Exercise sheet 7
Systems Biology class 2014

May 14, 2014

Print and return to during classes, tutorials or office hours to Jean Hausser until May 18th 2014.

1 Optimality of LacZ expression

In the class, we learned about the cost and benefit of the lac system of E. coli under defined experimental conditions. The cost was

$$c(Z) = \frac{\eta Z}{1 - Z/M}$$

where η is a constant and M is the upper limit of expression. The benefit was

$$b(Z, L) = \delta Z \frac{L}{K + L}$$

where K is the Michaelis-Menten constant and δ is the maximum growth advantage per Z molecule. Fitness, defined as normalized exponential growth rate, is $f = b - c$.

1. Find an expression for the optimal protein level Z_{opt} as a function of L. Note that the optimal Z_{opt} can be found by the point at which $\frac{df}{dZ} = 0$. Sketch this function.
2. Find the minimal lactose level at which Z_{opt} is greater than zero, L_c. Explain why, if $L < L_c$, you might expect the cells to eventually lose the lac system.
3. How does L_c depend on the parameters η and δ? Explain the biological implication.
4. A mutant arises which increases the value of M. What would happen to Z_{opt}? Explain the biological implication.
5. We run an experiment in which we perform serial dillutions of E. coli into fresh medium. At every dillution, we measure the average amount of protein Z per bacteria. We start on day d_0 with a population of wildtype E. coli and a concentration of lactose larger than what bacteria are exposed to in their normal environment. On day d_1, we notice that the average amount of protein Z per bacteria does not change from one dillution to the next anymore. At that time, we alter the the medium so that the lactose concentration is lower than the concentration bacteria are exposed to in their normal environment.

   Sketch the average amount of protein Z per bacteria as a function of time.

2 Limiting substrate

Protein X is an enzyme that acts on a substrate to provide fitness to the organism. The substrate concentration is L.

1. Write the fitness function $f(X, L)$ assuming linear cost, $c(X) = \eta X$, and a benefit that is a Michaelis–Menten term, $b(L, X) = b_0 L \frac{X}{X+K}$, appropriate for cases where the substrate, rather than the enzyme X, is limiting. Calculate the optimal enzyme level as a function of L and K.
2. What is the minimal substrate level L_c required for maintenance of the gene for X by the organism? When is the gene lost? Explain.

3 Optimal expression of a subunit

Multiple units of protein X act together in a multi-unit complex. The benefit is a Hill function,

$$b(X) = b_0 \frac{X^n}{K^n + X^n}$$

and the cost function is $c(X) = \eta X$. The relative fitness is $f = b - c$.

In the case of this relative fitness function f, there is no explicit analytical expression for the amount of protein X_{opt} that maximizes f. Therefore, we will approach this optimality problem in two steps: we will start by a qualitative analysis to get an intuitive understanding of the problem, and then verify our intuition numerically with Matlab.

1. On the same plot, sketch the cost and benefit as a function of X. Explain qualitatively how the optimal protein level X_{opt} depends on η. For values of η that lead to an optimal protein level X_{opt} larger than 0, propose a reasonable lower bound for X_{opt} based on the parameters (b_0, n, η, K). Hint: one parameter may be sufficient to get a rough estimate of X_{opt}.

2. Using Matlab, find the optimal protein concentration X_{opt} assuming $n = 3, b_0 = 10, \eta = 2, K = 2$. Is X_{opt} in the range of the rough estimate you proposed in the previous question?

   Hints: use the `fminsearch` function in Matlab, which finds the *minimum* of a given function. The script `findMin.m` on the course website shows how to use `fminsearch`. Remember that maximizing $f = b - c$ is equivalent to minimizing $-f = c - b$.

3. Now assume that protein X brings benefit to the cell only when its concentration exceeds X_0, so that $b(X) = b_0\theta(X \geq K)$, where θ is the step function:

   $$\theta(X \geq K) = \begin{cases} 1 & X \geq K \\ 0 & X < K \end{cases}$$

   Determine graphically the optimal expression level of X. Is it comparable to the values you obtained in the two previous questions?