20.430/6.561/10.539/2.795
Fields, Forces, and Flows in Biological Systems
Fall 2015

Problem Set # 1 (Chemical Sub-System) **Issued: 9/14/15**
Due: 5pm -- 9/25/15

Problem Sets should be turned in to the 20.430 FFF drop-off boxes, located to the right of the elevators on the 2nd floor of Building 16. Please turn Problems 1 & 2 into Box 1, and Problems 3 & 4 into Box 2.

Please state any additional assumptions you feel are necessary to solve the problems.

Reading Assignment: Chapter 1, Pages 1-10 from FFF by AJ Grodzinsky

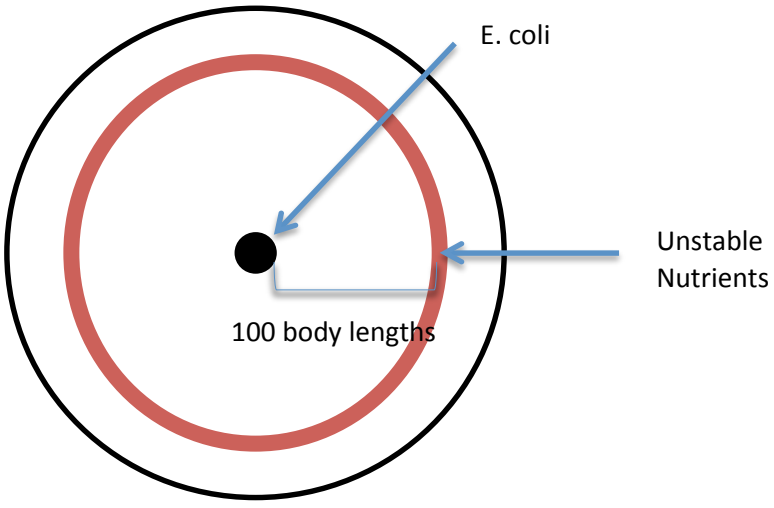
Problem 1: Bacterial chemotaxis

Bacteria such as *E. coli* swim and tumble stochastically in order to increase their search radius for nutrients in their environment. In order to chemotax toward a food source, *E. coli* are able to modulate their frequency of tumbling as well as the distance they can move in a single burst. Suppose that you have grown a population of *E. coli* at the center of a petri dish and then placed a ring of nutrients (at $t = 0$) around the colony 100 body lengths away. The nutrients degrade over time with a half-life of one minute.

On average, what is the time interval (τ) and swimming distance (δ) required for the population of *E. coli* to reach the food before 95% of it has degraded, and each *E. coli* can travel 10 body lengths per second?

With these values, what is the effective diffusion coefficient (D_{eff}) of *E. coli*?

How do these values change if the nutrients are 1,000 body lengths away?



Problem 2: Statistical mechanics of a molecular trap

In lecture we analyzed free diffusion of a molecule undergoing Brownian motion. In single-molecule spectroscopy, a laser is used to apply a restoring force on a polystyrene bead that is used to "trap" single molecules such as molecular motors, proteins, and RNAs to understand their conformational and binding dynamics, where the 1D potential energy of the trapped particle is, $U(x) = 1/2\ kx^2$, when located at any position x.

a. Assuming that this system is in thermal equilibrium on long time-scales of observation, compute the mean-squared displacement $< x^2 >$ of the particle using the Boltzmann distribution in 1D continuous space.

Hints:

- The trapped particle's position x represents a microstate that takes on continuous values. Therefore, the partition function takes the form of an integral, $Z = \int \exp(-U / k_B T) dx$ over all states (here, $-\infty < x < \infty$).
- Recall from elementary probability theory that the mean of any random variable α is simply $< \alpha >= \int \alpha P(\alpha) dx$, where the integral is over all values of α, and the probability distribution must be normalized.
- The integrals in the following link may be useful: https://en.wikipedia.org/wiki/Gaussian_integral

b. Explain how this mean-squared displacement expression differs from that of a free particle, and how the observation time-window over which the mean-squared displacement is measured experimentally impacts your interpretation of the particle's free versus trapped motion. Does your mean-squared displacement expression depend on lag-time? Why or why not?

Hints:

- Sketch the mean-squared displacement of the particle over time including times that are much smaller than the diffusional time corresponding to $\sqrt{< x^2 >}$ and also for times much larger than this time-scale.

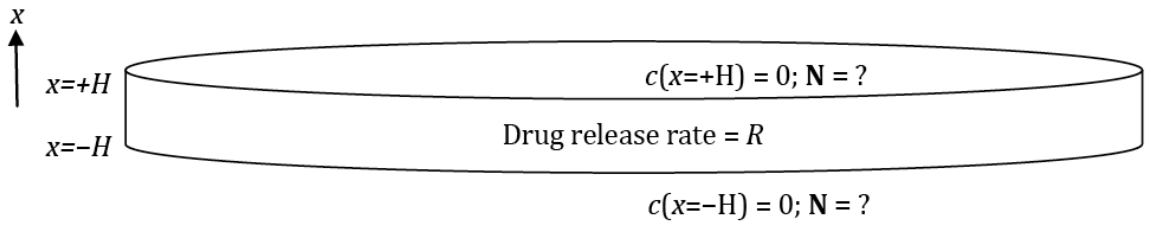
Problem 3: Diffusion of drug from a cylindrical disk

Drug-eluting materials are often used for controlled release of drugs over extended time periods. The implant is often in the form of a disk-shaped polymer implant that can be easily inserted subcutaneously. For a thin disk (thickness, $2H$ << radius, a), diffusion from the disk into the surrounding tissues can be treated as a one-dimensional problem in the direction perpendicular to the surface of the disk, except near the edges. Remember to state any assumptions in your analysis.

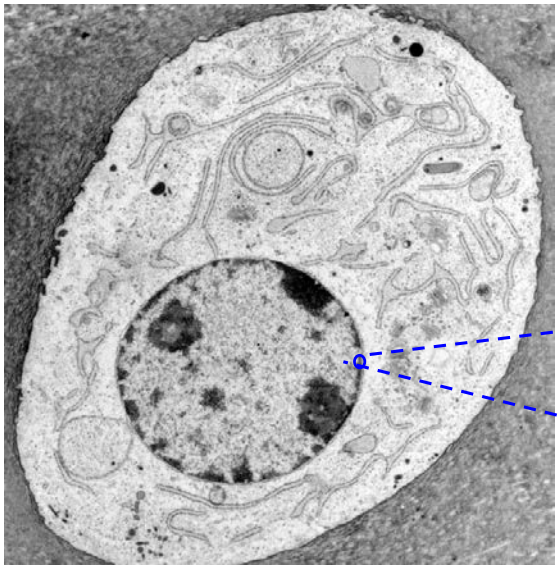
(a) A drug is being released uniformly from the material contained in the disk at a fixed rate R. Find an expression for the pseudo-steady-state concentration profile of drug inside the disk. You may assume that drug diffuses so freely in the surrounding tissue relative to within the disk, that the surface concentrations, c(x=-H) and c(x=H) can both be assumed to be zero. The diffusion coefficient inside the disk is D.

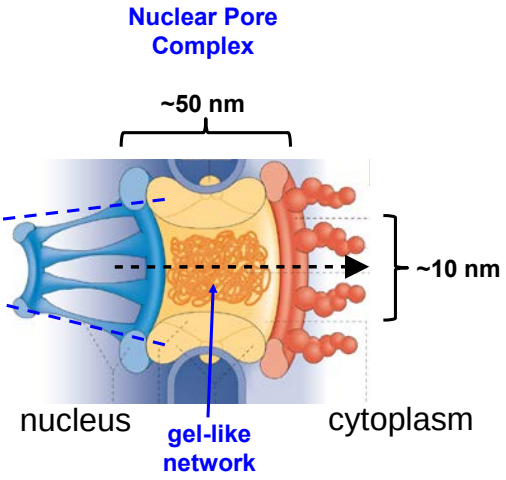
(b) Plot the concentration profile c(x) obtained in (a).

(c) Compute the steady flux of drug out of the disk at x = -H and x = $+H$, as well as the total rate of drug release from the disk. (Hint: typical units for rate of drug release would be mol/s).



Problem 4: Kinetics of nuclear-cytoplasmic molecular diffusion across nuclear pores



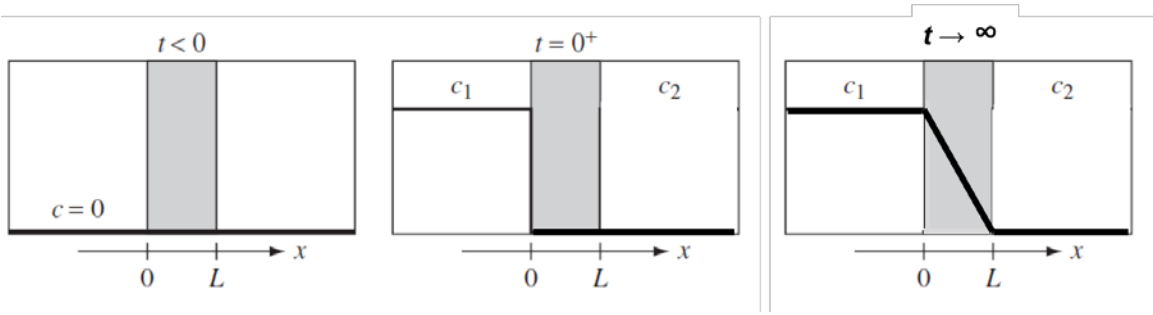


The ~50 nm thick nuclear membrane in eukaryotic cells consists of two lipid bilayers in which there reside as many as ~2,000 nuclear pores (each ~10 nm diameter) that control the passage of small and large molecules between the nucleus and cytoplasm. Small molecules and proteins with a M.W. < 40 kDa can rapidly transport across nuclear pores and equilibrate between nucleus and cytoplasm. (Other molecules (e.g., mRNA and tRNA) require facilitated transport to pass through the nuclear pore to the cytoplasm where they participate in protein synthesis.)

In an early paper (BioTechniques, 1998), Chatterjee and Stochaj devised a method to transfect HeLa cells (the famous immortalized cell line named after Henrietta Lacks) with a 29 kDa green fluorescent protein (the chimeric or fusion protein was called "NP-GFP"). This protein preferentially accumulated within the nucleus of the cells by means of facilitated transport. However, lowering the temperature eliminated such facilitated transport, and the protein was then able to freely diffuse from the nucleus outward into the cytoplasm (which was characterized by fluorescence microscopy).

The objective of this problem is to develop a simple 1-D continuum model of the initial kinetics of the spatial-temporal evolution of NP-GFP transport into the interior of the gel-like matrix within the nuclear pore complex, as the NP-GFP begins to diffuse from the nucleus into the pore and ultimately across to the cytoplasm. In the figure below, c_1 = NP-GFP concentration in the nucleus and c_2 = NP-GFP concentration in the cytoplasm,

and all the nuclear pores are lumped together and represented as the 1-D shaded region from $x = 0$ to $x = L$:



Accumulation of NP-GFP in the nucleus results in the initial nucleus concentration c_1 at $t = 0^+$ shown in the middle figure. (This is the initial condition for the solution of your diffusion equation.) As diffusion across the pore occurs, you can assume that the volume of the cytoplasm is so large (relative to the nucleus) that the concentration of NP-GFP in the cytoplasm is "diluted" to $c_2 \sim 0$ throughout the diffusion times of interest here. Thus, for experimental times of interest, you can assume that the boundary conditions on NP-GFP at the inner and outer edges of the nuclear pores are: c = c_1 at $x = 0$ and c = c_2 = 0 at $x = L$. (We know that for much longer times, the concentration of NP-GFP in the cytoplasm will eventually equal that in the nucleus, as true equilibrium is reached. But we are focusing here on the initial diffusion kinetics within the nuclear pore gel-matrix.

(a) Combine Fick's laws (flux and continuity) to form the overall diffusion equation of interest, with D = diffusivity of NP-GFP.

(b) Solve the diffusion equation to find $c(x,t)$ inside the nuclear pore ($0 < x < L$) valid from $t = 0^+$ to times long enough that the concentration profile reaches the linear profile within the pore matrix labeled as "$t = \infty$".

(c) What is the characteristic diffusion time for transport of NP-GFP across the nuclear pore of thickness L? (Note that we are assuming that this time constant is much shorter than the time needed for NP-GFP to eventually equilibrate between the cytoplasm and nucleus. We will calculate that (longer) time constant in a future problem.)

Hints:

i The space-time evolution of $c(x,t)$ for this problem is similar to that for IGF-1 in Fig 1.18 on page 26 of the text, except in this homework problem, there is no binding of NP-GFP to anything (by assumption).

ii Show that your answer is the same as Eqn. 1.72 on page 28 of the text, except that D_{eff} in (1.73) and 1.74) = D (no binding here). Note that any numerical constants that appear in the characteristic time constant (e.g., Eq. 1.74) are associated with the particular boundary conditions that are specified in the problem.

But: please note that there is a typo in Eq. (1.72): In the right most term, the factor (1/n) shown as outside the summation sign should be inside the summation, directly multiplying $sin(n\pi x/L)$.

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