CALIFORNIA INSTITUTE OF TECHNOLOGY
Biology and Biological Engineering (BBE)

BE 150

M. Elowitz and R. M. Murray
Spring 2014

Problem Set #5

Issued: 1 May 2014
Due: 15 May 2014

1. (Stochastic simulations)

   For this problem, we return to our standard model of transcription and translation process.

$$0 \underset{\delta_m}{\overset{k_1}{\rightleftharpoons}} \mathrm{M}$$
$$\mathrm{M} \xrightarrow{\gamma} M + \mathrm{P}$$
$$\mathrm{P} \xrightarrow{\delta_p} 0$$

   where M is the mRNA concentration, P is the protein concentration.

   (a) Simulate the stochastic system above until time $T = 100$ using Simbiology or Matlab. Use the following parameters: $k_1 = 1, \delta_m = 0.5, \gamma = 5, \delta_p = 0.1$. Plot the resulting number of mRNAs and protein over time. (Hint: In Simbiology, you need to make sure all the kinetic rates are Mass Action, and set the solver to stochastic (Simulation Settings $\rightarrow$ Solver $\rightarrow$ stochastic)).

   (b) Now assume that the proteins are degraded much more slowly than mRNA and the rate of protein degradation is 0.01. To maintain similar protein levels, the translation rate is now 0.5. Simulate this system as above. What difference do you see in protein level? Comment on the effect of protein degradation rates on noise.

   (c) Take the final value of the protein concentration in parts (a) and (b) and create a histogram showing the distribution of expression levels. Fit this to a gamma distribution and compute the mean and variance of the resulting gamma distribution.

2. (Selection stringency and noise)

   Consider a population of cells that express a flourescent protein. Flourescent protein expression level is controlled by one of types of two promoters. While the mean expression level of the promoters is roughly the same, their noise level is different. This problem explores the effect of different selection stringencies on the noise in a population of cells under selective pressure.

   (a) To create a population of cells, start with 100 cells where each cell has a genotype (μ_i, σ_i). Draw each μ_i from a normal distribution with a mean of 100 and a standard deviation of 5. To simulate the "high noise" and "low noise" populations, draw σ_i randomly from one of two normal distributions (mean = 5, standard deviation = 0.5 OR mean = 15, standard deviation = 1.5).

   "Grow" the population of cells from this starter population by generating 100 different phenotypes for each genotype using a normal distribution with mean, μ_i and standard deviation, σ_i. Let each of these values correspond to the FP expression level of a cell

single cell. Make sure you keep track of the genotype of each of the descendant cells. Plot a histogram of FP levels for your population of cells.

(b) Perform "selections" of varying stringency on your cell population by taking the cells with the top 1%, 5% and 25% of FP levels. "Regrow" these cells in an unbiased manner until you reach your initial population level (i.e. pick a parent from your selected population at random then use it's genotype to generate a new cell phenotype, you can assume that the genotype stays the same).

(c) What is the mean expression level for each of your new populations? What is $< \sigma_i >$ for each of them? Plot a histogram of σ_i to compare the differences in noise between selection conditions. What is effect does selection stringency have on noise levels? (You might want to run this a few times to confirm trends)

(d) Explain how this might affect how you do selections in a directed evolution experiment.

3. (Two-sided diffusion; Alon 8.1)

A morphogen is produced at both boundaries of a region of cells that ranges from $x = 0$ to $x = L$. The morphogen diffuses into the region and is degraded at rate α.

(a) What is the steady state concentration of the morphogen as a function of position? Assume that the concentration at the boundaries is $M(0) = M(L) = M_o$. Under what conditions is the concentration of morphogen at the center of the region very small compared to M_o?

Hint: The morphogen concentration obeys the following reaction-diffusion equation at steady state:

$$D\frac{d^2M}{dx^2} - \alpha M = 0$$

The solutions of this equation are of the form

$$M(x) = Ae^{-x/\lambda} + Be^{x/\lambda}.$$

Find λ, A, and B that satisfy the diffusion-degradation equation and the boundary conditions.

(b) Simulate the system and create a plot of the morphogen profile with three different initial amounts of M_0. It should be a graph of position versus morphogen concentration. How do different concentrations of initial morphogen affect the distribution profile?

(c) Now simulate the system when λ is halved. Again simulate with three different initial concentrations of M_0. What changes do you observe?

4. (Polynomial self-enhanced degradation; Alon 8.3)

Find the steady state concentration profile of a morphogen produced at x=0. The morphogen diffuses into a field of cells, with nonlinear self-enhanced degradation described by:

$$\frac{dM}{dt} = D\frac{d^2M}{dx^2} - \alpha M^n$$

When is patterning with this profile robust to the level of M at the boundary, M_o?

Hint: Try a solution of the form $M(x) = a(x+b)^m$ and find the parameters a and b in terms of D, M_o, and α.

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Bi 250b

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   (a) Say you perform a selection by picking out the top $n\%$ brightest cells and regrowing the population. How would you expect the tightness of your selection (i.e. picking the top 5% brightest cells vs. picking the top 25% brightest cells) to affect your mean fluoresence levels if you grow each population to the same level as your initial population? How would this affect the expression noise level of each population?

   To get a better idea of the numbers involved you can estimate the number of cells that will be selected for a certain percentile using the following command in MATLAB:

```
5000*(1-normcdf(X,mu,sigma))
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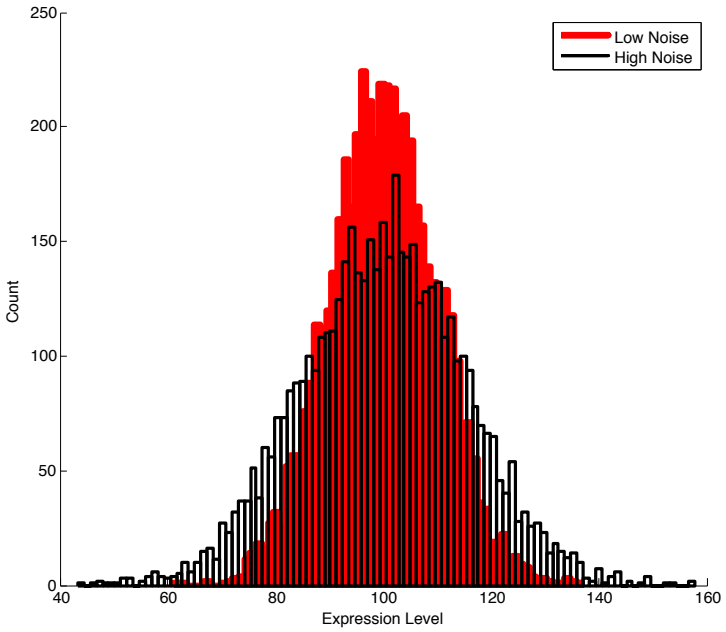
where X is the fluorescent protein expression cutoff you want, mu=100 , and sigma=10 for the low noise population and 15 for the high noise population. What is the ratio between high-noise cells and low-noise cells if your protein expression level cutoff is 110 units? 130 units?



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