Understanding Pharmacokinetic Compartment Models

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Executive Summary

Pharmacokinetics is “the study of the time course of drug absorption, distribution, metabolism, and excretion” (American Society of Health-System Pharmacists n.d.). It is essential to understand how different drugs and medications interact in the bloodstream. Pharmacokinetics is modeled through the use of compartment models, where various complex biological systems are divided into multiple interconnected sections. These compartments describe the continuous rates of change of drug concentrations throughout the body allowing medical personnel the ability to predict drug concentrations in various tissues in order to optimize patient dosing.

We aim to develop a concrete understanding of the fundamentals of one and two-compartment models, how to derive them, and apply them to examples in order to depict the usefulness of this modeling technique. To gauge a solid understanding we learned how to manually calculate drug initial concentration rates and interaction rates over time within different compartment models. The model revealed that regardless of the quantity of compartments the initial concentration is always the same value, as it starts in the center region, while all other compartments are initialized at zero.

As the healthcare and pharmaceutical sector continues to grow in America, we further explored the behavior and effects in a modeling simulation of Gentamicin, an antibiotic drug, and discussed a research study of Apramycin, another antibiotic, to bridge our understanding of pharmacokinetics. The two-compartment model revealed the drug capacity peak concentration levels and rates of change between compartments. This information and data may improve patient care and optimize drug regimens.

Abstract

In studying pharmacokinetic (PK) compartment models, we focused on describing drug distribution through one and two-compartment models. Each method is characterized by differential equations representing the drug's absorption, distribution, and elimination in the body. We developed an understanding of how to quantify the influence the model parameters, such as volume of distribution (V) and the rate constants (k_{10}, k_{12}, k_{21}), have on overall drug concentration. One-compartment models offer the most simplistic approach, although they are commonly only used for drugs that quickly reach equilibrium in the body. For drugs that have more complex distribution dynamics, two-compartment models are utilized to capture the uneven drug distribution. These models provide insights that enable medical personnel to precisely predict drug behavior, ultimately leading to optimal dosing strategies.

Keywords: Pharmacokinetics, Compartments Models, Gentamicin

Introduction

Over 131 million Americans utilize prescription medication, and this number is increasing annually, showcasing the popularity of the healthcare sector (Georgetown University n.d.) In 2022, it was recorded that over 1.25 million people were severely injured and 175,00 died from adverse drug reactions (Kommu 2022) highlighting the urgency and magnitude of the issue of improper drug dosing. Therefore, to guarantee appropriate dosage and reduce the source of negative risks, it is essential to assess and quantify the efficacy of drug administration and interactions in the bloodstream. The study of how the body interacts with administered substances for the entire duration of drug exposure is called Pharmacokinetics (Grogan, Preuss 2023). This process follows the course of "drug absorption, distribution, metabolism, and excretion" with the primary goal of decreasing the toxicity of a patient's drug therapy and effective therapeutic management of drugs (American Society of Health-System Pharmacists n.d.).

A variety of modeling approaches are used to predict and explore the effects of drug absorption and its long-term behavior and effects. Distributed Parameter Models, for instance, capture continuous information across spatial dimensions utilizing partial differential equations and require boundary conditions to craft a more detailed representation of the human body (Fivable Inc. 2024). Meanwhile, Artificial Neural Networks are more complex and dense time series models that fit patient data using machine learning techniques to train and test the model to predict drug performance and efficacy levels (Ogami, et al 2021). Despite the strengths and advanced concepts of these methods, a rudimentary comprehension of drug dynamics is needed.

Thus, the foundation and methods of this drug modeling process are represented by compartment models that transport the drug material in bodily systems such as chemical

reactions and biological processes through a collection of interlinked chambers (Science Direct 2022). Compartment models are a generalized modeling technique that divides various aspects of the human body into a series of interconnected sections. The model setup deploys differential equations to describe the continuous rates of change of drug concentrations throughout the body, so the model can predict the continuous nature of drug distribution.

Therefore the significance of this issue affects many people, so it is critical to examine the properties and features of compartment models. Thus, we aim to develop a concrete understanding of the fundamentals of compartment models on a small scale, using a basic model to depict drug movements in the singular compartment. While these simple models unveil unique insight, a gap in knowledge exists in our understanding of how basic one-compartment models scale to predict accurate patient drug responses in real-world applications. Therefore this research aims to fill the gap in building a concrete understanding to scale basic compartment models in order to provide a basis for more complex applications. An investigation into a large-scale case study of real pharmacokinetic intricacies will address scalability issues, and practical applications of medication efficacy used through improved and nuanced pharmacokinetic modeling to optimize patient care.

Methods

There are numerous pharmacokinetics (PK) models that range in complexity from one compartment to dozens. We will focus on deriving and understanding one and two-compartment PK models. To simplify the following models, we did not account for the rate of drug infusion into the system. Instead, we made the assumption that the Central compartment has a given drug concentration initialized at time t=0.

The one-compartment model is the most basic compartment model. This model assumes all the tissues within the body are contained in a single compartment called the Central compartment. To derive the formula for a one-compartment model, we define these parameters and let:

- C(t) be the concentration of the drug in the body at time t, with $C(t) = \frac{A(t)}{V}$
- 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:

$$\frac{dC(t)}{dt} = -kC(t)$$

(See Appendix A)

(Holz, Fahr 2001)

While this model is cost-efficient it ultimately is not the most accurate due to the assumption that the observed drug is equally and evenly distributed throughout the entire body.

The next model is a two-compartment model, which is made up of both Central and Peripheral compartments. The Central compartment in this model consists of plasma, blood, and highly perfused tissues (i.e. the kidneys and the liver). While the Peripheral compartment is composed of poorly perfused tissues (i.e. muscles). This distinction is made since a drug is distributed unevenly amongst sections of the body where the blood flow rates differ. The main assumption for this model is that the drug is administered into the Central compartment and the drug is eliminated from the Central compartment. However, as noted above, in this derivation we do not account for the rate of drug infusion into the system through the central compartment and is initialized at zero. To derive the system of differential equations for a two-compartment PK model, we define these parameters and let:

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

The rate of change of the drug in the Central compartment is given by:

$$A_1(t) = C_1(t) * V_1$$

The differential equation for the Central compartment is:

$$dA_1(t)/dt = -k_{10}A_1(t) - k_{12}A_1(t) + k_{21}A_2(t)$$

The rate of change of the drug in the peripheral compartment is given by:

$$A_2(t) = C_2(t) * V_2$$

The differential equation for the peripheral compartment is

$$dA_2(t)/dt = k_{12}A_1(t) - k_{21}A_2(t)$$

(Holz, Fahr 2001)

Additionally, there are more complex models outside the scope of this class, such as the Physiologically Based Pharmacokinetic Model (PBPK), which consists of multiple, highly dense compartments for every organ in the body. These models are more traditionally used for highly detailed studies and are very accurate, yet computationally expensive.

After deriving the differential equations listed above, we utilize the function ode45 in Matlab to be able to numerically solve for the drug concentration at any given time t. This provides a simpler method for modeling pharmacokinetics. Without it, you would need to implement other numerical methods, such as Euler's method, to solve ordinary differential equations. These approximations are not always as accurate, thus, the ode45 function is the optimal method in the implementation of compartment models. Overall, compartment models are the most utilized method in pharmacokinetics because they are a simple, yet effective way to predict drug concentrations. They provide a great balance between accuracy and time and space complexity. This allows for a better understanding of drug behavior in patients, which ultimately helps with safe and effective drug prescription and use.

Examples

Before simulating drug movement in different compartments, we must manually ascertain the principle values of the initial drug concentration throughout a specified time t. Given a set of predetermined parameters, we will use the differential equations for the one-compartment model to compute the initial drug concentration at time t=0 and compare it to drug concentration levels after 12 hours of drug interaction. We will then replicate the initial conditions and use Matlab programming to model (See Appendix B) the time at 12 hours for the two-compartment model since the calculations are complex and time-consuming to perform by hand. The methods section above mentioned the differential equations that were used. The given parameters are:

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

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

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

The initial concentration at time t=0 is 50mg/L.

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

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

Substituting the values:

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

Therefore after 12 hours the drug's concentration in the bloodstream is approximately 4.54 mg/L. Next, in order to calculate the two-compartment model's initial drug concentration with the same parameters we follow the same method of deploying the differential equations and plugging in the associated variable values for the rates of elimination and transformation between states. Thus:

The initial concentration in the central compartment is calculated as:

$$C1 = \frac{A_0}{V} = \frac{500}{10} = 50mg/L$$

The initial concentration for the peripheral compartment does not exist as the drug has not been transferred into that region at time t=0:

$$C2 = 0\, mg/L$$

Therefore, these hand calculations uncover how both one and two-compartment models start at the same level of initial concentration in the central compartment (50mg/L) as it is the first section the drug is administered and interacts with. Therefore, it logically concludes that any other compartments in a two, three, or multiple-compartment model in other centers like peripheral tissues (C2), organs (C3), or fats (C4) would be

initialized at 0mg/L as the drug has not transferred into these regions, and takes time to disperse front the central compartment.

Given the unprecedented levels of prescription drug use among Americans, it was vital to investigate the delivery of a commonly used medication such as Gentamicin. This is an injection-based antibiotic used to treat bacterial infections (Cleveland Clinic, 2024). A more thorough and intricate examination of the drug's rates of absorption and elimination over a given period of time can be achieved by employing the framework of a two-compartment model simulation through Matlab programming (See Appendix C). The Graduate College of Oklahoma State University published a book containing a medical study of pharmacokinetics and Gentamicin parameters were listed (Sester 1983). Taking this information we were able to apply the parametric data to simulate a two-compartment model of the drug treatment. The model consisted of the definition of parameters listed below:

- $k_{12} = 0.4\ hr^{-1}$ (Central to Peripheral transfer rate)
- $k_{21} = 0.25\ hr^{-1}$ (Peripheral to Central transfer rate)
- $ke = 0.15\ hr^{-1}$ (Elimination rate constant from the central compartment)
- $Vc = 18L$ (Central compartment volume)
- $D = 100\ mg$ (Dosage)
- $C_0 = \frac{D}{Vc}\ mg/L$ (Initial concentrations: Central, Peripheral)

Then the order of differential equations function deployed follows this formula:

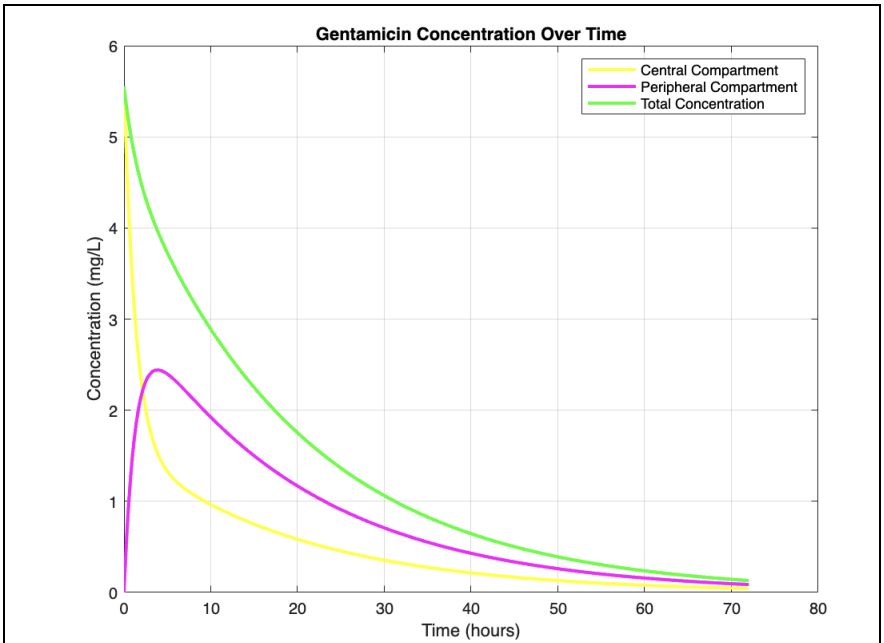
$$Central\ (C1) = -ke * C(1) - k_{12} * C(1) + k_{21} * C(2)$$

$$Peripheral\,(C2) = k_{12} * C(1) - k_{21} * C(2)$$

$$ODE\,(C1 + C2) = -ke * C(1) - k_{12} * C(1) + k_{21} * C(2) + k_{12} * C(1) - k_{21} * C(2)$$

We initialized our time span vector from zero to twenty-four hours by experimenting with various time intervals after entering the variables' corresponding values. Our graph did not, however, fully depict the magnitude of the drug's use during this time period when we tried to display the model. Since the drug is usually administered every day, we extended the duration to 72 hours, which is an extension of the original 24-hour period. To observe the overall drug concentration levels a patient encounters over the course of seventy-two hours, we defined the compartments and added them together after applying and initializing the ODE function to analyze the total concentration behavior. To investigate this further, we computed descriptive analytics and visualized the outcomes that each compartment simulated. Gentamicin's peak concentration levels in each compartment were measured, the system's time to equilibrium was assessed, and the area under the curve (AUC) component was used to identify the best-performing compartment and model. The two-compartment models' outcomes consisted of:

- Peak concentration C1= 5.56 *mg/L at* 0.00 *hours*
- Peak concentration C2= 2.44 *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 an equilibrium




```
Peak concentration in the central compartment: 5.56 mg/L at 0.00 hours
Peak concentration in the peripheral compartment: 2.44 mg/L at 3.96 hours
System does not reach equilibrium within the time frame.
Final ratio of peripheral to central concentrations: 2.00
AUC for central compartment: 36.19 mg·hr/L
AUC for peripheral compartment: 57.52 mg·hr/L
```

(Figure 1.1)

Since we assumed that the rate of diffusion in the central compartment (C1) was initialized at zero as depicted in Figure 1.1, the results show that the central compartment (C1) reaches its peak concentration level instantaneously at 0.00 hours. Gentamicin demonstrates a slower diffusion rate between the central and peripheral compartments, reaching its absorption capacity 3.96 hours after injection in contrast to the peripheral compartment (C2). Gentamicin accumulated more in the peripheral compartment during the seventy-two-hour period, as shown by the final drug distribution rate of 2.00. Gentamicin's dynamics and behavior in the simulation were monitored during the model's equilibrium testing, which revealed that there was still some kind of imbalance, error, or inaccuracy in Gentamicin's removal and absorption because it never achieved the critical point. This error could have arisen from our simplification of the model by

assigning the central compartment a zero value. However, in order to evaluate the model's performance, we looked at the area under the curve, which showed that the patient's peripheral tissues had a higher concentration level of Gentamicin for a longer period of time 57.52 $\frac{mg*hr}{L}$. then the central compartment 36.19 $\frac{mg*hr}{L}$.

Applications

There are numerous real-world applications of pharmacokinetic compartment models. They are constantly implemented in research studies to gain insights about new drugs like how they interact within the bloodstream. This allows researchers to adequately recommend dosage for individuals. In practice, pharmacokinetic models are usually paired with pharmacodynamic models, called pharmacokinetic-pharmacodynamic (PKPD) models. While "pharmacokinetic (PK) models describe the relationship between dose and concentration… pharmacodynamic (PD) models describe the relationship between concentration and effect" (Standing 2017). Thus, when used together, PKPD models provide researchers with insights into the relationship between the drug, its concentration, and its effect.

The following study "Model-Informed Drug Development for Antimicrobials: Translational PK and PK/PD Modeling to Predict an Efficacious Human Dose for Apramycin" illustrates how compartment models can be implemented in real-world situations. Apramycin is an antibiotic that has been shown to be effective against aminoglycoside-resistant bacteria. In an attempt 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). The results found in this study were that " a daily dose of 30 mg/kg for patients with a typical CrCL of 80 mL/minute" is recommended. This value can then be used to optimize dosage during testing (Sou, et al 2020). Altogether, PK models can be used in a variety of ways with the most common being PKPD models.

Class Activity 1: One-Compartment Model (Hand Calculation)

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

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:

- Initial Dose $A_0 = 40mg$
- Elimination rate constant $k = 0.2hr^{-1}$
- Volume of distribution V = 8L
- Time t = 2 hours

Class Activity 2: Two -Compartment Model (MATLAB)

Problem Statement: With the following parameters simulate the drug's movement in a two-compartment model for 72 hours. The drug starts in the central compartment, which then distributes to the peripheral compartment, then returns to the central compartment where it undergoes elimination and dispels the drug.

- Initial dose: $A_0 = 200mg$
- Elimination rate constant: $k_{10} = 0.3\ hr^{-1}$
- Rate constant from central to peripheral: $k_{12} = 0.1\ hr^{-1}$
- Rate constant from peripheral to central: $k_{21} = 0.05\ hr^{-1}$
- Volume of central compartment: $V_1 = 10\ L$
- Volume of peripheral compartment: $V_2 = 5L$

Task: Writing by hand or pseudocode

1. Write the ODE function describing the system
2. Solve the system for 72 hours using MATLAB's ode45
3. Find the Total Drug Concentration over 72 hours (Central & Peripheral)
4. Plot the amount of drug in both compartments over time

```
A0 = 200;  % Initial dose (mg)
k10 = 0.3; % Elimination rate constant (hr^-1)
k12 = 0.1; % Rate constant from central to peripheral (hr^-1)
k21 = 0.05; % Rate constant from peripheral to central (hr^-1)
V1 = 10; % Volume of the central compartment (L)
V2 = 5;  % Volume of peripheral compartment (L)

% Task 1: Define the system of differential equations

%%%%%

% dA1/dt (central compartment)
% dA2/dt (peripheral compartment)
A_init = [A0; 0];  % Initial amounts in A1 and A2

% Task 2: Time vector (0 to 72 hours)

%%%%%
[t, A] = ode45(odefun, tspan, A_init);

%Task 3: Total Drug Concentration (Central and Peripheral)
%%%%%
A1 = A(:,1);  % Amount in central compartment (mg)
A2 = A(:,2);  % Amount in peripheral compartment (mg)

% Task 4: Plot the results

%%%%%
```

Activity 1 Solution

Steps to Solve:

1. Calculate Initial Concentration:

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

   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:

   $$C(2) = 5 * e^{(0.2*2)} = 5 * e^{(0.4)} \approx 5 * 0.60703 = 3.3515\, mg/L$$

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

   See Appendix D to confirm solutions with Matlab programming.

Activity 2 Solution

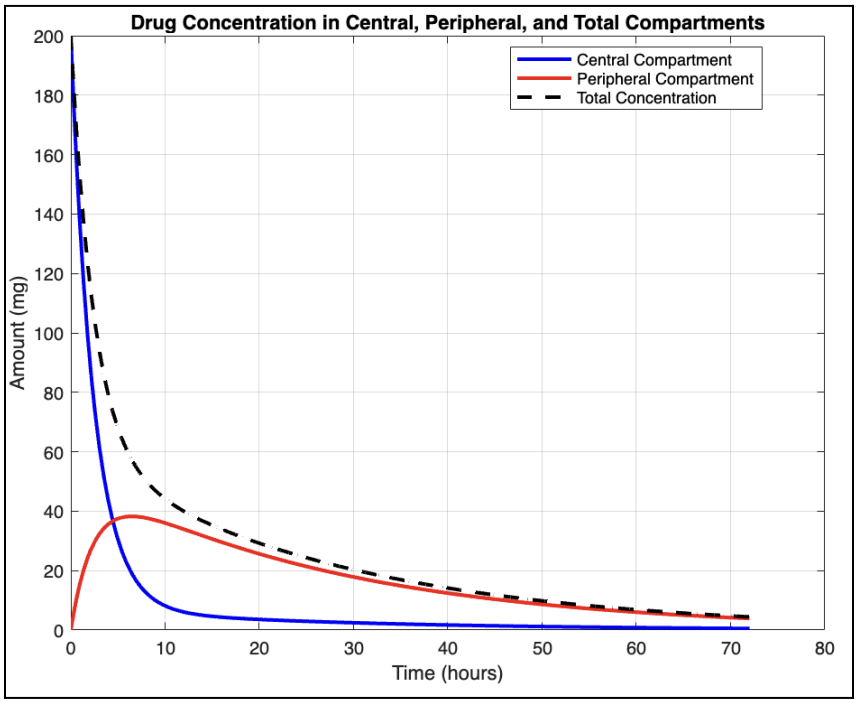
The specific sections of code relevant to this task are displayed below. For the complete solution, please refer to Appendix E.

```
% Task 1: Define the system of differential equations
odefun = @(t, A) [
   -k10*A(1) - k12*A(1) + k21*A(2);    % dA1/dt (central compartment)
   k12*A(1) - k21*A(2)                 % dA2/dt (peripheral compartment)
];
% Task 2: Time vector (0 to 72 hours)
tspan = [0 72];  % Time from 0 to 72 hours


% Task 3: Total Drug Concentration
TotalConcentration = A1 + A2;


% Task 4: Plot the model
figure;
plot(t, A1, 'b', 'LineWidth', 2, 'DisplayName', 'Central Compartment');
hold on;
plot(t, A2, 'r', 'LineWidth', 2, 'DisplayName', 'Peripheral
Compartment');
plot(t, Total, 'k--', 'LineWidth', 2, 'DisplayName', 'Total
Concentration');
hold off;
xlabel('Time (hours)');
ylabel('Amount (mg)');
title('Drug Concentration in Central, Peripheral, and Total
Compartments');
legend('Location', 'best');
```

```
grid on;
```



(Figure 1.2)

Given that the drug is excreting itself and moving into the peripheral compartment, the graph illustrates how the model and central compartment gradually decrease in the model. As it starts to stabilize and level off after receiving additional medication from the central compartment, the peripheral compartment demonstrates an increase in drug concentration levels over time.

Conclusion

In conclusion, the research and modeling simulation of Gentamicin as a small case example, connects to larger case studies of pharmacokinetics and bridges our understanding of how compartment models are developed and deployed 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.

Therefore, by understanding the foundational ideas of how these drug dosage models are utilized, we have gained valuable insights into the role they play in optimizing drug treatments or tailoring medication to specific patients. We learned the important factors between singular and multimodal compartment models and their initialization rates for drugs after consumption shift between regions in the body of peripheral compartments like fats, tissues, and organs.

Ultimately, this research and experimentation modeling different drug interactions was a simplified version of a complex process, to solidify comprehension of these complex systems and processes. The examples and applications clearly depict the importance of understanding long-term drug behavior and mirror how our Gentamicin modeling example is reflected in clinical and medical studies like the Apramycin clinical trial which undergoes mathematical modeling using PBPK models to effectively analyze the drug's behavior. Therefore, bridging the gap between theoretical modeling and real-world applications highlights the importance of our research in pharmacokinetic modeling.

Appendix A

Methodology: Derivation of Functions

The rate of change of drug concentration is given by:

$$dC(t)/dt = -kC(t)$$

Since,

$$A(t) = C(t) * V$$

We get,

$$dA(t)/dt = d/dt\,[C(t) * V]$$

$$dA(t)/dt = V * [-k * (A(t)/V)]$$

$$dA(t)/dt = -kA(t)$$

As this is a differential equation, we can integrate both sides of the equation. This results in

$A(t) = A_0\, e^{-kt}$, where A_0 is the initial amount of drug administered.

Since $C(t) = A(t)/V$, the concentration, C(t), of the drug at any time t is given by the formula:

$$C(t) = (A_0 / V)e^{-kt}$$

Appendix B

Example 1: Drug concentration levels in a two-compartment system after 12 hours using Matlab programming.

```
% Parameters for the 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 (C1)
C2_t_two = C_vals(end, 2);            % peripheral concentration
(C2)
```

```
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 displayed from the Matlab programming reveal that our hand calculations for the one-compartment model were accurate. It also displays the drug concentration level at 12 hours for both compartments and shows how the central (C1) compartment has less concentration 6.02 mg/L in comparison to the peripheral (C2) compartment 12.90 mg/L at 12 hours since the majority of the drug has been transferred into the second region depleting the volume in the center region throughout the twelve-hour timeframe.

Appendix C

Example 2: Gentamicin Matlab Programming and Results

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

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;

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;

% Model data analysis and performance evaluation

[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));

%source: https://www.mathworks.com/help/signal/ug/peak-analysis.html


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
```

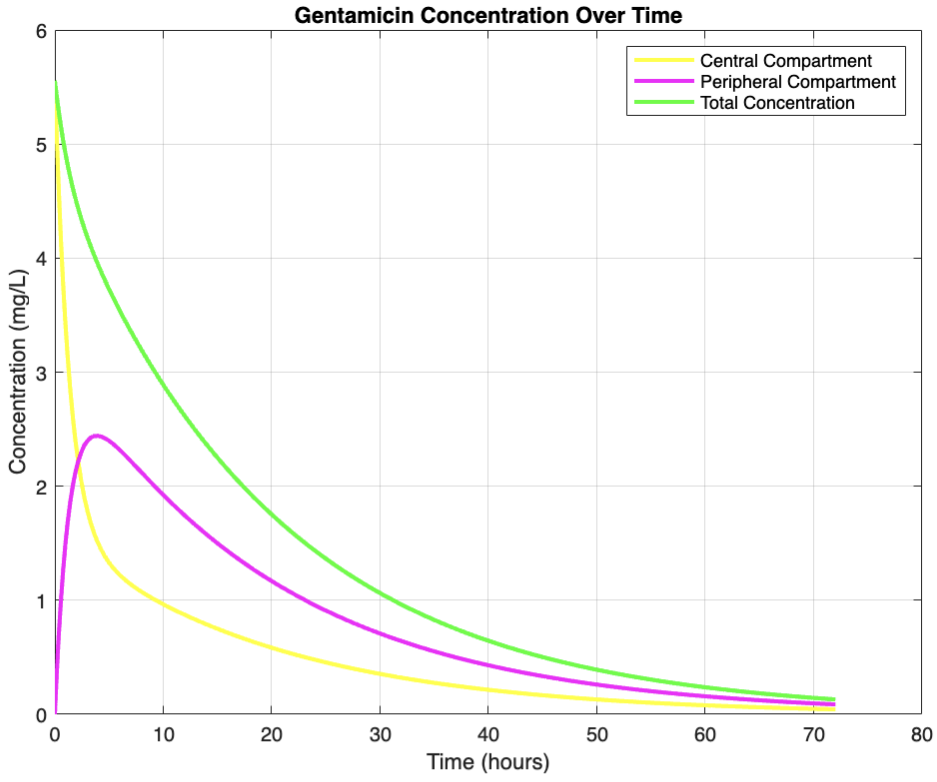
```
AUC_C2 = trapz(t, C2); % AUC for the peripheral compartment

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

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

% source: The model with greater area under the curve is generally the
better one.

%https://developers.google.com/machine-learning/crash-course/classificat
ion/roc-and-auc#:~:text=AUC%20is%20a%20useful%20measure,is%20generally%2
0the%20better%20one.
```




```
Peak concentration in the central compartment: 5.56 mg/L at 0.00 hours
Peak concentration in the peripheral compartment: 2.44 mg/L at 3.96 hours
System does not reach equilibrium within the time frame.
Final ratio of peripheral to central concentrations: 2.00
AUC for central compartment: 36.19 mg·hr/L
AUC for peripheral compartment: 57.52 mg·hr/L
```

Appendix D

Activity 1: Hand Calculation Verification with Matlab Programming

```
% Given values
A0 = 40;     % Initial dose in mg
V = 8;       % Volume of distribution in L
k = 0.2;     % Elimination rate constant in hr^-1
t = 2;       % Time in hours
% Step 1: Calculate the initial concentration
C0 = A0 / V;
% Step 2: Calculate concentration after 2 hours using the
one-compartment model
C_t = C0 * exp(-k * t);
% Display results
fprintf('Initial concentration: %.2f mg/L\n', C0);
fprintf('Concentration after %.1f hours: %.2f mg/L\n', t, C_t);
```

The results from the Matlab programming match the solutions to the hand calculations.

```
Initial concentration: 5.00 mg/L
Concentration after 2.0 hours: 3.35 mg/L
```

Appendix E

The final solution code for class Activity 2 Two-Compartment modeling using Matlab is:

```
% Given parameters
A0 = 200;  % Initial dose (mg)
k10 = 0.3; % Elimination rate constant (hr^-1)
k12 = 0.1; % Rate constant from central to peripheral (hr^-1)
k21 = 0.05; % Rate constant from peripheral to central (hr^-1)
V1 = 10;   % Volume of central compartment (L)
V2 = 5;    % Volume of peripheral compartment (L)

% Task 1: Define the system of differential equations
odefun = @(t, A) [
   -k10*A(1) - k12*A(1) + k21*A(2); % dA1/dt
   k12*A(1) - k21*A(2)];            % dA2/dt

A_init = [A0; 0];

% Task 2: Time vector
tspan = [0 72];

[t, A] = ode45(odefun, tspan, A_init);
A1 = A(:,1);  % Amount in central compartment (mg)
A2 = A(:,2);  % Amount in peripheral compartment (mg)

% Task 3: Calculate total concentration (sum of both compartments)
Total = A1 + A2;
```

```
% Task 4: Plot results

figure;

plot(t, A1, 'b', 'LineWidth', 2, 'DisplayName', 'Central
Compartment');

hold on;

plot(t, A2, 'r', 'LineWidth', 2, 'DisplayName', 'Peripheral
Compartment');

plot(t, Total, 'k--', 'LineWidth', 2, 'DisplayName', 'Total
Concentration');

hold off;

xlabel('Time (hours)');

ylabel('Amount (mg)');

title('Drug Concentration in Central, Peripheral, and Total
Compartments');

legend('Location', 'best');

grid on;
```

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