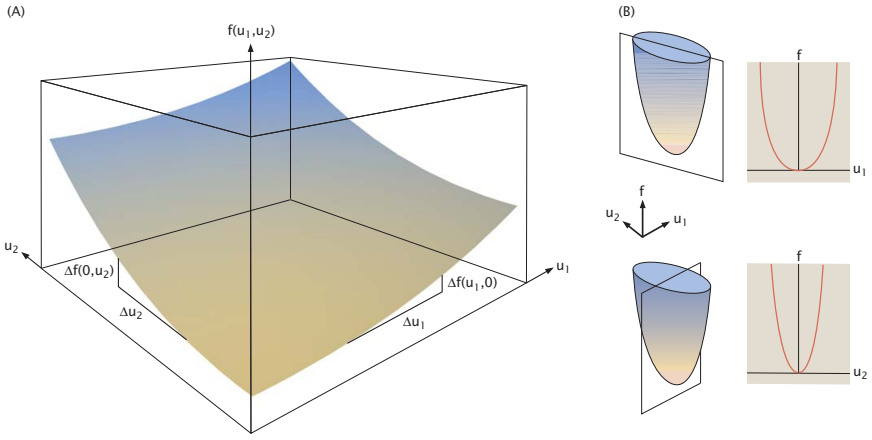


Figure 2: Illustration of the concept of a partial derivative. (A) The plot shows the function $f(u_1, u_2)$ which depends upon the variables u_1 and u_2. If u_2 is held fixed, the surface is reduced to a curve and the partial derivative is nothing more than the ordinary derivative familiar from calculus, but on this particular curve. (B) Planar cuts through the function $f(u_1, u_2)$.

(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 $t \to 0$, 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 $D = 10$ μm^2/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.

(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 μm? 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.