Linear Genetic Network Modeling

Problem 1: Two Gene Network

Let’s first model protein A acting as an activating transcription factor for gene B.

The change in concentration of protein B, \( c_B \), can be written as the balance of generation of protein B and the degradation/dilution of protein B:

\[
\frac{dc_B}{dt} = G_B(t) - D_B c_B(t) \tag{1}
\]

where \( D_B \) stands for a degradation constant and \( G_B \) stands for the generation of B, induced by the basal promoter rate and transcription factor A. The generation term that is dependent on the transcription factor A is usually modeled by a non-linear Hill equation. However, for our linear model we’ll approximate that

\[
G_B(t) = G_0 + x(t)c_A(t) \tag{2}
\]

where \( x(t) \) is a scaling factor from 0 to 1 that represents the efficiency of protein A as a transcription factor and \( G_0 \) is basal promoter production rate.

We will further simplify that there is no basal promoter production. We will also assume that the scaling factor is time-invariant, i.e. a constant value, \( X \):

\[
G_B(t) = Xc_A(t) \tag{3}
\]

leaving us with

\[
\frac{dc_B}{dt} = Xc_A(t) - D_B c_B(t). \tag{4}
\]

Assume the initial concentration of protein B is 0 and that \( D_B \) is a positive non-zero number.

Figure 1: The top shows the gene network; the bottom diagram shows the equivalent linear systems block diagram.

\begin{align*}
\textbf{a: } & \text{ Find the Laplace transfer function, } H_{AB}(s), \text{ of this system.} \\
\textbf{b: } & \text{ Find the output response (i.e., the concentration } c_B(t) \text{ of protein B) for this system. } \text{Hint: express your answer in terms of the protein A concentration over time, } c_A(t), \text{ which can in principle be any waveform.} \\
\textbf{c: } & \text{ Is this system stable? Explain.} \\
\textbf{d: } & \text{ What if we assumed the system did not generate protein A, and we exogenously added protein A to our system at } t = 0. \text{ Assuming that protein A is not degraded/consumed, we could model this as a step } c_A(t) = H(t) \text{ where the step (Heavyside) function } H(t) = 0 \text{ for } t < 0, \text{ and } H(t) = 1 \text{ for } t > 0. \text{ What is now the response in the concentration } c_B(t) \text{ of protein B?}
\end{align*}
Problem 2: Adding Negative Autoregulation

Now protein B, in addition to protein A, acts as a transcription factor on its own gene.

The generation equation of protein B due to activated protein B acting as a repressor is similar to equation 3 but with a negative sign and a constant (positive) scaling factor, $Y$:

$$G_B(t) = X_{cA}(t) - Yc_B(t).$$  \hfill (5)

The overall differential equation then becomes

$$\frac{dc_B}{dt} = X_{cA}(t) - (D_B + Y)c_B(t)$$ \hfill (6)

Assume the initial concentration of protein B is 0 and that $D_B$ is a positive non-zero number.

![Gene network and system diagram](image)

**Figure 2:** The gene network and system diagram of Figure 1; now with negative autoregulation.

**a:** Simplify the box diagram in figure 2 by finding the overall Laplace transfer function, $H_{neg}(s)$, of this system based on equation 6, as shown in the following figure.

![New simplified system block diagram](image)

**Figure 3:** New simplified system block diagram.

**b:** Find the output response (i.e., the concentration of protein B over time $c_B(t)$) as you did in Problem 1b (in terms of protein A).

**c:** Is this system stable?

Problem 3: Negative Feedback Loop

Assume we have a system where protein A is an activator for gene B. Protein B is an activator for gene C. Protein C acts a repressor for gene B. **Assume the initial concentrations of protein B and protein C are 0.**
Figure 4: Gene network and system diagram, now with a third gene exerting negative feedback.

a: Write the differential equation for the change in concentration of protein B and another differential equation for the change in protein C. Use Y as the scaling factor for the efficiency of protein C as a transcription factor (repressor) for gene for protein B. Use Z as the scaling factor for protein B as a transcription factor (activator) on the gene for protein C.

b: Simplify the block model and find the new overall transfer function, $H_{feed}$, of the system as depicted in the figure below.

![Figure 5: New simplified system block diagram.](image)

c: Find the damping coefficient and the damping frequency.

d: Assume that the scaling factors are all unity ($X = Y = Z = 1$), and the degradation constants are all equal $D_B = D_C = D$. Use Matlab to plot 3 separate Bode plot sets for following cases: when the degradation constant $D$ for each of the proteins is equal to 1, 0.1, and 0.01. Compare what happens at low, resonance, and high frequencies for each set.