Compartment Models and Pharmacokinetic Modeling

MATH 3700

Sarah Brongiel & Kayley Reith

Compartment Models

- Represent the transport of material in systems such as chemical reactions and biological processes (Science Direct 2022)
- A collection of compartments that are inter-linked by material flows of different order (Science Direct 2022)

Pharmacokinetics

- The study of how the body interacts with administered substances for the entire duration of exposure (Grogan, Preuss 2023)

Motivation

- Over 131 million Americans utilize prescription medication (Georgetown University n.d.)
- Over 1.25 million people were severely injured, and 175,00 died from adverse drug reactions (Kommu 2022)
- The urgency and magnitude of the issue of improper drug dosing makes it critical to further explore

Methodology

Understanding Compartment PK models:

- PK models range in complexity from 1 compartment to dozens
- We will focus on one and two compartment PK models

Methodology

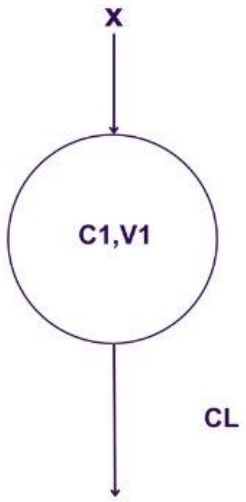

Figure 1 One-compartment intravenous model.
X: Dose; C_1: Central compartment concentration; V_1: Central compartment volume; CL: Clearance

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How to Derive 1 Compartment Models:

- To simplify the model, assume the Central compartment has a given drug concentration at time t=0.

Let,

- C(t) be the concentration of the drug in the body at time t, with C(t) = A(t)/V
- A(t) be the drug amount at time t, where A(t) = C(t) * V
- V be the volume of distribution
- k be the first-order elimination rate constant, k > 0

The rate of change of drug concentration is given by:
dC(t)/dt = -kC(t)

(Standing 2017)

Methodology

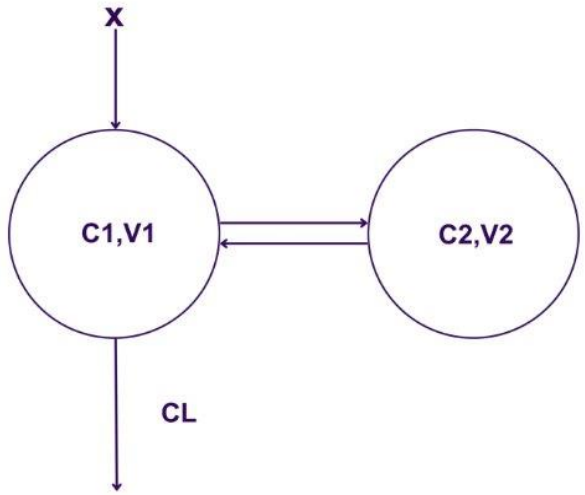

Figure 2 Two-compartment intravenous model.
X: Dose; C_1: Central compartment concentration; V_1: Central compartment volume; C_2: Peripheral compartment concentration; V_2: Peripheral compartment volume; CL: Clearance; Q: Intercompartment clearance

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How to Derive 2 Compartment Models:

- To simplify the model, assume the Central compartment has a given drug concentration at time t=0.

Let,

- $C_1(t)$: the drug concentration in the central compartment at time t
- $C_2(t)$: the drug concentration in the peripheral compartment at time t
- K_{12}: the rate of drug transfer to the peripheral compartment
- K_{21}: the rate of drug transfer from the peripheral compartment
- K_{10}: the elimination rate from the central compartment
- V_1: the volume of distribution of the central compartment
- V_2: the volume of distribution of the peripheral compartment

The differential equation for the Central compartment is:

$$\frac{dA1(t)}{dt} = -k_{10}A1(t) - k_{12}A1(t) + k_{21}A2(t)$$

The differential equation for the peripheral compartment is:

$$\frac{dA2(t)}{dt} = k_{12}A1(t) - k_{21}A2(t)$$

(Standing 2017)

Example 1: Initial Drug Concentration

- One-compartment Model: Initial Drug Concentration and at 12 hours
- Two-compartment Model: Initial Drug Concentration at 12 hours

Parameters:

- $A_0 = 500\,mg\ (Intial\ Dose)$
- $V = 10L\ (Volume)$
- $k = 0.2hr^{-1}(Elimination\ rate)$
- $t = \ 12\ (hours)$
- $k_{12} = \ 0.4hr^{-1}(Central\ to\ Peripheral\ transfer\ rate)$
- $k_{21} = \ 0.25\ hr^{-1}(Peripheral\ to\ Central\ transfer\ rate)$
- $ke = \ 0.2\ hr^{-1}(Elimination\ rate\ constant\ from\ the\ central\ compartment)$
- $C1 \ = \frac{A0}{V}\ (Initial\ concentrations:\ Central, Peripheral)$
- $C2 \ = \ 0$

Example 1: Initial Drug Concentration

In order to calculate the initial concentration level of the **one-compartment model** we follow these formulas:

$$C(0) = \left(\frac{A_0}{V}\right) = \left(\frac{500}{10}\right) = 50\ \frac{mg}{L}\ at\ 0\ hours$$

Now to calculate the drug concentration level at time t=12 we follow this formula:

$$C(t) = C_0 * e^{-kt}$$

$$C(12) = 50 * e^{-0.2*12} = 50 * e^{-2.4} \approx 50 * 0.09072 = 4.54\ \frac{mg}{L}\ at\ 12\ hours$$

Example 1: Initial Drug Concentration

To calculate the initial concentration level of the **two-compartment model** we focus on the two regions **central compartment (C1)** and the **peripheral compartment (C2):**

$$Central\ (C1) = \left(\frac{A_0}{V}\right) = \left(\frac{500}{10}\right) = 50mg/L$$

$$Peripheral\ (C2) = 0\ mg/L$$

The peripheral compartment (C2) is initialized at 0, because no drug material has transferred into that compartment yet from the center region. Therefore, all multi-compartment models will be initialized at the central region and others will assume to start at zero.

Example 1: Initial Drug Concentration

```
% Parameters for one-compartment model
A0 = 500;
V = 10;
k = 0.2;
t = 12;
k12 = 0.4;
k21 = 0.25;
ke = 0.2;
Vc = 10;
C1_0 = A0 / Vc;
C2_0 = 0;

% One-compartment model
C0 = A0 / V;                          % Initial concentration
C_t_one = C0 * exp(-k * t);           % Concentration after t hours


% Two-compartment model -- ODE45
ODE = @(t, C) [-ke * C(1) - k12 * C(1) + k21 * C(2);
               k12 * C(1) - k21 * C(2)];
[t_vals, C_vals] = ode45(ODE, [0 t], [C1_0 C2_0]);

C1_t_two = C_vals(end, 1);            % central concentration
C2_t_two = C_vals(end, 2);            % peripheral concentration


fprintf('One-compartment model:\n');
fprintf('  Initial concentration: %.2f mg/L\n', C0);
fprintf('  Concentration after %.1f hours: %.2f mg/L\n', t, C_t_one);

fprintf('\nTwo-compartment model:\n');
fprintf('  Final central concentration after %.1f hours: %.2f mg/L\n', t, C1_t_two);
fprintf('  Final peripheral concentration after %.1f hours: %.2f mg/L\n', t, C2_t_two);
```

```
One-compartment model:
  Initial concentration: 50.00 mg/L
  Concentration after 12.0 hours: 4.54 mg/L

Two-compartment model:
  Final central concentration after 12.0 hours: 6.02 mg/L
  Final peripheral concentration after 12.0 hours: 12.90 mg/L
```

The results of the two-compartment model after 12 hours reveal that as more time passes, the drug material transfers into more regions beyond the central, decreasing their volume and increasing others (C2).

Example 2: Gentamicin Two Compartment Model Simulation

- Gentamicin is a type of antibiotic that treats infections caused by bacteria (Cleveland Clinic 2024)
- The drug's parameters were found in a medical study (Sester 1983)
- Model and simulate Gentamicin interaction and elimination rates through two compartments (Central and Peripheral)
- Calculate drug concentration capacity

Example 2: Gentamicin Two Compartment Model Simulation

STEPS:

- Define the Compartment's parameter
- Configure ODE Function
- Set Time Span of Drug Administration
- Total Drug Concentration

```
% Parameters for gentamicin
k12 = 0.4; % hr^-1, Central to Peripheral transfer rate
k21 = 0.25; % hr^-1, Peripheral to Central transfer rate
ke = 0.15; % hr^-1, Elimination rate constant from the central compartment
Vc = 18; % L, Central compartment volume
D = 100; % mg, Dosage
C0 = [D / Vc; 0]; % Initial concentrations [Central, Peripheral] (mg/L)


odefun = @(t, C) [
    -ke * C(1) - k12 * C(1) + k21 * C(2); % Central compartment
    k12 * C(1) - k21 * C(2)     |         % Peripheral compartment
];

% Time span (0 to 72 hours)
tspan = [0 72];


[t, C] = ode45(odefun, tspan, C0);
C1 = C(:, 1); % Central compartment (mg/L)
C2 = C(:, 2); % Peripheral compartment (mg/L)

% Total drug concentration (Central + Peripheral)
TotalConcentration = C1 + C2;
```

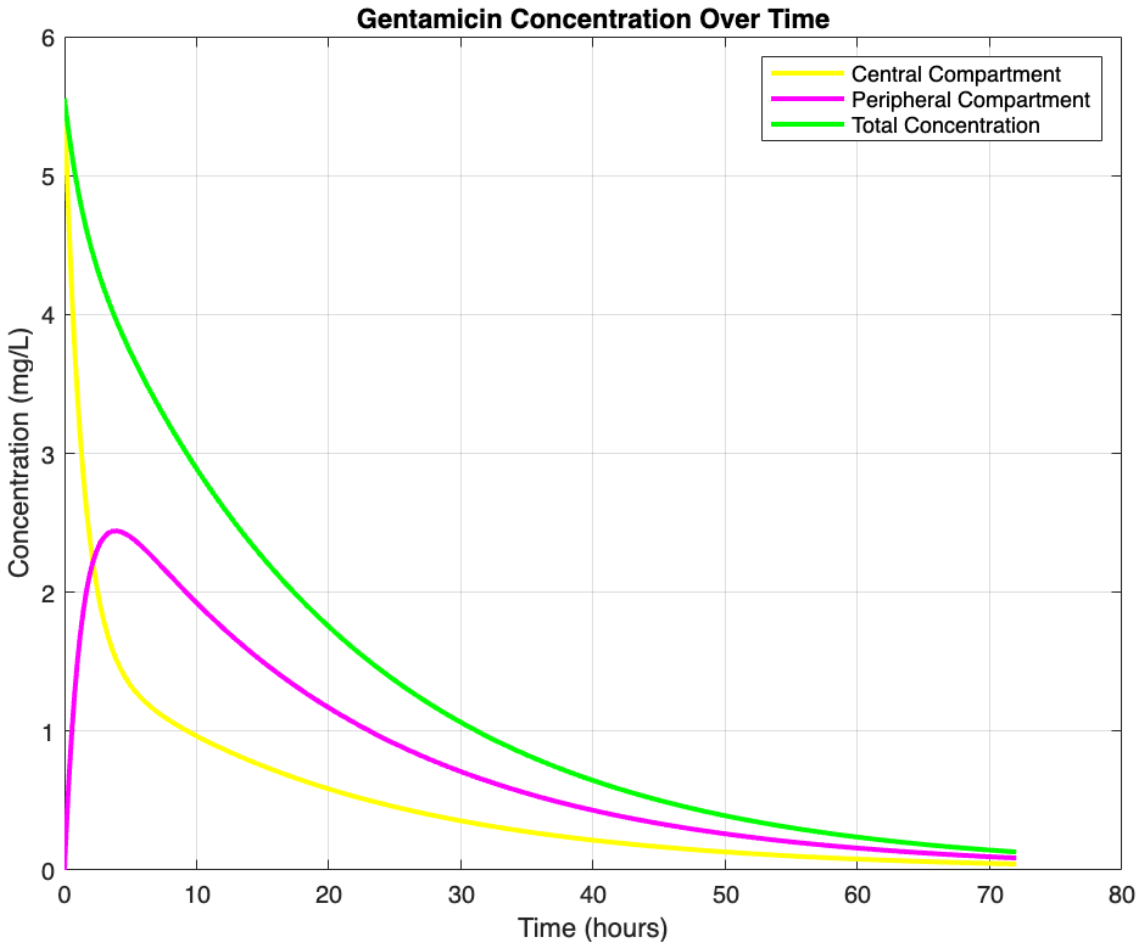
Example 2: Gentamicin Two Compartment Model Simulation

```
figure;
plot(t, C1, 'y-', 'LineWidth', 2); hold on;
plot(t, C2, 'm-', 'LineWidth', 2);
plot(t, TotalConcentration, 'g-', 'LineWidth', 2);
xlabel('Time (hours)');
ylabel('Concentration (mg/L)');
title('Gentamicin Concentration Over Time');
legend('Central Compartment', 'Peripheral Compartment', 'Total Concentration');
grid on;

[C1_max, idx_C1_max] = max(C1);
[C2_max, idx_C2_max] = max(C2);

fprintf('Peak concentration in the central compartment: %.2f mg/L at %.2f hours\n', C1_max, t(idx_C1_max));
fprintf('Peak concentration in the peripheral compartment: %.2f mg/L at %.2f hours\n', C2_max, t(idx_C2_max));


if abs(C1(end) - C2(end)) < 1e-3
    fprintf('System approaches equilibrium at %.2f mg/L\n', C1(end));
else
    fprintf('System does not reach equilibrium within the time frame.\n');
end

ratio_C2_C1 = C2 ./ C1;
fprintf('Final ratio of peripheral to central concentrations: %.2f\n', ratio_C2_C1(end));

AUC_C1 = trapz(t, C1); % AUC for the central compartment
AUC_C2 = trapz(t, C2); % AUC for the peripheral compartment

fprintf('AUC for central compartment: %.2f mg·hr/L\n', AUC_C1);
fprintf('AUC for peripheral compartment: %.2f mg·hr/L\n', AUC_C2);
```

STEPS

- Plot Results
- Calculate Peak Concentration
- Determine Equilibrium Satisfaction
- Calculate AUC

Example 2: Gentamicin Two Compartment Model Simulation



Results:

- Peak concentration C1 $= 5.56 \frac{mg}{L} at\ 0.00\ hours$
- Peak concentration C2 $= 2.44 \frac{mg}{L}\ at\ 3.96\ hours$
- Final ratio of peripheral (C2) to central (C1) = 2.00
- AUC for C1= $36.19\ \frac{mg*hr}{L}$
- AUC for C2= $57.52 \frac{mg*hr}{L}$
- System does not reach equilibrium

Practical Applications

- In practice, pharmacokinetic models are usually paired with pharmacodynamic models.
  - While “pharmacokinetic (PK) models describe the relationship between dose and concentration… pharmacodynamic (PD) models describe the relationship between concentration and effect” (Standing 2017)

Practical Applications

- One real world example of these models is “Model-Informed Drug Development for Antimicrobials: Translational PK and PK/PD Modeling to Predict an Efficacious Human Dose for Apramycin”
  - Apramycin is an antibiotic that has been shown to be effective against aminoglycoside-resistant bacteria.
  - The purpose of this study is to assist the drug’s transition from the preclinical to the clinical phase. The researchers scaled model parameters of apramycin found from studies using four different animal species (mouse, rat, guinea pig, and dog).
  - They were then able to use a PKPD model to find that “ a daily dose of 30 mg/kg for patients with a typical CrCL (creatinine clearance) of 80 mL/minute” is recommended.

  (Sou, et al 2020)

In Class Activity: One-Compartment Model

Problem: A patient is administered a drug with an initial dose of 40 mg. The elimination rate is constant k, where k = $0.2hr^{-1}$. The volume of distribution is V= 8L.

1. Calculate the initial concentration of the drug in the body.
2. Calculate the concentration of the drug in the body after 2 hours.

Given:

- $A_0 = 40$mg (Initial Dose)
- K = $0.2hr^{-1}$ (Elimination rate constant)
- V = 8L (The volume of distribution)
- T = 2 hours (The volume of distribution)

In Class Activity - Solutions

1. Calculate Initial Concentration:

- $C(0) = \frac{A_0}{V} = \frac{40}{8} = 5\ mg/L$

The initial concentration is **5 mg/L**.

2. Calculate Concentration After 2 Hours:

- Use the formula:

$$C(t) = C_0 * e^{-kt}$$

- Substituting the values:

$$C(2) = 5\ * e^{0.2*2} =$$

$$C(2) = \ 5\ * e^{0.4}\ \approx$$

$$C(2) = 5 * 0.60703 = 3.3515\ mg/L$$

After 2 hours, the concentration is approximately **3.35 mg/L**.

In Class Activity 2: Two-Compartment Model Matlab

Problem: A patient is administered a drug with an initial dose of 40 mg. The elimination rate is constant k, where k = $0.2hr^{-1}$. The volume of distribution is V= 8L.

1. Calculate the initial concentration of the drug in the body.
2. Calculate the concentration of the drug in the body after 2 hours.

Given:

- $A_0 = 40$mg (Initial Dose)
- K = $0.2hr^{-1}$ (Elimination rate constant)
- V = 8L (The volume of distribution)
- T = 2 hours (The volume of distribution)

Connection to Class

- Real-world problem simulations
- Order of Differential Equations (ODEs)
- SIR / Compartment Models
- Model Data Analysis

Summary

- Modeling simulation of Gentamicin as a small case example connects to larger case studies of pharmacokinetics
- Bridge our understanding of how compartment models are developed to model drug dynamics and behavior
- It was critical to explore this topic as the pharmaceutical industry is revolutionizing patient treatment and growing in popularity
- Simplified version of a complex process, to solidify comprehension of these complex systems

References

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