

**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:

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

- a) 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)  $\alpha > \beta_1$ .

i)  $\alpha < \beta_1$ :

$dX/dt > 0$  for all non-negative values of  $X$ : this system has no physically-meaningful fixed points and grows exponentially without bound. (No deduction for mentioning that there is a fixed point at  $X^* = -\frac{\beta_0}{\beta_1 - \alpha}$  or indicating that it is unstable, though this value of  $X$  is physically unrealizable.)

ii)  $\alpha = \beta_1$ :

Now  $dX/dt = \beta_0$ : the system grows linearly without bound; no fixed points.

iii)  $\alpha > \beta_1$

Setting  $dX/dt = 0$ , we get:

$$X^* = \frac{\beta_0}{\alpha - \beta_1}$$

This fixed point is stable since  $dX/dt > 0$  for  $X < X^*$  and  $dX/dt < 0$  for  $X > X^*$ .

- b) When the response time of  $X$  is well-defined, how does it compare to the response time of  $Z$ ?

From the above we conclude that the response time is only well-defined when  $\alpha > \beta_1$ , in which case the response time is the time  $\tau$  such that  $X(\tau) = \frac{\beta_0}{2(\alpha - \beta_1)}$ . Following a method analogous to that used on last week's problem set, we find an expression for  $X(t)$ :

$$\begin{aligned} \int \frac{dX}{\beta_0 + (\beta_1 - \alpha) X} &= \int dt \\ \frac{1}{\beta_1 - \alpha} \ln [\beta_0 + (\beta_1 - \alpha) X] &= t + c_0 \\ \beta_0 + (\beta_1 - \alpha) X &= c_1 e^{-(\alpha - \beta_1)t} \quad X(0) = 0 \implies c_1 = \beta_0 \\ X &= \frac{\beta_0 [1 - e^{-(\alpha - \beta_1)t}]}{\alpha - \beta_1} \end{aligned}$$

We can then solve for  $\tau$ :

$$\begin{aligned}\frac{\beta_0}{2(\alpha - \beta_1)} &= \frac{\beta_0 [1 - e^{-(\alpha - \beta_1)\tau}]}{\alpha - \beta_1} \\ e^{-(\alpha - \beta_1)\tau} &= \frac{1}{2} \\ \tau &= \frac{\ln 2}{\alpha - \beta_1}\end{aligned}$$

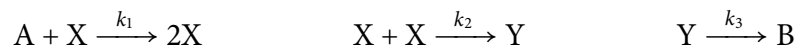
Because the denominator is smaller than in the simple regulation case, the response time is longer with positive feedback.

- c) Describe a biological scenario where positive regulation of this type would be preferable to simple regulation. Explain your reasoning.

Slowed responses can be used to institute a time delay, which may be useful for coordinating the timing of developmental processes.

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

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



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

- i) Write a differential equation model describing the concentrations of  $X$  and  $Y$ .

$$\begin{aligned}\frac{dX}{dt} &= f(X, Y) = k_1AX - 2k_2X^2 \\ \frac{dY}{dt} &= g(X, Y) = k_2X^2 - k_3Y\end{aligned}$$

- ii) Verify that the system has two steady states.

$$\begin{aligned}\frac{dX}{dt} &= X(k_1A - 2k_2X) = 0 \implies X = 0 \text{ or } \frac{k_1A}{2k_2} \\ X = 0 \text{ and } \frac{dY}{dt} &= 0 \implies Y = 0 \\ X = \frac{k_1A}{2k_2} \text{ and } \frac{dY}{dt} &= 0 \implies Y = \frac{k_1^2k_2A}{4k_2^2k_3}\end{aligned}$$

The fixed points are  $(0, 0)$  and  $(\frac{k_1A}{2k_2}, \frac{k_1^2k_2A}{4k_2^2k_3})$ .

- iii) Determine the system Jacobian at the steady states and characterize the local behavior of the system near these points.

$$J = \begin{pmatrix} \frac{df}{dX} & \frac{df}{dY} \\ \frac{dg}{dX} & \frac{dg}{dY} \end{pmatrix}_{(X^*, Y^*)} = \begin{pmatrix} k_1 A - 4k_2 X & 0 \\ 2k_2 X & -k_3 \end{pmatrix}_{(X^*, Y^*)}$$

Linearizing around the fixed point  $(0, 0)$  therefore gives

$$\frac{d}{dt} \begin{pmatrix} X \\ Y \end{pmatrix} = \begin{pmatrix} k_1 A & 0 \\ 0 & -k_3 \end{pmatrix} \begin{pmatrix} X \\ Y \end{pmatrix}$$

Since all constants in this system are non-negative, the Jacobian is guaranteed to have one positive and one negative eigenvalue:  $\lambda_1 = k_1 A > 0$  and  $\lambda_2 = -k_3 < 0$ . This means the origin is a *saddle*. (For comparison to part iv, we also mention that the eigenvector corresponding to  $\lambda_2$  is  $\mathbf{v}_2 = (0, 1)^T$ , so all trajectories where  $X = 0$  decay to the origin with time.)

Linearizing around the fixed point  $\left(\frac{k_1 A}{2k_2}, \frac{k_1^2 k_2 A}{4k_2^2 k_3}\right)$  gives

$$\frac{d}{dt} \begin{pmatrix} X \\ Y \end{pmatrix} = \begin{pmatrix} -k_1 A & 0 \\ k_1 A & -k_3 \end{pmatrix} \begin{pmatrix} X \\ Y \end{pmatrix}$$

For this fixed point, both eigenvalues  $\lambda_1 = -k_1 A$  and  $\lambda_2 = -k_3$  are negative, so this is a stable fixed point.

- iv) By referring to the network, provide an intuitive description of the system behavior from any initial condition for which  $[X] = 0$ .

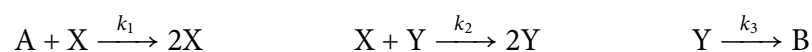
If  $[X]$  is initially zero, then it will stay zero forever, because the only reaction that produces  $X$  requires some  $X$  to already be present. This also means that no more  $Y$  will be produced, since  $Y$  is produced from  $X$ . However,  $Y$  is decaying into  $B$ : therefore,  $[Y]$  will approach zero as  $t \rightarrow \infty$ .

This matches our intuition from the formal stability analysis, since the origin is a saddle and trajectories along the  $y$ -axis approach the origin.

- v) Sketch a phase portrait for the system that is consistent with your expectations from (iii) and (iv).

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- b) 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.

$$\begin{aligned}\frac{dX}{dt} &= f(X, Y) = k_1AX - k_2XY \\ \frac{dY}{dt} &= g(X, Y) = k_2XY - k_3Y\end{aligned}$$

Find the steady states:

$$\begin{aligned}\frac{dX}{dt} = (k_1A - k_2Y) = 0 &\implies X = 0 \text{ or } Y = \frac{k_1A}{k_2} \\ \frac{dY}{dt} = Y(k_2X - k_3) = 0 &\implies Y = 0 \text{ or } X = \frac{k_3}{k_2}\end{aligned}$$

This gives two possible fixed points:  $(0, 0)$  and  $(\frac{k_3}{k_2}, \frac{k_1A}{k_2})$ .

$$J = \begin{pmatrix} \frac{df}{dX} & \frac{df}{dY} \\ \frac{dg}{dX} & \frac{dg}{dY} \end{pmatrix}_{(X^*, Y^*)} = \begin{pmatrix} k_1A - k_2Y & -k_2X \\ k_2Y & k_2X - k_3 \end{pmatrix}_{(X^*, Y^*)}$$

Linearizing around the fixed point  $(0, 0)$  therefore gives

$$\frac{d}{dt} \begin{pmatrix} X \\ Y \end{pmatrix} = \begin{pmatrix} k_1A & 0 \\ 0 & -k_3 \end{pmatrix} \begin{pmatrix} X \\ Y \end{pmatrix}$$

...and exactly as before, the origin has one positive and one negative eigenvalue, and is therefore a saddle.

Linearizing around the fixed point  $(\frac{k_3}{k_2}, \frac{k_1A}{k_2})$  gives

$$\frac{d}{dt} \begin{pmatrix} X \\ Y \end{pmatrix} = \begin{pmatrix} 0 & -k_3 \\ k_1A & 0 \end{pmatrix} \begin{pmatrix} X \\ Y \end{pmatrix}$$

This matrix has two purely imaginary eigenvalues, so solutions form closed loops around this fixed point.

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### 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  $\tilde{h}(s)$ .

$$O(t) = I(t) \otimes h(t) = \int_{-\infty}^{\infty} I(t - \tau)h(\tau) d\tau = \int_0^t I(t - \tau)h(\tau) d\tau$$

It is not necessary to prove that  $\tilde{O}(s) = \tilde{h}(s)\tilde{I}(s)$  as this is a property of the Laplace transform of the convolution integral which we stated in class. However, the derivation is given below for reference.

To narrow the limits on the convolution integral, we have used the fact that  $h(\tau)$  is nonzero only for positive  $\tau$ , and  $I(t - \tau)$  is nonzero only for  $\tau \leq t$ .

$$\begin{aligned}\tilde{O}(s) &= \int_0^{\infty} e^{-st} \left[ \int_0^t I(t - \tau)h(\tau) d\tau \right] dt \\ &= \int_0^{\infty} \left[ \int_0^t e^{-st} I(t - \tau)h(\tau) d\tau \right] dt \\ &= \int_0^{\infty} \left[ \int_{\tau}^{\infty} e^{-st} I(t - \tau)h(\tau) dt \right] d\tau \\ &= \int_0^{\infty} \left[ \int_{\tau}^{\infty} e^{-st} I(t - \tau) dt \right] h(\tau) d\tau\end{aligned}$$

Now, making the substitution  $\sigma = t - \tau$ ,  $d\sigma = dt$ :

$$\begin{aligned}\tilde{O}(s) &= \int_0^{\infty} \left[ \int_0^{\infty} e^{-s(\sigma+\tau)} I(\sigma) d\sigma \right] h(\tau) d\tau \\ &= \int_0^{\infty} \left[ \int_0^{\infty} e^{-s\sigma} I(\sigma) d\sigma \right] e^{-s\tau} h(\tau) d\tau \\ &= \int_0^{\infty} \tilde{I}(s) e^{-s\tau} h(\tau) d\tau \\ &= \tilde{h}(s)\tilde{I}(s)\end{aligned}$$

- 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:

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

$$\begin{aligned} \tilde{I}(s) &= \int_0^{\infty} e^{-st} \delta(t) dt \\ &= e^{-st} \Big|_{t=0} = 1 \end{aligned}$$

We have used the fact that the integrand is non-zero at only one point ( $t = 0$ ) and that the Dirac delta distribution is defined such that

$$\int_{-\infty}^{\infty} \delta(t) dt = 1$$

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

$$\begin{aligned} \tilde{I}(s) &= \int_0^{\infty} e^{-st} \theta(t) dt \\ &= \int_0^{\infty} e^{-st} dt = \left. \frac{-e^{-st}}{s} \right|_0^{\infty} \\ &= \int_{-\infty}^{\infty} e^{-s\tau} I(t-\tau) h(\tau) d\tau \\ &= 0 - \left( -\frac{1}{s} \right) = \frac{1}{s} \end{aligned}$$

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  $\tilde{I}(s)$ .

$$\begin{aligned} I(t) &= N\delta(t) \\ \tilde{I}(s) &= N \end{aligned}$$

d) Find an expression for  $\tilde{O}(s)$  (for the rest of the problem, you may consult a table of Laplace transforms<sup>1</sup>).

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

$$\tilde{O}(s) = \frac{A\omega}{(s + \alpha)^2 + \omega^2}$$

e) Find the impulse response  $h(t)$  by determining  $\tilde{h}(s)$  and finding the inverse Laplace transform.

$$\tilde{h}(s) = \frac{\tilde{O}(s)}{\tilde{I}(s)} = \frac{A\omega}{N[(s + \alpha)^2 + \omega^2]}$$

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  $\tilde{I}(s)$ ?

$$\tilde{I}(s) = \frac{M}{s}$$

f) Use  $\tilde{h}(s)$ , calculated in part (e), to express  $\tilde{O}(s)$  as a rational function in  $s$ .

$$\begin{aligned} \tilde{O}(s) &= \tilde{h}(s)\tilde{I}(s) \\ &= \frac{AM}{N} \frac{\omega}{s[(s + \alpha)^2 + \omega^2]} \end{aligned}$$

g) Determine  $O(t)$ . What value does  $O(t)$  approach as  $t \rightarrow \infty$ ?

$$\begin{aligned} \tilde{O}(s) &= \frac{AM}{N} \frac{\omega}{\alpha^2 + \omega^2} \left( \frac{\alpha^2 + \omega^2}{s[(s + \alpha)^2 + \omega^2]} \right) \\ &= \frac{AM}{N} \frac{\omega}{\alpha^2 + \omega^2} \left( \frac{(s + \alpha)^2 + \omega^2}{s[(s + \alpha)^2 + \omega^2]} - \frac{s(s + 2\alpha)}{s[(s + \alpha)^2 + \omega^2]} \right) \\ &= \frac{AM}{N} \frac{\omega}{\alpha^2 + \omega^2} \left( \frac{1}{s} - \frac{s + \alpha}{(s + \alpha)^2 + \omega^2} - \frac{\alpha}{\omega} \frac{\omega}{(s + \alpha)^2 + \omega^2} \right) \\ O(t) &= \frac{AM}{N} \frac{\omega}{\alpha^2 + \omega^2} \left( 1 - e^{-\alpha t} \cos \omega t - \frac{\alpha}{\omega} e^{-\alpha t} \sin \omega t \right) \\ &\rightarrow \frac{AM}{N} \frac{\omega}{\alpha^2 + \omega^2} \text{ as } t \rightarrow \infty \end{aligned}$$

