Estimating Rate Constants for an Open Two-Compartment Model

November 10th, 2020

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Abstract

The process of exponential peeling is described in a detailed process for obtaining estimates for coefficients of the sum of exponential terms by using data filling techniques. The exponential peeling method is used to obtain estimates for the least squares regression coefficients of each exponential term. Determining these coefficients enables estimations of rate constants through evaluation of a matrix equation. Using the matrix equation approximates the rate constants and enables for solving a system of differential equations and initial value problems to compare estimates with the data.

Introduction

Pharmacokinetics are modeled by separating physiological systems into compartments. The unique physiological compartments describe the absorption, distribution and elimination of the varying methods of drug intake into a physiological system. The compartment model that is analyzed is an open Two-Compartment model that describes the absorption, distribution and elimination of a single intravenous drug dose. The compartments and their rate constants can be characterized where x_1 is the concentration of the drug dose in the Central Compartment containing blood and extracellular water, x_2 is the concentration of the Tissue Compartment, k_{01} is the rate constant of the drug dose being eliminated from the system, k_{21} is the rate constant of the drug dose being distributed from the Central Compartment to the Tissue Compartment and k_{12} is the rate constant of the drug dose that is being distributed from the Tissue Compartment to the Central Compartment. Figure 1 depicts the open Two-Compartment Model. The open two-compartment system can be described by the following system:

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

or $\vec{x}' = \boldsymbol{K}\vec{x},$ so that

$$\boldsymbol{K} = \begin{pmatrix} K_{11} & K_{12} \\ K_{21} & K_{22} \end{pmatrix}\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} -(k_{01} + k_{21}) & k_{12} \\ k_{21} & -k_{12} \end{pmatrix}\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} \qquad (2)$$

This project aims to find the rate constants of absorption, distribution and elimination of a single intravenous drug dose of an open Two-Compartment model. Exponential peeling is the process in obtaining estimates of coefficients through a least squares regression of a sum of exponential terms enables in determine the values of the solution.

$$\vec{x}(t) \ = \ \alpha e^{\lambda_1 t}\,\vec{v_1} \ + \ \beta e^{\lambda_2 t}\,\vec{v_2} \qquad (3)$$

Obtaining values for λ_1 and λ_2 allow for evaluating a matrix equation to find the corresponding eigen-vectors with its respective eigenvalues. The eigenvectors enable computation of (2). With the estima-tions from (2) the system of differential equations can be evaluated and compared to the data in the open Two- Compartment model.

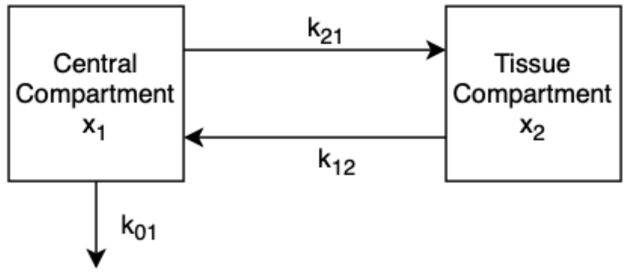


Figure 1: Open Two-Compartment Model of the single intravenous drug dose.

Determining the Amount of Solutions in the K Matrix

It is assumed that the rate constants k_{01}, k_{12} and k_{21} are positive to show that the eigenvalues of **K** are real, distinct and negative. To show that the eigenvalues, λ_1 and λ_2 are real, distinct and negative the discriminant of the characteristic polynomial of ***K*** is positive. It follows that:

$$\det(K - \lambda \mathrm{I}) = 0 \tag{4}$$
$$(-(k_{01} + k_{21}) - \lambda) - k_{12} - \lambda) - k_{12} k_{21} = 0 \tag{5}$$
$$-k_{12}(-k_{01} - k_{21}) + \lambda(k_{01} + k_{21}) + \lambda \mathrm{k}_{12} + \lambda^2 - k_{12} k_{21} = 0 \tag{6}$$
$$k_{12} k_{01} + \lambda \mathrm{k}_{01} + \lambda \mathrm{k}_{21} + \lambda \mathrm{k}_{12} + \lambda^2 = 0 \tag{7}$$
$$\lambda^2 + \lambda(k_{01} + k_{21} + k_{12}) + k_{12} k_{01} = 0 \tag{8}$$

Equation (8) is in the form of a quadratic equation. The discriminant of a quadratic equation is $b^2 - 4\,\mathrm{ac}$ where $a = 1$, $b^2 = (k_{01} + k_{21} + k_{12})$ and $c = k_{12} k_{01}$. To compute the discriminant of the quadratic equation we complete the following steps:

$$b^2 - 4\,a\,c = (k_{01} + k_{21} + k_{12})^2 - 4\,k_{12} k_{01} \tag{9}$$
$$= k_{01}^2 + k_{12}^2 + k_{21}^2 + 2\,k_{12} k_{21} + 2\,k_{21} k_{01} - 2\,k_{12} k_{01} \tag{10}$$
$$= (k_{01}^2 + k_{12}^2 - 2\,k_{12} k_{01}) + k_{21}^2 + 2\,k_{12} k_{21} + 2\,k_{21} k_{01} \tag{11}$$
$$= (k_{01} - k_{12})^2 + (k_{21}^2 + 2\,k_{12} k_{21} + 2\,k_{21} k_{01}) \tag{12}$$

Both parts of the discriminant in (12) will be positive, since all rate constants in the discriminant are positive and terms are squared to ensure a positivity. Since the discriminant is positive there exist two real solutions. By this, the quadratic equation $\lambda^2 + \lambda(K_{01} + K_{21} + K_{12}) + K_{12} K_{01} = 0$ can be factored, so that there exist two real numbers p and q, such that $p \cdot q = k_{12} k_{01}$ and $p + q = k_{01} + k_{21} + k_{12}$ so the following holds true:

$$(\lambda_1 + p)(\lambda_2 + q) = 0 \tag{13}$$
$$\lambda_1 + p = 0 \text{ and } \lambda_2 + q = 0$$
$$\lambda_1 = -p \text{ and } \lambda_2 = -q$$

Where λ_1 and λ_2 are negative and distinct values. In order to find the values of λ_1 and λ_2 we know there exists two real solutions because the discriminant was positive. When factoring a quadratic equation the sum of the two roots are the opposite of b, in this case, $-(\mathrm{k}_{01} + \mathrm{k}_{21} + \mathrm{k}_{12})$ and the product of the two roots are $k_{12} k_{01}$. This result will prove to be useful in identifying the eigenvalues and eigenvectors in the estimations.

Estimating Eigenvalues and Eigenvectors

The open Two-Compartment Model has recorded concentrations on a time interval starting from zero minutes to one hundred minutes characterized in the Figure 2. By previous work, it is assumed that the eigenvalues of **K** satisfy $\lambda_2 < \lambda_1 < 0$ and the eigenvectors of λ_1 and λ_2 are $\vec{v}_1 = \begin{pmatrix} v_{11} \\ v_{12} \end{pmatrix}$ and $\vec{v}_2 = \begin{pmatrix} v_{21} \\ v_{22} \end{pmatrix}$ respectively. The solution to (1) is denoted by the vector equation.

$$\vec{x}(t) = \alpha e^{\lambda_1 t} \vec{v_1} + \beta e^{\lambda_2 t} \vec{v_2} \tag{14}$$

Exponential peeling is used to find estimates of the eigenvalues and eigenvectors in (14). Exponential peeling is the interactive process of fitting data by a sum of exponential terms. The peeling method is used to obtain estimates of the coefficients for each exponential term using a Least Squares Regression Line. Finding the coefficients for the first exponential term requires initial exponential peeling methods. Taking the logarithm of the Two-Compartment data provides a linear region to complete a Least Squares Regression to find the slopes, λ_1, and the y - intercepts, $\ln(\alpha v_{11})$ and $\ln(\alpha v_{12})$ of each compartment concentration. Completing the Least Squares Regression on the closed time interval from 64.286 minutes to 100 minutes allows for the linear regression lines.

$$\begin{aligned} x_1(t) &= -1.58331 - 0.017221\, t \\ x_2(t) &= -1.3295 - 0.0172982\, t \end{aligned} \tag{15}$$

It is observed that the lines are parallel to indicate that the slope of the Least Squares Regression Lines are the same allowing for $\lambda_1 \approx -0.017$ to be used as the exponent in the first term of the sum in (14), and the intercepts can be used as $\vec{v_1}$. The Least Squares Regression Line for the first exponential term can be depicted in Figure 3.

The coefficients in the second exponential term, λ_2, $\ln(\beta v_{21})$ and $\ln(\beta v_{22})$ are found completing an additional exponential peeling using residual data , $x_r^*(t) = x^*(t) - \begin{pmatrix} 0.205294 \\ 0.26461 \end{pmatrix} e^{-0.017\, t}$, on the closed time interval on 14.286 minutes to 57.143 minutes. The residual data is computed on the interval by taking the difference between the data points in the compartments and the first exponential term with its estimates. After computing the residual data it is essential to take the logarithm of the data to find a linear region. Completing a Least Squares Regression of the linear region on the closed interval of 14.286 minutes to 57.143 minutes allowed for the linear regression lines to find the coefficients of the second exponential term.

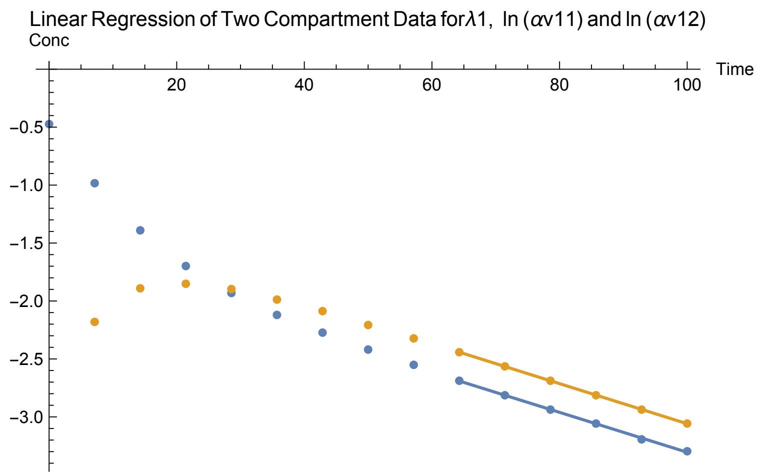
$$\begin{aligned} x_1^*(t) &= -1.02293 - 0.101472\,t \\ x_2^*(t) &= -1.37182 - 0.106002\,t \end{aligned} \tag{16}$$

The slope for the Least Squares Regression lines are approximately the same indicating that $\lambda_2 \approx -0.11$. Completing the exponential peeling process obtained the coefficients for (14) by finding the Least Squares Regression on intervals of the Two - Compartment data for the single intravenous drug dose. The estimated solution of (1) can be identified through the exponential peeling process. The estimation of the coefficients enable the computation and estimation of **K** by using the eigenvalues and their corresponding eigenvectors .

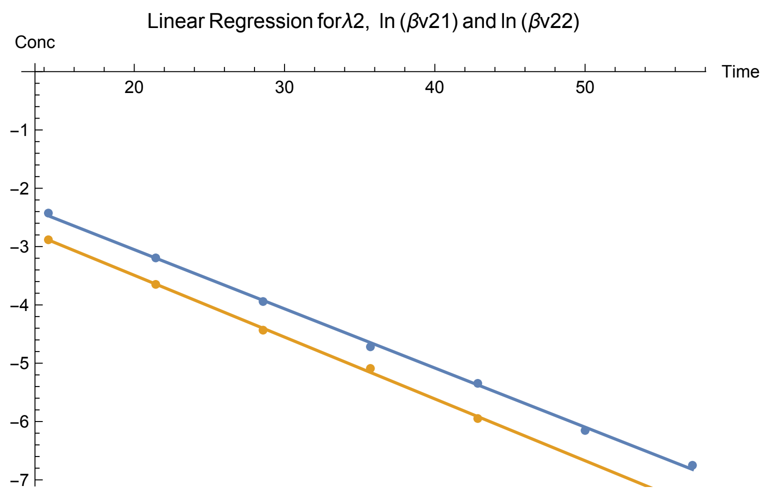
$$\vec{x}(t) = \begin{pmatrix} 0.205294 \\ 0.26461 \end{pmatrix} e^{-0.017\,t} + \begin{pmatrix} 0.35954 \\ 0.253645 \end{pmatrix} e^{-0.11\,t} \tag{17}$$

Time (minutes)	x1 (mg/mL)	x2 (mg/mL)
0	0.623	0
7.143	0.374	0.113
14.286	0.249	0.151
21.429	0.183	0.157
28.571	0.145	0.15
35.714	0.12	0.137
42.857	0.103	0.124
50	0.089	0.11
57.143	0.078	0.098
64.286	0.068	0.087
71.429	0.06	0.077
78.571	0.053	0.068
85.714	0.047	0.06
92.857	0.041	0.053
100	0.037	0.047

Figure 2: Open Two - Compartment concentration measurements



<u>Figure 3:</u> Linear Regression of the Two-Compartment Data to find the coefficients in the first exponential term.



<u>Figure 4:</u> Linear Regression of the Residual Open Two - Compartment Data to find the coefficients in the second exponential term

Computing Entries of **K** from its Eigenvalues and Eigenvectors

The corresponding eigenvalues and compartment concentration data are used to calculate an approximation of the eigenvectors $\vec{v}_1$ and $\vec{v}_2$. The matrix equations in (18) compute the approximations of $\vec{v}_1$ and $\vec{v}_2$. The matrix equation is an overdetermined solution set because there are more row than columns in each of the matrix equations. To find the approximate solutions for the corresponding vectors a Least Squares Regression is used to find the values that make the matrix equation consistent. The assumption is made that the eigenvalue estimations are known.

$$\begin{pmatrix} e^{-0.017*0} & e^{-0.11*0} \\ e^{-0.017*7.143} & e^{-0.11*7.143} \\ . & . \\ . & . \\ . & . \\ e^{-0.017*100} & e^{-0.11*100} \end{pmatrix} \begin{pmatrix} v_{11} \\ v_{12} \end{pmatrix} = \begin{pmatrix} 0.623 \\ 0.374 \\ . \\ . \\ . \\ 0.037 \end{pmatrix} \text{ and } \begin{pmatrix} e^{-0.017*0} & e^{-0.11*0} \\ e^{-0.017*7.143} & e^{-0.11*7.143} \\ . & . \\ . & . \\ . & . \\ e^{-0.017*100} & e^{-0.11*100} \end{pmatrix} \begin{pmatrix} v_{21} \\ v_{22} \end{pmatrix} = \begin{pmatrix} 0.000 \\ 0.113 \\ . \\ . \\ . \\ 0.047 \end{pmatrix} \quad (18)$$

Completing the Least Squares Regression for the matrix equations in (18) results in **V.**

$$\boldsymbol{V} = \begin{pmatrix} 0.205314 & 0.418607 \\ 0.261026 & -0.260609 \end{pmatrix} \quad (19)$$

Finding the approximation of **V** enables for the calculation of **K** using the equation **KV** = **VΛ** where $\mathbf{\Lambda} = \begin{pmatrix} \lambda_1 & 0 \\ 0 & \lambda_1 \end{pmatrix}$. The estimation of **K** is computed by the following equation $\boldsymbol{K} = \mathbf{V\Lambda}\boldsymbol{V}^{-1}$ so that $\boldsymbol{K} = \begin{pmatrix} -0.0794293 & 0.0491047 \\ 0.0388661 & -0.0475707 \end{pmatrix}$. By having **K** this provides the basis for identifying estimations for the rate constants.

Entries of **K**

The estimates of **K** are denoted by $\hat{\boldsymbol{K}}_{\mathrm{ij}}$ and the estimates $\hat{\lambda}_1$ and $\hat{\lambda}_2$ are the eigenvalues of **K**. Equation (2) will be used to determine the estimate value of $\hat{k}_{01}$ of k_{01}. It follows that $\boldsymbol{K} = \begin{pmatrix} K_{11} & K_{21} \\ K_{12} & K_{22} \end{pmatrix} = \begin{pmatrix} -k_{01} - k_{21} & k_{12} \\ k_{21} & -k_{12} \end{pmatrix}$. Through this, the rate constants k_{12} and k_{21} are easily estimated to be 0.048 and 0.0388661 respectively since there values are represented in **K** .To calculate the rate constant $\hat{k}_{01}$ the following is needed.

$$\begin{aligned} \hat{k}_{01} &= -0.0388661 + 0.0794293 \\ \hat{k}_{01} &= 0.403632 \end{aligned} \quad (20)$$

By previous work, it is a fact that $\lambda_1 + \lambda_2 = -(k_{01} + k_{12} + k_{21})$ and $\lambda_1 \lambda_2 = k_{12}\, k_{01}$. These equations can be used to verify that the estimated rate constants are true estimation of the Two - Compartment model. Let $(-0.017 + -0.11) = -(0.403632 + 0.048 + 0.0388661)$ such that $-0.127 = -0.127429$ are approximate estimations and are approximately the same. Now, let $(-0.017)(-0.11) = (0.048)(0.0403632)$ such that $0.00187 = 0.00194703$ are estimations that are close to each other. These calculations are evidence that the rate constant estimate $\hat{k}_{01} = 0.403632$. It holds true that the rate constants are all positive. By finding estimations of the rate constants this provides the opportunity to compare our estimated solution (17) through exponential peeling to the solution through solving the system of differential equations and the initial value problem.

System of Differential Equations

To determine the validity of the process that has been completed the rate constants computed in the aforementioned section will be used in (2) is evaluated with the initial conditions such that $x_1(0) = 0.623$ and $x_2(0) = 0.000$.

$$\begin{aligned} x_1' &= -0.0794293\, x_1 + 0.048\, x_2 \\ x_2' &= 0.0388661\, x_1 - 0.048\, x_2 \end{aligned} \tag{21}$$

Solving the differential equation and the initial value problem created a solution that was close to the estimations that were calculated in the previous sections. The solution to the system of differential equations is shown below compared to the estimated solution to (2) made in the previous sections. The solution to the system of differential equations.

$$\vec{x}(t) = \begin{pmatrix} 0.204997 \\ 0.263408 \end{pmatrix} e^{-0.0177525\, t} + \begin{pmatrix} 0.418003 \\ 0.263408 \end{pmatrix} e^{-0.109677\, t} \tag{22}$$

The estimated solution of the system of differential equations.

$$\vec{\hat{x}}(t) = \begin{pmatrix} 0.205314 \\ 0.263408 \end{pmatrix} e^{-0.017\, t} + \begin{pmatrix} 0.418607 \\ -0.260609 \end{pmatrix} e^{-0.11\, t} \tag{23}$$

The two solutions (22) and (23) are close by inspection alone. This indicates that the data and the lines that the solution created should fit the Two - Compartment data points. Figure 5 depicts the relationship between the solution of the system of differential equations with the two - compartment concentration data points.

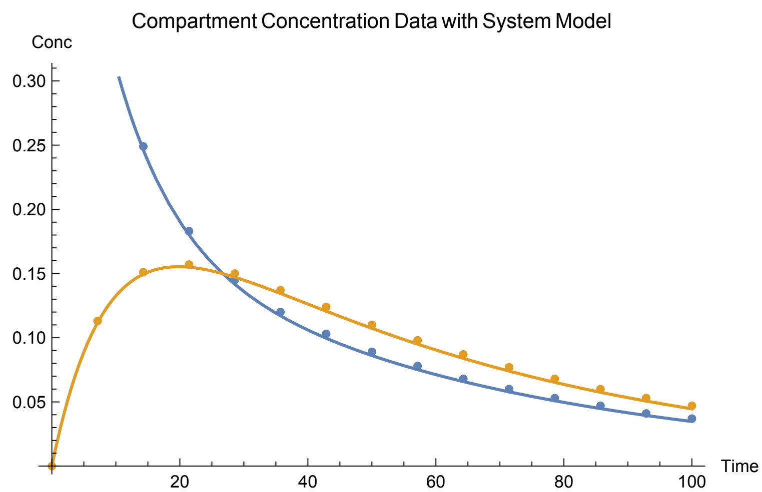


Figure 5: Two - Compartment Concentration Data with the solution of the system of differential equations.

Conclusion

The estimation of the rate constants in the open Two - Compartment model was approximated through the process of exponential peeling to find the coefficients in the sum of the exponential terms providing an estimated solution of (1). The estimations of λ_1 and λ_2 provided opportunities to find approximations of their corresponding eigenvectors to compute an estimation of **K.** These estimations provided the necessary information, the rate constants, to solve the system of differential equations to compare the solutions to each other and the data.

This process revealed that the estimated solution (17) and (22) show that the rate constants are consistent with the data.

References

Smith, L. B. (1969). PEEL - A Program to Perform Exponential “Peeling” (Fitting) On-Line. CGTM, 73.

Appendix

Question 2:

a.) Explain why the graphs of lnx1[t] and lnx2[t] should be approximately straight lines with slopes equal to λ1 and intercepts lnαv11 and lnαv21, respectively. Thus estimate of λ1, αv11 and αv21 may be obtained by fitting straight lines to the data lnx1*[tn] and lnx2*[tn] corresponding to values of tn, where the graphs of the logarithms of the data are approximately linear.

In[∘]:=
```
x1andx2data = {{0, 0.623, 0}, {7.143, 0.374, 0.113}, {14.286, 0.249, 0.151},
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  {42.857, 0.103, 0.124}, {50, 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, 0.037, 0.047}}
```

Out[∘]=
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{{0, 0.623, 0}, {7.143, 0.374, 0.113}, {14.286, 0.249, 0.151},
 {21.429, 0.183, 0.157}, {28.571, 0.145, 0.15}, {35.714, 0.12, 0.137},
 {42.857, 0.103, 0.124}, {50, 0.089, 0.11}, {57.143, 0.078, 0.098},
 {64.286, 0.068, 0.087}, {71.429, 0.06, 0.077}, {78.571, 0.053, 0.068},
 {85.714, 0.047, 0.06}, {92.857, 0.041, 0.053}, {100, 0.037, 0.047}}
```

In[∘]:=
```
Grid[x1andx2data]
```

Out[∘]=

0	0.623	0
7.143	0.374	0.113
14.286	0.249	0.151
21.429	0.183	0.157
28.571	0.145	0.15
35.714	0.12	0.137
42.857	0.103	0.124
50	0.089	0.11
57.143	0.078	0.098
64.286	0.068	0.087
71.429	0.06	0.077
78.571	0.053	0.068
85.714	0.047	0.06
92.857	0.041	0.053
100	0.037	0.047

In[•]:=
```
ReplacePart[%45,
 1 → Prepend[First[%45], {"Time (minutes)", "x1 (mg/mL)", "x2 (mg/mL)"}]]
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Out[•]=

Time (minutes)	x1 (mg/mL)	x2 (mg/mL)
0	0.623	0
7.143	0.374	0.113
14.286	0.249	0.151
21.429	0.183	0.157
28.571	0.145	0.15
35.714	0.12	0.137
42.857	0.103	0.124
50	0.089	0.11
57.143	0.078	0.098
64.286	0.068	0.087
71.429	0.06	0.077
78.571	0.053	0.068
85.714	0.047	0.06
92.857	0.041	0.053
100	0.037	0.047

In[•]:=
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  Dividers → {Black, {2 → Black}}, Frame → True, Spacings → {2, {2, {0.7}, 2}}}, 2]
```

Out[•]=

Time (minutes)	x1 (mg/mL)	x2 (mg/mL)
0	0.623	0
7.143	0.374	0.113
14.286	0.249	0.151
21.429	0.183	0.157
28.571	0.145	0.15
35.714	0.12	0.137
42.857	0.103	0.124
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57.143	0.078	0.098
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78.571	0.053	0.068
85.714	0.047	0.06
92.857	0.041	0.053
100	0.037	0.047


```
Insert[%47, {Background → {None, {GrayLevel[0.7], {White}}},
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In[•]:=
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x1data = {{0, 0.623}, {7.143, 0.374}, {14.286, 0.249},
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  {50, 0.089}, {57.143, 0.078}, {64.286, 0.068}, {71.429, 0.060},
  {78.571, 0.053}, {85.714, 0.047}, {92.857, 0.041}, {100, 0.037}}
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In[•]:=
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x2data = {{0, 0}, {7.143, 0.113}, {14.286, 0.151}, {21.429, 0.157}, {28.571, 0.150},
  {35.714, 0.137}, {42.857, 0.124}, {50, 0.110}, {57.143, 0.098}, {64.286, 0.087},
  {71.429, 0.077}, {78.571, 0.068}, {85.714, 0.060}, {92.857, 0.053}, {100, 0.047}}
```

In[•]:=
```
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```

In[•]:=
```
Show[%50, AxesLabel → {HoldForm[Tme], RawBoxes[RowBox[{"Conc", "."}]]},
 PlotLabel → HoldForm[Two - Compartment Data], LabelStyle → {GrayLevel[0]}]
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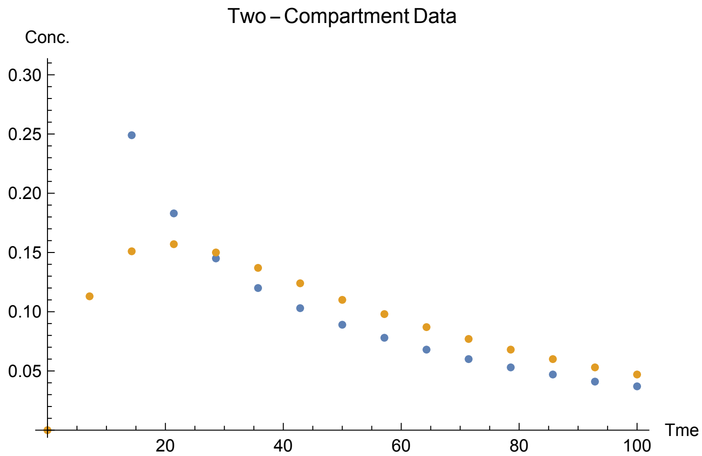
Out[•]=



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  {42.857, Log[0.103]}, {50, Log[0.089]}, {57.143, Log[0.078]},
  {64.286, Log[0.068]}, {71.429, Log[0.060]}, {78.571, Log[0.053]},
  {85.714, Log[0.047]}, {92.857, Log[0.041]}, {100, Log[0.037]}}
```

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 {28.571, -1.93102}, {35.714, -2.12026}, {42.857, -2.27303},
 {50, -2.41912}, {57.143, -2.55105}, {64.286, -2.68825}, {71.429, -2.81341},
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In[•]:=
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  {42.857, Log[0.124]}, {50, Log[0.110]}, {57.143, Log[0.098]},
  {64.286, Log[0.087]}, {71.429, Log[0.077]}, {78.571, Log[0.068]},
  {85.714, Log[0.060]}, {92.857, Log[0.053]}, {100, Log[0.047]}}
```

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{{0, -∞}, {7.143, -2.18037}, {14.286, -1.89048}, {21.429, -1.85151},
 {28.571, -1.89712}, {35.714, -1.98777}, {42.857, -2.08747},
 {50, -2.20727}, {57.143, -2.32279}, {64.286, -2.44185}, {71.429, -2.56395},
 {78.571, -2.68825}, {85.714, -2.81341}, {92.857, -2.93746}, {100, -3.05761}}
```

In[•]:=
```
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```

In[∘]:=
```
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       "of", " ", "Two", " ", "Compartment", " ", "Data", " ", "forλ1"}],
     ",", " ", RowBox[{"ln", RowBox[{"(", "αv11", ")"}], " ", "and", " ",
       "ln", RowBox[{"(", "αv12", ")"}]}]}]}]], LabelStyle → {GrayLevel[0]}]
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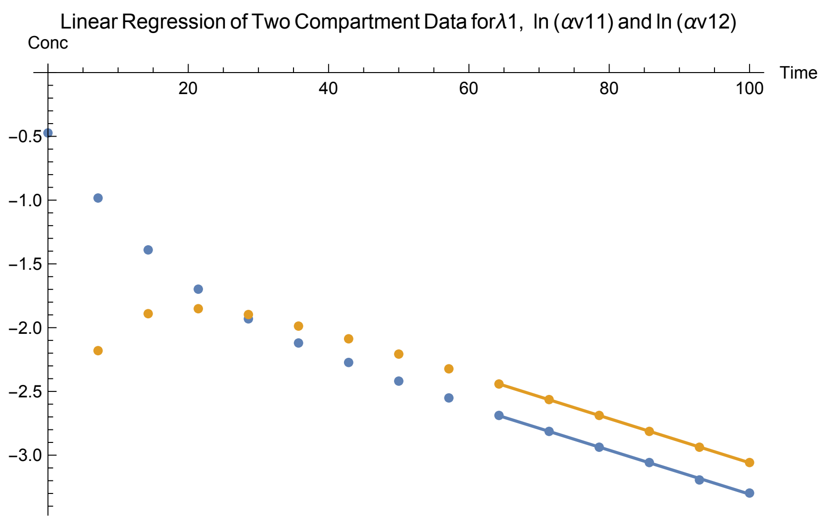
Out[∘]=



In[∘]:=
```
SubGroupLogx1Dataλ1 =
 {{64.286, Log[0.068]}, {71.429, Log[0.060]}, {78.571, Log[0.053]},
  {85.714, Log[0.047]}, {92.857, Log[0.041]}, {100, Log[0.037]}}
```

Out[∘]=
```
{{64.286, -2.68825}, {71.429, -2.81341}, {78.571, -2.93746},
 {85.714, -3.05761}, {92.857, -3.19418}, {100, -3.29684}}
```

In[∘]:=
```
SubGroupLogx2Dataλ1 =
 {{64.286, Log[0.087]}, {71.429, Log[0.077]}, {78.571, Log[0.068]},
  {85.714, Log[0.060]}, {92.857, Log[0.053]}, {100, Log[0.047]}}
```

Out[∘]=
```
{{64.286, -2.44185}, {71.429, -2.56395}, {78.571, -2.68825},
 {85.714, -2.81341}, {92.857, -2.93746}, {100, -3.05761}}
```

In[∘]:=
```
x1lineλ1 = Normal[LinearModelFit[SubGroupLogx1Dataλ1, t, t]]
```

Out[∘]= $-1.58331-0.0172218\,t$

In[∘]:=
```
Exp[-1.58331]
```

Out[∘]= 0.205294

In[∘]:=
```
x2lineλ1 = Normal[LinearModelFit[SubGroupLogx2Dataλ1, t, t]]
```

Out[∘]= $-1.3295-0.0172982\,t$

In[∘]:=
```
Exp[-1.3295]
```

Out[∘]= 0.26461

---

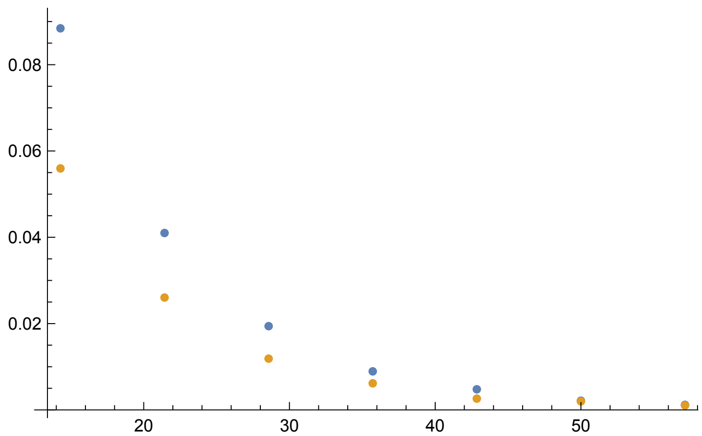
b.) Given that both components of the data x*[tn] are accurately represented by a sum of exponential functions of the form (i), explain how to find the estimates of $\lambda 2$, βv12 and βv22 using the residual data where estimates of $\lambda 1$ and αv11 and αv21 are used.

In[•]:=
```
f[t_] = Exp[-1.58331] * Exp[-0.0172 * t]
```
Out[•]=
```
0.205294 e^(-0.0172 t)
```

In[•]:=
```
g[t_] = Exp[-1.3295] * Exp[-0.0172 * t]
```
Out[•]=
```
0.26461 e^(-0.0172 t)
```

In[•]:=
```
Residualx1Data = {{14.286, 0.249 - f[14.286]}, {21.429, 0.183 - f[21.429]},
  {28.571, 0.145 - f[28.571]}, {35.714, 0.120 - f[35.714]},
  {42.857, 0.103 - f[42.857]}, {50, 0.089 - f[50]}, {57.143, 0.078 - f[57.143]}}
```
Out[•]=
```
{{14.286, 0.0884306}, {21.429, 0.0409944}, {28.571, 0.0194098},
 {35.714, 0.00892957}, {42.857, 0.00477067}, {50, 0.00212717}, {57.143, 0.00117073}}
```

In[•]:=
```
Residualx2Data = Abs[{{14.286, 0.151 - g[14.286]}, {21.429, 0.157 - g[21.429]},
   {28.571, 0.150 - g[28.571]}, {35.714, 0.137 - g[35.714]},
   {42.857, 0.124 - g[42.857]}, {50, 0.110 - g[50]}, {57.143, 0.098 - g[57.143]}}]
```
Out[•]=
```
{{14.286, 0.0559622}, {21.429, 0.0260348}, {28.571, 0.0118766},
 {35.714, 0.00616166}, {42.857, 0.00261043}, {50, 0.00197272}, {57.143, 0.00102731}}
```

In[•]:=
```
ListPlot[{Residualx1Data, Residualx2Data}]
```
Out[•]=


In[•]:=
```
LogResidualx1Data = {{14.286, Log[0.249 - f[14.286]]},
  {21.429, Log[0.183 - f[21.429]]}, {28.571, Log[0.145 - f[28.571]]},
  {35.714, Log[0.120 - f[35.714]]}, {42.857, Log[0.103 - f[42.857]]},
  {50, Log[0.089 - f[50]]}, {57.143, Log[0.078 - f[57.143]]}}
```
Out[•]=
```
{{14.286, -2.42554}, {21.429, -3.19432}, {28.571, -3.94198},
 {35.714, -4.71839}, {42.857, -5.34527}, {50, -6.15296}, {57.143, -6.75013}}
```

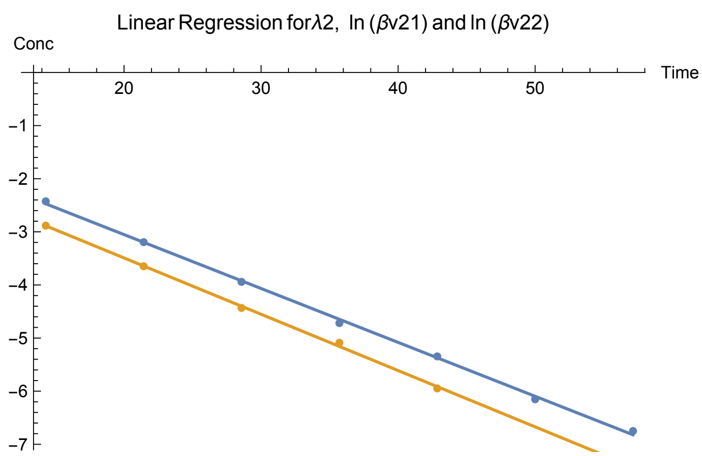
In[•]:=
```
LogResidualx2Data = {{14.286`, Log[0.05596218159845728`]},
   {21.429`, Log[0.026034832998461016`]}, {28.571`, Log[0.011876561539305941`]},
   {35.714`, Log[0.006161659675570474 4`]}, {42.857`, Log[0.0026104283793260685`]}}
```

Out[•]=
```
{{14.286, -2.88308}, {21.429, -3.64832},
 {28.571, -4.43319}, {35.714, -5.08941}, {42.857, -5.94824}}
```

In[•]:=
```
Show[ListPlot[{LogResidualx1Data, LogResidualx2Data}],
 Plot[{x1lineλ2, x2lineλ2}, {t, 14.286, 57.143}]]
```

In[•]:=
```
Show[%42, AxesLabel → {HoldForm[Time], HoldForm[Conc]},
 PlotLabel → RawBoxes[RowBox[{RowBox[{"Linear", " ", "Regression", " ", "forλ2"}],
     ",", " ", RowBox[{"ln", RowBox[{"(", "βv21", ")"}], " ", "and", " ",
       "ln", RowBox[{"(", "βv22", ")"}]}]}]], LabelStyle → {GrayLevel[0]}]
```

Out[•]=



In[•]:=
```
x1lineλ2 = Normal[LinearModelFit[LogResidualx1Data, t, t]]
```

Out[•]=
```
-1.02293 - 0.101472 t
```

In[•]:=
```
Exp[-1.02293]
```

Out[•]=
```
0.35954
```

In[•]:=
```
x2lineλ2 = Normal[LinearModelFit[LogResidualx2Data, t, t]]
```

Out[•]=
```
-1.37182 - 0.106002 t
```

In[•]:=
```
Exp[-1.37182]
```

Out[•]=
```
0.253645
```

Question 3:

Assume that the eigenvalues and the corresponding eigenvector of **K** are know. Show that the entries of the matrix **K** must satisfy the following equations.

In[•]:=
```
Quit[]
```

```
In[•]:= x1[t_] = Exp[-0.017 * t]
Out[•]= e^(-0.017 t)

In[•]:= x2[t_] = Exp[-0.11 * t]
Out[•]= e^(-0.11 t)

In[•]:= EigenvalueEquations =
         {{x1[0], x2[0]}, {x1[7.143], x2[7.143]}, {x1[14.286], x2[14.286]},
          {x1[21.429], x2[21.429]}, {x1[28.571], x2[28.571]}, {x1[35.714], x2[35.714]},
          {x1[42.857], x2[42.857]}, {x1[50], x2[50]}, {x1[57.143], x2[57.143]},
          {x1[64.286], x2[64.286]}, {x1[71.429], x2[71.429]}, {x1[78.571], x2[78.571]},
          {x1[85.714], x2[85.714]}, {x1[92.857], x2[92.857]}, {x1[100], x2[100]}}
Out[•]= {{1., 1.}, {0.885652, 0.455787}, {0.78438, 0.207742},
         {0.694688, 0.0946859}, {0.615262, 0.0431613}, {0.544908, 0.0196724},
         {0.482599, 0.00896641}, {0.427415, 0.00408677}, {0.378541, 0.0018627},
         {0.335256, 0.000848993}, {0.29692, 0.00038696}, {0.262972, 0.000176391},
         {0.232902, 0.0000803965}, {0.20627, 0.0000366437}, {0.182684, 0.0000167017}}

In[•]:= x1 = {0.623, 0.374, 0.249, 0.183, 0.145, 0.120,
          0.103, 0.089, 0.078, 0.068, 0.060, 0.053, 0.047, 0.041, 0.037}
Out[•]= {0.623, 0.374, 0.249, 0.183, 0.145, 0.12, 0.103,
         0.089, 0.078, 0.068, 0.06, 0.053, 0.047, 0.041, 0.037}

In[•]:= solV11andV12 = LeastSquares[EigenvalueEquations, x1] // MatrixForm
Out[•]//MatrixForm=
```

$$\begin{pmatrix} 0.205314 \\ 0.418607 \end{pmatrix}$$

```
In[•]:= x2 = {0, 0.113, 0.151, 0.157, 0.150, 0.137,
          0.124, 0.110, 0.098, 0.087, 0.077, 0.068, 0.060, 0.053, 0.047}
Out[•]= {0, 0.113, 0.151, 0.157, 0.15, 0.137, 0.124,
         0.11, 0.098, 0.087, 0.077, 0.068, 0.06, 0.053, 0.047}

In[•]:= solv21andv22 = LeastSquares[EigenvalueEquations, x2] // MatrixForm
Out[•]//MatrixForm=
```

$$\begin{pmatrix} 0.261026 \\ -0.260609 \end{pmatrix}$$

```
In[•]:= VMatrix = {{0.205314, 0.418607}, {0.261026, -0.260609}} // MatrixForm
Out[•]//MatrixForm=
```

$$\begin{pmatrix} 0.205314 & 0.418607 \\ 0.261026 & -0.260609 \end{pmatrix}$$

```
In[•]:= EigenvalueMatrix = {{-0.017, 0}, {0, -0.11}} // MatrixForm
Out[•]//MatrixForm=
```

$$\begin{pmatrix} -0.017 & 0 \\ 0 & -0.11 \end{pmatrix}$$

In[•]:=
```
InverseVMatrix = Inverse[{{0.205314, 0.418607}, {0.261026, -0.260609}}]
```
Out[•]=
```
{{1.60105, 2.57171}, {1.60361, -1.26134}}
```

In[•]:=
```
K = Dot[{{0.205314, 0.418607}, {0.261026, -0.260609}},
   {{-0.017, 0}, {0, -0.11}}, {{1.6010482067210876`, 2.571706988902511`},
    {1.6036100411251284`, -1.2613440499550412`}}] // MatrixForm
```
Out[•]//MatrixForm=

$$\begin{pmatrix} -0.0794293 & 0.0491047 \\ 0.0388661 & -0.0475707 \end{pmatrix}$$

Question 4:

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

In[•]:=
```
K
```
Out[•]//MatrixForm=

$$\begin{pmatrix} -0.0794293 & 0.0491047 \\ 0.0388661 & -0.0475707 \end{pmatrix}$$

In[•]:=
```
k12 = 0.048
```
Out[•]=
```
0.048
```

In[•]:=
```
k21 = 0.0388661
```
Out[•]=
```
0.0388661
```

In[•]:=
```
k01 = - (-0.0794293) - k21
```
Out[•]=
```
0.0405632
```

In[•]:=
```
-k21 - (-0.0792293)
```
Out[•]=
```
0.0403632
```

In[•]:=
```
- (k01 + k12 + k21)
```
Out[•]=
```
-0.127429
```

In[•]:=
```
-0.017 + -0.11
```
Out[•]=
```
-0.127
```

In[•]:=
```
k12 * k01
```
Out[•]=
```
0.00194703
```

In[•]:=
```
-0.017 * -0.11
```
Out[•]=
```
0.00187
```

Question 5:

Table 3.P.1 lists drug concentration measurements made in blood and tissue compartments over a period of 100 minutes. Use the method described in Problem 2 through 4 to estimate the rate coeffi-

cients k01, k12, and k21 in the system model 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.

In[∘]:=
```
sol = Expand[DSolve[{x1'[t] == -0.0794293 * x1[t] + 0.048 * x2[t], x2'[t] ==
    0.0388661 * x1[t] - 0.048 * x2[t], x1[0] == 0.623, x2[0] == 0}, {x1[t], x2[t]}, t]]
```

Out[∘]=
$$\{\{x1[t] \to 0.418003\, e^{-0.109677\, t} + 0.204997\, e^{-0.0177525\, t},\ x2[t] \to -0.263408\, e^{-0.109677\, t} + 0.263408\, e^{-0.0177525\, t}\}\}$$

In[∘]:=
```
Show[ListPlot[{x1data, x2data}], Plot[
  {0.4180030483040753` e^(-0.10967684125131547` t) + 0.20499695169592466` e^(-0.01775245874868453` t),
   -0.2634075926406902` e^(-0.10967684125131547` t) +
    0.2634075926406902` e^(-0.01775245874868453` t)}, {t, 0, 100}]]
```

In[∘]:=
```
Show[%11, AxesLabel → {HoldForm[Time], HoldForm[Conc]},
 PlotLabel → HoldForm[Compartment Concentration Data with System Model],
 LabelStyle → {GrayLevel[0]}]
```

Out[∘]=