Quantitative Understanding in Biology Module III: Linear Difference Equations Computer Laboratory

Transformation Matrices

Consider the 2x2 matrix below.

$$M = \begin{pmatrix} \cos\theta & -\sin\theta \\ \sin\theta & \cos\theta \end{pmatrix}$$

For θ=π/10, compute the eigenvalues of this matrix. You don't need to do this by hand, feel free to use MATLAB for this and in other problems in this laboratory – make up reasonable values for constants when necessary. Express the eigenvalues in both 'rectangular' form (a + bi) and 'polar' form ($r \cdot e^{i\theta}$). What does this tell you about the evolution of a system that is modeled by

$$\begin{pmatrix} x \\ y \end{pmatrix}_{n+1} = M \begin{pmatrix} x \\ y \end{pmatrix}_n$$

For a few different initial conditions, plot fifteen or so steps of the evolution of this system. Do this by plotting (x,y) points for fifteen steps. What is the geometrical interpretation of this matrix? Confirm this for different values of θ.

Difference Equations Including Constant Terms

Difference equations as we have used them so far express the new value of each variable as a linear combination of the previous values of the variables in the system. In equation form, this is…

$$x_i' = \sum_j a_{i,j} \cdot x_j$$

…where x' is the new value of x.

This form does not allow for a constant term to be included in the equation. However, this can be achieved by augmenting the system with an extra state variable that starts out (and remains) at one. For example, consider this system:

$$\begin{pmatrix} x \\ y \\ 1 \end{pmatrix}_{n+1} = \begin{pmatrix} 1 & 0 & X \\ 0 & 1 & Y \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} x \\ y \\ 1 \end{pmatrix}_n$$

Choose non-zero values for X and Y, as well as an initial condition, then simulate and plot the evolution of this system for fifteen or so steps. What is the geometrical interpretation of this matrix?

Combining Matrices

Consider the following system:

$$\begin{pmatrix} x \\ y \\ 1 \end{pmatrix}_{n+1} = \begin{pmatrix} 1 & 0 & X \\ 0 & 1 & Y \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} \alpha & 0 & 0 \\ 0 & \alpha & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} \cos\theta & -\sin\theta & 0 \\ \sin\theta & \cos\theta & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} 1 & 0 & -X \\ 0 & 1 & -Y \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} x \\ y \\ 1 \end{pmatrix}_{n}$$

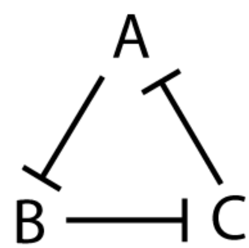
The transformation matrix, M, for each iteration of the model is a product of four matrices. Can you predict what the behavior of the system will be, and explain the role of each parameter: X, Y, α, and θ.

Choose some reasonable values for the parameters and an initial condition, then simulate and plot for a few steps.

Compute the eigenvectors and eigenvalues of the system for three cases where α<1; α=1; and α>1. Comment on the results.

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: $\tau = 0.005$; $\alpha_0 = 4$; $\alpha = 1$; $\beta = 0.01$. 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 $\alpha=2.5$.

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?