

Problem 1: Positive Feedback (adapted from Alon 3.4, 15 points)

In last week's problem set, you showed that a gene Z with simple regulation described by

$$\frac{dZ}{dt} = \beta_0 - \alpha Z, \quad Z(0) = 0$$

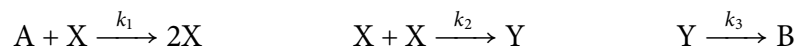
has a response time (i.e., time required to reach half of its steady-state expression level) given by $\tau = \frac{\ln 2}{\alpha}$. Now consider a protein X which positively regulates its own expression:

$$\frac{dX}{dt} = \beta_0 + \beta_1 X - \alpha X, \quad X(0) = 0$$

- Identify any fixed points of this system and determine their stability. Consider the three cases (i) $\alpha < \beta_1$, (ii) $\alpha = \beta_1$, and (iii) $\alpha > \beta_1$.
- When the response time of X is well-defined, how does it compare to the response time of Z ?
- Describe a biological scenario where positive regulation of this type would be preferable to simple regulation. Explain your reasoning.

Problem 2: Global dynamics from local stability analysis (Ingalls 4.8.6, 35 points)

- Consider the chemical reaction network with mass-action kinetics:



Assume that $[A]$ and $[B]$ are held constant.

- Write a differential equation model describing the concentrations of X and Y .
 - Verify that the system has two steady states.
 - Determine the system Jacobian at the steady states and characterize the local behavior of the system near these points.
 - By referring to the network, provide an intuitive description of the system behavior from any initial condition for which $[X] = 0$.
 - Sketch a phase portrait for the system that is consistent with your expectations from (iii) and (iv).
- Repeat for the related system



In this case, you'll find that the nonzero steady state is a center: it is surrounded by concentric periodic trajectories.

Problem 3: Practice with Laplace transforms (adapted from Meister 2009, 50 points)

Absorption of a single photon by a photoreceptor neuron triggers a biochemical cascade that results in a change in current across the neuron's membrane called the "single photon response," which lasts for a few hundred milliseconds before decaying away. The neuron's photon detection system is approximately linear and time-invariant: when several photons get absorbed, the resulting current is simply the sum of all their single photon responses.

- a) We will represent the single photon response for a photon absorbed at time $t = 0$ by $h(t)$. What is the photoreceptor's response $O(t)$ to an arbitrary time-varying light stimulus, in which the rate of photon absorptions varies with time as $I(t)$, where

$$I(t) dt = \text{number of photons absorbed in short interval } dt ?$$

Write the answer as a convolution integral, then apply a Laplace transform to find $\tilde{O}(s)$ in terms of $\tilde{I}(s)$ and $\tilde{h}(s)$.

- b) One way to investigate a system's behavior is to apply a well-defined "test" input and study the resulting output timecourse. Determine the Laplace transforms $\tilde{I}(s)$ for the two common types of test inputs given below, showing your work:

i) $I(t) = \delta(t) = \begin{cases} \infty, & t = 0 \\ 0, & t \neq 0 \end{cases}$ (Dirac delta/unit impulse)

ii) $I(t) = \theta(t) = \begin{cases} 0, & t < 0 \\ 1, & t \geq 0 \end{cases}$ (Heaviside step function)

When a very brief flash of light consisting of N photons is delivered to a photoreceptor, the photon detection system's output is:

$$O(t) = \begin{cases} 0, & t < 0 \\ A \sin(\omega t) e^{-\alpha t}, & t \geq 0 \end{cases}$$

- c) Write an expression for $I(t)$ in this case, and then apply a Laplace transform to find an expression for $\tilde{I}(s)$.
- d) Find an expression for $\tilde{O}(s)$ (for the rest of the problem, you may consult a table of Laplace transforms¹).
- e) Find the impulse response $h(t)$ by determining $\tilde{h}(s)$ and finding the inverse Laplace transform.

An input of the form

$$I(t) = \begin{cases} 0, & t < 0 \\ M \text{ photons per second}, & t \geq 0 \end{cases}$$

is then applied. Below you will determine what output $O(t)$ was expected under the assumption that the photon detection system is linear and time-invariant.

- e) What is $\tilde{I}(s)$?
- f) Use $\tilde{h}(s)$, calculated in part (e), to express $\tilde{O}(s)$ as a rational function in s .
- g) Determine $O(t)$. What value does $O(t)$ approach as $t \rightarrow \infty$?

¹A thorough table is available at <http://www.dartmouth.edu/~sullivan/22files/New%20Laplace%20Transform%20Table.pdf>.