CALIFORNIA INSTITUTE OF TECHNOLOGY
Biology and Biological Engineering (BBE)

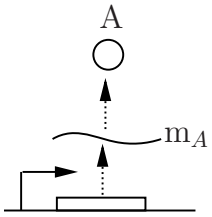
BE 150

M. Elowitz and R. M. Murray
Spring 2014

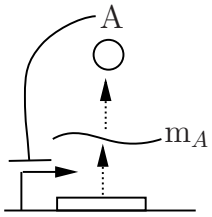
Problem Set #1

Issued: 31 March 2014
Due: 9 April 2014

1. (Negative autoregulation) Consider the two simple circuits shown below (from BFS, Figure 2.7), where the protein A is taken as LacI:



Unregulated expression



Negative autoregulation

β_m	mRNA production rate
γ_m	mRNA degradation rate
β_p	protein production rate
γ_p	protein degradation rate

   (a) Write down an ODE model for the *lacI* repressor circuit in the left figure, including dynamics for transcription and translation of *lacI*. Find the steady state value of the mRNA and protein concentration as a function of the parameters.

   (b) Write down an ODE model for the *lacI* negative autoregulated circuit in the right figure. Assume that the repressor can be modeled as a Hill function with Hill coefficient n, activation constant K and maximum rate of transcription α.

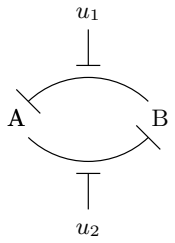
   (c) Pick parameters such that the open loop and closed loop systems have the same steady state. You can use the BioNumbers website `http://bionumbers.org/` as reference for picking parameters (be careful with units).

   (d) Write a MATLAB program (using the 'ode45' function) to simulate both systems starting from zero initial concentrations (of mRNA and protein), and plot concentrations of mRNA and protein for unregulated and regulated circuits as a function of time.

   (e) What is the response time of the *lacI* protein for unregulated and regulated circuits? Define the response time as the time it takes to reach 90% of the final steady state value, starting from zero initial concentration. Which circuit provides faster response?

2. (Toggle switch)

   Consider a positive transcriptional feedback loop composed of two negative interactions (from BFS, Figure 1.27), shown to the right. We will ignore the role of the inducers u_1 and u_2 for now. This system has two equilibrium states: one where the expression of A is high and B is low, and another where the expression of B is high and A is low.



   (a) Write an ODE model for the system above, modeling just the protein dynamics (no mRNA). Assume that the two transcription/repression mechanisms have the same dynamics and both proteins are degraded at the same rate $\gamma = 0.2$. Let the basal (unrepressed) transcription rate be $\beta_0 = 1$ and take the parameters of the Hill function to be $K = 2$ and $n = 2$.

(b) To solve for the steady states, create a two dimensional plot with the concentration of A on the x axis and the concentration of B on the y axis. Plot the *nullclines* for the system by solving $dA/dt = 0$ and $dB/dt = 0$ (i.e. solve for $A = g_1(B)$ from $dA/dt = 0$ and for $B = g_2(A)$ from $dB/dt = 0$ and then plot both solution curves). The steady states are given by the intersections of the two nullclines. (See BFS Section 3-5 for a brief discussion of nullcline analysis, if more information is needed.)

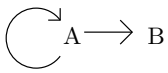
(c) Using the plot you created in part (b), shade the regions of initial conditions for which the solution will tend to each individual equilibrium point (use different colors or shading patterns for each equilibrium point that you find). A hand drawn sketch is fine (though you are welcome to use MATLAB or Mathematica if you want to get fancy).

(d) Use MATLAB to create a simulation model of the system and plot the time response of X and Y using the following two initial conditions:

$$(X(0), Y(0)) = (1, 4) \qquad (X(0), Y(0)) = (4, 1).$$

Draw these two trajectories on the plot you created in part (b) and verify that the solutions converge to the proper equilibrium point.

3. Consider the circuit shown below, in which the protein A positively autoregulates itself, as well as activates the expression of a second protein B.



Assume that A must dimerize in order to function as an activator (so A_2 is the actual activator).

(a) Using the MATLAB Simbiology toolbox, build a model for this system. You should hand in a printout of the reactions that you use in your model as well as the parameter values.

(b) Include a set of simulations showing the response of your system to different initial concentrations of the protein A using the appropriate parameters for *E. coli*. Empirically determine how many equilibrium points the system has, supported by your simulations.

(c) Find a set of parameters such that when the initial concentration of A is sufficiently low the circuit stays in the "off" state (low expression of B), while for sufficiently high initial concentration of A the circuit switches to the "on" state.

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Bi 250b

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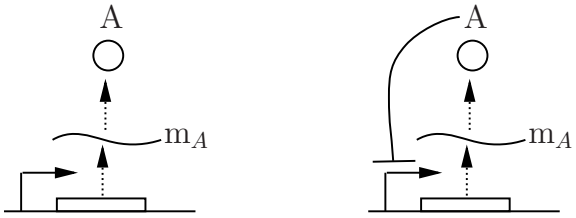


Unregulated expression Negative autoregulation

β_m	mRNA production rate
γ_m	mRNA degradation rate
β_p	protein production rate
γ_p	protein degradation rate

   (a) Build a SimBiology model of the unregulated system in the left figure. List the reactions for your model and indicate which of the parameters listed above correspond to the rate constants in your model.

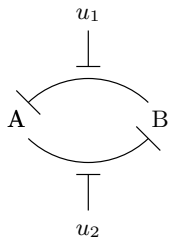
   (b) Build a SimBiology model of the negatively autoregulated system in the right figure. List the reactions for your model and describe the parameters, as you did for the unregulated system.

   (c) Use the BioNumbers website `http://bionumbers.org/` to find a realistic set of parameters for the circuits, assuming they are expressed in *E. coli*. Plot the concentration of the mRNA and protein as a function of time for each circuit and make sure that they make sense in terms of your understanding of gene expression dynamics in *E. coli*.

   (d) Estimate the response time of the *lacI* protein for unregulated and regulated circuits. Define the response time as the time it takes to reach 90% of the final steady state value, starting from zero initial concentration. Which circuit provides faster response?

2. (Toggle switch)

   Consider a positive transcriptional feedback loop composed of two negative interactions (from BFS, Figure 1.27), shown to the right. We will ignore the role of the inducers u_1 and u_2 for now. This system has two equilibrium states: one where the expression of A is high and B is low, and another where the expression of B is high and A is low.



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(c) Using the plot you created in part (b), plot arrows in the different regions of the plot indicating how the individuals concentrations of the proteins will change (increase or decrease, based on the sign of dA/dt and dB/dt). Use these arrows to shade the regions of initial conditions for which the solution will tend to each individual equilibrium point (use different colors or shading patterns for each equilibrium point that you find). A hand drawn sketch is fine (though you are welcome to use MATLAB or Mathematica if you want to get fancy).

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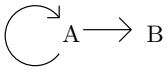

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