BE/APh161: Physical Biology of the Cell
Homework 3
Due Date: Wednesday, January 28, 2026

"Champions aren't made in gyms. Champions are made from something they have deep inside them - a desire, a dream, a vision. They have to have the skill, and the will. But the will must be stronger than the skill." - Muhammad Ali

1'. $Stuff(t)$ and the Science and Mathematics of Change

Obviously, I am intensely dedicated to this idea that much of what different parts of science have focused on is the science of change. In the world of geology, huge emphasis was placed on the development of our modern notion of "Deep Time." In physics, over and over again, we learn about dynamical laws, whether the original insights of $F = ma$ or Maxwell's dynamical theory of the electromagnetic field, or the heat equation, etc. In chemistry, we have a beautiful and well-crafted theory of chemical reaction dynamics based upon the law of mass action.

(a) Give three one sentence examples of some time dependent phenomenon that you find interesting that qualify as examples of $stuff(t)$.

(b) Explain in a few sentences what I mean by the update rule paradigm mathematically. Show how to write an update rule for some dynamical problem.

1. Post-Translational Modifications and "nature's escape from genetic imprisonment"

In a very interesting article ("Post-translational modification: nature's escape from genetic imprisonment and the basis for dynamic information encoding"), Prof. Jeremy Gunawardena discusses how we should think about post-translational modifications as a way of expanding the natural repertoire of the 20-letter amino acid alphabet. Similarly, Prof. Christopher Walsh wrote a whole book entitled "Posttranslational Modifications of Proteins: Expanding Nature's Inventory," again making the point that by adding

chemical groups to proteins we can significantly change their properties.

(a) Provide at least one mechanistic idea about how adding a chemical group to a protein can alter its structure or function. Your answer should be offered in less than a paragraph, but should be concrete in its assertions about how these modifications change the protein. Why does Gunawardena refer to this process of post-translational modification as "escape from genetic imprisonment"?

(b) As a toy model of the combinatorial complexity offered by post-translational modifications, imagine that a protein has N residues that are able to be phosphorylated. NOTE: comment on which residues these are and how the dominant phosphorylation chemistry differs between bacteria and eukaryotes. How many distinct proteins can be generated as a result of the N residues that can be phosphorylated? Make an approximate estimate of the mass associated with a phosphate group and what fraction of the total mass this group represents for a typical protein. Similarly, give some indication of the net charge introduced by a phosphate group at physiological pH. What ideas do you have about how we can go about measuring these different states of phosphorylation?

(c) In this part of the problem, make a crude estimate of the number of sites on a protein that are subject to phosphorylation. To do so, imagine that the protein is a sphere with N residues packed at roughly constant density as shown in Figure 1. How does the radius of that sphere depend upon the number of residues in the protein? Given that estimate, what is the scaling of the number of residues that are on the surface with N? Given that number, what fraction of those are phosphorylatable? Remember, these are crude estimates. Work out these results for a concrete case of a typical protein with roughly 400 amino acids.

(d) Let's close out these estimates by thinking about a bacterial cell. If all 3×10^6 proteins in such a cell can be phosphorylated with the number of different phosphorylation states that you estimated above, how many distinct cells could we make with all of these different states of phosphorylation? State clearly any independence assumptions you are making when you combine phosphorylation states across proteins.

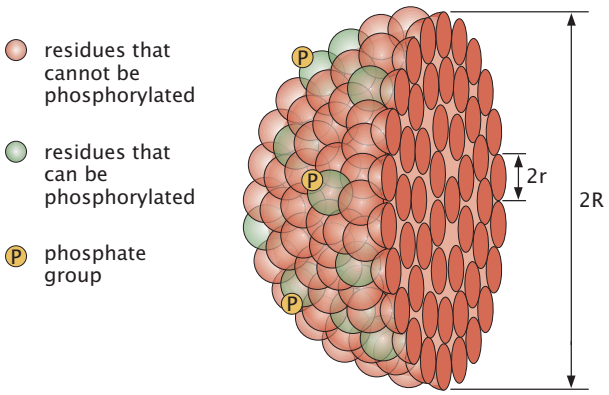

Figure 1: Schematic of a protein showing the surface residues that are available for phosphorylation.

2. 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 ocnsuming energy. Figure 2 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. This is one of those problems for which no AI is permitted.

(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. Don't find 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.

3. Computing With the Update Rule

In class, we discussed the rate equation protocol shown in Figure 3. We used that protocol to work out the temporal dynamics of the average number of mRNAs in a population of cells assuming that the promoter of interest

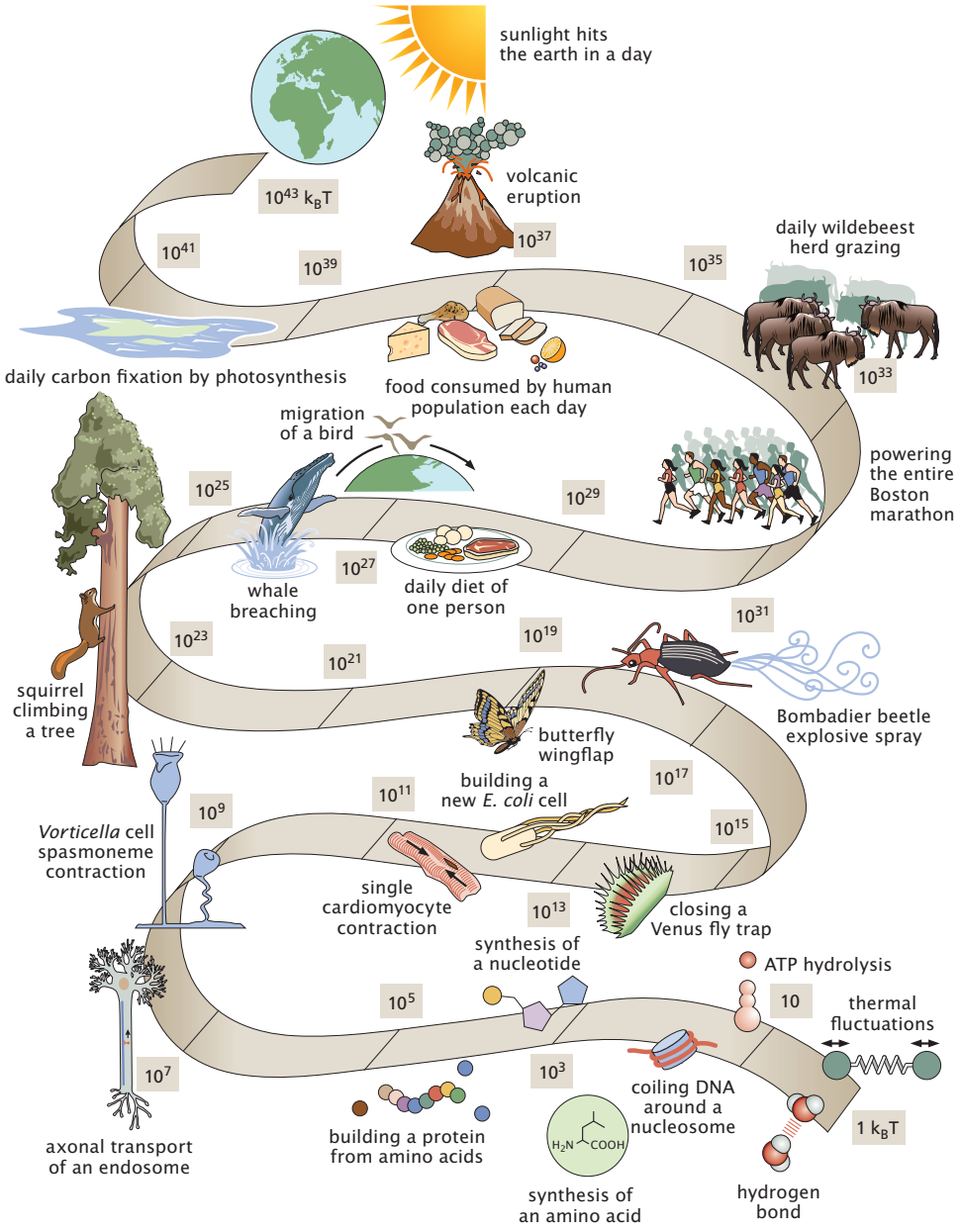

Figure 2: Energy scales of biology. From top to bottom, the energetic cost of the process of interest increases. All energies are measured in units of k_BT.

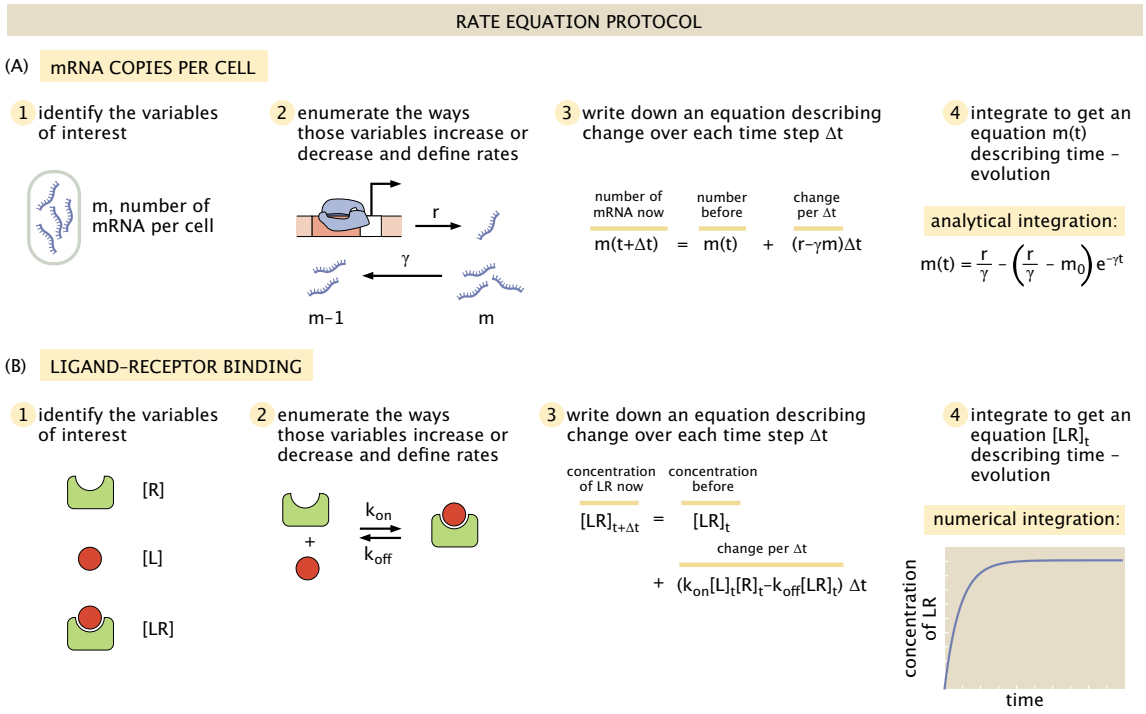

Figure 3: The rate equation protocol. To write dynamical equations for the time evolution of quantities of biological interest, there is a progression of steps.

was constitutively expressed. In this problem, we are going to take an opportunity to compare analytic and numerical calculations of the behavior not only of the constitutive promoter, but also, of the simplest genetic switch.

(a) Go through all of the steps of the rate equation protocol shown in Figure 3(A) by explaining what the dynamical variables are, showing how to write down the update rule, reinterpreting that update rule as a differential equation and then demonstrating that the solution to that differential equation is

$$m(t) = \frac{r}{\gamma} - \left(\frac{r}{\gamma} - m_0\right) e^{-\gamma t} \tag{1}$$

as shown in the figure. Make sure you explain the $t \to 0$ and $t \to \infty$ limits.

(b) Write a code in Python that uses the update rule in its simplest form

shown in Figure 3 to find the number of mRNA as a function of time. For concreteness, let's take typical numbers such as that the degradation rate is $\gamma = 1/3$ min^{-1} and $r = 1/3$ min^{-1}. Feel free to use your chatbot of choice to help you with the coding, but make sure you use Rob's rules for code produced in this context. We are NOT going for efficiency. I don't want you using a differential equation integrator, I want to do the truly naive Euler forward integration shown in the rate equation protocol. The goal is to make a plot of $m(t)$. Make sure you submit your code with your homework. The code must be commented to demonstrate that you know precisely what is going on. This should be a very simple code. Comment on how long you had to run your numerical integration to reach saturation in terms of the parameters r and γ.

(c) As we have already discussed in class a number of times, most genes are regulated. This means that unlike the constitutive promoter, there is feedback. The simplest example of that behavior is perhaps the auto-activation switch shown in Figure 4. The simplest model we can write of this equation is to imagine that the promoter produces mRNA with a higher rate r_∞ when it is self-activated. We write an equation of this form as

$$\frac{dA}{dt} = -\gamma A + r_0 \frac{1}{1 + \left(\frac{A}{K}\right)^2} + r_\infty \frac{\left(\frac{A}{K}\right)^2}{1 + \left(\frac{A}{K}\right)^2}. \tag{2}$$

Sketch a diagram of the rates vs A as I have done in class. In particular, your graph should show the degradation term and then the production term and beneath it put a phase portrait that shows which direction the vectors are pointing. Using your diagram, make statements about the fixed point solutions of this equation and comment on their stability. Does this make sense?

(d) Use your code from part (b) but now modified to account for the more complex right hand side to integrate the equations of motion for the auto-activation switch. Let's keep the same value of γ, and consider $r_0 = 1/10$ min^{-1} and $r_\infty = 5$ min^{-1}. We also need an equilibrium constant and in my dimensionless units, consider $K = 5$. Solve for $A(t)$ for several different initial conditions to show that for low initial A, the solution converges to the small A fixed point and for large initial A, the solution converges to the high A

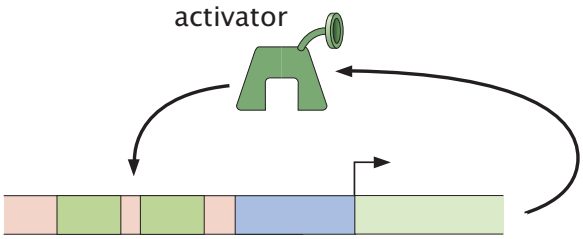

Figure 4: Architecture of the auto-activation gene circuit. The activator has a binding site (labeled in green) on its own promoter such that when there is sufficient level of activator present, the level of transcription will be enhanced relative to its basal value.

fixed point.

4. Equation of Motion for Mean Cytoskeletal Filament Length

In class we discussed the rate equation protocol shown in Figure 3. Our application of the protocol in class was to the problem of a constitutive promoter and provided a dynamical equation for the average number of mRNAs per cell as a function of time. In this problem, you are going to imitate that analysis, but this time thinking about the average length of a cytoskeletal filament as a function of time. Imagine a situation in which we have a closed box in which a single cytoskeletal filament has been nucleated (using a nucleating factor, for example) and which is bathed in a reservoir of monomers, with the initial number of monomers being given by N_{tot}. Our goal is to compute $L(t)$, where L is the length of the filament as a function of time. The rate at which monomers attach is $k_{on}n_{free}$, where n_{free} is the number of free monomers and the rate at which monomers detach from the tip of the growing filament is k_{off}. Write a dynamical growth equation for the dynamics of $L(t)$ and find the solution. What is the steady-state length of the filament? Make a plot of the length as a function of time - you can attempt to figure out reasonable choices of the parameters by looking at book.bionumbers.org or by looking at PBoC, but give an explanation of your choices. Also, compare and contrast the analysis here with that done in class for the constitutive promoter.