Mathematical Material

Calculus
Differentiation
Integration
Laplace Transforms

Calculus: Objectives

- To understand and use differential processes and equations (de's)
- To understand Laplace transforms and their use in the integration of de's (analytical integration)
- To understand Euler’s method of numerical integration
- To understand integration as a summation process

Calculus

- Pharmacokinetics is the study of the rate of drug movement and transformation
  - Studied using differential calculus
- Drug performance is related to total amount of drug absorbed
  - Studied using integral calculus
Differential Equations

- Most (but not all) rate processes are first or zero order
  - Write differential equations from diagram
  - Convert differential equation into integrated form
    - Numerical methods - Euler’s method and others
    - Analytical method - Laplace transform

Diagram of Rate Process

- Draw the diagram

\[
\begin{array}{c}
  \text{k0} \\
  1 \\
  \text{k1} \\
  2 \\
  \text{k2} \\
  3 \\
\end{array}
\]

Zero order rate constant: k0
First order rate constants: k1 and k2

Diagram of Rate Process

- Write the de - Component 1

\[
\begin{array}{c}
  \text{k0} \\
  1 \\
  \text{k1} \\
  2 \\
  \text{k2} \\
  3 \\
\end{array}
\]
Diagram of Rate Process

• Write the de - Component 1

Positive Rates - arrow into component

Negative Rates - arrow away from component

\[
\begin{align*}
\frac{dX_1}{dt} &= +k_0 - k_1 \cdot X_1 \\
\text{Zero order} &\quad \text{just enter rate constant} \\
\text{First order} &\quad \text{multiply rate constant by component at the END of the arrow}
\end{align*}
\]
Diagram of Rate Process

- Write the de - Component 2

\[
\frac{dX_2}{dt} = + k_1 \cdot X_1 - k_2 \cdot X_2
\]

Zero order: just enter rate constant
First order: multiply rate constant by component at the END of the arrow

Diagram of Rate Process

- Write the de - Component 3

\[
\frac{dX_3}{dt} = + k_2 \cdot X_2
\]

Zero order: just enter rate constant
First order: multiply rate constant by component at the END of the arrow

Another example

- Write the de - Component 1

where \( k_1 \) is a first order rate constant

AL
Another example

- Write the de - Component 1

\[ \frac{dX_1}{dt} = -k_1 \cdot X_1 \]

Rate of Change of Amount

\[ \frac{dX_1}{dt} = -k_1 \cdot X_1 \]

Initial Condition
Bolus Dose = \( X_1(0) \)

Amount Remaining - \( X_1 \)

\[ \frac{dX_1}{dt} = -k_1 \cdot X_1 \]

Slope = \( k_1 \cdot X_1 \)
Numerical Integration - Euler

• Point-Slope Method
• Point
  – Initial Value - $X_i(0)$
• Slope
  – Differential Equation - $k_1 \cdot X_i$

The Equation

$$\frac{dX_i}{dt} = -k_1 \cdot X_i$$

An Example - Euler’s Method

• Choose stepsize (ss) = 0.1

$$X_i(\text{new}) = X_i(\text{old}) + \text{slope} \times \text{ss}$$
$$= X_i(\text{old}) + (-k_1 \cdot X_i(\text{old})) \times \text{ss}$$
$$= 100 + (-0.25 \times 100) \times 0.1$$
$$= 100 - 2.5 = 97.5$$

$X_i(0) = 100 \quad k_1 = 0.25$

An Example - Euler’s Method

<table>
<thead>
<tr>
<th>Time</th>
<th>$\Delta X_i$</th>
<th>$X_i$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>0.1</td>
<td>-2.50</td>
<td>97.50</td>
</tr>
<tr>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$X_i(0) = 100 \quad k_1 = 0.25$
Analytical Integration using Laplace Transform

- Laplace transform converts Differential Equation into the Laplace s domain
- Equation can be rearranged algebraically
- Back transform provide the solution
- Similar to ‘how’ logarithms convert multiplication and division into addition and subtraction

Laplace Transform - General Method

- Write the differential equation(s)
- Transform to the Laplace, s, domain
- Rearrange to solve for variable(s) of interest
- Take the back transform to the time domain to get the integrated equation

Laplace Integral

- Laplace transform is based on the Laplace Integral

\[ E(t) = \int_0^\infty e^{-st} \cdot f(t) \cdot dt \]

where \( f(t) \) is the function to be transformed from the time (t) domain to the Laplace (s) domain

- for the mathematicians in the class
Three Useful Transforms

- Transform of the constant $A$
  $$\mathcal{L}(A) = \frac{A}{s}$$

- Transform of variable such as drug amount
  $$\mathcal{L}(A \cdot X) = A \cdot \mathcal{X}$$

- Transform of a differential equation
  $$\mathcal{L}\left(\frac{dX}{dt}\right) = s\cdot \mathcal{X} - X_0$$

Laplace Transform Table

<table>
<thead>
<tr>
<th>Function: $f(t)$</th>
<th>Laplace: $F(s)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1$</td>
<td>$\frac{1}{s}$</td>
</tr>
<tr>
<td>$A$</td>
<td>$\frac{A}{s}$</td>
</tr>
<tr>
<td>$A \cdot e^{-at}$</td>
<td>$\frac{A}{s+a}$</td>
</tr>
<tr>
<td>$\frac{A}{a} \cdot (1-e^{-at})$</td>
<td>$\frac{A}{s+a}$</td>
</tr>
<tr>
<td>$\frac{A}{(b-a)} \cdot (e^{-bt} - e^{-at})$</td>
<td>$\frac{A}{s(a+b)}$</td>
</tr>
<tr>
<td>$\frac{A}{a} \cdot t - \frac{A}{2} \cdot (1-e^{-at})$</td>
<td>$\frac{A}{s(a+b)}$</td>
</tr>
</tbody>
</table>

Example - I.V. Bolus

- One compartment Model - I.V. Bolus
  $$\frac{dX}{dt} = -kel \cdot X$$

- Transform d.e. and variable
  $$s\cdot \mathcal{X} - X_0 = -kel \cdot \mathcal{X}$$

- Solve for $\mathcal{X}$
  $$s\cdot \mathcal{X} + kel \cdot \mathcal{X} = X_0 = \text{Dose}$$
Example - I.V. Bolus

- Rearrange and solve for $X$
  $$X = \frac{Dose}{s + kel}$$

- Back transform using Laplace Table
  $$X = Dose \cdot e^{-kel}$$

- Divide by $V$ to Determine $Cp$
  $$Cp = \frac{X}{V} = \frac{Dose}{V} \cdot e^{-kel}$$

Example - I.V. Infusion

- One compartment Model - I.V. Infusion
  $$\frac{dX}{dt} = k0 - kel \cdot X$$

- Transform d.e. and variable
  $$s \cdot X_X0 = \frac{k0}{s} - kel \cdot X$$

- Solve for $X$
  $$s \cdot X + kel \cdot X = \frac{k0}{s}$$
  Since $X0_0 = 0$

Example - I.V. Infusion

- Rearrange and solve for $X$
  $$X = \frac{k0}{s \cdot (s + kel)}$$

- Back transform using Laplace Table
  $$X = \frac{k0}{kel} \cdot (1 - e^{-kel})$$

- Divide by $V$ to Determine $Cp$
  $$Cp = \frac{X}{V} = \frac{k0}{V \cdot kel} \cdot (1 - e^{-kel})$$
Integration of Cp versus Time

- Integration of \( \frac{dC_p}{dt} \) give \( C_p \) versus time
- Integration of \( C_p \) gives Area under the Time versus \( C_p \) curve (AUC)

\[ \text{Integration} \quad \frac{dC_p}{dt} \quad C_p \quad \text{AUC} \quad \text{Differentiation} \]

- Acceleration \( \rightarrow \) Speed \( \rightarrow \) Distance

Integration of \( C_p \) versus Time

- AUC is used a measure the dosage form performance
- If the model or equation is known then an analytical solution is possible
- One model independent, numerical method is the trapezoidal rule

Area under the Curve (AUC)

Add time slices to calculate the total area

\[ \text{AUC} = \int_{t=0}^{t=\infty} C_p \cdot dt \]
AUC - Analytical Solution

\[
AUC = \int_{0}^{\infty} C_p \cdot dt
\]

if \( C_p = \frac{Dose}{V} \cdot e^{-ke_l \cdot t} \)

\[
AUC = \int_{0}^{\infty} \frac{Dose}{V} \cdot e^{-ke_l \cdot t} \cdot dt
\]

taking the constants (\( \frac{Dose}{V} \)) outside the integral

\[
AUC = \frac{Dose}{V} \int_{0}^{\infty} e^{-ke_l \cdot t} \cdot dt
\]

AUC - Analytical Solution...

\[
AUC = \frac{Dose}{V} \int_{0}^{\infty} e^{-ke_l \cdot t} \cdot dt
\]

now taking the integral using Math Tables gives

\[
AUC = \frac{Dose}{V} \left[ e^{\frac{-ke_l \cdot t}{-ke_l}} \right]_{0}^{\infty}
\]

that is integration from 0 to \( \infty \)

expanding using both limits gives

\[
AUC = \frac{Dose}{V} \left[ 1 - e^{\frac{-ke_l \cdot 0}{-ke_l}} \right]
\]

AUC - Analytical Solution ...

\[
AUC = \frac{Dose}{V} \left[ e^{\frac{-ke_l \cdot \infty}{-ke_l}} - e^{\frac{-ke_l \cdot 0}{-ke_l}} \right]
\]

since \( e^{\frac{-ke_l \cdot \infty}{-ke_l}} = 0 \) and \( e^{\frac{-ke_l \cdot 0}{-ke_l}} = 1 \)

\[
AUC = \frac{Dose}{V} \left[ 0 - \frac{1}{-ke_l} \right]
\]

and

\[
AUC = \frac{Dose}{V} \cdot \frac{1}{-ke_l} \cdot \frac{Dose}{V \cdot ke_l} = \frac{Cp(0)}{ke_l}
\]
AUC - Numerical Solution

One segment - Shape of a Trapezoid

AUC - One Segment

\[ \text{AUC}_{1-10} = \frac{C_p(3) + C_p(4)}{2} \cdot (t(4) - t(3)) \]

AUC - 0 to Last Data Point

\[ \text{AUC}_{0-\text{last}} = \frac{C_p(0) + C_p(1)}{2} \cdot (t(1) - t(0)) + \frac{C_p(1) + C_p(2)}{2} \cdot (t(2) - t(1)) + \ldots + \frac{C_p(6) + C_p(\text{last})}{2} \cdot (t(\text{last}) - t(6)) \]
AUC - Zero to Infinity

\[ \text{AUC} = \text{AUC}_{(t=0)}^{(t=\infty)} = \text{AUC}_{(t=0)}^{(t=\infty)} + \text{AUC}_{(t=\text{last})} \]

with \[ \text{AUC}_{(t=\text{last})} = \int_{t=\text{last}}^{t=\infty} C_p \cdot dt = \frac{C_p(\text{last})}{k_e} \]

AUC - Example Calculation

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Cp (µg/ml)</th>
<th>ΔAUC</th>
<th>AUC (µg.hr/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>71</td>
<td>85.5</td>
<td>85.5</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>60.5</td>
<td>146.0</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>10</td>
<td>3.1</td>
<td>9.3</td>
<td>283.0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>8.9*</td>
<td>291.9</td>
</tr>
</tbody>
</table>

* estimated by back-extrapolated * using \( k_e = 0.348 \text{ hr}^{-1} \)