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

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Abstract

In this project, we will be studying a two-compartment open model of a physiological system. Physiological systems are frequently used to describe the evolution in time of a single intravenous drug dose or a chemical tracer.

In this two-compartment model, the goal is to find the appropriate parameters for the model sot that we can describe a sample of compartment concentration measurements of a particular drug. First, we will use exponential peeling to simplify the problem as it is a method that can be extended to when there are more than two exponential functions required to represent the component concentrations. Next, we will use a least-squares regression to calculate suitable parameters.

The results we get at the end signify that using the parameters we have calculated makes the model better suited to predict long-term behavior of the drug than short-term behavior.

1 Introduction

Pharmacokinetics refers to the rate and extent of distribution of a drug to different tissues, and the rate of elimination of the drug. Pharmacokinetics can be reduced to mathematical equations, which describe the transit of the drug throughout the body, a net balance sheet from absorption and distribution to metabolism and excretion [Oikonen 2019].

Pharmacokinetic two-compartment model divided the body into central and peripheral compartment. The central compartment (compartment 1) consists of the plasma and tissues where the distribution of the drug is practically instantaneous. The peripheral compartment (compartment 2) consists of tissues where the distribution of the drug is slower [Oikonen 2019]. The idea here is that the rate at which the concentration of a compartment changes is proportional to the current concentration. In this project problem's context, this leads to a simple linear model which can be described by just two equations.

Our goal is to estimate the rate constants by using time-dependent measurements of concentrations to estimate the eigenvalues and eigenvectors of the rate matrix $\mathbf{K}$, from which estimates of all the rate constants can be computed. We will be using exponential peeling to reduce the system so we can first study its long-term behavior. The method of exponential peeling has also been compared with the least squares method for simple linear regression [J. Mazumdar 1991]. In this project, we will convert the problem to a linear system and then use that linear system to perform a least-squares regression on in order to estimate the parameters using python.

2 Problem 1

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

$$\begin{aligned} \dot{x}_1 &= -(k_{01} + k_{21})x_1 + k_{12}x_2, \\ \dot{x}_2 &= k_{21}x_1 - k_{12}x_2. \end{aligned} \tag{1}$$

This can also be expressed in the matrix form $\dot{\vec{x}} = \mathbf{K}\vec{x}$ where

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

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

2.1 Part a

Using Equation 2, I can find the characteristic polynomial by determining the determinant of $\mathbf{K}$. The characteristic polynomial of $\mathbf{K}$ is

$$\mathbf{K} = \lambda^2 + (k_{12} + k_{01} + k_{21})\lambda + k_{01}k_{12}, \tag{3}$$

So the discriminant will be:

$$\begin{aligned} \Delta &= (k_{12} + k_{01} + k_{21})^2 - (4)(1)(k_{01}k_{21}) \\ &= (k_{01}^2 + k_{12}^2 + k_{21}^2 + 2k_{01}(k_{21} - k_{12}) + 2k_{12}k_{21} \end{aligned} \tag{4}$$

I know that the eigenvalues of $\mathbf{K}$ are real and distinct when $\Delta > 0$. To check that the discriminant is greater than 0, I have to rewrite the discriminant equation until it's obvious that the only positive values will result.

So I can rewrite the equation to be:

$$\begin{aligned} \Delta &= (k_{01}^2 + k_{12}^2 + k_{21}^2 + 2k_{01}(k_{21} - k_{12}) + 2k_{12}k_{21} \\ &= (k_{01}^2 + k_{12}^2 + k_{21}^2 + 2k_{01}k_{21} - 2k_{01}k_{12} + 2k_{12}k_{21} \\ &= (k_{01} - k_{21})^2 + k_{12}^2 + 2k_{01}k_{21} + 2k_{12}k_{21} \end{aligned} \tag{5}$$

The discriminant is always positive because:

- $(k_{01} - k_{21})^2$ is squared, thus it will always be positive regardless of the difference in the two constants,
- k_{12} is given to be positive, and
- it is assumed that $k_{01}, k_{12}, k_{21} > 0$.

That means that the eigenvalues are real and distinct because the discriminant is greater than 0. In order for the eigenvalues to be negative, it must be that

$$(k_{01} + k_{12} + k_{21}) > \sqrt{(k_{01} + k_{12} + k_{21})^2 - 4k_{01}k_{12}}.$$

Squaring both sides, we get

$$\begin{aligned} (k_{01} + k_{12} + k_{21})^2 &> (k_{01} + k_{12} + k_{21})^2 - 4k_{01}k_{12}, \\ 0 &> -4k_{01}k_{12}, \end{aligned}$$

so the inequality is true. Therefore, the eigenvalues of $\mathbf{K}$ are real, distinct, and negative.

2.2 Part b

(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 $\lambda_1\lambda_2 = k_{12}k_{01}$.

Suppose λ_1 and λ_2 are the eigenvalues of $\mathbf{K}$. Since $p_{\mathbf{K}}$ is quadratic, the eigenvalues are given by

$$\lambda_1 = \frac{-(k_{12} + k_{01} + k_{21}) + \sqrt{\Delta}}{2}, \qquad \lambda_2 = \frac{-(k_{12} + k_{01} + k_{21}) - \sqrt{\Delta}}{2}.$$

Then,

$$\begin{aligned}
\lambda_1 + \lambda_2 &= \frac{-(k_{12} + k_{01} + k_{21}) + \sqrt{\Delta}}{2} + \frac{-(k_{12} + k_{01} + k_{21}) - \sqrt{\Delta}}{2}, \\
&= \frac{-(k_{12} + k_{01} + k_{21}) + \sqrt{\Delta} - (k_{12} + k_{01} + k_{21}) - \sqrt{\Delta}}{2}, \\
&= \frac{-2(k_{12} + k_{01} + k_{21})}{2},
\end{aligned}$$

so $\lambda_1 + \lambda_2 = -(k_{12} + k_{01} + k_{21})$.

Now for the other expression,

$$\begin{aligned}
\lambda_1\lambda_2 &= \frac{-(k_{12} + k_{01} + k_{21}) + \sqrt{\Delta}}{2} \frac{-(k_{12} + k_{01} + k_{21}) - \sqrt{\Delta}}{2}, \\
&= \frac{k_{01}^2 + 2k_{01}k_{12} + k_{12}^2 + 2k_{01}k_{21} + 2k_{12}k21 + k_{21}^2 - \Delta}{4}, \\
&= \frac{(k_{01} + k_{12} + k_{21})^2 - \Delta}{4}, \\
&= \frac{(k_{01} + k_{12} + k_{21})^2 - \left[(k_{12} + k_{01} + k_{21})^2 - 4k_{01}k_{12}\right]}{4},
\end{aligned}$$

so $\lambda_1\lambda_2 = k_{01}k_{12}$.

3 Problem 2

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 concentration in each of the compartments. We assume that the eigenvalues of $\mathbf{K}$ satisfy $\lambda_1 < \lambda_2 < 0$. Denote the eigenvalues of λ_1 and λ_2 by

$$\vec{v_1} = \begin{pmatrix} v_{11} \\ v_{21} \end{pmatrix}, \qquad \vec{v_2} = \begin{pmatrix} v_{12} \\ v_{22} \end{pmatrix},$$

respectively.

Then the solution of Equation 1 can be expressed as

$$\vec{x}(t) = \alpha e^{\lambda_1 t}\vec{v_1} + \beta e^{\lambda_2 t}\vec{v_2} \tag{6}$$

where α and β are assumed to be nonzero and depend on initial conditions. Note that we can also write Equation 6 as $\vec{x}(t) = e^{\lambda_1 t}\left(\alpha\vec{v_1} + \beta e^{(\lambda_2 - \lambda_1)t}\vec{v_2}\right)$. Then, as $t \to \infty$, $e^{(\lambda_2 - \lambda_1)t} \to 0$.

So the solution can be approximated as

$$\vec{x}(t) = \alpha e^{\lambda_1 t}\vec{v_1} \tag{7}$$

for large values of t.

The goal is to determine the coefficients in Equation 1 so that we can accurately describe the data.

Using the approximation for large t given in Equation 7, we have the equations

$$x_1(t) = \alpha v_{11} e^{\lambda_1 t}, \qquad x_2(t) = \alpha v_{21} e^{\lambda_1 t}.$$

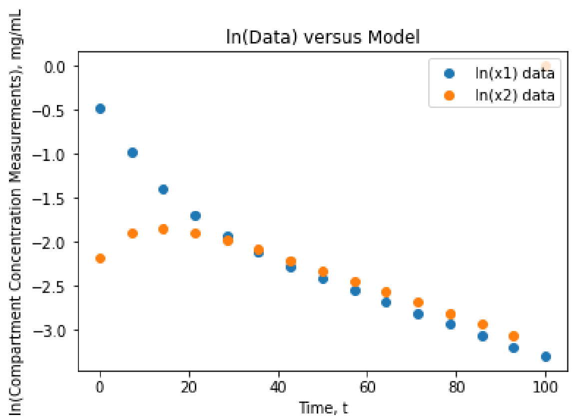

Figure 1: Graphs of the data $\ln x_1$ and $\ln x_2$ are approximately straight lines for values of t such that $e^{(\lambda_2-\lambda_1)t} \approx 0$.

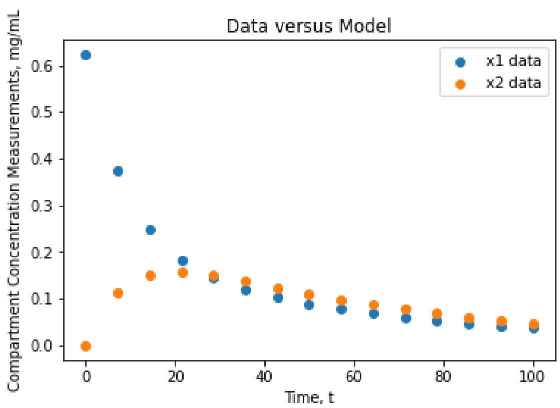

Figure 2: Plot of the compartment concentration measurements in Table 1.

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

Table 1: Compartment concentration measurements.

Now we can take the natural log of both equations and get the following:

$$\ln x_1(t) = \ln(\alpha v_{11}) + \lambda_1 t, \qquad \ln x_2(t) = \ln(\alpha v_{21}) + \lambda_1 t,$$

so we can use the slopes of the graphs of $\ln x_1$ and $\ln x_2$ to approximate λ_1. We choose $t = 50.000$ as the start of the fitting, based on Figure 1.

Next, we should go on to do a least squares regression using both the $\ln x_1$ and $\ln x_2$ data to approximate λ_1, αv_{11}, and αv_{21}. We will choose λ_1 to be the average of the results. So,

$$\lambda_1 = -0.0174, \qquad \alpha v_{11} = 0.2132, \qquad \alpha v_{21} = 0.2603.$$

By Equation 6, we have $\beta e^{\lambda_2 t}\vec{v_2} = \vec{x}(t) - \alpha e^{\lambda t}\vec{v_1}$. This gives the equations

$$x_1(t) - \alpha v_{11} e^{\lambda_1 t} = \beta v_{12} e^{\lambda_2 t}, \qquad x_2(t) - \alpha v_{21} e^{\lambda_1 t} = \beta v_{22} e^{\lambda_2 t}.$$

Since we now have approximations for λ_1, αv_{11}, and αv_{21}, we can take the natural log of both equations to obtain linear expressions with which we can fit to the data to obtain approximations for λ_2, βv_{12}, and βv_{22}:

$$\ln\left(x_1(t) - \alpha v_{11} e^{\lambda_1 t}\right) = \ln(\beta v_{12}) + \lambda t, \qquad \ln\left(x_2(t) - \alpha v_{21} e^{\lambda_1 t}\right) = \ln(\beta v_{22}) + \lambda t.$$

This time we fit from $t = 0.000$ *until* $t = 50.000$ since we're trying to find the residual before the behavior becomes approximately linear. Again, we choose λ_2 to be the average of the results from the two equations. So,

$$\lambda_2 = -0.1324, \qquad \beta v_{12} = 0.5371, \qquad \beta v_{22} = 0.2953.$$

4 Problem 3

3. Computing the Entries of K from Its Eigenvalues and Eigenvectors. Let's denote the matrix $\mathbf{V}$ whose columns are the eigenvectors $\vec{v_1}$ and $\vec{v_2}$ of $\mathbf{K}$. That is,

$$\mathbf{V} = \begin{pmatrix} \vec{v_1} & \vec{v_2} \end{pmatrix} = \begin{pmatrix} v_{11} & v_{12} \\ v_{21} & v_{22} \end{pmatrix}.$$

Since $\mathbf{K}$ is a square matrix, we can apply eigenvalue decomposition to obtain

$$\mathsf{K} = \mathsf{V}\Lambda\mathbf{V}^{-1}, \text{ where } \Lambda = \begin{pmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{pmatrix}. \tag{8}$$

If we assume λ_1 and λ_2 are good estimates, then we have

$$\begin{pmatrix} e^{\lambda_1 t_1} & e^{\lambda_2 t_1} \\ e^{\lambda_1 t_2} & e^{\lambda_2 t_2} \\ e^{\lambda_2 t_3} & e^{\lambda_2 t_3} \\ \vdots & \vdots \end{pmatrix} \mathbf{V} = \begin{pmatrix} x_1(t_1) & x_2(t_1) \\ x_1(t_2) & x_2(t_2) \\ x_1(t_3) & x_2(t_3) \\ \vdots & \vdots \end{pmatrix},$$

and so we can solve for $\mathbf{V}$ using least squares and then find $\mathbf{K}$ by applying Equation 8. This gives

$$\mathbf{V} = \begin{pmatrix} 0.2259 & 0.2540 \\ 0.4055 & -0.2594 \end{pmatrix}.$$

So using Equation 8, we get the following entries for the matrix $\mathbf{K}$ gives

$$\mathbf{K} = \begin{pmatrix} -0.0907 & 0.0408 \\ 0.0749 & -0.0591 \end{pmatrix}.$$

5 Problem 4

From Equation 2, we got the $\mathbf{K}$ matrix to be:

$$\mathbf{K} = \begin{pmatrix} -k_{01} - k_{21} & k_{12} \\ k_{21} & -k_{12} \end{pmatrix} = \begin{pmatrix} -0.0907 & 0.0408 \\ 0.0749 & -0.0591 \end{pmatrix}.$$

Since there is a difference in what k_{12} is, we can take k_{12} to be the mean of the values calculated by the least squares instead. Note that the values we found for k_{01}, k_{12}, k_{21} are indeed greater than 0, so it matches up with the requirements/assumptions we made from the very beginning.

After taking the mean of the values calculated by the least squares for k_{12}, we get the following values for the parameters: $k_{01} = 0.0158, k_{12} = 0.0500$, and $k_{21} = 0.0749$.

Now, to find the general solution parameters α and β in Equation 6, we will use the first line of Table 1. Using $t = 0.000$ and $x_1 = 0.623$, so we have the simple linear system

$$0.623 = 0.2259\alpha + 0.2540\beta,$$
$$0.000 = 0.4055\alpha - 0.2594\beta.$$

Solving gives $\alpha = 1.0000$ and $\beta = 1.5635$.

6 Problem 5

So to summarize, these are the values we got so far: $k_{01} = 0.0158$, $k_{12} = 0.0500$, $k_{21} = 0.0749$, $\alpha = 1.0000$, and $\beta = 1.5635$.

Using these parameters to put into 6, we get the following approximation for the long-term behavior:

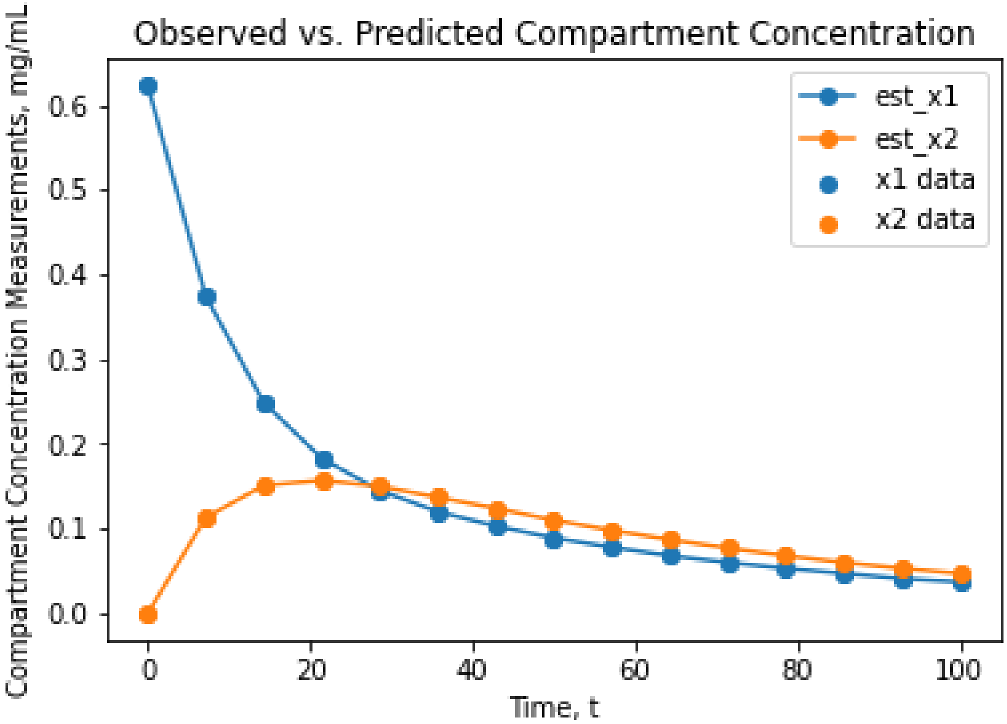

Figure 3: Graph of the model solution in Equation 6 with parameters with the data from Table 1.

7 References

References

J. Mazumdar M. Banerjee, L. Y. Teng (1991). "A mathematical study of simple exponential modelling in biochemical processes." In: https://pubmed.ncbi.nlm.nih.gov/1789775/.

Oikonen, Vesa (2019). "Pharmacokinetic two-compartment model". In: http://www.turkupetcentre.net/petanalysis/pk_2cm.html.