CALIFORNIA INSTITUTE OF TECHNOLOGY
Biology and Biological Engineering (BBE)

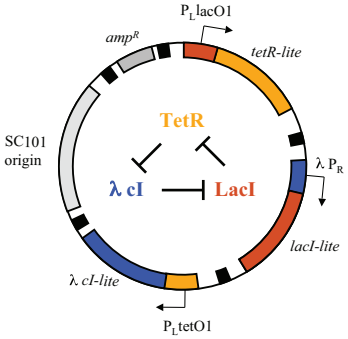
BE 150

M. Elowitz and R. M. Murray
Winter 2013

Problem Set #3

Issued: 23 Jan 2013
Due: 30 Jan 2013

1. (Repressilator modeling and robustness) The repressilator is a synthetic genetic transcriptional circuit that is design to produce a sustained oscillation in cells. A schematic diagram and simple differential equation model are shown below:



$$\frac{dm_1}{dt} = \frac{\alpha}{1+(\frac{p_3}{K_m})^n} - \delta m_1 \qquad \frac{dp_1}{dt} = \beta m_1 - \gamma p_1$$

$$\frac{dm_2}{dt} = \frac{\alpha}{1+(\frac{p_1}{K_m})^n} - \delta m_2 \qquad \frac{dp_2}{dt} = \beta m_2 - \gamma p_2$$

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   (a) Build a SimBiology model of the represssilator that captures the mRNA and protein dynamics shown to the right and simulate the system using the following parameters: $\alpha = 0.5$, $n = 2$, $K_m = 40$, $\delta = 0.0058$, $\gamma = 0.0012$, $\beta = 0.116$. (Note: you should use the "unknown" kinetic law in SimBiology to implement these dynamics.) Show that some (reasonable) initial conditions generate sustained oscillations while other initial conditions do not.

   (b) Suppose the protein half-life suddenly decreases by half. Which parameter(s) will change and how? Simulate what happens. What if the protein half-life is doubled? How do these two changes affect the oscillatory behavior?

   (c) Now assume that there is leakiness in the transcription process. How does the system's ODE change? Simulate the system with a small leakiness (say, 5×10^{-3}) and comment on how it affects the oscillatory behavior.

2. (Autoinhibition with transcriptional delay; based on Lewis, J., 200x, DOI 10.1016/S0960-9822(03)00534-7) Consider the following delayed differential equations:

$$\frac{dm(t)}{dt} = f(p(t-T_m)) - \delta m(t) \qquad \frac{dp(t)}{dt} = \beta m(t-T_p) - \gamma p(t)$$

   with

$$f(p) = \frac{k}{1+p^2/p_0^2}.$$

   The function $f(p)$ represents the action of the inhibitory protein as a dimer and the variables m and p are mRNA and protein concentrations. The parameter T_m is the delay from initiation of transcription and the arrival of mature mRNA into the cytoplasm, T_p is the delay from initiation of translation to the emergence of a complete functional protein. The parameters δ and γ are degradation of and mRNA and protein.

(a) Implement the delayed differential equation model above in MATLAB. Specifically, write a function which takes in the current and delayed protein and mRNA levels (assume these are known) as input and returns the vector $[dm/dt; dp/dt]$. Choose parameters from the paper to obtain sustained oscillations and plot the mRNA and protein concentrations. You can implement your own numerical integrator or use `dde.m` from the course website, which takes a function as one of its arguments.

(b) Comment on the robustness of sustained oscillations with respect to reduction in protein synthesis rate.

(c) Leave parameters as in a) and change only one parameter to obtain damped oscillations and plot mRNA and protein concentrations. Do not change the protein synthesis rate. Comment on how the change of parameter might affect damping of the oscillation.

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Bi 250b

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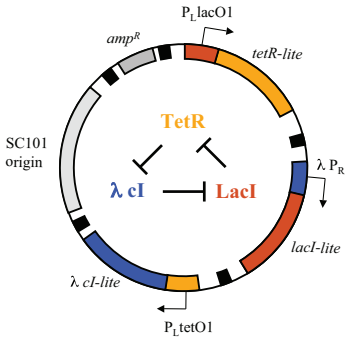

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