7.32/7.81J/8.591J: Systems Biology

Fall 2013

Exam #1

Instructions
1) Please do not open the exam until instructed to do so.
2) This exam is closed-book and closed-notes.
3) Please do all problems.
4) Use the back of sheets if you need more space.

Name:

Scores

1: (out of 9)

2: (out of 14)

3: (out of 16)

4: (out of 12)

5: (out of 10)

6: (out of 14)

7: (out of 11)

8: (out of 14)

Total (out of 100):

1) Negative autoregulation (9 points)

Consider a gene X which represses its own expression. We will use the logic approximation, such that the concentration rate of production is β when $[X] < K$ and 0 otherwise. Let α be the effective degradation of protein X. For what values of α, β, and K is $[X]_{eq}$ robust against variations in α, β, and K?

Variations in α (3 pt):

Variations in β (3 pt):

Variations in K (3 pt):

2) Oscillations in Negative autoregulation (14 points, 2 pages)

a. Consider a protein represses its own expression such that the differential equation describing the concentration of p is: $\dot{p} = \frac{\alpha}{1+p^n} - p$

Under what parameter range will this self-repression lead to oscillations? Is the fixed point stable or unstable? (4 pt)

b. Now consider the slightly more complicated model in which we directly model transcription:

$$\dot{m} = \frac{\alpha}{1 + p^n} - m$$
$$\dot{p} = -\beta(p - m)$$

What is the fixed point of this pair of equations? (2 pt)

c. Use linear stability analysis to determine the conditions (if any) in which this fixed point becomes unstable, leading to oscillations. (6 pt)

d. How could this model be modified to enhance the ability to lead to oscillations? (2 pt)

3) Network growth (16 points plus 5 points extra credit, 2 pages)

Consider the Barabasi model of network growth that leads to power law distributions of the degree distribution. Starting with m_0 nodes, at each time point add one node and randomly connect it to m existing nodes with probabilities proportional to the existing number of edges (first round connect at random).

a. What is the total number of edges in the network at time t? (2 pt)

b. What is the sum of the number of connections (i.e. degree) over all nodes at time t? (2 pt)

c. If node i was added to the network at time t_i then how does the expected number of edges from that node (k_i) grow with time? (6 pt)

Now we will consider a model in which there is network growth but no preferential attachment. Instead, we will assume that new nodes attach to the existing nodes with equal probability independent of the number of connections that a node has

d. Does this model without preferential attachment lead to a random Erdos-Renyi Network? Why or why not? (2 pt)

e. In this new model, if node i was added to the network at time t_i then how does the expected number of edges from that node (k_i) grow with time? (4 pt)

EXTRA CREDIT. Demonstrate that for long times this model does not lead to a power law distribution but instead to a distribution that falls off exponentially with the number of connections. (5 pt extra credit)

4) Analysis of network motifs (12 points). For this problem, an arrow will signify either positive or negative regulation. In Uri Alon's book/paper, he studied the transcriptional network of E. coli, which had N = 424 nodes (genes) and E = 514 edges (interactions). For each of the four examples given below, answer the following three questions:

    a. Draw the sub-network (1 pt for each)

    b. Given a random Erdos-Renyi network, how many of each of the following sub-graphs do you expect to see? (1 pt for each)

    c. Is the indicated subgraph a network motif in this system? (1 pt for each)

As a reminder, $\langle N_G \rangle = \frac{1}{a} N^n p^g$, where p is the probability of an edge being realized.

a. Autoregulation (3 pt)

b. Toggle-switch (3 pt)

c. Repressilator (3 pt)

d. Feed-forward loop (3 pt)

5) Pulse generation (10 points total)

a. Which Feed Forward Loop can generate a pulse of Z in response to the signal Sx appearing? (3 pt)

b. In this network motif, how should the transcription factors X and Y levels be combined at the Z promoter? Please fill in the logic table below. (2 pt)

X	Y	Z
0	0	
0	1	
1	0	
1	1	

c. If at time t= 0 the signal Sx appears and activates the transcription factor X (which is already at steady state), draw the following as a function of time: X, X*, Y* (assume Sy always present), Z. (5 pt)

6) Protein bursts (14 points total)

Assume that after an mRNA is transcribed that it is degraded at rate δ and translated at rate r.

a. What is the (normalized) probability distribution $p_{first}(t)$ that describes the time in which the first of these reactions will occur? (3 pt)

b. What is the probability ρ that a protein will be translated before the mRNA is degraded? (2 pt)

c. What is the probability distribution p(n) describing the probability that the mRNA will produce n proteins? (3 pt)

d. Assume that the probability ρ from part (b) is 0.5. In addition, assume that two mRNA are produced in quick succession. The resulting protein burst is then from the proteins transcribed from both of these mRNA. What is the probability that the combined protein burst has the following sizes? (6 pt)

P(n=0):

P(n=1):

P(n=2):

P(n=3):

P(n=k):

7) Master Equation (11 points total)

Consider the following model of negative autoregulation:

$$\dot{n} = \frac{\beta K}{K+n} - \alpha n,$$

where n is the number of proteins in the cell and K is the number of proteins at which there is half repression of the promoter.

a. Using the Master Equation formalism, write an expression for how the probability of having n proteins changes with time. (2 pt)

b. Assume that β = 1 min^{-1}, α = 0.1 min^{-1}, and K = 10 proteins. If at time t = 0 we are told that the cell starts such that p(n=20) = 0.5, p(n=21) = 0.5, what is the probability distribution of states a short time Δt = 0.01 min later? Keep all terms that are on the order of Δt. (5 pt)

c. If we now wait a long time until the system reaches equilibrium, what is the ratio $\dfrac{p(n=20)}{p(n=21)}$?

(4 pt)

8) Cooperatively binding transcription factor (14 points total)

a. Consider a transcription factor X that dimerizes with dissociation constant K_X (units of concentration). What is the concentration of the dimer $[X_2]$ as a function of $[X]_T$, the total concentration of X? Simplify in the limit $[X]_T \ll K_X$ and in the limit $[X]_T \gg K_X$. Draw $[X_2]$ as a function of $[X]_T$. (7 pt)

b. Now assume that the dimer X_2 activates expression of gene Y, where the rate of expression is proportional to the fraction of time that the promoter is bound by the dimer. Assuming that the binding of the dimer has dissociation constant Kp and the maximal rate of expression is β, what is the mean rate of expression as a function of $[X]_T$? (3 pt)

c. Draw the mean rate of expression of gene Y as a function of $[X]_T$, for $K_p \ll K_x$ and for $K_p \gg K_x$. **Comment**. (4pt)

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