BE/APh161: Physical Biology of the Cell
Homework 4
Due Date: Wednesday, February 5, 2020

"I learned a lot from studying and watching Muhammad. One of the main takeaways was that you have to work hard in the dark to shine in the light." - Kobe Bryant, speaking of Muhammad Ali

1. Solving the Diffusion Equation

We have been interested in making estimates of the time scale associated with a number of biological processes. One of the most ubiquitous processes is diffusion, which is our "go to" null hypothesis for how molecules get around in cells.

In class I noted that the time scale for diffusing a distance L is given by $t = L^2/D$, where D is the diffusion constant. In this problem, we will formally derive this result. Note that parts (a) and (b) are effectively problem 13.2 of PBoC. Also, reading much of chap. 13 of PBoC will be very helpful for doing this problem.

(a) Our goal is to find the diffusive profile for some molecular species as a function of time. If we are given an initial concentration, we can use the diffusion equation to determine the concentration distribution at a later time. To that end, consider the one-dimensional diffusion equation in free space given by

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

In particular, consider that the initial concentration distribution is given by $c(x,0) = \delta(x)$, where $\delta(x)$ is the Dirac delta function and basically means that there is a spike at the origin. In particular, you will show that

$$G(x,t) = \frac{1}{\sqrt{4\pi Dt}} e^{-\frac{x^2}{4Dt}}, \tag{2}$$

where we introduce the Green function $G(x,t)$ to signify that this is the concentration profile for the special case in which the initial concentration is the spike at the origin as represented by the delta function.

To obtain the solution, we will Fourier transform the diffusion equation in the spatial variable x according to the Fourier transform convention

$$\tilde{f}(k) = \frac{1}{2\pi}\int_{-\infty}^{\infty} f(x)e^{-ikx}dx, \tag{3}$$

and

$$f(x) = \int_{-\infty}^{\infty} \tilde{f}(k)e^{ikx}dk. \tag{4}$$

Using these definitions, Fourier transform both sides of the diffusion equation to arrive at the ordinary differential equation

$$\frac{d\tilde{c}(k,t)}{dt} = -Dk^2\tilde{c}(k,t). \tag{5}$$

Note that to do this Fourier transform of the right side, you will need to use integration by parts twice. Solve the differential equation that emerges from your Fourier transform to obtain $\tilde{c}(k,t)$ and make sure to use the initial condition $c(x,0) = \delta(x)$ to find $\tilde{c}(k,0)$. Then invert the Fourier transform on $\tilde{c}(k,t)$ to find $c(x,t)$. NOTE: You will need to use completion of the square to carry out the inversion. Make sure you explain all of your steps. We are big on having you not only do the analysis correctly, but also to explain what you are doing and why you are doing it. Also, explain why I said this is the solution for "free space". Why would this solution fail to describe diffusion in a finite box?

(b) Using the solution we obtained above, find $\langle x\rangle$ and $\langle x^2\rangle$. In general, we have that

$$\langle x^n\rangle = \frac{\int_{-\infty}^{\infty} x^n c(x,t)dx}{\int_{-\infty}^{\infty} c(x,t)dx}. \tag{6}$$

Explain what you find for both the first and second moments of the distribution as a function of time and explain how it relates to the estimated diffusion time $t = L^2/D$ which we use to find the time scale for diffusion over a length L. Using the Einstein-Stokes relation given by

$$D = \frac{k_B T}{6\pi\eta a}, \tag{7}$$

where η is the viscosity which for water is $\eta_{water} = 10^{-3}\ Pa\ s$ and a is the radius of the diffusing particle, estimate the diffusion constant for a protein

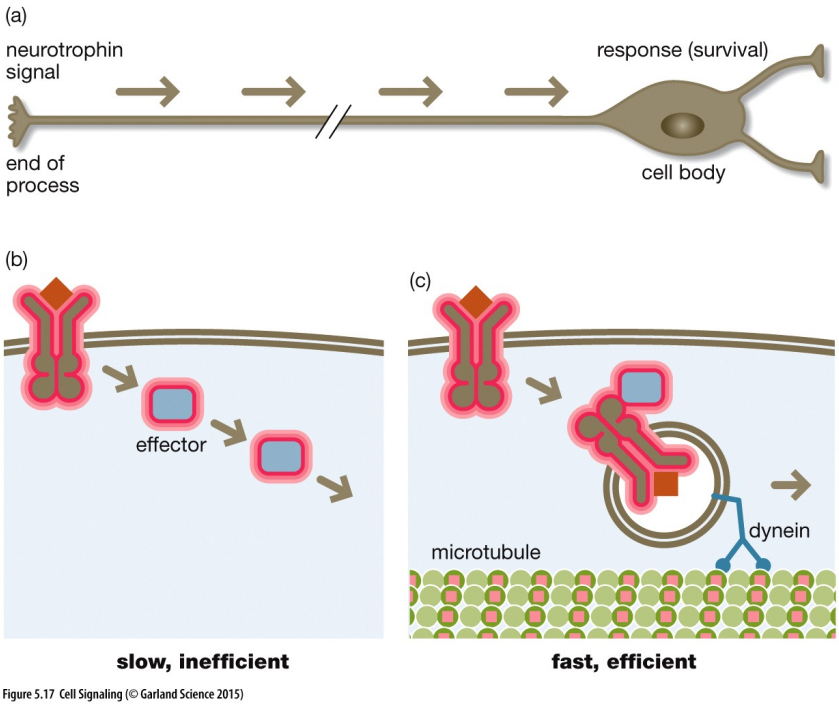

Figure 1: Comparison between passive diffusion and active transport in neurons. (a) Schematic of a neuron. (b) An effector molecule is activated and then diffuses along the axon to the cell body. (c) Receptor is incorporated into a vesicle and then actively transported by a dynein molecule along a microtubule.

in water and make a log-log plot of diffusion time vs distance (with distances ranging from 1 nm to 100 mm) and comment on its biological significance. Also, make a plot of the solution for the point source as a function of time by showing $c(x,t)$ at various times t using the same diffusion constant.

(c) In their book "Cell Signaling", Lim, Mayer and Pawson give the classic story about diffusion in neurons and how diffusion will take prohibitively long times. See Figure 1 for their depiction of the comparison between passive diffusion and active transport. Using what we have learned about diffusion, work out the time for diffusion of a protein over the 10 cm length of a neuron. Compare this to the time for a molecule to be transported actively by

a motor. Do you agree with their assessment that active transport is efficient?

2. Diffusive speed limits: It's not just a good idea, it's the law

In order for a chemical reaction to take place, the reactants must be at the same place at the same time. A very interesting calculation explores the way in which diffusion can control the on rate for reactions. Imagine some reaction in which A and B come together to form the complex AB. To simplify the problem, we are going to imagine B as a sphere of radius a that is fixed at the origin of our coordinate system. Further, we are going to imagine that very far away the concentration of A is held at c_0. What I really mean by this is that $lim_{r\to\infty} c(r) = c_0$, where $c(r)$ is the concentration of reactant A as a function of distance from the origin. Our goal is to compute the so-called "diffusion-limited on rate" for the reaction. We begin by working out the steady-state solution to the diffusion equation with the boundary condition that $c(a) = 0$, which corresponds to the physical statement that the sphere is a "perfect absorber". What this really means is that every time a molecule of A arrives at the sphere, the reaction occurs. (Note that this tells us that the diffusion-limited on rate is the fastest that a reaction could occur. It could be true that after the molecule arrives, it has to wait for some favorable orientation to occur, for example, which would make the rate of the reaction even slower).

(a) Solve the diffusion equation

$$\frac{\partial c(\mathbf{r},t)}{\partial t} = D\nabla^2 c(\mathbf{r},t) \tag{8}$$

in steady state and find the concentration profile $c(r)$ as a function of c_0 and a. Explain why we can write the concentration only as a function of the *scalar* r as opposed to the vector $\mathbf{r}$.

(b) Use that result to compute the diffusive flux $J(a)$ at the surface of the sphere. Here you need to invoke Fick's law relating flux and concentration, but acknowledging that you are working in spherical coordinates.

(c) Use the result of part (b) to write an equation for dn/dt, the rate at which A molecules arrive at the sphere and thus the rate of production of AB. The function $n(t)$ simply tells me how many molecules have arrived at

the "perfect absorber" during the time between $t = 0$ and the time t.

(d) Now, use the result of part (c) to write an equation of the form

$$\frac{dn}{dt} = k_{on} c_0, \tag{9}$$

and hence write an expression for k_{on}. This is the so-called Smoluchowski rate.

(e) Find a numerical value for this diffusion limited on rate, k_{on}. Justify the units it has and provide an actual numerical value by estimating the relevant parameters that determine k_{on}.

3. Spread the Butter Diffusion Style.

(a) In class I sketched how to derive the master equation for diffusion as a limiting process by thinking of one-dimensional line as discretized into boxes of width a, and with a jump probability $k\Delta t$. Given that at $t = 0$ we have $p(0, 0) = 1$ (i.e. all the probability is concentrated at the origin), work out the probability after time Δt by hand. That is, figure out $p(0, \Delta t)$, $p(a, \Delta t)$ and $p(-a, \Delta t)$. Why do we not consider any points farther from the origin after a single time step?

(b) In this part of the problem, you will write a code to carry out the discrete spread the butter that you began by hand above. The goal is to work out the time evolution of the probability distribution for the initial condition when all the probability is concentrated at the origin. What you need to hand in is a plot that shows how the probability distribution changes over time.

(c) Now do the same thing as in part (b), but for the case in which the diffusion is in a finite box. The novelty here is figuring out what happens because of the boundaries. Intuitively, what will happen in the long-time limit given that you started out with a delta function at the origin? Hand in a plot of how the probability changes as a function of time. Make sure you explain what is going on in the long-time limit.

(d) One-dimensional FRAP via spread the butter. In this part of the problem, we build on what you did in the previous part to consider fluorescence-

recovery-after-photobleaching for a one-dimensional cell. Consider the one-dimensional finite box with an initially uniform distribution of intensity throughout the "cell". Now, photobleach (i.e. just set the probability to zero) a region symmetrically displaced around the origin. If the cell runs from $-L$ to L then photobleach the region from $-a$ to a. How does the recovery time depend upon the diffusion constant?