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

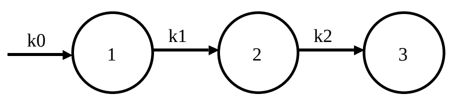
- Pharmacokinetics is the study of the rate of drug movement and transformation
  - Studied using differential calculus
- Drug performance is related to total amount of drug absorbed
  - Studied using integral calculus

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



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

Diagram of Rate Process

- Write the de - Component 1

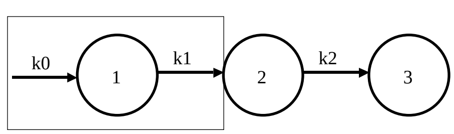


Diagram of Rate Process

- Write the de - Component 1

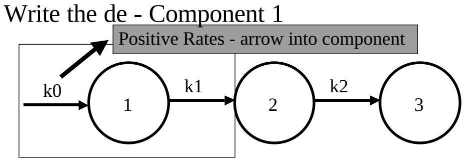


Diagram of Rate Process

- Write the de - Component 1

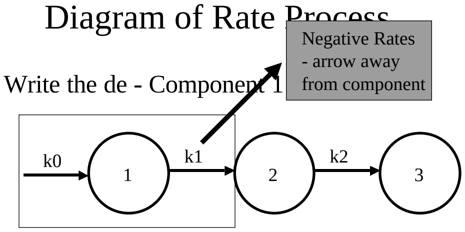
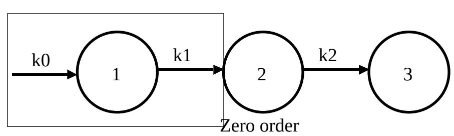


Diagram of Rate Process

- Write the de - Component 1

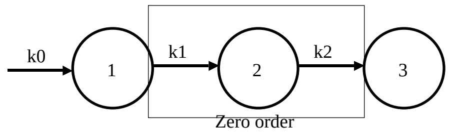


$$\frac{dX_1}{dt} = +k0 - k1 \cdot X_1$$

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 2

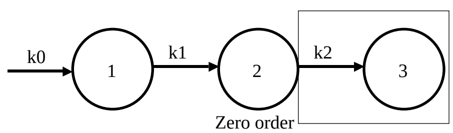


Zero order
just enter rate constant
First order
multiply rate constant by component at the END of the arrow

$$\frac{dX_2}{dt} = +k1 \cdot X_1 - k2 \cdot X_2$$

Diagram of Rate Process

- Write the de - Component 3

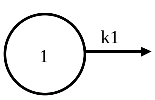


Zero order
just enter rate constant
First order
multiply rate constant by component at the END of the arrow

$$\frac{dX_3}{dt} = +k2 \cdot X_2$$

Another example

- Write the de - Component 1

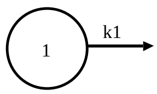


where k1 is a first order rate constant

AL

Another example

- Write the de - Component 1



$$\frac{dX_1}{dt} = -k1 \cdot X_1$$

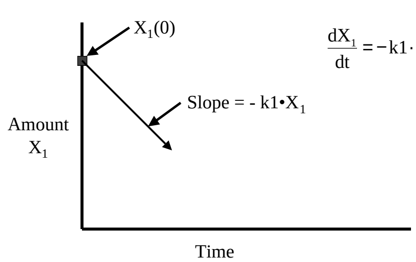
Rate of Change of Amount

$$\frac{dX_1}{dt} = -k1 \cdot X_1$$

Initial Condition

Bolus Dose = $X_1(0)$

Amount Remaining - X_1



$$\frac{dX_1}{dt} = -k1 \cdot X_1$$

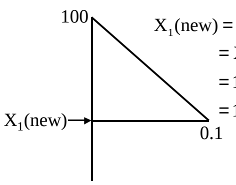
Numerical Integration - Euler

- Point-Slope Method
- Point
  - Initial Value - $X_1(0)$
- Slope
  - Differential Equation - $k1 \bullet X_1$

The Equation $\frac{dX_1}{dt} = -k1 \cdot X_1$

An Example - Euler's Method

- Choose stepsize (ss) = 0.1



$$
\begin{aligned}
X_1(new) &= X_1(old) + slope \bullet ss \\
&= X_1(old) + (-k1 \bullet X_1(old)) \bullet ss \\
&= 100 + (-0.25 \bullet 100) \bullet 0.1 \\
&= 100 - 2.5 = 97.5
\end{aligned}
$$

$X_1(0) = 100$ k1 = 0.25

An Example - Euler's Method

Time	ΔX_1	X_1
0.0		100
0.1	-2.50	97.50
0.2		
0.3		
0.4		
0.5		

$X_1(0) = 100$ k1 = 0.25 AL

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

$$\overline{L}f(t) = \int_0^\infty e^{-s\cdot t} \cdot f(t) \cdot dt$$

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

$$\bar{L}(A) = \frac{A}{s}$$

- Transform of variable such as drug amount

$$\bar{L}(A \bullet X) = A \bullet \bar{X}$$

- Transform of a differential equation

$$\bar{L}\left(\frac{dX}{dt}\right) = s \bullet \bar{X} - X_0$$

Laplace Transform Table

Function: f(t)	Laplace: f(s)
1	$\frac{1}{s}$
A	$\frac{A}{s}$
$A \bullet e^{-a \bullet t}$	$\frac{A}{(s+a)}$
$\frac{A}{a} \bullet \left(1 - e^{-a \bullet t}\right)$	$\frac{A}{s \bullet (s+a)}$
$\frac{A}{(b-a)} \bullet \left(e^{-a \bullet t} - e^{-b \bullet t}\right)$	$\frac{A}{(s+a) \bullet (s+b)}$
$\frac{A}{a} \bullet t - \frac{A}{a^2} \bullet \left(1 - e^{-a \bullet t}\right)$	$\frac{A}{s^2 \bullet (s+a)}$

From Table I, Mayersohn and Gibaldi, Amer. J. Pharm. Ed., 34(4) 608-614 (1970)

As a PDF file

Example - I.V. Bolus

- One compartment Model - I.V. Bolus

$$\frac{dX}{dt} = -kel \bullet X$$

- Transform d.e. and variable

$$s \bullet \bar{X} - X_0 = -kel \bullet \bar{X}$$

- Solve for $\bar{X}$

$$s \bullet \bar{X} + kel \bullet \bar{X} = X_0 = Dose$$

Example - I.V. Bolus

- Rearrange and solve for $\overline{X}$

$$\overline{X} = \frac{Dose}{s + kel}$$

- Back transform using Laplace Table

$$X = Dose \bullet e^{-kel \bullet t}$$

- Divide by V to Determine Cp

$$Cp = \frac{X}{V} = \frac{Dose}{V} \bullet e^{-kel \bullet t}$$

Example - I.V. Infusion

- One compartment Model - I.V. Infusion

$$\frac{dX}{dt} = k0 - kel \bullet X$$

- Transform d.e. and variable

$$s \bullet \overline{X} - X_0 = \frac{k0}{s} - kel \bullet \overline{X}$$

- Solve for $\overline{X}$

$$s \bullet \overline{X} + kel \bullet \overline{X} = \frac{k0}{s} \qquad \text{Since } X_0 = 0$$

Example - I.V. Infusion

- Rearrange and solve for $\overline{X}$

$$\overline{X} = \frac{k0}{s \bullet (s + kel)}$$

- Back transform using Laplace Table

$$X = \frac{k0}{kel} \bullet \left(1 - e^{-kel \bullet t}\right)$$

- Divide by V to Determine Cp

$$Cp = \frac{X}{V} = \frac{k0}{V \bullet kel} \bullet \left(1 - e^{-kel \bullet t}\right)$$

Integration of Cp versus Time

- Integration of dCp/dt give Cp versus time
- Integration of Cp gives Area under the Time versus Cp curve (AUC)

Integration →

dCp/dt ↔ Cp ↔ AUC

← Differentiation

Acceleration ↔ Speed ↔ Distance

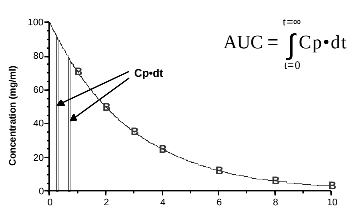
Integration of Cp versus Time

- 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

$$AUC = \int_{t=0}^{t=\infty} Cp \bullet dt$$



AUC - Analytical Solution

$$AUC = \int_{t=0}^{t=\infty} Cp \bullet dt$$

$$\text{if} \quad Cp = \frac{Dose}{V} \bullet e^{-kel \bullet t}$$

$$AUC = \int_{t=0}^{t=\infty} \frac{Dose}{V} \bullet e^{-kel \bullet t} \bullet dt$$

taking the constants (Dose/V) outside the integral

$$AUC = \frac{Dose}{V} \bullet \int_{t=0}^{t=\infty} e^{-kel \bullet t} \bullet dt$$

AUC - Analytical Solution...

$$AUC = \frac{Dose}{V} \bullet \int_{t=0}^{t=\infty} e^{-kel \bullet t} \bullet dt$$

now taking the integral
using Math Tables gives

$$AUC = \frac{Dose}{V} \bullet \left[\frac{e^{-kel \bullet t}}{-kel} \right]_{t=0}^{t=\infty}$$

that is integration from 0 to ∞
expanding using both limits gives

$$AUC = \frac{Dose}{V} \bullet \left[\frac{e^{-kel \bullet \infty}}{-kel} - \frac{e^{-kel \bullet 0}}{-kel} \right]$$

AUC - Analytical Solution ...

$$AUC = \frac{Dose}{V} \bullet \left[\frac{e^{-kel \bullet \infty}}{-kel} - \frac{e^{-kel \bullet 0}}{-kel} \right]$$

since $e^{-kel \bullet \infty} = 0$ and $e^{-kel \bullet 0} = 1$

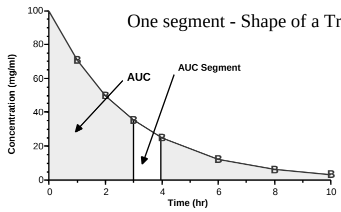
$$AUC = \frac{Dose}{V} \bullet \left[\frac{0}{-kel} - \frac{1}{-kel} \right]$$

and

$$AUC = \frac{Dose}{V} \bullet \frac{1}{kel} = \frac{Dose}{V \bullet kel} = \frac{Cp(0)}{kel}$$

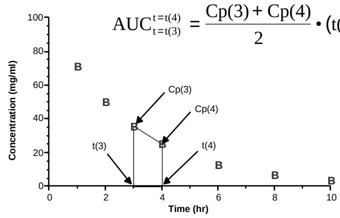
AUC - Numerical Solution

One segment - Shape of a Trapezoid



AUC - One Segment

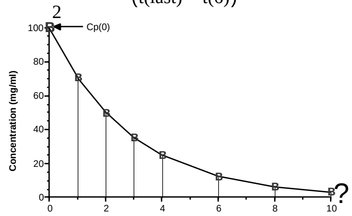
$$AUC_{t=t(3)}^{t=t(4)} = \frac{Cp(3)+Cp(4)}{2} \bullet (t(4)-t(3))$$



AUC - 0 to Last Data Point

$$AUC_{t=0}^{t=t(last)} = \frac{Cp(0)+Cp(1)}{2} \bullet t(1) + \frac{Cp(1)+Cp(2)}{2} \bullet (t(2)-t(1)) +$$

$$+ \frac{Cp(6)+Cp(last)}{2} \bullet (t(last)-t(6))$$



AUC - Zero to Infinity

$$AUC = AUC_{t=0}^{t=\infty} = AUC_{t=0}^{t=t(last)} + AUC_{t=t(last)}^{t=\infty}$$

with $$AUC_{t=t(last)}^{t=\infty} = \int_{t=t(last)}^{t=\infty} Cp \bullet dt = \frac{Cp(last)}{kel}$$

AUC - Example Calculation

Time (hr)	Cp (µg/ml)	ΔAUC	AUC (µg.hr/ml)
0	100*		
1	71	85.5	85.5
2	50	60.5	146.0
…	…	…	…
10	3.1	9.3	283.0
Total		8.9#	291.9

* estimated by back-extrapolated # using kel = 0.348 hr^{-1}