# MCB137L/237L: Physical Biology of the Cell
# Spring 2024
# Homework 6
# (Due 3/5/24 at 2:00pm)

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"Mathematics, rightly viewed, possesses not only truth, but supreme beauty cold and austere, like that of sculpture, without appeal to any part of our weaker nature, without the gorgeous trappings of painting or music, yet sublimely pure, and capable of a stern perfection such as only the greatest art can show. The true spirit of delight, the exaltation, the sense of being more than Man, which is the touchstone of the highest excellence, is to be found in mathematics as surely as in poetry." - Bertrand Russel in *Study of Mathematics*

## 1 Ion channel currents

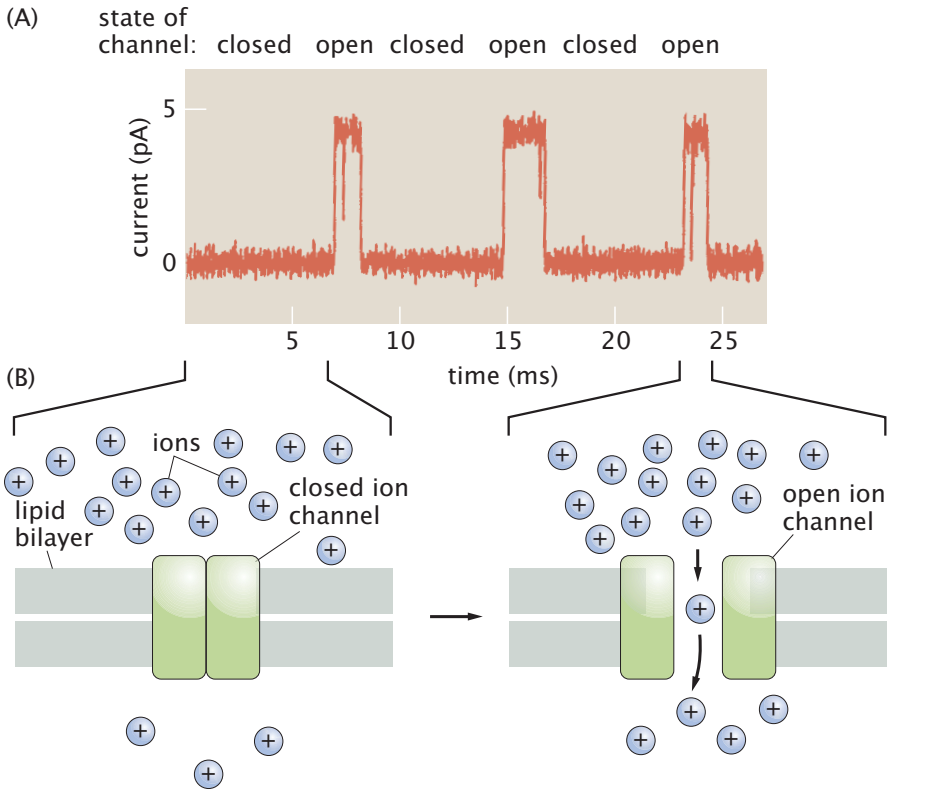
Figure 1A shows a single-channel recording of the current passing through a voltage-gated sodium channel. The data reveal that the channel transitions between open and closed states as shown in Figure 1B. When in the open state, $Na^+$ ions can flow from one side of the membrane to the other, resulting 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 $1.6 \times 10^{-19}$ C (Coulomb), and that 1 A = 1 C/s (Ampere = Coulomb/second). Compare your estimate to the current measured in Figure 1A.

## 2 Creating morphogen gradients

One of the most important ideas for how positional information arises in multicellular organisms is the idea of a morphogen gradient (another serious contender is a Turing pattern). In this problem we will use a steady-state solution to the reaction-diffusion equation for




(C)

$D_{small\ ions} = 1000\ \mu m^2/s$

| 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)

Bicoid to understand how the exponential profile shown in Figure 2 is set up. Stated simply, the development of the Bicoid gradient can be thought of as resulting from a competition between the diffusion of Bicoid protein that is synthesized at the anterior end of the embryo (the mother deposits localized *bcd* mRNA there as shown in Figure 3) and the degradation of this protein while it is diffusing around.

**(a)** Give a brief description (a paragraph or less) of the Bicoid gradient in *Drosophila* and how it is relevant to fly development.

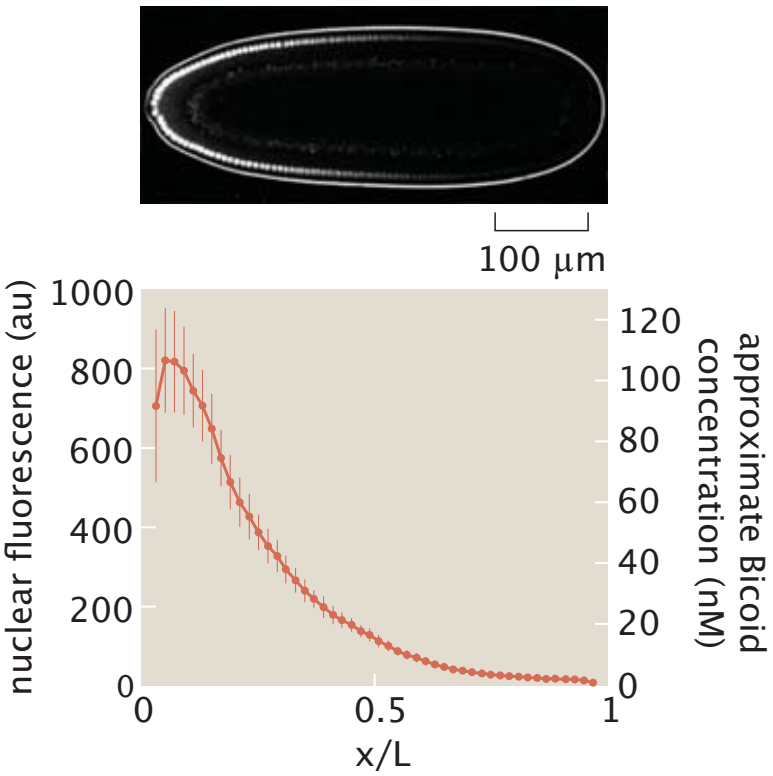



Figure 2: The Bicoid morphogen. The Bicoid activator is distributed in an exponential gradient. (Adapted from F. Liu *et al.*, Proc Natl Acad Sci USA 110:6724 2013.)

**(b)** Make a derivation of the reaction-diffusion equation and use it to justify the form

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

Make sure you explain carefully where all of these terms come from. To do so, you can build on the derivation of the diffusion equation we did in class based on particules jumping between adjacent boxes. Specifically, begin with the usual way by considering a one-dimensional concentration profile and by finding the rate of change of the number of Bicoid molecules in the box at position $x$ by considering the flux into $(kN(x-a,t) + kN(x+a,t))$ and out of $(2kN(x,t))$ the box, with $a$ being the size of the box and $k$ the rate of jumping of a particle, using arguments like those made in class. However, you need to generalize that treatment by accounting for the fact that a Bicoid molecule has the probability $r\Delta t$ of degrading in time interval $\Delta t$, where $r \approx 1/\tau$ with $\tau$ being the degradation time.

**(c)** Now, show that $Bcd(x,t) = Bcd_0 e^{-x/\lambda}$, with $\lambda$ being a decay length and $Bcd_0$ being the Bicoid concentration at $x = 0$, is a solution of the reaction-diffusion equation 1 in steady-state. How is $\lambda$ determined by the model parameters $D$ and $\tau$?

(**c, EXTRA CREDIT**) Solve this equation in steady-state by finding the general solution subject to the boundary condition that $J(0,t) = j_0$ and $J(L,t) = 0$. Remember that you can use Fick's law to relate the flux to a change in Bicoid concentration over time. Make

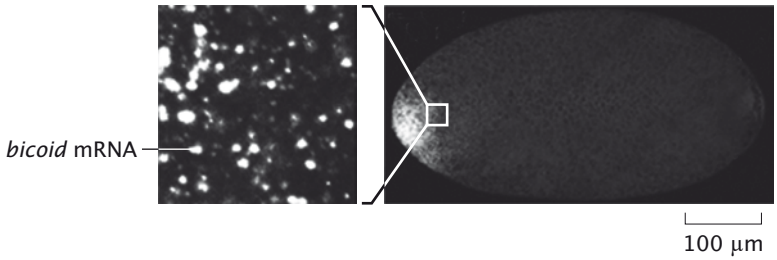



Figure 3: *bicoid* mRNA distribution. Using single molecule mRNA FISH, the localization of individual *bicoid* mRNA molecules at the anterior end of the embryo can be revealed. (Adapted from Petkova et al. (2014), *Current Biology* 24:1283.)

sure you explain what these boundary conditions mean relative to the biology of the problem. Suggest approximations that can be made to simplify the result, specifically, can you exploit the fact that the embryo is much larger than the decay length to simplify the solution?

(**d**) What is the value of the decay constant $\lambda$ for the gradient shown in Figure 2? To estimate this magnitude, you can just fit "by eye" by plotting your solution for different values of $Bcd_0$ and $\lambda$. Now, compare the measured $\lambda$ value with that you can predict by plugging in realistic values of $D$, $\tau$ into your solution. To make this possible, read the papers by Abu-Arish *et al.* and Drocco *et al.*, provided on the course website. Remember that you already delved into the experiment by Drocco *et al.* in the context of Homework 4.

# 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.