MCB137L/237L: Physical Biology of the Cell
Spring 2025
Homework 14 – Extra Credit
(Due 5/13/25 at 2:00pm)

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This homework draws from biological phenomena and physical models we explored throughout the semester. Note that this homework is for extra credit and that it is completely optional. As we are already going to drop your two lowest-scoring homework, if you complete this homework, we will use it to replace your third lowest-scoring homework. However, we will only do so if it actually *improves* your grade.

1 Energy and Life

One of the strongest things we can say about the properties of living organisms that distinguish them from inorganic materials such as the rocks that make up the face of Half Dome is that they are always consuming energy. Figure 1 shows a number of biological processes as viewed through the prism of energy consumption.

(a) Write a brief, thoughtful paragraph about the meaning of the energy scale k_BT .

(b) In this problem, choose three of the entries in the figure and make your own calculation of the relevant energy scale and see to what extent you agree with the reported numbers. Make sure that at least two of the problems you choose do not correspond to examples we explored in class. Further, dont nd a way to get the same numbers as are in the figure. Rather, do this yourself and get your own number. Make sure you carefully report your thought process and assumptions.

2 Leaky Membranes: The Cost of Defying Diffusion

As we saw in class, some ionic species are at a higher concentration inside the cell than outside the cell. As a result of this concentration gradient, there will be a flux of ions leaving the cell given by the concentration difference and the permeability which can be written as

$$\text{flux} = P(c_{in} - c_{out}) \tag{1}$$

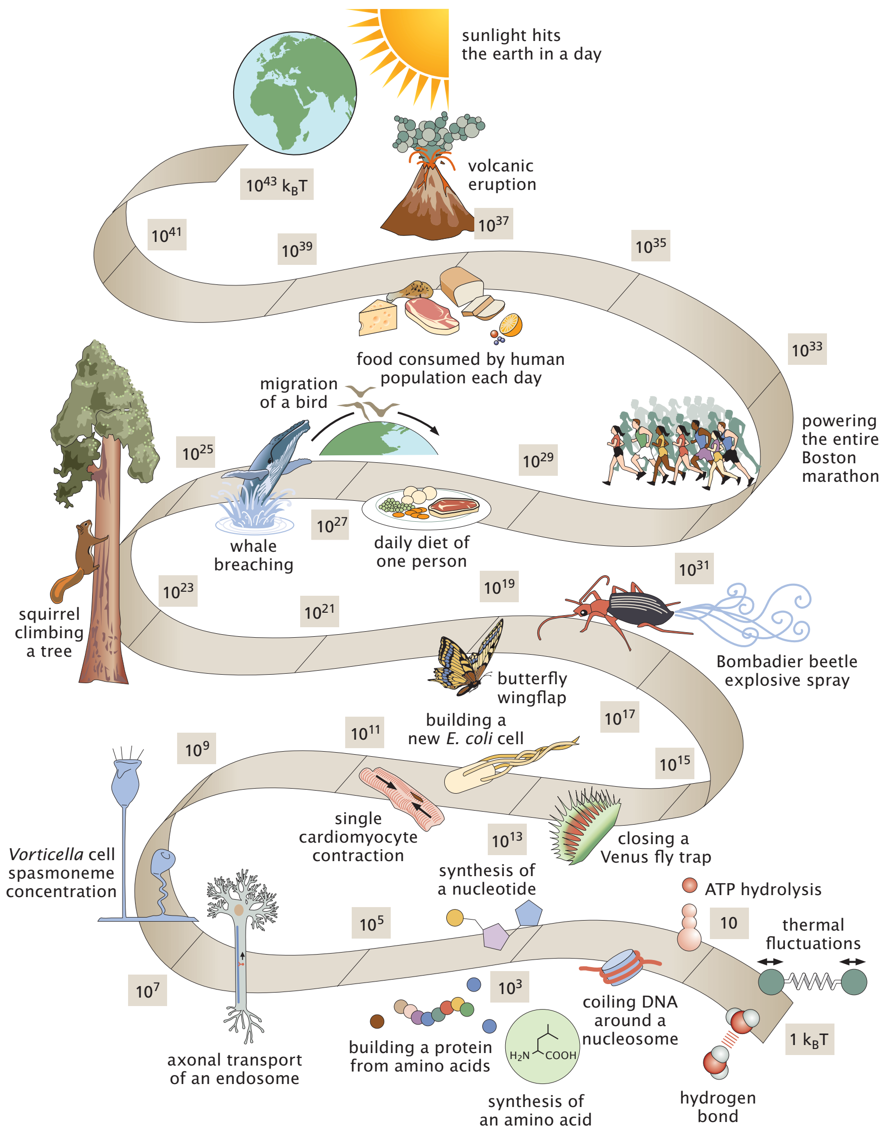

Figure 1: Energy scales of biology. From top to bottom, the energetic cost of the process of interest increases. All energies are measured in units of k_BT.

where P is the permeability as illustrated in Figure 2.

(a) Calculate the number of ions of a species such as K^+ that leave the cell per second due to the permeability of the membrane. Essentially, this tells us about the leakiness of the cell membrane to ions which will over time lead to a complete dissipation of the gradient. You might find it useful to read up on permeability in Section 11.1.3 of PBoC2.

(b) Using ideas worked out in class about the protonmotive force, make an estimate of the power in ATP/s or k_BT/s that it costs to maintain the concentration gradient against the perpetual leakiness of the membrane. Make sure you spell out the quantitative details of how you make this estimate.

(c) How does the energy necessary to maintain the K^+ gradient compare to that required to build a bacterial cell?

3 A minimal genetic switch

In class, we introduced how genetic switches can be constructed using two repressors that repress each other's gene expression. Here, we consider a simpler regulatory architecture that can also result in a genetic switch. Specifically, we will model the self-activation of an activator molecule. For this problem, you might find it useful, to review the phase portrait concept we described in class for the case of mRNA production and degradation, as well as the phase diagram of the logistic equation you had to draw earlier on in the semester.

Figure 3(A) presents a regulatory architecture, where an activator activates its own production. Figure 3(B) shows the states and weights for our model. In this problem, we will ignore mRNA and associate the rate indicated in the figure with the rate of protein production. Here, a promoter has two activator binding sites in its vicinity. In the absence of activators, or in the presence of only one activator, the rate of protein production is r_0. When both activators are bound, the rate is r. The activators bind with a dissociation constant K_d and interact with a cooperativity factor $\omega = e^{-\beta\varepsilon_{int}}$, where ε_{int} is the interaction energy between activators. A is the concentration of activator.

(a) Write down an equation describing the temporal evolution of the number of activators. Consider the rate of production stemming from the model shown in Figure 3, as well as a rate of protein degradation γ. Hint: Remember that the overall rate of production $\langle r \rangle$ of a system is given by

$$\langle r \rangle = \sum_i p_i r_i, \qquad (2)$$

where p_i is the probability of the system being in state i, and r_i is the rate of production when the system is in that state.

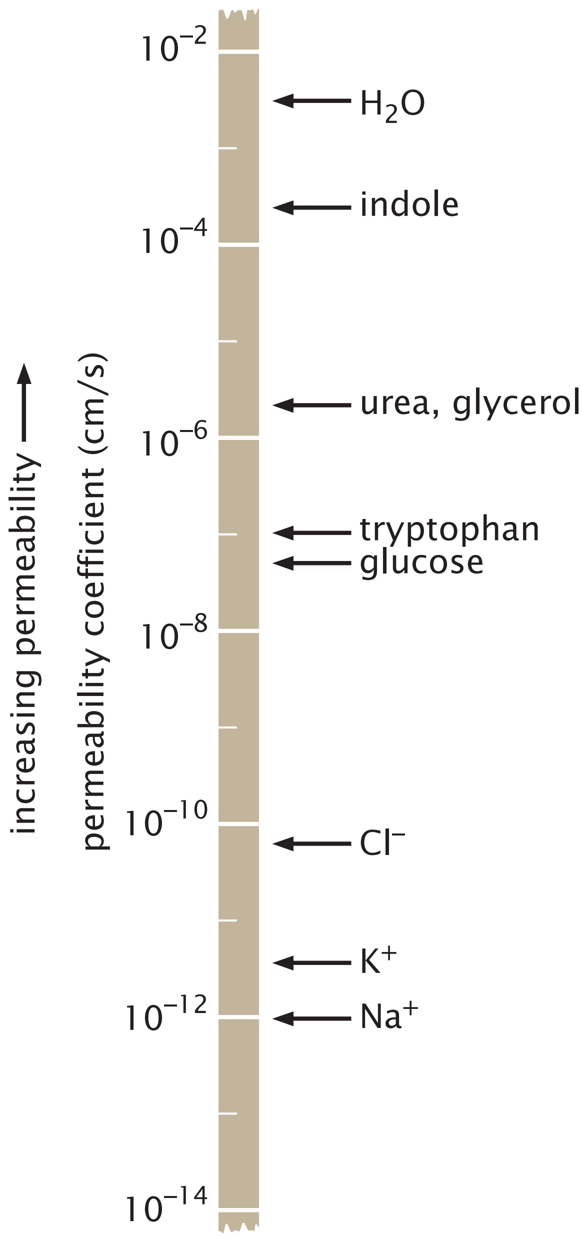

Figure 2: Permeability of various ions and molecules across membranes.

(b) Plot the phase diagram for this equation in order to find how many equilibria the system can support. Namely, plot the rates of production and degradation as a function of the activator concentration. Use $K_d = 5$ nM, $\gamma = 0.1$/min, $r_0 = 0.01$ nM/min, and $r = 0.5$ nM/min. Make plots for $\omega = 1$ and $\omega = 10$.

(c) Draw vectors indicating the direction of the concentration change under your plots as we did in class for the mRNA production and degradation case, and as you explored in the homework in the context of the logistic equation. How many equilibrium points do you find? Indicate whether these points correspond to stable or unstable equilibria. You can review the concept of phase portraits by reading "Computational Exploration: Growth Curves and the Logistic Equation" on page 103 of PBoC2, paying special attention to vectors drawn on the lower part of Figure 3.10.

(d) Solve the equation you derived in (a) for different initial conditions, and plot all of them on the same graph. Choose initial conditions that help illustrate how the system can converge to different levels of activator in steady state.

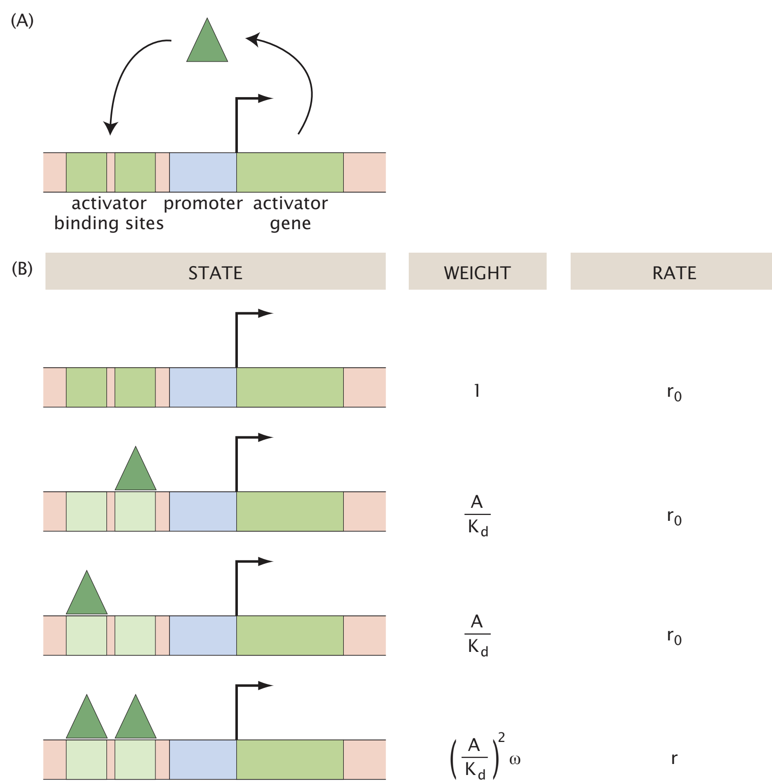

Figure 3: A simple autoactivation switch model. (A) Cartoon of the autoactivation switch. (B) States, weights and rates for the autoactivating genetic switch model.

4 Random walks and biological polymers

Physicists know how to solve just a handful of problems. Fortunately, many dissimilar phenomena in physics and biology alike can be mapped onto such problems for which we know a solution. Here, we explore the mathematical connection between diffusion and the spatial arrangement of polymers such as DNA, actin, and microtubules.

(a) Read the introduction to Section 8.2 of PBoC ("Random Walk Models of Macromolecules View Them as Rigid Segments Connected by Hinges") to learn more about how polymers can be thought of as chains of connected rigid segments. Pay close attention to Figures 8.1 and 8.2. Here, the Kuhn length a is defined as the length of the segments. Look up the Kuhn length for DNA, actin, and microtubules in order to get a feeling for these polymers. Note that you might find reference to the persistence length $\xi_p = a/2$ instead of the Kuhn length.

(b) Now, think of a polymer chain of N segments in 1D. As shown in Figure 8.3 of PBoC each segment can either be pointing to the right of to the left. Given n_R and n_L segments pointing to the right and left, respectively, the position of the end of the chain is given by $L = (n_R - n_L)\, a$. Map this problem onto the diffusion problem we solved in class where we calculated the $\langle x \rangle$ and $\langle x^2 \rangle$ of a random walker that start at the origin shown in Figure 4. To make this possible, note that each segment can be randomly pointing to the left or right. In particular, calculate $\langle n_R - n_L \rangle$ and $\langle (n_R - n_L)^2 \rangle$ and show that the size of the polymer is given by

$$\text{size} \approx \sqrt{\langle L^2 \rangle} = a\sqrt{N} \tag{3}$$

by repeating graphical the derivation we did in class.

(c) Think of the size of the polymer you derived in (b) as the linear dimension of the blob the polymer will make on a surface such as shown in the figures below. Use the derived formula to estimate the genome length (in μm and bp) of the bacteriophage T2 shown in Figure 1.16 of PBoC and of the *E. coli* in Figure 8.5 of PBoC. How well did your estimate do?

All relevant figures from PBoC can also be found in Figures 5 and 6 below.

5 The French flag model

One of the most important and interesting ideas to come out of the idea of positional information contained in morphogen gradients was the so-called French flag model which we will explore here. This model posits that the Bicoid concentration dictates the position of the cephalic furrow. As seen in Figure 7, the idea of the model is that boundaries in the embryo are determined by threshold values of the morphogen. The model predicts that, if the gene dosage of the morphogen gets changed, as seen in the mutant profile, the boundary will still occur at the same value of the morphogen. That hypothesis is enough to determine the shift

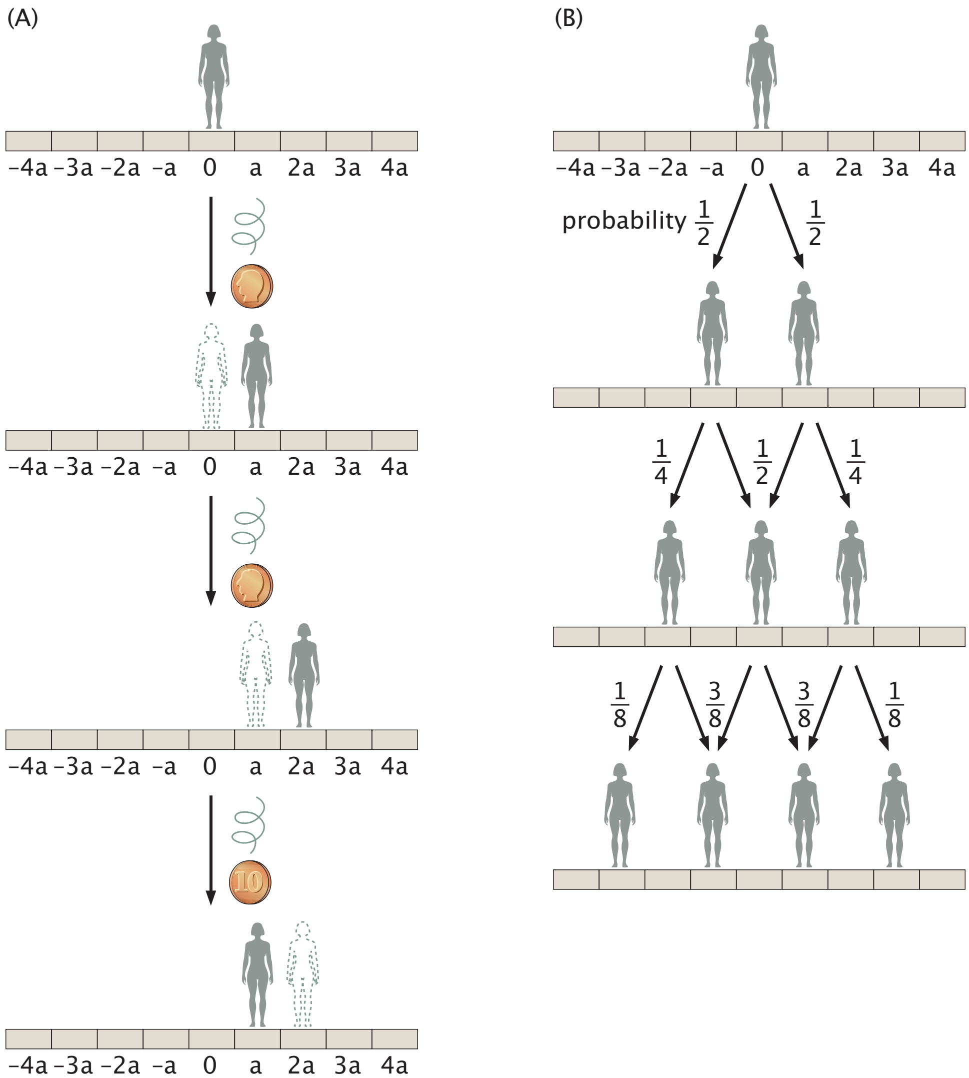

Figure 4: Coin flips and diffusion. (A) Stochastic "simulation" of a coin flipping process with the random walker stepping to the right when a heads is flipped and stepping to the left when a tails is flipped. (B) Scheme for calculating the probability of each and every possible outcome after a total of N steps.

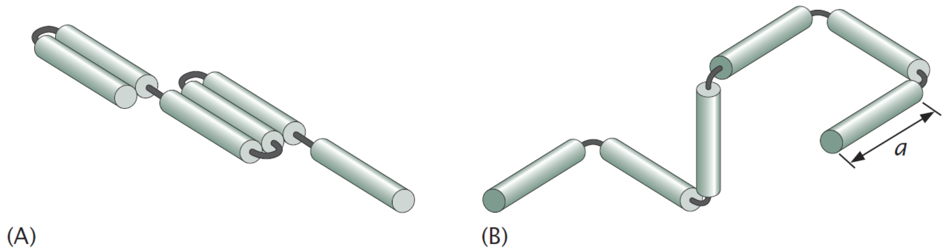

Figure 8.1: Random walk model of a polymer. Schematic representation of (A) a one-dimensional random walk and (B) a three-dimensional random walk as an arrangement of linked segments of length *a*.

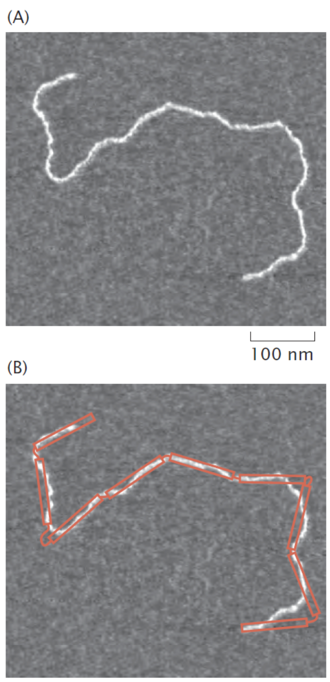

Figure 8.2: DNA as a random walk. (A) Structure of DNA on a surface as seen experimentally using atomic-force microscopy. (B) Representation of the DNA on a surface as a random walk. (Adapted from P. A. Wiggins et al., *Nat. Nanotech.* 1:37, 2006.)

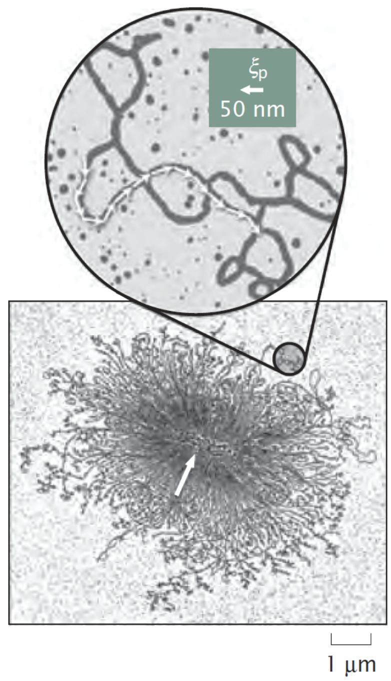

Figure 8.5: Illustration of the spatial extent of a bacterial genome that has escaped the bacterial cell. The expanded region in the figure shows a small segment of the DNA and has a series of arrows on the DNA, each of which has a length equal to the persistence length in order to give a sense of the scale over which the DNA is stiff. (Adapted from an original by Ruth Kavenoff.)

Figure 1.16: Electron microscopy image of a bacteriophage genome that has escaped its capsid. Simple arguments from polymer physics can be used to estimate the genomic size of the DNA by examining the physical size of the randomly spread DNA. We will perform these kinds of calculations in Chapter 8. (Adapted from G. Stent, Molecular Biology of Bacterial Viruses. W. H. Freeman, 1963.)

Figure 5: Figures 8.1, 8.2, 8.5 and 1.16 from PBoC.

in boundary position with gene dosage.

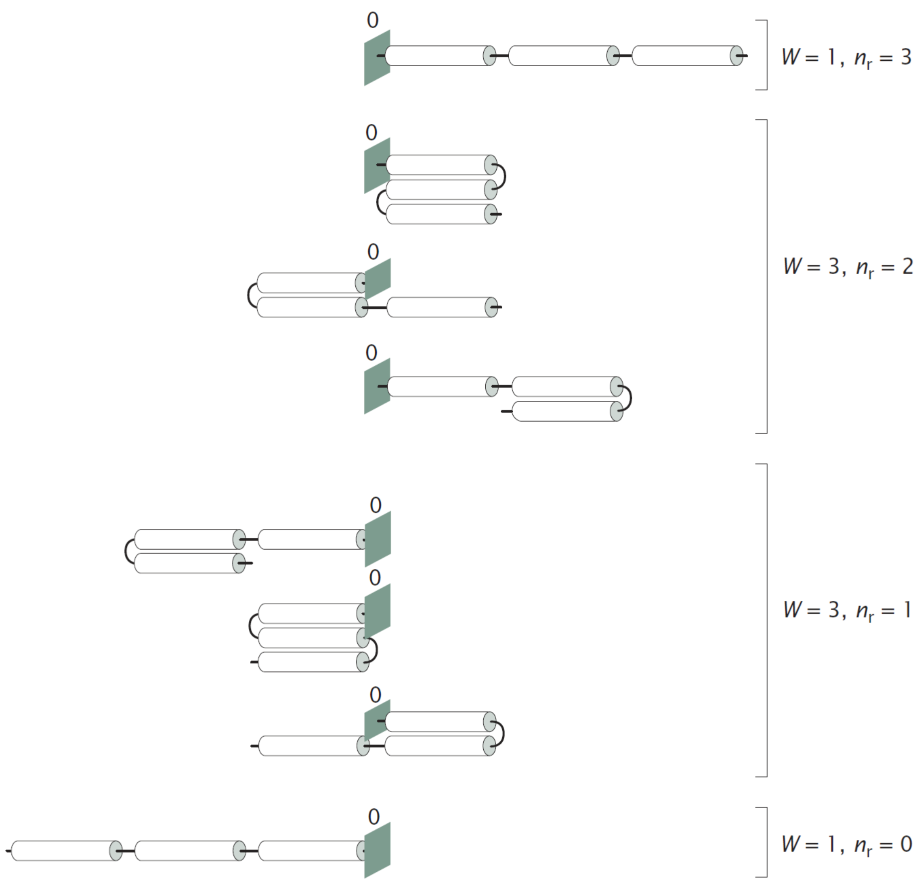

Figure 8.3: Random walk configurations. The schematic shows all of the allowed conformations of a polymer made up of three segments ($2^3 = 8$ conformations) and their corresponding degeneracies.

Figure 6: Figure 8.3 from PBoC.

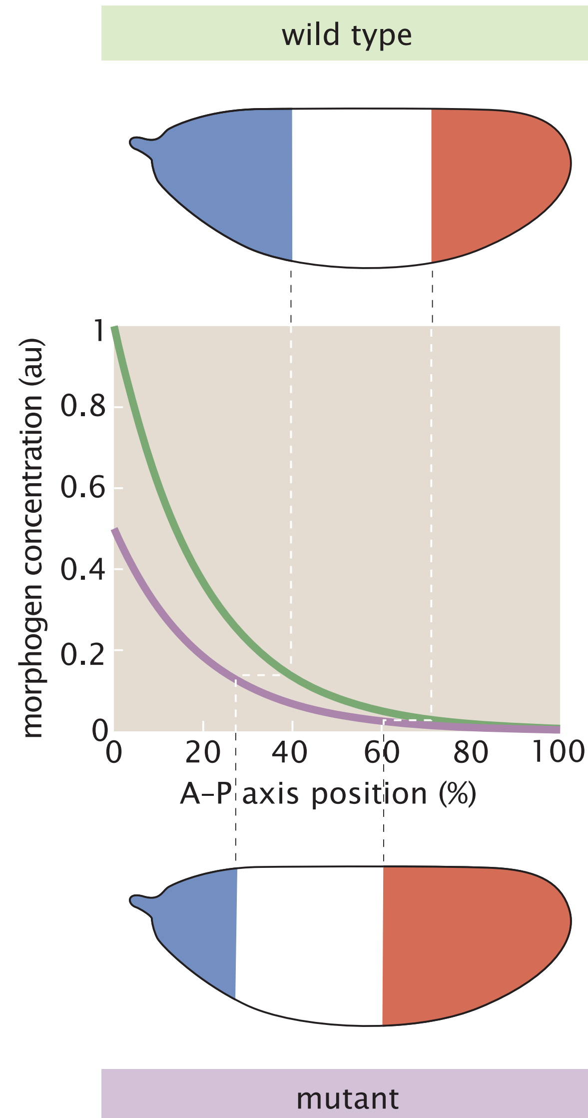

Figure 7: Concept of the French flag model.

To test this model, we will analyze several experiments (Nusslein-Vohlhard and Driever. and Liu *et al.*) where they measured cephalic furrow position as a function of different dosages of the *bicoid* gene in embryos. An exponential gradient of Bicoid is described by

$$Bcd(x, \lambda, \alpha, Bcd_0) = Bcd_0\, \alpha\, e^{-x/\lambda}, \tag{4}$$

where x is the position along the embryo, Bcd_0 is the Bicoid concentration at $x = 0$, λ is the decay constant of the gradient and α is the Bicoid dosage, with $\alpha = 1$ corresponding to the wild-type.

(a) Work out a model that predicts the position of the cephalic furrow x_{new} as a function of the gene dosage α, the morphogen gradient decay length λ and the position of the wild-type cephalic furrow, x_{CF}.

(b) Note that, given a measured $x_{CF} \approx 32\%$ of the embryo length, your model has no free parameters. Compare the prediction from your model with the data for x_{new} vs. α obtained by Nusslein-Vohlhard, and by Driever and Liu *et al.* (provided on the course website). Comment on how well your prediction matches the data that is provided with the homework. What could be going on?