

Questions are listed below, and all answers must use your own words, no plagiarism, and cite the sources if necessary

1. Modeling a negative feedback system that uses tetramers for repression

Description and assumptions:

- Protein monomers dimerize, dimers bind to other dimers to form tetramers, and tetramers bind to DNA acting as repressors. Monomers and dimers do not bind to DNA
- Only monomers degrade and dimer/tetramer degradation is negligible
- Total amount of DNA, RNA polymerase, and Ribosomes is constant
- There is some level of basal expression (transcription rate β) when no repressors are bound
- Transcription is negligible when repressors are bound

- a) Draw a diagram/schematic of the feedback system
- b) Write down the reaction list for this system
- c) Write down the full mass action/ODE system of equations
- d) Write down the simplified 1-equation ODE system

(Note: do not focus on derivations, just guess at the correct answer in non-dimensionalized form, if you prefer. It will look somewhat similar to the form presented in the next question below. If you are interested, you can mathematically simplify equations to mRNA/Protein dynamics using QEA, then simplify equations to Protein only dynamics)

- e) In **short/plain language**, what assumptions were made in (d)?

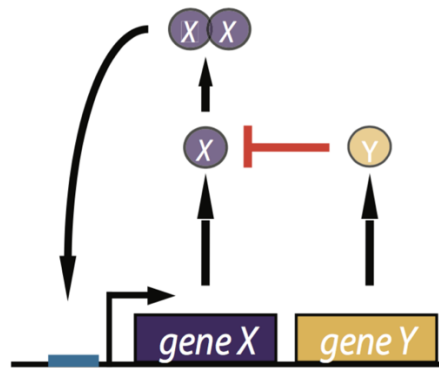
2. Positive feedback and bistability

This is a continuation of the exploration in the attached reference file. For the non-dimensionalized “+” feedback system below:

$$\dot{x} = \frac{(1 + ax^2)}{1 + x^2} - gx$$

- a) What type of feedback system(s) does this equation represent? Describe how the value of parameter “a” changes the behavior of the feedback system.
- b) Make a plot of the differential equation \dot{x} for values $a = 50$, $g=10, 13, 16, 19, 22, 25$ in Matlab
- c) Numerically find the fixed points (steady states) for **each of these curves**
- d) Determine which fixed points are stable/unstable and explain the reason.

3. Exploring oscillations in an activator-repressor system



- a) Write down the reaction list for the above positive/negative feedback system. mRNA dynamics description can be neglected if desired.

Hint: You can assume that monomers degrade and dimer degradation is negligible. You can assume the total amount of DNA, RNA polymerase, and Ribosomes is constant. Assume some level of basal expression (transcription rate β) when no activator (X_2) is bound to DNA.

- b) (short answer) Simplify the dynamics to protein only equations for x & y (monomers).

Hint: Since we didn't focus on derivations, just descriptively explain how things get simplified to this form below. mRNA dynamics can be assumed to be on a fast timescale compared to protein dynamics. m_{xy} is a scaling term that comes from non-dimensionalization - please explain the interpretation of each other term in the equations below:

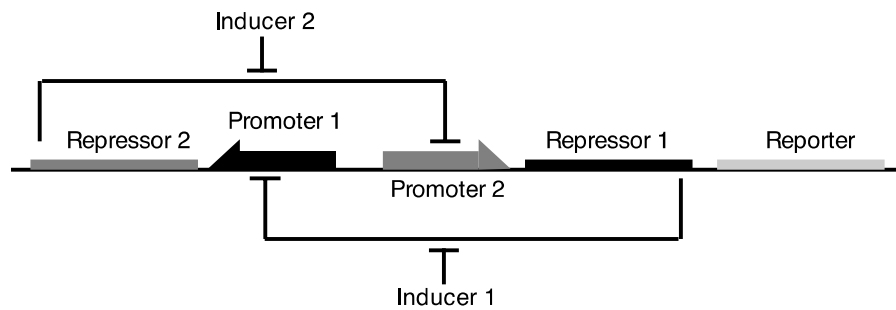
$$\dot{x} = \frac{1+ax^2}{1+x^2} - \gamma_x x - \gamma_{xy} xy \quad \dot{y} = \frac{m_{xy}(1+ax^2)}{1+x^2} - \gamma_y y$$

- c) Simulate the system using ode23 function in Matlab for two sets of parameters: one that oscillates and one that does not. Make a plot of x vs t . Parameter set [$a = 100, g_x = 0.5, g_y = 0.05, g_{xy} = 0.1, m_{xy} = 1$] can be used as a reference.

- d) Make a plot of phase portraits (x vs. y) for same two sets of parameters: one that oscillates and one that does not. (in Matlab)

4. Exploring a bistable toggle switch

See the diagram below showing a bistable toggle-switch from Gardner et al., Nature 2000



- a) In the paper, the authors have derived equations below. Explain in words what each term and parameter represent.

$$\frac{du}{dt} = \frac{\alpha_1}{1+v^\beta} - u \quad \frac{dv}{dt} = \frac{\alpha_2}{1+u^\gamma} - v$$

- b) Explore numerically and list some general requirements for conditions that leads to bistability of the system. In other words, what approximate conditions should each parameter in the equations above need to satisfy?
- c) In words, explain how a system that uses bistability as above acts as a “toggle switch”.
- d) Determine how the authors created Fig. 2c and reproduce this heat map for bistability/monostability as a function of a α_1 and α_2 .