BE/APh161: Physical Biology of the Cell
Homework 5
Due Date: Wednesday, February 24, 2021

"Thinking, analyzing, inventing are not anomalous acts; they are the normal respiration of the intelligence." - Jorge Luis Borges

1. Synthetic Oscillators in Bacteria.

I gave a vignette on oscillatory gene regulatory circuits and how to write rate equations for genetic oscillators. During that vignette, I showed an experimental realization of such an oscillator that had one more regulatory feedback than the architecture I considered in the vignette. In this problem, your goal is to use your code that you have written for integrating ordinary differential equations and to repurpose it to solve for the coupled activator and repressor dynamics of that oscillatory circuit.

(A) Draw a schematic of the regulatory circuit in the paper by Hasty *et al.* included with this homework. More importantly, explain what the various features in the regulatory circuit do.

(B) Write down the states, weights and rates for the activator gene and the repressor gene. (Note: you can ignore the gene for the fluorescent protein). Make sure you justify in detail the way you constructed your statistical weights.

(C) Using those states, weights and rates, write down the two coupled differential equations for the activator $A(t)$ and repressor $R(t)$ as a function of time.

(D) Integrate those equations over time and plot $R(t)$ and $A(t)$.

2. What Living Organisms Must Fight.

In the vignette on the "calculus of equilibrium" we talked about how systems will tend towards the state of maximum entropy. In this problem, you are going to flesh out the details of the calculations leading to the graphs in that

vignette and will provide your own graphs.

(A) Equilibrium with respect to mass transport. Consider a system partitioned equally into two parts, each of which contains Ω lattice sites. We want to write the total entropy as $S_{tot}(L) = S_L(L) + S_R(L_{tot} - L)$. Show that these contributions to the entropy can be written as

$$S_L(L) = k_B \log \frac{\Omega^L}{L!} \tag{1}$$

for the left side and

$$S_R(L_{tot} - L) = k_B \log \frac{\Omega^{L_{tot}-L}}{(L_{tot} - L)!} \tag{2}$$

for the right side. Using the Stirling approximation, derive the expression

$$S_{tot}(L) = -k_B L_{tot} \left[\frac{L}{L_{tot}} \ln \frac{L}{L_{tot}} + \left(1 - \frac{L}{L_{tot}}\right) \ln \left(1 - \frac{L}{L_{tot}}\right) - \left(\ln \frac{L_{tot}}{\Omega} - 1\right) \right] \tag{3}$$

for the total entropy. Plot the entropy of the left part, the right part and the total entropy as a function of the number of ligands in the left side of the container which can run from $L = 0$ to $L = L_{tot}$. To make this plot, you will need to assume a certain number of lattice sites. Imagine a container with $\Omega = 10^9$ lattice sites. If each such lattice site has a volume of 1 nm^3, then the total volume of each side is 1 μm^3.

(B) We next consider the case in which the partition between the two sides is mobile. In this case, we are interested in how the entropy on the left side and the right side play against each other, conspiring to give a total entropy of the form

$$S_{tot}(x) = S_L(x) + S_R(x), \tag{4}$$

where x is the label used to characterize the position of the interface. As usual, the entropy is given by the Boltzmann formula which in this case takes the form

$$S_L(x) = k_B \log W_L(x) \tag{5}$$

and

$$S_R(x) = k_B \log W_R(x). \tag{6}$$

To make progress, we now need to reckon the number of states as a function of the position x of the partition. When the partition is at the midpoint, each of the subcompartments has a volume V. The volume swept out by the motion of the partition by a distance x is xA, where A is the cross-sectional area of that partition. As a result, show that the number of states added or subtracted due to the motion of the partition is xA/v, leading to the results

$$W_L(x) = \frac{(\frac{V+xA}{v})^{L_L}}{L_L!}, \tag{7}$$

and

$$W_R(x) = \frac{(\frac{V-xA}{v})^{L_R}}{L_R!}. \tag{8}$$

Use these results to show that

$$S_{tot}(x) = k_B L_L \log \frac{V+xA}{v} - k_B \log L_L! + k_B \log \frac{V-xA}{v} - k_B \log L_R!, \tag{9}$$

and make a plot of the resulting entropy of the two sides and the total entropy as a function of the position of the partition x.

3. Dynamics of A $\rightarrow$ B reactions.

One of the most interesting topics in science is how we have learned to probe deep time. Surprisingly, DNA sequence has permitted us to explore deep time in the biological setting. Of course, biology and the dynamics of the Earth are not independent phenomena and the point of the rest of this problem is to better understand the details of how scientists figure out how old the Earth is as well as how old various fossil-bearing strata are. To that end, we will first consider a simple model of the radioactive decay process for potassium-argon dating methods, recognizing that there are many other dating methods that complement the one considered here.

Potassium-Argon dating

Potassium-argon dating is based upon the decay of ^{40}K into ^{40}Ar. To a first approximation, this method can be thought of as a simple stopwatch in which at t = 0 (i.e. when the rocks crystallize), the amount of ^{40}Ar is zero, since it is presumed that all of the inert argon has escaped. We can write an

equation for the number of potassium nuclei at time $t + \Delta t$ as

$$N_{\mathrm{K}}(t + \Delta t) = N_{\mathrm{K}}(t) - (\lambda \Delta t) N_{\mathrm{K}}(t). \tag{10}$$

Stated simply, this means that in every small time increment Δt, every nucleus has a probability $\lambda \Delta t$ of decaying, where λ is the decay rate of ^{40}K into ^{40}Ar. We also employ the important constraint that the number of total nuclei in the system must remain constant, so that

$$N_{\mathrm{K}}(0) = N_{\mathrm{K}}(t) + N_{\mathrm{Ar}}(t), \tag{11}$$

where $N_{\mathrm{K}}(0)$ is the number of ^{40}K nuclei present when the rock is formed, $N_{\mathrm{K}}(t)$ is the number of ^{40}K nuclei present in the rock at time t, and $N_{\mathrm{Ar}}(t)$ is likewise the number of ^{40}Ar nuclei present in the rock at time t. In this part of the problem you will use equations 10 and 11 to construct differential equations to find the relationship between $N_{\mathrm{K}}(t)$, $N_{\mathrm{Ar}}(t)$, and t.

(A) Using equations 10 and 11 as a guide, write differential equations for $N_{\mathrm{K}}(t)$ and $N_{\mathrm{Ar}}(t)$. How do these two expressions relate to one another?

(B) Next, we note that the solution for a linear differential equation of the form $\frac{dx}{dt} = kx$ is given by $x(t) = x(0)e^{kt}$. Use this result to solve for $N_{\mathrm{K}}(t)$.

(C) Use the constraint encapsulated by equation 11 to write an equation for the lifetime of the rock, t, in terms of the ratio $\frac{N_{\mathrm{Ar}}}{N_{\mathrm{K}}}$.

Age of the Galapagos Islands

The potassium-argon dating method described above has been used in several contexts central to some of the most important evolutionary questions in biology. As we go from West to East in the Galapagos Archipelago, the ages of the islands increase, with Santa Cruz older than Isabella, for example. But how are these numbers known and what evidence substantiates these claims when naturalist guides make them? In a beautiful article from Science Magazine in 1976 (Science, New Series, Vol. 192, No. 4238 (Apr. 30, 1976), pp. 465-467), Kimberly Bailey tells us of her efforts to determine the ages of the islands of Santa Cruz, San Cristobal and Espanola. We will now use her data to find out the K-Ar ages of several of these islands ourselves.

(D) Read Bailey's short paper and give a brief synopsis (1 paragraph) of her approach and findings.

(E) Use the results from Sample H70-130 and JD1088 of Table 1 to determine ages for Santa Cruz Island and Santa Fe Island. To do this, you will need to navigate a few subtleties. First, note that the amount of Argon is presented in moles, and so you can use those numbers directly. To determine the number of moles of ^{40}K, you will need to use the weight percentage that is K_2O and use that in combination with the mass of the sample to figure out how much K is present. Note that not all of the potassium in the sample will be the isotope ^{40}K, so you will need to use the ratio of ^{40}K to total potassium, $\frac{^{40}\mathrm{K}}{\mathrm{K_{total}}} \approx 1.2\times10^{-4}$. Additionally, use the decay constant $\lambda \approx 5.8\times10^{-11}$ yr^{-1}.

Determining Lucy's age

In 1974, a fossil of *Australopithecus afarensis* (shown in Figure 1) was discovered in Ethiopia. This specimen, which was dubbed "Lucy," marks an important step in understanding human evolution because at the time of its discovery, it was the earliest known species to show evidence of bipedal locomotion. Because Lucy was found in an area that was rich in volcanic rock, potassium-argon dating was an ideal method for determining Lucy's age (Aronsen 1977).

Unfortunately for us, real-world K-Ar dating data are generally not neatly presented in the form of N_{Ar} and N_{K}. Instead, geologists will measure a concentration of ^{40}Ar in mol/g and a weight percent of K_2O. These data must be used to identify the number of ^{40}Ar and ^{40}K nuclei in the sample. In this part of the problem, we will look at such measurements from an actual paleontological specimen as reported in Aronsen (1977) in order to determine its age.

(F) Using the table of ^{40}Ar and K_2O measurements below (Aronsen 1977), obtain an estimate for Lucy's age. Be sure to explain the steps you take to obtain your answer. Since each sample is taken from the area in which Lucy was found, we expect each sample to give you roughly the same answer; you will need to take the mean of the ages of each sample to obtain an estimate for Lucy's age.

Figure 1: The remains of Lucy, a specimen of *Australopithecus afarensis*.

Assume that each sample has a total mass of 1 g. Also, note that not all of the potassium in the sample will be the isotope ^{40}K, so you will need to use the ratio of ^{40}K to total potassium, $\frac{^{40}\mathrm{K}}{\mathrm{K_{total}}} \approx 1.2 \times 10^{-4}$. Additionally, use the decay constant $\lambda \approx 5.8 \times 10^{-11}$ yr^{-1}.

Reactions of the form

$$\mathrm{A} \rightarrow \mathrm{B}. \tag{12}$$

are ubiquitous in the natural world. Thus far, we examined these equations in the context of radioactive decay, a phenomena central to biology because

Sample Number	^{40}Ar $\times 10^{-12}$ mol/g	wt. % K_2O
1	2.91	0.657
2	3.18	0.755
3	3.08	0.680

Table 1: Outcome of measurements of potassium and argon for dating the rocks in the vicinity of Lucy.

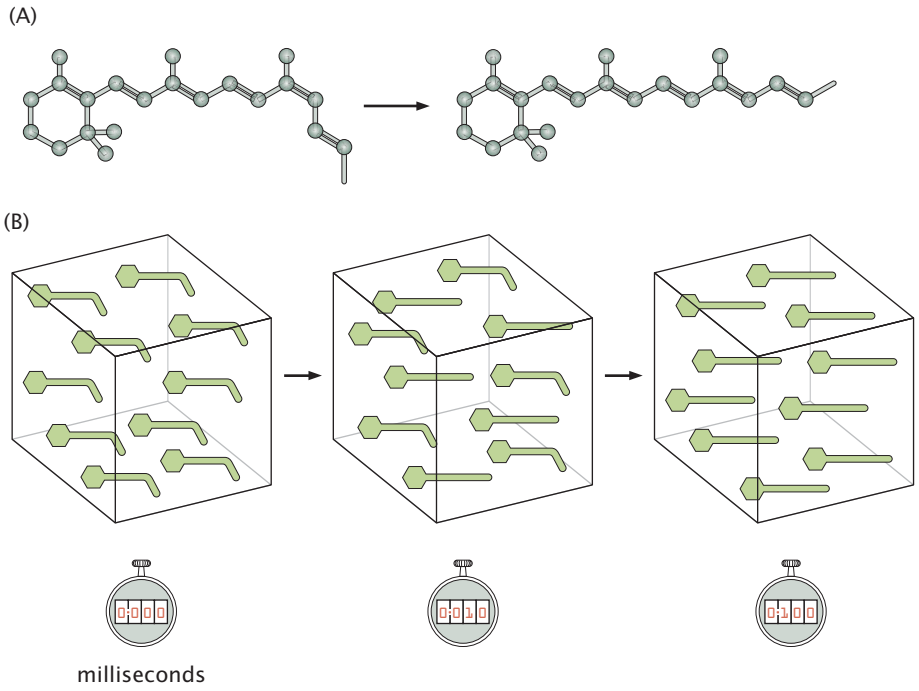

Figure 2: Different views of the isomerization process. (A) Schematic of an isomerization process where species A is decaying into species B. In this case, we use the two forms of retinal to characterize the process. (B) Schematic of the change in the populations of the two species over time.

it provides a way of understanding biological evolution. Part of the intention of this problem is to illustrate the broad reach of these reactions in problems ranging from the dating of incredibly important fossils such as the famed Lucy to the molecules of vision.

(G) Apply the results from your analysis of radioactive dating to now write an equation for the decay of 13-*cis*-retinal to all-*trans*-retinal, as is illustrated in Figure 2. The half-life of this reaction is $\tau = 2\,\mathrm{s}$. Make sure you write down a formal relationship between the rate constants to use in your rate equation and the half-life of the reaction.

4. The Failure of Equilibrium Fidelity.

In the vignette on "Fidelity as Defiance," I worked out in words that for a

simple two amino-acid view of protein translation, that the error rate is given by the ratio of the K_ds of the wrong and the right tRNAs. In this problem, flesh out the entire argument given in that vignette, and generalize beyond the case done in class to the case in which the concentration of the wrong and right tRNAs is different. That is, find an expression for the error rate in this case. Make sure you put in some approximate (but well justified) numbers. Explain why this model *fails* as a picture of translational fidelity.