

APh161: Physical Biology of the Cell
Homework 5, part B
Due Date: Monday, March 9, 2009

“A traveler who refuses to pass over a bridge until he has personally test the soundness of every part of it is not likely to go far; something must be risked, even in mathematics.” – Horace Lamb

Reading:

Read section 19.3 of Physical Biology of the Cell (PBOC).

- 1. Repressilator (handed out as HW5, part A).**
- 2. Computing the messenger RNA distribution moments.**

In class, I worked out the master equation for the mRNA distribution for a one-state promoter. In this problem, you will do a few manipulations to further explore this idea.

(a) Write a pedagogical derivation of the master equation for the one-state model. Then, show that the Poisson distribution is a solution to our master equation. This means that we are testing the trial solution

$$p(m) = \frac{e^{-\lambda} \lambda^m}{m!}. \quad (1)$$

I am asking you to plug this into the master equation and verify that this solves the master equation. What choice do you have to make for the parameter λ in order for this to work out?

(b) Compute both the mean and the variance of this distribution. The way I would do this is by the trick of differentiation with respect to a parameter - in this case take a derivative with respect to λ . (If you don't recall this idea of differentiating with respect to a parameter, see the solutions to problem 3(c) on homework 4 and also look at eqn. 13.36 of PBoC for using the trick

in the case of an integral, rather than the sum you will do here).

(c) In class, we also sketched how the calculation of the moments of the mRNA distribution would go in the case of a promoter that has two states, an active state and an inactive state. Assume that in the inactive state there is no transcription. Write the two master equations for $p_A(m, t)$ and $p_I(m, t)$. Now generalize the steps we took for the one-state promoter leading to the various moments, now using the notation $\mu_A^{(j)}$ and $\mu_I^{(j)}$ for the j^{th} “partial moments”. In particular, find the equations that link the different moments in steady state and find expressions for the zeroth, first and second moments. Compare and contrast the ratio of the variance to the mean in this case. In particular, prove that the ratio of the variance to the mean can be written as

$$\frac{\sigma^2}{\mu^{(1)}} = 1 + \mu^{(1)} \times \frac{k_{off}}{k_{on}} \times \frac{\gamma}{(k_{on} + k_{off} + \gamma)}. \quad (2)$$

Examine the paper by Golding *et al.* posted with the homework. From the first part of the problem, you should notice that the ratio of the variance to the mean for the one-state promoter (i.e. for a Poisson process) is 1. However, the experiments of Golding *et al.* shown in their fig. 2D illustrates that the ratio of the variance to the mean is a value closer to four which they interpret as saying that there are several processes in play, namely, the switching back and forth between the active and inactive states and the production of mRNA when in the active state. Examine fig. 2D and fig. 3A. Fig. 2 sheds light on the rates that appear in our expression for the ratio of the variance and the mean for the two-state promoter when the promoter is fully induced. Is our model consistent with the observation by Golding *et al.*?

3. Scaling and the Fly Embryo?

In this problem, we will begin to explore one of my favorite problems in biology. In particular, when multiple cells interact (for example in multicellular organisms, but even in biofilms which are bacterial collectives), different patterns of gene expression are observed at different points in the organism. This raises the question of what mechanisms lay down positional information. This is a hot research topic that is laden with all sorts of controversy and polemics. As a result, our goals are more humble. We will try to see how one of the early ideas in the field, that of a morphogen gradient, characterizes

the laying down of positional information. Our window onto the topic will be to contrast the patterns of gene expression in different species of flies.

To get started read section 19.3.4 of PBoC (and the discussion in section 2.3.3 in PBoC) to learn a little bit about the laying down of the fly body plan along its long axis (the so-called anterior-posterior axis). Then, read the paper from PNAS by Gregor *et al.* posted with this homework and write a one paragraph summary of the experiment and what they learned. We are going to think about one particular feature of this experiment. One of their intriguing findings is the property of “scaling”, namely, that different fly species have patterns of gene expression that appear at the same *fractional* coordinate along the anterior-posterior axis of the fly (see their fig. 2). In this problem, you will explore why this is a challenging observation when viewed from the perspective of the morphogen gradient model and some of the ideas that have been put forth to think about this problem and what their shortcomings are.

The morphogen idea (see Lewis Wolpert, 1969) argues that there is some diffusible substrate that provides the “signal” that sets the threshold for gene expression. In the fly case, the bicoid protein has been implicated in the patterning along the anterior-posterior axis and our aim is to think about bicoid using the morphogen idea. The first idea we will pursue is to use a “reaction-diffusion” equation to consider the claim that if the genes are turned on for all values of the morphogen greater than some critical value, then as we pass from anterior to posterior along the fly, we will reach a point at which the gene is no longer turned on because the morphogen concentration has fallen below the critical concentration.

(a) Explain in your own words and by doing the relevant math the logic culminating in eqn. 19.70. Let’s now assume that once the concentration falls below some concentration (for the sake of argument, let’s say $[Bcd]_0/2$), the genes of interest will be turned off. This is actually not quite correct since the expression patterns we are really interested in are stripes, but for simplicity, we are going to work with this simple argument. Consider a species with an embryo of length L and make a sketch of the distribution of bicoid along the long axis and label the value of x at which the concentration falls below the threshold. Now, make a second sketch, this time for a species with length

$2L$ and *assuming* (explain why these might be reasonable assumptions) that the diffusion constant and degradation rate are the same as those for an embryo of length L , and sketch where along the fly the concentration will have dropped below threshold. What do you conclude from this result? What suggestions do you have about what might be going wrong with this model and how might you test these ideas (and what do Gregor *et al.* have to say about it)? One idea that has been pursued is the idea that the gradient is read out before steady-state is reached (to learn more about that see the paper by Bergmann *et al.* from PLoS Biology also posted with this homework).

(b) One of the ideas that people considered as a fix for the shortcomings of the approach described in part (a) concerning the behavior of the reaction-diffusion process is to include a *nonlinear* degradation so that the relevant equation now becomes

$$D \frac{d^2[Bcd]}{dx^2} - \alpha[Bcd]^2 = 0. \quad (3)$$

First, show that the trial solution

$$[Bcd](x) = A(x + \epsilon)^\gamma \quad (4)$$

satisfies the differential equation for a particular choice of γ . Assume that the concentration of bicoid at the origin is $[Bcd]_0$ and solve for the unknown constants ϵ and A . Then sketch the concentration (you might want to use Mathematica or Matlab to actually plot the function first to see what it looks like) and discuss the issue of scaling in this case. To learn more about this you can consult chap. 8 of the book by Uri Alon that is one of the “suggested reading” books for the course.

4. Membrane Biophysics.

Do problem 11.6 from PBoC.

5. Chap. 17 problem - biological electricity.

do problem 17.5 of PBoC.