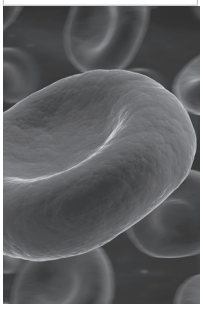
PROJECTS



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Project 1 Estimating Rate Constants for an Open Two-Compartment Model

Physiological systems are often modeled by dividing them into distinct functional units or compartments. A simple two-compartment model used to describe the evolution in time of a single intravenous drug dose (or a chemical tracer) is shown in Figure 3.P.1. The central compartment, consisting of blood and extracellular water, is rapidly diffused with the drug.

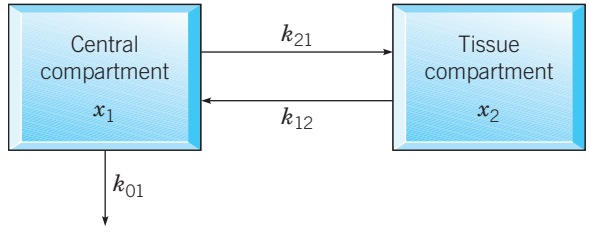

FIGURE 3.P.1 A two-compartment open model of a physiological system.

The second compartment, known as the tissue compartment, contains tissues that equilibriate more slowly with the drug. If x_1 is the concentration of drug in the blood and x_2 is its concentration in the tissue, the compartment model is described by the following system:

$$\begin{aligned} x_1' &= -(k_{01} + k_{21})x_1 + k_{12}x_2 \\ x_2' &= k_{21}x_1 - k_{12}x_2, \end{aligned} \tag{1}$$

or $\mathbf{x}' = \mathbf{K}\mathbf{x}$, where

$$\mathbf{K} = \begin{pmatrix} K_{11} & K_{12} \\ K_{21} & K_{22} \end{pmatrix} = \begin{pmatrix} -k_{01} - k_{21} & k_{12} \\ k_{21} & -k_{12} \end{pmatrix}. \tag{2}$$

Here, the rate constant k_{21} is the fraction per unit time of drug in the blood compartment transferred to the tissue compartment; k_{12} is the fraction per unit time of drug in the tissue compartment transferred to the blood; and k_{01} is the fraction per unit time of drug eliminated from the system.

In this project, we illustrate a method for estimating the rate constants by using time-dependent measurements of concentrations to estimate the eigenvalues and eigenvectors of the rate matrix $\mathbf{K}$ in Eq. (2) from which estimates of all rate constants can be computed.

Project 1 PROBLEMS

1. Assume that all the rate constants in Eq. (1) are positive.

(a) Show that the eigenvalues of the matrix $\mathbf{K}$ are real, distinct, and negative.

Hint: Show that the discriminant of the characteristic polynomial of $\mathbf{K}$ is positive.

(b) If λ_1 and λ_2 are the eigenvalues of $\mathbf{K}$, show that $\lambda_1 + \lambda_2 = -(k_{01} + k_{12} + k_{21})$ and $\lambda_1\lambda_2 = k_{12}k_{01}$.

2. Estimating Eigenvalues and Eigenvectors of K from Transient Concentration Data. Denote by $\mathbf{x}^*(t_k) = x_1^*(t_k)\mathbf{i} + x_2^*(t_k)\mathbf{j}$, $k = 1, 2, 3, \ldots$ measurements of the concentrations in each of the compartments. We assume that the eigenvalues of $\mathbf{K}$ satisfy $\lambda_2 < \lambda_1 < 0$. Denote the eigenvectors of λ_1 and λ_2 by

$$\mathbf{v_1} = \begin{pmatrix} v_{11} \\ v_{21} \end{pmatrix} \quad \text{and} \quad \mathbf{v_2} = \begin{pmatrix} v_{12} \\ v_{22} \end{pmatrix},$$

respectively. The solution of Eq. (1) can be expressed as

$$\mathbf{x}(t) = \alpha e^{\lambda_1 t}\mathbf{v}_1 + \beta e^{\lambda_2 t}\mathbf{v}_2, \qquad \text{(i)}$$

where α and β, assumed to be nonzero, depend on initial conditions. From Eq. (i), we note that

$$\mathbf{x}(t) = e^{\lambda_1 t}\left[\alpha\mathbf{v}_1 + \beta e^{(\lambda_2-\lambda_1)t}\mathbf{v}_2\right] \sim \alpha e^{\lambda_1 t}\mathbf{v}_1 \quad \text{if } e^{(\lambda_2-\lambda_1)t} \sim 0. \qquad \text{(ii)}$$

(a) For values of t such that $e^{(\lambda_2-\lambda_1)t} \sim 0$, explain why the graphs of $\ln x_1(t)$ and $\ln x_2(t)$ should be approximately straight lines with slopes equal to λ_1 and intercepts equal to $\ln \alpha v_{11}$ and $\ln \alpha v_{21}$, respectively. Thus estimates of λ_1, αv_{11}, and αv_{21} may be obtained by fitting straight lines to the data $\ln x_1^*(t_n)$ and $\ln x_2^*(t_n)$ corresponding to values of t_n, where graphs of the logarithms of the data are approximately linear, as shown in Figure 3.P.2.

(b) Given that both components of the data $\mathbf{x}^*(t_n)$ are accurately represented by a sum of exponential functions of the form (i), explain how to find estimates of λ_2, βv_{12}, and βv_{22} using the residual data $\mathbf{x}_r^*(t_n) = \mathbf{x}^*(t_n) - \hat{\mathbf{v}}_1^{(\alpha)} e^{\hat{\lambda}_1 t_n}$, where estimates of λ_1 and $\alpha\mathbf{v}_1$ are denoted by $\hat{\lambda}_1$ and $\hat{\mathbf{v}}_1^{(\alpha)}$, respectively.[7]

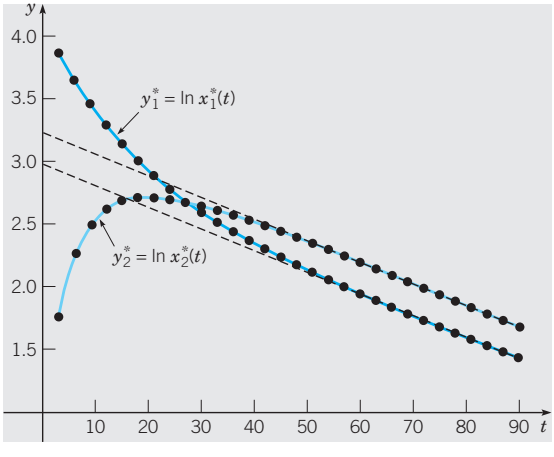

FIGURE 3.P.2 Graphs of the data $y_{1n}^* = \ln x_1^*(t_n)$ and $y_{2n}^* = \ln x_2^*(t_n)$ are approximately straight lines for values of t_n such that $e^{(\lambda_2-\lambda_1)t_n} \sim 0$.

3. Computing the Entries of K from Its Eigenvalues and Eigenvectors. Assume that the eigenvalues λ_1 and λ_2 and corresponding eigenvectors $\mathbf{v}_1$ and $\mathbf{v}_2$ of $\mathbf{K}$ are known. Show that the entries of the matrix $\mathbf{K}$ must satisfy the following systems of equations:

$$\begin{pmatrix} v_{11} & v_{21} \\ v_{12} & v_{22} \end{pmatrix}\begin{pmatrix} K_{11} \\ K_{12} \end{pmatrix} = \begin{pmatrix} \lambda_1 v_{11} \\ \lambda_2 v_{12} \end{pmatrix} \qquad \text{(iii)}$$

and

$$\begin{pmatrix} v_{11} & v_{21} \\ v_{12} & v_{22} \end{pmatrix}\begin{pmatrix} K_{21} \\ K_{22} \end{pmatrix} = \begin{pmatrix} \lambda_1 v_{21} \\ \lambda_2 v_{22} \end{pmatrix}, \qquad \text{(iv)}$$

or, using matrix notation, $\mathbf{KV} = \mathbf{V\Lambda}$, where

$$\mathbf{V} = \begin{pmatrix} v_{11} & v_{12} \\ v_{21} & v_{22} \end{pmatrix} \quad \text{and} \quad \mathbf{\Lambda} = \begin{pmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{pmatrix}.$$

4. Given estimates $\hat{K}_{ij}$ of the entries of $\mathbf{K}$ and estimates $\hat{\lambda}_1$ and $\hat{\lambda}_2$ of the eigenvalues of $\mathbf{K}$, show how to obtain an estimate $\hat{k}_{01}$ of k_{01} using the relations in Problem 1(b).

5. Table 3.P.1 lists drug concentration measurements made in blood and tissue compartments over a period of 100 min. Use the method described in Problems 2 through 4 to estimate the rate coefficients k_{01}, k_{12}, and k_{21} in the system model (1). Then solve the resulting system using initial conditions from line 1 of Table 3.P.1. Verify the accuracy of your estimates by plotting the solution components and the data in Table 3.P.1 on the same set of coordinate axes.

TABLE 3.P.1 Compartment concentration measurements.

time (min)	x_1 (mg/mL)	x_2 (mg/mL)
0.000	0.623	0.000
7.143	0.374	0.113
14.286	0.249	0.151
21.429	0.183	0.157
28.571	0.145	0.150
35.714	0.120	0.137
42.857	0.103	0.124
50.000	0.089	0.110
57.143	0.078	0.098
64.286	0.068	0.087
71.429	0.060	0.077
78.571	0.053	0.068
85.714	0.047	0.060
92.857	0.041	0.053
100.000	0.037	0.047

[7]The procedure outlined here is called the **method of exponential peeling**. The method can be extended to cases where more than two exponential functions are required to represent the component concentrations. There must be one compartment for each exponential decay term. See, for example, D. Van Liew (1967), *Journal of Theoretical Biology* ***16***, 43.