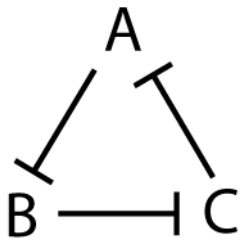
Quantitative Understanding in Biology Modules III & IV: Difference and Differential Equations Computer Laboratory

A Network of Interacting Genes

Consider a simple network of interacting genes:



This seemingly simple picture describes a somewhat elaborate model for the interactions of genes and their products. It says that the product of gene A inhibits the expression of gene B. In turn, the product of gene B inhibits the expression of C. Similarly, the product of gene C inhibits the expression of gene A.

A little thought reveals that this system may have some interesting dynamic characteristics. As the expression of gene A increases, we expect the expression of B to decrease. This is turn will lead to an increase in the expression of gene C (because its inhibitor, B, is present in decreasing quantities). But that, in turn, should lead to a decrease in the expression of A. Our thought experiment indicates that this system has the potential to exhibit oscillatory behavior.

We will proceed to build a simple, linearized, mathematical model of this system. In fact, such a system was expressed in bacteria using GFP as a reporter (Elowitz and Leibler, *Nature*, 2000). You can actually see the intensity of GFP vary over time in the bacteria.

In order to explore this system more formally, we would begin by writing the differential equations corresponding to each biochemical reaction implied in the diagram. It is important to realize that there are two such species implied for each gene: its transcribed mRNA product, and its translated protein product. We'll denote the concentrations of mRNAs as m_A, m_B, and m_C; similarly the protein products will be denoted as p_A, p_B, and p_C.

A differential equation for the concentration of mRNA of A can be written as:

$$\frac{dm_A}{dt} = \alpha_0 - m_A - \alpha \cdot p_C$$

In the first term, α_0 represents a basal level of expression of mRNA. The second term represents degradation of the mRNA of A over time; this is simply proportional to the amount of mRNA present (you might include a coefficient here to capture the rate of degradation, but it is not necessary for our purposes).

The third term represents the inhibition of the expression of mRNA of gene A by the protein product of gene C. Protein C is a transcription factor that binds to the promoter region of the DNA encoding for A and prevents transcription. The degree of inhibition is given by the coefficient α. A key assumption in our model is that this relationship is linear. Does this seem reasonable?

We can turn this differential equation into a difference equation by considering a short time interval, τ. Our difference equation is:

$$m_A' - m_A = \tau(\alpha_0 - m_A - \alpha \cdot p_C)$$

We can write similar equations for m_B and m_C.

A second set of differential equations comes from consideration of the protein products. We write:

$$\frac{dp_A}{dt} = \beta(m_A - p_A)$$

The term containing m_A indicates that the production of the protein is proportional to the amount of mRNA present. The negative p_A term represents degradation of the protein.

This equation can be written in terms of differences using the same reasoning as we followed for mRNA, and similar logic can be applied to the protein products of genes B and C.

Note that we use the same parameters, α_0, α and β for all three genes. In reality, they are probably different, but this simplified model will still be sufficient to capture the essential dynamic character of the system.

Show that the system as modeled above can be represented by the matrix equation:

$$\begin{pmatrix} m_A \\ p_A \\ m_B \\ p_B \\ m_C \\ p_C \\ 1 \end{pmatrix}_{n+1} = \begin{pmatrix} (1-\tau) & 0 & 0 & 0 & 0 & -\tau\alpha & \tau\alpha_0 \\ \tau\beta & (1-\tau\beta) & 0 & 0 & 0 & 0 & 0 \\ 0 & -\tau\alpha & (1-\tau) & 0 & 0 & 0 & \tau\alpha_0 \\ 0 & 0 & \tau\beta & (1-\tau\beta) & 0 & 0 & 0 \\ 0 & 0 & 0 & -\tau\alpha & (1-\tau) & 0 & \tau\alpha_0 \\ 0 & 0 & 0 & 0 & \tau\beta & (1-\tau\beta) & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} m_A \\ p_A \\ m_B \\ p_B \\ m_C \\ p_C \\ 1 \end{pmatrix}_n$$

Using the following values for the model parameters, **simulate the system**: τ = 0.005; α_0 = 4; α = 1; β = 0.01. For your initial condition, use a unit amount of protein A only. Note that the time-step, τ, is fairly small. You don't need to collect and plot data for every single time-point. **How can you do this efficiently?**

Compute the eigenvalues and eigenvectors for this model. Comment.

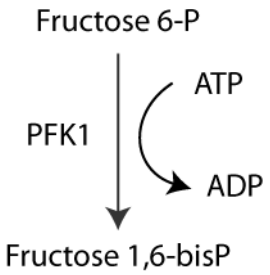
Repeat both a simulation and the computation and interpretation of eigenvalues and eigenvectors for α=2.5.

Without running additional simulations, can you determine a value for α that would give a sustained, periodic oscillation of mRNAs and proteins? How sensitive is this model to this parameter? Do you think a system such as this can be used as a biological clock?

The Sel'kov Model of Glycolysis

Reference: Keener and Sneyd (Chapt. 1)

One step in the glycolytic pathway is the phosphorylation of fructose 6-phosphate to fructose 1,6 bisphosphate, which it catalyzed by the enzyme phosphofructokinase (PFK1). This reaction transforms a molecule of ATP to a molecule of ADP; this is the source of the phosphate that is added to the fructose. This process is drawn as…



The enzyme involved, PFK1, exhibits properties of allosteric regulation which are quite complex and which we will not cover here (see your favorite biochemistry text for the gory details). A simplified model of this allosteric regulation, proposed by Sel'kov, is to view PFK1 as being activated by some number, γ, molecules of ADP.

$$PFK1_{inactive} + \gamma ADP \leftrightarrow PFK1_{active}$$

The fact the phosphorylation reaction produces a product that actives the enzyme that catalyzes the reaction can lead to some interesting dynamics, which we will investigate here.

When we have modeled chemical reactions before, we have considered the system to be closed; that is we modeled the system with some amount of starting material and investigated how the concentrations of those materials would evolve over time, but we never added or took away material during the simulation. In this case, we will model an open system. We will provide our simulated system with a steady supply of ATP, and we will continuously remove ADP at a rate proportional to its concentration. You can think about these two steps as a very, very gross model of many other reactions that might be going on in the cell to regulate the concentrations of ATP and ADP.

This system can be modeled by the following set of chemical reactions, as proposed by Sel'kov:

$$\xrightarrow{v_1} ATP$$

$$\gamma ADP + PFK1_{inactive} \xleftrightarrow{k_3, k_{-3}} PFK1_{active}$$

$$ATP + PFK1_{active} \xleftrightarrow{k_1, k_{-1}} PFK1_{complex} \xrightarrow{k_2} PFK1_{active} + ADP$$

$$ADP \xrightarrow{v_2}$$

Note that the 3rd equation does not include the fructose reactant or product!

Apply the law of mass action to write a system of differential equations that can be used to simulate this system.

Take the constants in the model to be:

γ=2.0
v_1 = 0.003
v_2 = 2.5·v_1
k_1 = 0.1
k_{-1} = 0.2
k_2 = 0.1
k_3 = 0.2
k_{-3} = 0.2

Find any steady states for this system, and investigate stability.

Hint: Matlab's symbolic math tools can be your friend. See the `solve` *function.*

Consider an initial condition where only ATP, ADP, and inactive enzyme are present in the following amounts.

[ATP] = 1.0

[ADP] = 2.0

[$PFK1_{inactive}$] = 1.4

Simulate the system numerically. Prepare appropriate plots, and compare your results to your steady-state analysis.

