

Cold Spring Harbor Laboratory: Physical Biology of the Cell Homework 1 Due Date: Tuesday, March 4, 2015

“Doubt is the father of creation.” - Galileo Galilei

1. Number of mRNA

In this problem, we are going to work our way through an estimate of the number of mRNA molecules found in a bacterium and in a yeast cell. The idea of the estimate is to try to figure out over the entire set of genes in the organism, how many *total* copies of mRNA will be found in the cell. To do the estimate, we will first consider the case of a bacterium and then for yeast, we will make the assumption that things play out the same way and simply scale up our bacterial estimate. Our starting point is the number of proteins in a cell, which for a bacterium we take to be 3×10^6 . This means that in order to make a new cell, this many proteins have to be synthesized in the 1000-3000 s of the cell cycle (depending upon growth conditions). If the ribosome translates at a rate of 20 aa/s, figure out a range of values for how many proteins each mRNA can crank out per minute. The range comes from how tightly packed the ribosomes are. What is the highest rate at which translation could occur (hint: think about the size of the ribosome and how tightly packed they can be)? Now use this to estimate the total number of mRNAs that are needed to supply the protein needed during a cell cycle. Provide estimates for both bacteria and budding yeast.

2. Hill functions, the good, the bad and the ugly.

As discussed in class, a Hill function is of the form

$$p(x) = \frac{\left(\frac{x}{K_d}\right)^n}{1 + \left(\frac{x}{K_d}\right)^n}. \quad (1)$$

This function is used generically in the biological literature for a host of different processes where x is concentration and $p(x)$ could be the binding probability as a function of concentration, the activity of some molecule as a function of concentration or the probability that a ligand-gated ion channel is open as a function of concentration. Said differently, people are very

indiscriminate in their uses of this function which ultimately makes it little more than an unsubstantiated fitting scheme.

(a) Plot such a function for the cases of $n = 1, 2$ and 4 . Comment on what the “Hill coefficient” tunes.

(b) Imitating the argument for p_{bound} given in class and provided in Section 6.4.1 of PBOC2, consider a reaction involving a receptor with two binding sites. Imagine the reaction



where the notation L_2R means that the receptor is doubly bound. If we define the dissociation constant as

$$K_d^2 = \frac{[L]^2[R]}{[L_2R]}, \quad (3)$$

imitating the argument given in Section 6.4.1 of PBOC2, show that we find

$$p_{bound}([L]) = \frac{\left(\frac{[L]}{K_d}\right)^2}{1 + \left(\frac{[L]}{K_d}\right)^2}. \quad (4)$$

Interpret what it means to assume the chemical reaction in eqn. 2. Specifically, what does this whole procedure say about the states of single occupancy?

(c) Now let’s redo the problem “correctly” by accounting for all of the states and their corresponding weights. What are the allowed states of this two-site receptor? Using our statistical mechanics approach described in class for simple ligand-receptor binding, work out the states and weights and find expressions for the probability of the empty state $p_0([L])$, the singly-occupied states $p_1([L])$ and the doubly occupied state $p_2([L])$. For the energy of the doubly occupied state, consider a total energy of the form $2\epsilon_b + \epsilon_{int}$, where ϵ_{int} is an “interaction energy” that imposes cooperativity in the binding. To do this problem and to make plots you will need to ascribe actual energies. Consider the case where $\epsilon_b = -5 k_B T$ and $\epsilon_{int} = -2 k_B T$. Make a single plot using Matlab that has p_0 , p_1 and p_2 . Use a log axis on the x-axis.