CALIFORNIA INSTITUTE OF TECHNOLOGY
Bioengineering

Bi 250b

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Winter 2012

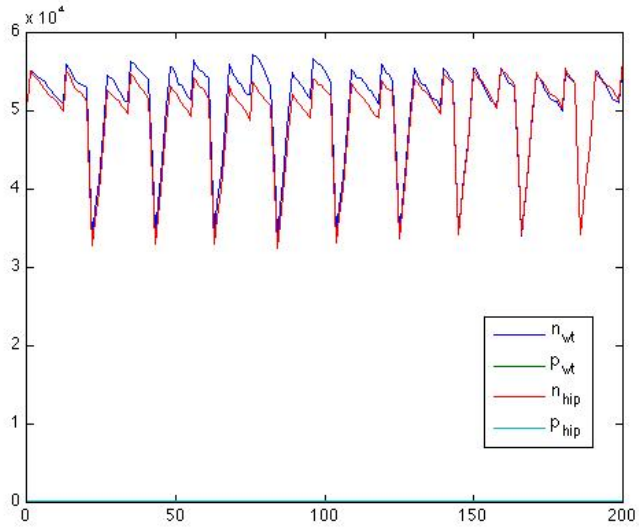
Problem Set #6

Issued: 16 Feb 2012
Due: 24 Feb 2012

1. *Bacterial persistence.* (Based on Kussell et al., Genetics, 2005.)

   Suppose you are conducting an experiment in which you are studying the evolution of a wild type and hipQ mutant strain of *E. coli* in the presence of two possible environments, corresponding to the presence of antibiotic (stress condition) or absence of antibiotic (growth condition). This population consists of normal and persister bacterial cells that are able to switch to the other type spontaneously. The hipQ strain exhibits a 1000-fold higher rate of switching from normal cell to persister.

   The plot below is the result of a simulation of the evolutionary dynamics of wild type and hipQ normal and persister cells given that there is a cycle of a 20.5 hour growth condition followed by a 2.5 hour stress condition, starting with 50,000 wild type cells and 50,000 hipQ cells for 200 hours.



   (a) Describe the results of the simulation. Describe in a few sentences the algorithm for this simulation (see paper).

   (b) Explain the differences between the stochastic simulation results from the paper and deterministic simulation from part a).

2. *Coordinated Response and Frequency Modulation* (Based on Cai et al., Nature, 2008.)

   One alternate explanation to the coordinated gene response observed in the paper is if the downstream genes controlled by Crz1 all have the same input function. How would you experimentally distinguish between this and a model that uses frequency modulation?

3. *Selection Stringency and Gene Expression Noise*

Consider a population of cells that express a fluorescent protein. Fluorescent 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) 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:

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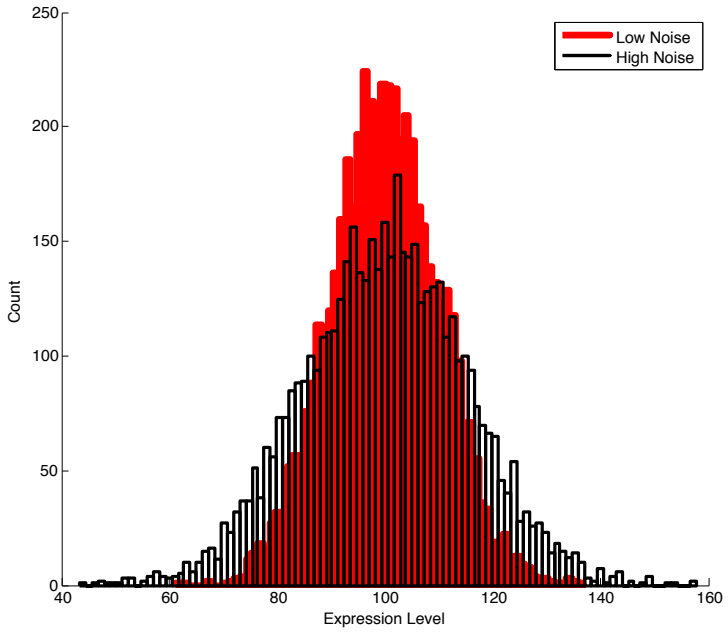
where X is the fluorescent protein expression cutoff you want, mu=100 , and sigma=10 for the low noise population and 15 for the high noise population. What is the ratio between high-noise cells and low-noise cells if your protein expression level cutoff is 110 units? 130 units?



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