

# Exercise sheet 11

## Systems Biology class 2014

June 18, 2014

Return to during classes, tutorials, office hours to Jean Hausser or in the envelope outside room 612 in the Wolfson building until June 22th 2014.

### 0 The demand rule applied to different systems

1. Which mode of regulation would you predict according to the demand rule?
  - (a) a transport system that brings an amino acid (aa) into the cell when the aa is rare in the environment
  - (b) a transport system that brings an aa into the cell when the aa is common in the environment
  - (c) a biosynthesis system that makes an aa from scratch when the aa is rare in the environment
  - (d) a biosynthesis system that makes an aa from scratch when the aa is common in the environment
2. What can you say about the mode of regulation of a transport system and a biosynthesis system for the same aa, regardless of whether the aa is common or rare?
3. What can you say about the mode of regulation of a transport system for a sugar and the mode regulation of an enzyme that cuts the sugar into smaller pieces for use in metabolism regardless of whether the sugar is common or rare?
4. Many bacterial genes with common function are transcribed on the same mRNA, called an operon. How does this correspond to demand rules?
5. A gene is regulated by three transcription factors, each with its own binding site.
  - (a) In the environment, the gene is needed at its maximal level most of the time. What is the predicted mode of the three regulators. which expression state is most error prone?
  - (b) The gene is regulated by two repressors and an activator. They have an additive effect: the expression level is 8 when only the activator is bound, none of regulators binding leads to level 5, and every repressor binding drops expression by one unit.  
What is the most common expression level in the environment? What is the most error prone expression level?

### 1 Optimization versus historical precedent

Imagine a population of organisms with a regulatory mechanism in place for a certain gene. Conditions change, and the demand for the gene in the new environment is  $p$  ( $0 \leq p \leq 1$ ). Expressing the gene in high amount when it should be lowly expressed yields a penalty on the fitness  $\Delta f_0$  compared to when the regulator binds the promoter. On the other hand, failing to express the gene when it is needed in high amount gives a penalty  $\Delta f_1$ , relative to when the regulator is bound to the promoter. Mutants with the opposite mode of regulation arise in the population, but they can only replace the original population if their fitness advantage exceeds a minimal value  $s_{\min}$ .

1. Assuming that the gene is initially regulated by a repressor, show that a mutant that regulates the gene by an activator will take over the population if

$$p > \frac{s_{\min} + \Delta f_0}{\Delta f_1 + \Delta f_0}$$

2. Assuming that the gene is initially regulated by an activator, show that a mutant that regulates the gene by a repressor will take over the population if

$$p < \frac{\Delta f_0 - s_{\min}}{\Delta f_1 + \Delta f_0}$$

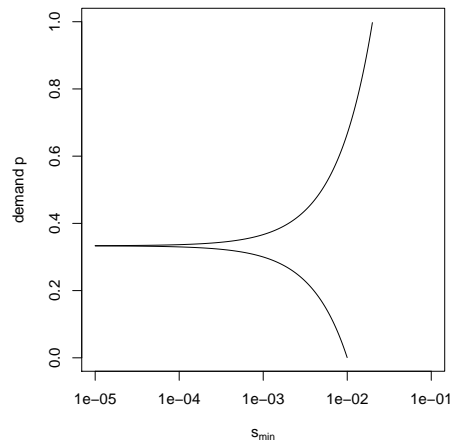


Figure 1:

Figure 1 represents the curves  $p = \frac{s_{\min} + \Delta f_0}{\Delta f_1 + \Delta f_0}$  and  $p = \frac{\Delta f_0 - s_{\min}}{\Delta f_1 + \Delta f_0}$  as a function of the minimum fitness advantage  $s_{\min}$  for  $\Delta f_1 = 2\%$  and  $\Delta f_0 = 1\%$ .

3. Label each area of the plane with the regulator that will be preferred. When is the mode of regulation determined by historical precedent? In 1 – 2 sentences, propose a biological interpretation.
4. In *E. coli*,  $s_{\min}$  is typically in the  $10^{-7} - 10^{-8}$  range. Under these conditions, is it likely that the historical precedent will determine the mode of regulation?

## 2 Demand rules for developmental genes

Consider a cell which, during the developmental process of the organism, can assume either fate *A* or fate *B*. A set of genes  $G_A$  is expressed in fate *A* and not in fate *B*, and a different set  $G_B$  is expressed in fate *B* and not in *A*. This cell-fate decision is regulated by two transcription-factors *X* and *Y*. *X* activates its own transcription and represses the transcription of *Y*, whereas *Y* activates its own transcription and represses the transcription of *X*. Furthermore, *X* transcriptionally activates  $G_A$  and represses  $G_B$ , and *Y* has the opposite effect, activating  $G_B$  and repressing  $G_A$ . Finally, the activity of *X* and *Y* also depends on environmental signals like hormones, but we will neglect those in this exercise.

1. Draw the transcription network in this case.
2. Explain the mode of regulation of the genes *X*, *Y*,  $G_A$  and  $G_B$  in terms of the demand rule.

## 3 Error-load of variability in protein expression (optional)

The expression of proteins varies from cell to cell due to different factors, such as intrinsic the randomness in the chemistry of gene expression. As a result, cells deviate from the optimal expression level. In this exercise we will calculate the average reduction in fitness due to these variations for the case of the *lac* system (see Figure 2). The fitness function for this exercise is  $f(Z) = \gamma Z - \frac{\eta Z}{1 - Z/M}$ , similar to the function we studied in lecture 7, where  $\gamma$  is the benefit per protein *Z*,  $\eta$  is the cost of producing *Z*, and *M* is the maximum expression capacity.

1. Show that the average reduction in fitness due to small cell-cell variations of *Z* around  $Z_{\text{opt}}$  is

$$\Delta f = C \langle (Z - Z_{\text{opt}})^2 \rangle$$

where *C* is the curvature of the fitness function near its maximum  $C = \frac{1}{2} \frac{d^2 f}{dZ^2}$  and the brackets  $\langle \rangle$  denote a population average. Hint: use a Taylor expansion of *f* near its maximum  $Z_{\text{opt}}$ .

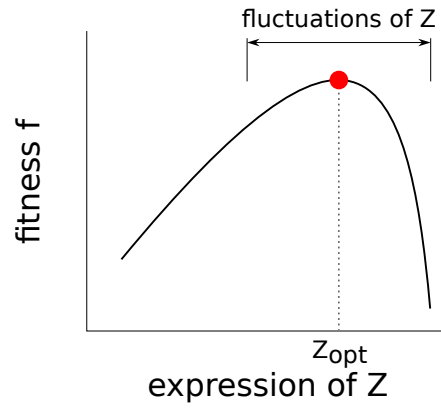


Figure 2:

2. Assuming that the lac system is fully induced ( $Z = Z_{max}$ ) and that the average value of  $Z$  in the population is  $Z_{max}$ , compute the mean reduction in fitness due to variations in  $Z$  in the fully induced state. When the *lac* promoter is fully induced, the coefficient of variation (standard deviation divided by the mean) in the expression of the  $Z$  protein is about  $V = 0.1$  (Elowitz et al., Nature 2002). The other parameters are  $\gamma = 0.17Z_{max}^{-1}$ ,  $\eta = 0.02Z_{max}^{-1}$  and  $M = 2Z_{max}$ .