MATH492: Statistics Dissertation
An Introduction to the Single-Subject and Population Pharmacokinetics of Oral and Bolus Dosing Regimes

Author: James Robinson
Advisor: Dr Fang Wan

January 7, 2025

Abstract

A brief introduction to Pharmacokinetics (PK) is given. The use of the ADME scheme is described and the method of compartmental modelling is defined. A brief argument for the case of multiple doses follows. The data considered in a PK analysis setting is outlined, and from there the basics of the PK properties of a drug are defined. Definitions of bolus and oral dosing is given, and their concentration functions are derived for 1-compartment models, in both single dose and multiple dose cases. Some of the numerical methods employed in PK analysis are given, and then simulations are performed to explore the concepts mentioned. These simulations are discussed with relevant research articles references. A concluding section recaps all that was discussed, and points towards how these concepts can be built on as well as discusses viable alternative approaches.

Contents

1 Introduction

During pre-clinical and phase I clinical trials, one of our aims is to quantify the studied drug's safe doses, and whether a repeating dose regime continues to fall within our desired safe-zone [1]. This is known as the pharmacokinetic study of the drug. The data from these studies is sent to an ethics committee, alongside all clinical trial data, where it is reviewed and ensured to be ethical as well as statistically sound.

Pharmacokinetics, abbreviated to PK, is the field of both statistics and pharmacology which describes how the body and its biological processes effect an administered drug [2]. This is closely related to, but not to be confused with, Pharmacodynamics (PD), which is the study of how a drug effects a body [2]. These are often studied in tandem through the aptly called process of PKPD modelling. PK analysis uses ordinary differential equations (ODEs) as well as some more traditional statistical methods, whereas PD analysis is more chemistry and evidence based. Of course, there is overlap between the two areas of study, such as in Toxicology, where we aim to study the drugs toxicity effects at different concentrations [3].

The basis of PK analysis is breaking down the processes that a drug undergoes when 'travelling' through a body. At a base level, these are as follows: absorption, where the drug enters the blood stream; distribution, where the substance is dispersed/disseminated into the fluids/tissue of the body; metabolism, which describes the chemical changes the drug undergoes via biological processes in the body, and finally, excretion, which describes the removal of the drugs from the body. When we consider these processes, we commonly referred to it as the 'ADME scheme' [4]. Due to the complexity of most bodies we would study during a clinical trial, this scheme can be extended to include other processes that may occur, such as the 'LADME' scheme [5], where the L stands for liberation, the changing of the drug from its dosage form.

When observing the ADME processes, we can begin to abstract a large, complex body down into smaller parts which enact the different processes. These smaller parts are known as 'compartments', and this method of abstraction is known as compartmental modelling [6]. A drug moving through the stomach and out into the blood stream can be viewed compartmentally using 1 compartment, where the blood stream is viewed as the compartment, and the drug passes through the stomach lining into this compartment. We can also include the stomach as a compartment if we are to consider the liberation of the drug, such that we'd use a 2-compartment model, where the drug passes into the stomach then to the blood stream. Naturally, for something as complex as an entire body, we could abstract it down into a great many compartments, but this would be overly complex and essentially impossible to model, so we choose the lowest number of compartments that still accurately describe the processes and areas of the body we are considering. The two common and simple compartmental models are the 1-compartment and 2-compartment models, visualised below:

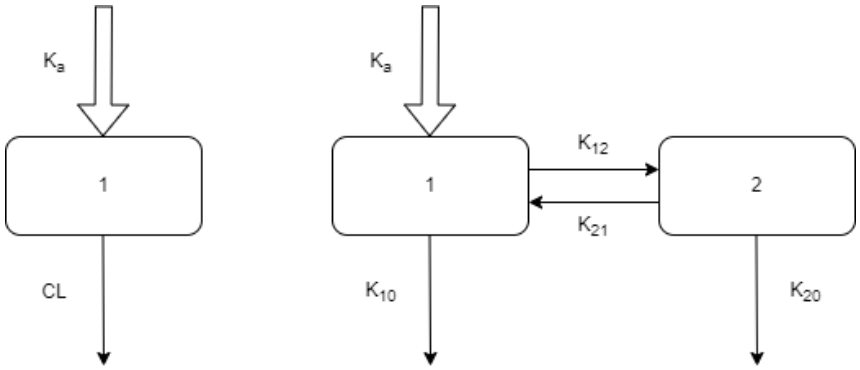

Figure 1: A diagram outlining a 1-compartmental (left) and 2-compartmental (right) model. K_a and CL represent uptake and clearance rates from the compartments, whereas the constants K_{ij} represent the transfer rates from compartment i to j, where $j = 0$ refers to elimination.

The compartment from which we draw the blood samples from can be labelled as the 'observation compartment', which in Figure 1 is compartment 1 for the 1-compartment model, and can be either of the compartments in the 2-compartment model. On top of any assumptions we make a priori, the type of compartmental model being used effects how we define our functions for describing the PK properties of the drug, such as the plasma concentration.

Generally, most medications are needed to be taken multiple times in order to achieve their desired effects, where some are only needed to be taking over a set course, whereas others may be needed to be taken indefinitely.

An example of a widely used drug that is taken over a set course is the antibiotic amoxicillin, a semisynthetic penicillin that can be used to treat a wide variety of bacterial infections. A study conducted by Daniel A. Spyker et al. [7] explored the Pharmacokinetics of amoxicillin, specifically centered at its dose dependence, when it was still a newly developed drug. The study looked at intravenous, oral, and intramuscular doses of 250, 500, and 1000 milligrams. It assumed a 2-compartment model, which was found to be a useful descriptor of the distribution and excretion of amoxicillin. This study is a useful insight into the processes that go into the study of a newly developed drug, especially when it comes to the differentiation between dosage types for the same drug, as well as drugs needed at a high dosage for therapeutic effects to occur.

Another drug widely used but is usually to be taken 'indefinitely' is the antidepressant Sertraline, also known by the brand name Zoloft. Sertraline is a Selective Seratonin Reuptake Inhibitor (SSRI) used to treat major depressive disorders, panic disordres, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD), amongst other psychological conditions relating to mood and stress. A study conducted by Ali A. Alhadab and Richard C. Brundage [8] looked into the population pharmacokinetics of sertraline in a model-based meta-analysis, focusing on IV infusion and oral dosing. This study quantified the changing bioavailability of the drug, that is, the amount of drug actually available to be absorbed, as well as looking at how the area under curve (AUC) increased with proportion to dose. This study is useful for exploring the pharmacokinetics of a pre-established drug, especially when

it comes to the changing bioavailability of the drug, the population pharmacokinetics, and the use of AUC computing and calculations of max conentrations achieved.

The data that comes from a clinical trial will consist of its design variables, such as doses given and time intervals between consecutive doses, as well as its measurements, which is the blood plasma concentration of the drug at the time of measurement. From these measurements alone we can establish several pharmacokinetic properties of the drug being administered, as well as how these properties change with differing dosing regimes. Furthermore, we can study these properties and drug properties in relation to a therapeutic safe zone, that is, the concentration zone where we maximise the desired therapeutic effects and minimise the risk of adverse effects. The design variables and measurements taken are as follows:

Metric	**Symbol**	**Unit**
Dose given	D	moles (mol)
Time	t	seconds (s)
Time interval between consecutive doses	τ	seconds (s)
Plasma concentration of drug at time t	$C(t)$	Molarity (mol/litre)
The maximum/minimum concentration of drug	C_{max} / C_{min}	Molarity (mol/litre)
Time the maximum/minimum concentration of drug achieved	t_{max} / t_{min}	seconds (s)

Table 1: Outlining the basic parameters and measurements made immediately during a trial. Here, M refers to the molarity (moles/litre). If instead we were to use mass instead of amount of substance, mol would be replaced with grams (g) and M would be replaced with grams per litre (g/L).

The AUC of a concentration curve is one of the most important values calculated during any PK analysis. The AUC represents the exposure of the body to the drug over a considered time period. As briefly outlined, the AUC is proportional to the dose administered when following linear kinetics, and also dependant on the elimination rate from the body as well as the dose administered. If one considers the PK properties we will define later, it is easy to see that a change in the AUC for a specific subject can allow for the description of changing PK properties in certain clinical sections, such as if the patient becomes diseased or if covariates such as weight drastically change.

Throughout this dissertation, we will make reference to a plasma concentration curve, sometimes referring to it as a concentration-time graph or a plasma concentration profile. Generally, the shape of this curve changes drastically with different dose types. Two arbitrarily generated concentration profiles for a single bolus dose and a single oral dose are given below:

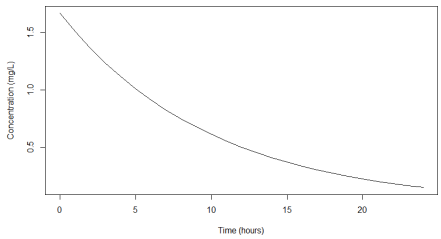

Figure 2: Concentration profile of a bolus dose.

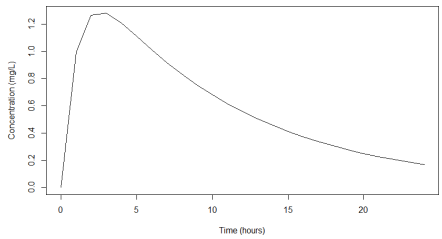

Figure 3: Concentration profile of an oral dose.

In this dissertation, we will define the PK properties we are considering throughout, and then derive plasma concentration functions using these properties for bolus and oral dosing cases. We will derive these functions for both single dose cases and multiple dose regimes. We will then go on to define the surface of the numerical and analytical methods employed in PK analysis, and then demonstrate these with appropriate simulations. We will then discuss these simulations, what they showed and where they were limited, using the limitations to link with real pk studies with real clinical data. When we conclude this dissertation, we will also discuss alternative paths for PK analysis, again making reference to possible further reading.

2 Background

2.1 Useful PK Properties

As mentioned previously, from just the plasma concentration measured and the time it was measured at, alongside the design variables such as the dose given and time interval between consecutive doses, we can calculate numerous different PK properties of the drug being studied. which we begin to explore here. We focus mainly on the properties that help us derive a function that gives the plasma concentration at a time t.

The most important metric we are aiming to estimate is the exposure of a body to a drug by estimating the area under the curve of the plasma concentration-time graph, the plot of the plasma concentration against time. When using a single dose, or considering the entirety of the concentration-time graph, this is given by:

$$AUC_{\infty} = \int_0^{\infty} C(t)dt$$

where we can solve this equation both numerically and analytically in order to estimate this exposure. We can also estimate the area under the curve during a specific time interval by:

$$AUC_{t,\tau} = \int_t^{t+\tau} C(t)dt$$

where time t in this case is the time at the beginning of the interval and time τ is the time over which the interval occurs. This particular method of calculating an AUC is useful for when we're only concerned about the AUC from the moment the drug has been fully 'loaded' into a body, that is, after the initial absorption phase is finished. It is also useful when using multiple dosing, as we aim to quantify the AUC only when the concentration has reached a certain threshold, which we will define fully later.

To begin deriving the rest of the functions and properties we need, we consider the relationship between the amount of drug in the body at a given time and the rate at which the drug is being both absorbed and elimintated from the body. This is given by the following equation:

$$M'(t) = a(t) - e(t)$$

where $M(t)$ is the amount of drug in the body, $a(t)$ is the uptake/absorption rate and $e(t)$ is the elimination rate. This equation is commonly referred to as the 'mass-balance' equation, and this general formulation has many applications outside the field of Pharmacokinetics. Taking a closer look at the elimination function, $e(t)$, we can define another useful property based on the assumption that the drug is being eliminated at a rate proportional to the concentration of the drug at the given time t. This proportion, called the clearance $CL(t)$, is defined by:

$$e(t) = CL(t)C(t)$$

where we assume that $CL(t)$ has some limit (say CL) as t tends to infinity. In this definition the clearance is time dependant, which is a valid assumption, but we may

also want to assume time-independence in order to make our model more simple. We can calculate an average clearance by:

$$CL_{avg} = \frac{D}{AUC}$$

where we use this average clearance as the constant clearance for our time-independence assumption. The equation relies on having calculated the AUC, which we may not be able to achieve if we rely solely on using the clearance in the derivation of our concentration function.

Next, we define the relationship between the amount of drug in the body to the plasma concentration of the drug. This quantity is known as the apparent volume the drug is distributed in, and is defined as the proportionality function $V(t)$ given below:

$$M(t) = V(t)C(t)$$

where again we have defined it in the case of time-dependence. We can compute this volume by integrating the mass-balance equation:

$$V(t) = \frac{\int_t^\infty CL(s)C(s)\ ds}{C(t)}$$

From this, we can compute a specific case of the volume, known as the volume of the central compartment, V_c. This is given at time $t = 0$, by:

$$V(0) = \frac{D}{C(0)} = V_c$$

This quantity is also referred to as the volume of distribution. Intuitively, this calculated volume could reach values which make no sense when attempting to interpret biologically. This 'volume' is more of a mathematical abstraction rather than a biological measurement, however it one can interpret it biologically by applying some ideas from pharmacodynamics.

The final quantity we wish to define is known as the bio-availability of the drug, labelled F. This quantity describes the ratio (or percentage) of the drug that actually becomes available for its intended purpose. That is, the amount of drug from the dose that is absorbed into the body. For this dissertation, we will continue to assume a bio-availability of 1, that is the entire drug is absorbed. The limitations of this will be discussed later.

Now that we have defined these values, we have all the tools we need to derive the plasma concentration functions of bolus doses and oral doses. As some of these quantities are mathematical abstractions, we can define different quantities and re-parameterise the equations appropriately, but using these parameters are generally straight forward.

2.2 Concentration Function for Bolus Dosing

A bolus dose refers to a dose given in a short time frame such that the absorption phase is considered to have been bypassed, and that the concentration of the drug is raised to an effective level as soon as possible. Working with a 1-compartment model, we do not have to account for the absorption rates between different compartments.

As we can assume that there is no absorption necessary in this dosing type, deriving the function for the concentration relies only on the assumption that the change in the remaining concentration is proportional to the current remaining concentration, that is:

$$C'(t) = -k_e C(t)$$

where k_e is the elimination rate of the drug. Solving this equation and assuming that the initial conditions are that the concentration is at its peak, the equation for the remaining plasma concentration for a bolus dose is:

$$C(t) = C(0)e^{-k_e t}$$

When considering the initial concentration $C(0)$, we know that this will be equal to the amount of drug available in the body divided by the concentration that the drug is being distributed in. So the complete equation for the remaining plasma concentration is:

$$C(t) = \frac{FD}{V} e^{-k_e t}$$

To derive the function in the case of multiple bolus doses, we can look at the geometric summation series for each consecutive dose. For a dosing interval τ, we can see that the concentration at the end of this first dosing interval is given by:

$$C_1^{end} = C_0 e^{-k_e \tau}$$

where we have switched to the notation C_n for the concentration of the interval of dose n. The concentration at the start (sta) of the second dose interval will rely on C_0, as the consecutive doses will have an accumulative effect on the concentration and we can assume an instantaneous uptake, and C_0 is the concentration after the dose is given. Thus we have:

$$\begin{aligned} C_2^{sta} &= C_0 e^{-k_e \tau} + C_0 \\ C_2^{end} &= \big(C_0 e^{-k_e \tau} + C_0\big) e^{-k_e \tau} \end{aligned}$$

where the relationship continues on for all n. In order to get this series into the form of a geometric series, we define the common ratio as r to be the term concerning the elimination of the drug after τ. Thus we can reformulate the relationship as:

$$\begin{aligned} C_1^{end} &= rC_0 \\ C_2^{sta} &= rC_0 + C_0 \\ C_2^{end} &= r\big(rC_0 + C_0\big) = r^2 C_0 + rC_0 \\ C_3^{sta} &= r^2 C_0 + rC_0 + C_0 \\ C_3^{end} &= r\big(r^2 C_0 + rC_0 + C_0\big) = r^3 C_0 + r^2 C_0 + rC_0 + C_0 \\ &\cdots \\ C_n^{sta} &= C_0 + rC_0 + \cdots + r^{n-1} C_0 \\ C_n^{end} &= rC_0 + \cdots r^n C_0 \end{aligned}$$

The terms for the start and end concentrations of the n^{th} doses are most clearly a geometric series up to the n^{th} term. Thus they can be rewritten as:

$$C_n^{sta} = C_0\left(\frac{1-r^n}{1-r}\right) = C_0\left(\frac{1-e^{-nk_e\tau}}{1-e^{-k_e\tau}}\right)$$
$$C_n^{end} = rC_0\left(\frac{1-r^n}{1-r}\right) = C_0\left(\frac{1-e^{-nk_e\tau}}{1-e^{-k_e\tau}}\right)e^{-k_e\tau}$$

From here, it becomes clear how to move forward with calculating the concentration remaining for any time t and dose n. Combining the two equations above we arrive at the formula for the concentration at a specific dose n:

$$\begin{aligned} C_{bolus,n}(t) &= C_n^{start}e^{-k_et} \\ &= C_0\left(\frac{1-e^{-nk_e\tau}}{1-e^{-k_e\tau}}\right)e^{-k_et} \end{aligned}$$

2.3 Concentration Function for Oral Dosing

An oral dose is any dose given orally, such as a tablet (which then passes into the stomach) or a form of gas, like an inhaler (where it passes into the lungs). We know that a drug would pass from the area of administration into the blood at a rate proportional to the amount of drug at the site of administration, governed by a constant absorption coefficient denoted k_a. We can also assume that is eliminated from the blood stream, with constant elimination coefficient denoted k_e. We assume $k_a > k_e$, such that the drug has a surplus in the blood plasma. We can see that the quantity of drug in each of these areas can be defined by

$$\begin{aligned} S(t+\Delta t) &= S(t) - k_aS(t) \\ B(t+\Delta t) &= B(t) - k_eB(t)\Delta t + k_aS(t)\Delta t \end{aligned}$$

from here, we can derive the rates of change of the amount of drug in the site of administration by

$$\frac{dS(t)}{dt} = -k_aS(t)$$

as $S(0) = FD$ and assuming $S \to 0$ as $t \to \infty$, we see that

$$S(t) = FDe^{-k_at}$$

and now that we have a formulation for $S(t)$, the rate of change of drug in the blood is given by the differential equation

$$\frac{dB(t)}{dt} = -k_eB(t) + k_aFDe^{-k_at}$$

which, when solving and utilising the same type of boundary conditions as the previous equations, yields

$$B(t) = \frac{FDk_a}{k_a - k_e}\left(e^{-k_et} - e^{-k_at}\right)$$

now, we can can give a formula for the concentration in a 1-compartment model:

$$C(t) = \frac{B(t)}{V} = \frac{FDk_a}{V(k_a - k_e)}\left(e^{-k_e t} - e^{-k_a t}\right)$$

We can also derive a formula for the concentration in a 1-compartmental model when considering multiple dosing, for both cases of the same amount being dosed every time, or the dose differing at each dose time. Going back to the earlier derivation, if the time between doses is given by a set time interval τ, we have

$$\begin{aligned} B(t + n\tau) &= \frac{FDk_a}{k_a - k_e} \sum_{i=0}^{n} \left(e^{-k_e(t+i\tau)} - e^{-k_a(t+i\tau)}\right) \\ &= \frac{FDk_a}{k_a - k_e}\left[\frac{e^{-k_e t}}{1 - e^{-k_e \tau}} - \frac{e^{-k_a t}}{1 - e^{-k_a \tau}}\right] \\ \therefore C(t + i\tau) &= \frac{FDk_a}{V(k_a - k_e)}\left[\frac{e^{-k_e t}}{1 - e^{-k_e \tau}} - \frac{e^{-k_a t}}{1 - e^{-k_a \tau}}\right] \end{aligned}$$

where $t \in [0, tau)$. Supposing we have a differing dose, say d_i at time i, we instead have

$$C(t) = \frac{FDk_a}{V(k_a - k_e)} \sum_{i=0}^{n} d_i\left[e^{-k_e(t-t_i)} - e^{-k_a(t-t_i)}\right]$$

where t lies between two consecutive dosing times, $t_{i,i+1}$. These formulae accommodate for equal periods between doses, where we instead use τ as before.

From these equations, we can see that for large i, or as t tends to infinity, the concentration of the drug at that time does not depend on the concentration resulting from doses previously given, meaning our drug concentration has reached an equilibrium, known as steady state. This comes from the assumption that $k_a > k_e$, such that the accumulation of the drug over time allows us to reach steady state. If this weren't the case, the drug wouldn't accumulate appropriately, which wouldn't result in the desired therapeutic effects.

2.4 Multiple Dosing and Steady State

As before, it is clear that each consecutive dose adds to the accumulated plasma concentration. The previously derived equation for $C(t + i\tau)$ in the oral case and $C_n(t)$ in the bolus case are indeed the equations for the plasma concentration at steady state, but they don't describe the whole concentration curve, rather they describe the concentrations over a certain time interval. Of course, to describe the whole curve we would simply sum the functions over all of the time periods. Hence, the accumulated plasma concentration (or the accumulated plasma concentration remaining, we use the latter term interchangeably here) is:

$$C(t) = \sum_{i=0}^{n} C(t - \tau_i)$$

where τ_i is the i^{th} dose interval, and $C(t - \tau_i)$ is the concentration over the dose interval. Summing these concentrations for each dose interval results in the total

accumulated plasma concentration. In the oral dose case, for a particular n^{th} dose, consider the time interval τ_n for dose number n:

$$C_n(t) = \sum_{i=0}^{n} C(t + \tau_n - \tau_i)$$

The formulae derived previously describe the plasma concentration when it has, or rather eventually does, reach steady state. Another way of viewing this concept using the two equations described above, where we take the limit as t tends to infinity:

$$C_n(t) \to C_{ss}(t) \text{ as } t \to \infty$$

where $C_{ss}(t)$ is the plasma concentration in steady state for a given time t and is labeled as such for clarity. Here, $C_{ss}(t)$ is given by the concentration derived earlier, and so we continue using the label $C(t + i\tau)$ or $C_{bolus,n}(t)$.

In order to continue describing the relationship between plasma concentration and steady state, require a function in the form $C(t)$ such that we can integrate it with respect to only one variable, t. Summing our function for $C(t + i\tau)$ over all i as outlined:

$$C_{oral}(t) = \frac{FDk_a}{V(k_a - k_e)}\left[\frac{e^{-nk_e t}}{1 - e^{-k_e\tau}} - \frac{e^{-nk_a t}}{1 - e^{-k_a\tau}}\right]$$

and of course for the bolus case we have:

$$C_{bolus}(t) = \frac{FD}{V}\sum_{i=1}^{n} C_0\left(\frac{1 - e^{-ik_e\tau}}{1 - e^{-k_e\tau}}\right)e^{-k_e t}$$

As discussed, we aim to achieve a steady state such that it falls within a safe interval. If the steady state reaches too high a concentration we can be at risk of drug toxicity and hazardous adverse effects, and if it reaches too low a concentration we would fail to achieve any of the desired or potential therapeutic results. Translating this relationship into an equation:

$$C_l \leq C_{min} \leq C_{max} \leq C_u$$

where $C_l,\ C_u$ are the lower and upper bounds of the safe therapeutic concentration levels, and $C_{min},\ C_{max}$ are the minimum and maximum concentration levels achieved when we reach steady state. In order to satisfy these constraints, we alter the dosing regime either by altering the dose given, altering the time between doses, or a combination of both.

While we can theoretically pick out the maximum and minimum concentrations in steady state by hand, this is a tedious process and we can instead calculate the maximum and minimum concentrations directly. To derive a formula for the time taken to reach the maximum concentration in the oral case, we begin by differentiating $C(t + i\tau)$ and setting it to equal 0, relabeling it as C_t for notation purposes:

$$C_t' = \frac{FDk_a}{V(k_a - k_e)}\left[\frac{k_a e^{-k_a t}}{1 - e^{-k_a\tau}} - \frac{k_e e^{-k_e t}}{1 - e^{-k_e\tau}}\right] = 0$$
$$\implies \frac{k_a e^{-k_a t}}{1 - e^{-k_a\tau}} - \frac{k_e e^{-k_e t}}{1 - e^{-k_e\tau}} = 0$$

Solving the above equation for t, labelling it t_{max}, we see that:

$$t_{max} = \frac{\log(k_a(1 - e^{-k_e\tau})) - \log(k_e(1 - e^{-k_a\tau}))}{k_a - k_e}$$

Next, to calculate the maximum concentration achieved, we simply plug it into our equation for the concentration:

$$C_{o,max} = \frac{FDk_a}{V(k_a - k_e)}\left[\frac{e^{-k_e t_{max}}}{1 - e^{-k_e\tau}} - \frac{e^{-k_a t_{max}}}{1 - e^{-k_a\tau}}\right]$$

Note that, in this derivation, τ is as defined, which is the length of the dosing interval. This means, for now, we are assuming that we have equal timings between consecutive doses. Another important point to note that the max concentration here is independent of the number of doses given. This further solidifies the idea that the steady state concentration doesn't rely on the history of doses given.

As for the minimum concentration of steady state, we can take a slightly different approach to differentiation. Logically, the minimum concentration of steady state will occur at the time the end of the interval between consecutive doses. This means we can plug τ back into our equation to solve for the minimum concentration:

$$C_{o,min} = \frac{FDk_a}{V(k_a - k_e)}\left[\frac{e^{-k_e\tau}}{1 - e^{-k_e\tau}} - \frac{e^{-k_a\tau}}{1 - e^{-k_a\tau}}\right]$$

Another useful metric related to these measurements is the average concentration during steady state. This can also be compared to the maximum and minimum concentrations, as well as to the desired interval. In a similar vain to the calculation of the maximum concentration, the average concentration can be calculated by integrating from, 0 to the time interval value τ, the equation for the plasma concentration and dividing it by τ. Doing this and then tidying up the result, we can see that:

$$C_{o,avg} = \frac{\int_0^\tau C(t)\ dt}{\tau} = \frac{FD}{Vk_e\tau}$$

Looking at the bolus case, we see that the maximum and minimums are more simple to derive. For the maximum, this is achieved at the start of each consecutive dose in steady state as n has tended to infinity, that is:

$$C_{b,max} = \frac{FD}{V}\left[\frac{1}{1 - e^{-k_e\tau}}\right]$$

Now, the minimum concentration will be at the end of the same interval where maximum concentration was achieved:

$$C_{b,min} = \frac{FD}{V}\left[\frac{e^{-k_e\tau}}{1 - e^{-k_e\tau}}\right]$$

When comparing the average concentration the the maximum and minimum concentrations, we may be interested in quantifying how the maximum and minimum differs from the average. One method of doing this is using what is known as the fluctuation index (FI), defined as the ratio:

$$FI = \frac{C_{max} - C_{min}}{C_{avg}}$$

In order to assure that this ratio is accurate, we would require that C_{max} at the very least is sufficiently large. This is likely to be the case by definition, as at the very least, we can say that C_{max} is larger than C_{min}.

3 Numerical and Computational Methods

In this section, we are going to explore the analytical methods involved in pk analysis, as well as explain how we apply numerical methods for both equation estimation as well as on discrete data sets. Note that, when considering the numerical methods, there are multiple ways of arriving at the same result, as the methods we are considering aren't mathematically complex. We have simply chosen to take the route of some of the more popular numerical methods, mainly for their relative ease of use but also because other research papers will employ the same methods.

3.1 Single Dose AUC

When aiming to calculate the AUC of a concentration-time graph, we can use both analytical methods to solve for this quantity assuming we have the true values of the parameters, and numerical methods for estimation in the cases where we are unsure as to whether we have accurate estimates for the parameters. Of course, both methods can be used during the same analysis and then compared to one another. Starting with analytical integration, the area under the entire curve for both bolus and oral doses are given by:

$$\begin{aligned} AUC_{bolus,\infty} &= \left[-\frac{FDe^{-k_e t}}{Vk_e} \right]_0^{t_\infty} \\ &= \frac{FD}{V}\left[\frac{1}{k_e} - \frac{e^{-k_e t_\infty}}{k_e} \right] \\ AUC_{oral,\infty} &= \left[-\frac{DF}{k_e(k_e - k_a)}(k_e e^{-k_a t} - k_a e^{-k_e t}) \right]_0^{t_\infty} \\ &= \frac{DF}{k_e}\left[1 - \frac{1}{k_e - k_a}(k_e e^{-k_a t_\infty} - k_a e^{-k_e t_\infty}) \right] \end{aligned}$$

where we are using t_∞ to represent the final time we have a recorded concentration.

For numerically integrating either of the concentration functions, we can use a technique known as the trapezoidal method [9]:

$$\begin{aligned} \int_a^b f(x)\, dx &\approx \frac{b-a}{2n} \sum_{i=0}^{n} f(x_i) + f(x_{i+1}) \\ &= \frac{b-a}{2n}\left[f(x_0) + f(x_n) + 2\sum_{i=1}^{n-1} f(x_i) \right] \end{aligned}$$

where $[a, b]$ is the interval over which the area is being calculated and n is our chosen number of trapezoids. Naturally, the larger n is, the more accurate the approximation becomes.

An interesting application of the trapezoidal method arises when it comes to processing the data from the clinical trial directly, rather than working with theoretical observations from our simulations. With a data set, we are limited to a number of intervals equal to the length of the data set minus 1, as well as a height equal to the length of the data set divided by the number of intervals being considered.

This technically places limitations on the accuracy of our estimation, as we cannot exceed a number intervals due to the bounds of the length of the data set. A simple algorithm for implementing the trapezoidal rule onto the data set is given by:

Algorithm 1 Trapezoidal rule applied to data set

```
num_intervals = length(data_set) - 1
height = length(data_set) / num_intervals
temp_sum = 0
for x in range of 2 to num_intervals do
    temp_sum = temp_sum + data_set[x]      ▷ taking each data point in data set
end for
temp_sum_2 = (2 * composite) + data_set[length(data_set)]
estimate = 0.5 * height * sum
```

The algorithm can be used to estimate the entire AUC of a data set generated by any of our concentration functions, whether they are for single doses, multiple doses, or differing doses. Its limitation in this case is that it will only work for a single-subject data set. If this algorithm were to be applied as it was to an entire data set for a population study, we would end up with a large and of course erroneous number.

When we want to calculate the AUC over a specific time interval, say while the concentration is in a certain region, we would simply integrate the functions over the bounds t_1 and t_2, the start and endpoints of the time interval. Furthermore, the interval $[a, b]$ for the trapezium rule will instead be $[t_1, t_2]$. Before Algorithm 1 is implemented, one method of ensuring we are passing it the desired data from the interval is by obtaining the data subset for this time period, such that the algorithm itself doesn't need to be altered.

3.2 AUC of Multiple Doses

We now begin to look at calculating the AUC in the multiple dosing case. Considering equally spaced doses and equal dose amounts, recall the two functions we derived previously:

$$C_{bolus}(t) = \frac{FD}{V}\left[\frac{1-e^{-nk_e\tau}}{1-e^{-k_e\tau}}\right]e^{-k_et}$$
$$C_{oral}(t) = \frac{FDk_a}{V(k_a-k_e)}\left[\frac{e^{-nk_et}}{1-e^{-k_e\tau}} - \frac{e^{-nk_at}}{1-e^{-k_a\tau}}\right]$$

Naturally, calculating the AUCs here will require more work, as we will have to consider the number of administered doses n during the time interval we are integrating over. Here, we will integrate over a set time interval rather than from 0 to infinity, for ease of explanation. Integrating the above equations, we obtain:

$$AUC_{bolus.t_1,t_2} = \frac{FD}{V}\cdot\frac{1-e^{-nk_e\tau}}{1-e^{-k_e\tau}}\cdot\left[\frac{e^{-k_et_1}}{k_e} - \frac{e^{-k_et_2}}{k_e}\right]$$
$$AUC_{oral,t_1,t_2} = \frac{FDk_a}{V(k_a-k_e)}\left[e^{\tau k_a n-1}\left(\frac{e^{k_et-(k_e+k_a)t}}{k_ae^{\tau k_a-1}}\right) - e^{\tau k_e n-1}\left(\frac{e^{k_at-(k_e+k_a)t}}{k_ee^{\tau * k_e-1}}\right)\right]_{t_1}^{t_2}$$

where n is the total number of doses given in the interval $[t_1, t_2]$. For the entire AUC, we would consider the interval $[0, \infty)$, and if we were only interested in the area under the steady state segment, we would define the interval accordingly.

The trapezium rule defined previously will naturally also allow us to estimate these values. Again, we would need to considered the number of administered doses n corresponding the the interval we are considering.

4 Simulation

In this section, we will explore some of the ideas previously discussed and apply the numerical methods given. We will start with oral dosing, where we will explore the ideas of maximum and minimum concentrations at steady state, as well as the relationship between dose given and the log AUC. We will also introduce population modelling with random effects in the context of oral dosing. We will then move on to bolus dosing, where we explore the ideas of wanting the steady state concentrations to fall within a given therapeutic region through both a single-subject and population modelling lense.

4.1 Single-Subject Multiple Oral Dose

To begin, we start by exploring our methods of simulation and calculating the AUC on a data set containing simulated data for a single individual. Here, we are using the R package '*clinPK*' [10] to simulate our initial dataset. It is important to note that this package uses the clearance CL instead of an elimination rate constant k_e. As we have defined in earlier sections, we will bypass this by dividing the clearance by the volume to obtain our elimination rate constant.

We chose a simple set of parameters, as defined below. The chose of our bio-availability $F = 1$ is for ease of clarity and calculation, and dose interval $\tau = 12$ is chosen arbitrarily. We have chosen to 'measure' the concentration over a period of 120 hours (5 days), such that we get 10 doses measured. The function used to generate this data is '*pk_1cm_oral()*'. The corresponding table of values and plasma concentration profile is given below:

Property	**Value**
Dose	50 (mg)
Dosage Interval	12 (hrs)
Absorption Rate	0.5
Clearance Rate	1.0
Volume	30

From the graph, we can see the plasma concentration approaches steady state at roughly 80 hours into the dosing regime. To check this, we can implement the method for calculating time for both maximum and minimum dose concentration at steady state, and then plotting this on the graph (for visual clarity):

While we see that the graph this regime in particular does not reach steady state, it is obvious that it will reach steady state if the length of treatment is extended. Extending the length of treatment to 240 hours (10 days):

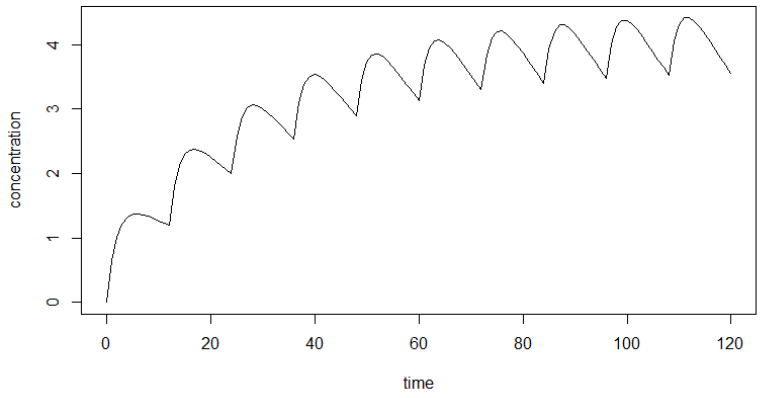

Figure 4: A basic plasma concentration profile for a dose interval of 12 hours and a bioavailibility of 1.

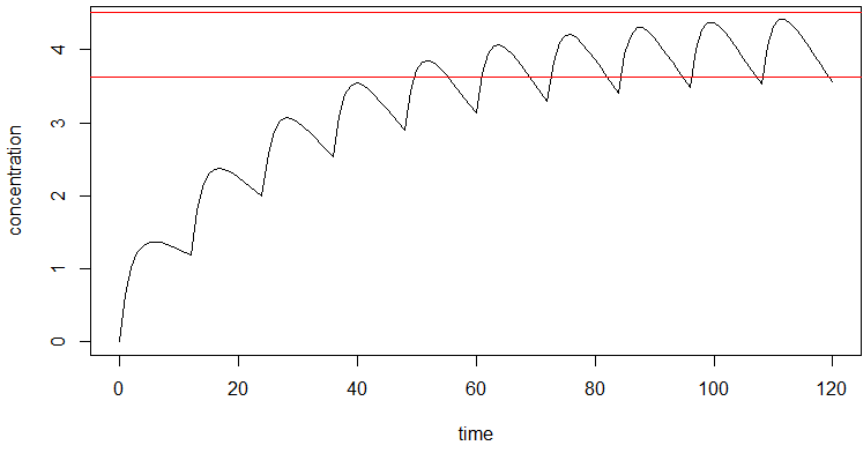

Figure 5: The same plasma concentration profile from figure 2, put with the estimated maximum and minimum plasma concentrations at steady state plotted.

To observe the effect of altering the dosage interval for this dosage, we will consider a 6 hour interval (twice as frequent dosing) and a 24 hour interval (half as frequent dosing). The steady state concentrations depend on the dosage interval, so they will have to be calculated again for the individual regimes. Plotting the concentrations together (for comparison) gives:

From this graph, we can see that increasing the interval decreases the eventual steady state concentrations, as well as the time taken to reach steady state, and vice versa. Intuitively, this makes sense, as a shorter interval between doses allows for less of the drug to be eliminated before the next dose, resulting in a greater amount accumulating in the body.

As stated before, the AUC of a plasma concentration profile describes the exposure of the body to the drug, and is dependent on the dose given and the elimination rate. In order to illustrate the relationship between the AUC and the dose given,

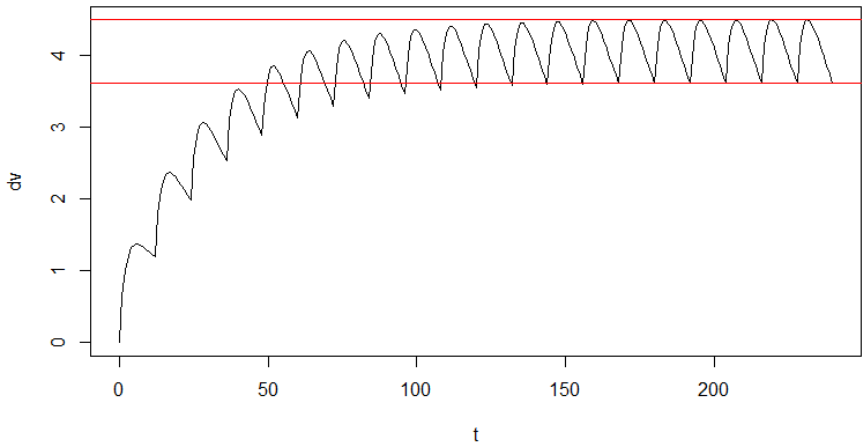

Figure 6: The dosing regime extended to cover 10 days, such that the concentration definitively reaches steady state.

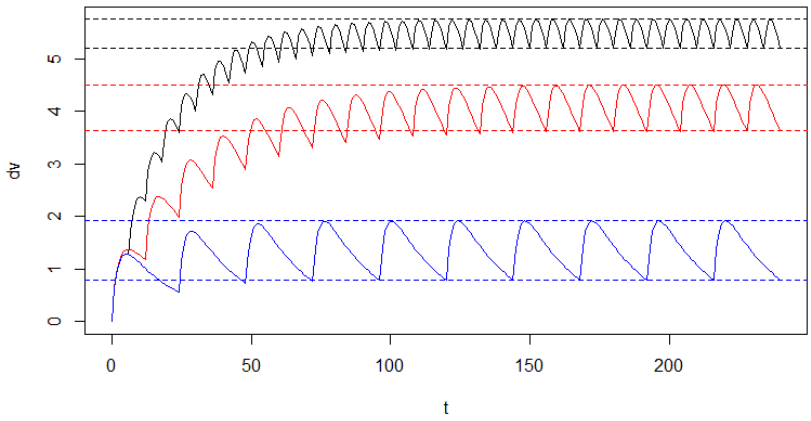

Figure 7: Concentration profiles (solid line) and steady state concentrations (dashed lines) for the following dosing regimes: 24 hours (blue), 12 hours (red), 6 hours (black).

we will simulate data for 5, 10, 25, 75, and 100 mg doses as well as use our data from the 50 mg dosage. Furthermore, we will continue using a dosage interval of 12 hours, over a period of 240 hours, as well as the values $k_a = 0.5,\ V = 30,\ CL = 1.5$ for consistency. The results of these simulations are given in the following table and plot:

From Figure 8, we can see that the relationship between Dose and the log(AUC) follows a roughly linear trend, shown by the red linear line plot. This is a concept known as dose-proportionality and is a tool we can use to estimate log(AUC) given a different dose. Of course, our example isn't necessarily the best illustration of this relationship, where we would need more simulations in order to give a more accurate model.

Dose (mg)	Est. AUC	Est. log(AUC)
5	62.2818	4.131669
10	124.5636	4.824817
25	311.4090	5.741107
50	893.4362	6.795075
75	934.2271	6.839720
100	1245.6361	7.127402

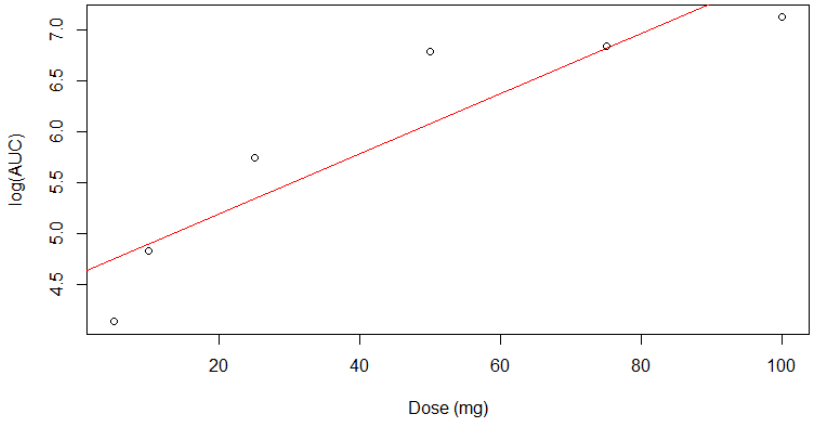

Figure 8: A plot for the simulated data, consisting of the dose given and the log values of the AUC estimates.

4.2 Population Multiple Oral Dose

When considering studies with multiple members, we may wish to incorporate some degree of randomness into our simulations, which we use to describe an individuals difference in results in comparison to the population average.

We can simulate random effect by including them into our terms for clearance, absorption, and elimination with the following:

$$\begin{aligned} Cl_i &= \exp(\beta_1 + b_{1,i}) \\ Ka_i &= \exp(\beta_2 + b_{2,i}) \\ Ke_i &= \exp(\beta_3 + b_{3,i}) \end{aligned}$$

where $(\beta_1, \beta_2, \beta_3)$ are some constants and the random effects $b_{j,i}$ have distribution:

$$b_{j,i} \sim \text{MVN}\big(\vec{0}, \Sigma\big)$$

with Σ being the corresponding covariance matrix.

In order to illustrate this random effect modelling, we use the '*PKPDsim*' package [11] alongside the following arbitrarily picked values: where here the matrix Ω is what we use to define our random effects. The clearance and absorption (and hence the elimination via the volume) define in the table are what the model will be using as the general population values, such that the individual concentrations will be generated by Ω.

Parameter	Value
Clearance	3.0
Volume	30
Absorption	0.5
Dose	50 mg
Interval	12
Pop. Size	10
Ω	$\begin{pmatrix} 0.1 & \\ 0.05 & 0.1 \end{pmatrix}$

Plotting the individual concentrations yielded from these calculations gives the resulting graph:

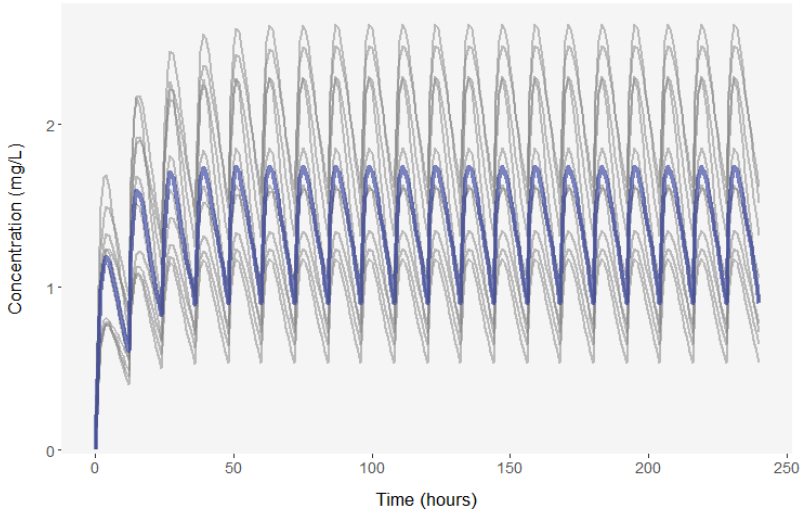

Figure 9: The simulated concentration profiles from a population of size 10 given the arbitrarily picked values.

Figure 9 shows the population average with the thick blue line, while the deviating population values of the individual subjects is plotted as shadows. As we can see, each subject has reached a steady state, the majority of which appear to happen at around the same time into the dosing regime. Generally, the maximum concentration at steady state for each of the subjects tend to appear to not deviate too far from the population average, however, in this case where we have no set upper bounds or desired safe levels for the maximum concentration, this is an arbitrary fact.

With the previous remark in mind, we can begin to explore how this sort of population modelling would interact with desired minimum and maximum steady state concentration levels. Say, for example, a safe region of 0.5mg/L to 2.5mg/L was desired. We can see from a plot whether the concentration levels consistently fall in this region when the curve (appears to) reach steady state. Simulating this trial again with the same values previously, but in turn simulating a new cohort, we have the following figure:

As we can see from Figure 10, some members of the cohort briefly peak above the maximum desired level. Occasionally, for drugs with a low risk of negative effects, this is allowable, especially if it has a low chance of occurring, that is, if there isn't

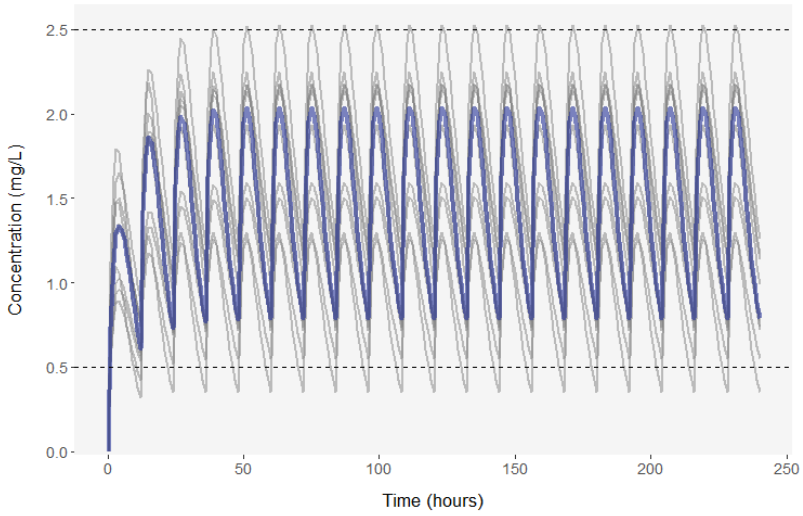

Figure 10: Population concentration-time graph for previously defined parameters, with a safezone of 0.5mg/L to 2.5mg/L included.

a great many individuals who peak above that line. This can be seen with drugs like [example]. On top of this, we can see that a fair few individuals actually trough below the desired minimum. In this case, while there probably isn't any negative side effects of the drug, the negative repercussion is that there may be less of a therapeutic effect for these individuals. It can be argued that the random effects simulated that allow these individuals to fall below the minimum may also need to be applied to this minimum specified, as indeed differing doses do work differently for people in the general population. At this point, however, we do not consider this, as it would be tedious to implement within the scope of this dissertation.

The aim would now be to alter the dosing regime in order to fit all individuals within this desired safe zone. We can do this by altering time intervals, dose levels, or a combination of both, usually going through a trial and error process to do so. It is here in particular that simulating trial data would come in handy, as it would be time consuming and possibly harming to an individual to repeat a trial and error process to alter the maximum and minimum concentrations.

In order to do this, we can take the random effects simulated for the individuals in the previous simulation and use these again. This is the same as using the same individuals in a real-life trial, as we are assuming the same biological differences from the previous simulation. Adjusting the dose interval to $\tau = 10$ yields the following:

where we can see that we have achieved steady state concentrations within the desired safe zone. Indeed, other methods of 'altering' the steady state concentration can be employed if a dosing regime of every 10 hours is found to be undesirable, such as altering the dose amount or experimenting with altering dose amounts after certain time periods. Note that, in Figure 11, there are only 9 patients, rather than the original 10. This is because this 10th patients plasma concentration profile far exceeded the maximum concentration before it had surely reached steady state. This case is a massive outlier, and we can estimate it to be rare, so we don't acknowledge it.

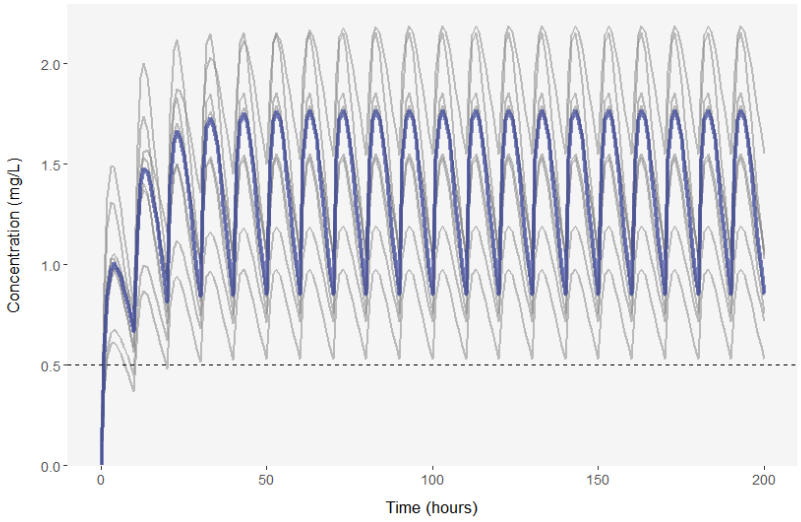

Figure 11: Plasma concentrations for $\tau = 10$. The upper limit of 2.5mg/L isn't plotted due to a technical limitation with the PKPDplot package.

4.3 Single-Subject Bolus Dosing

The concepts behind the simulations for oral dosing are much simpler when applied to the bolus method of dosing. This is partly due to the idea of an instantaneous uptake to reach an efficacious concentration immediately. Here, we will explore the ideas of altering time intervals and doses in order to have our steady state concentrations lie in our desired safe zone interval.

In order to begin exploring this concept, we can look at simulating a case for a single-subject study, and then building up a dosing regime from there. Again, say an efficacious and non-toxic range for a particular drug was found to be between 1.0mg/L and 2.5mg/L. Using the following values we achieve the also following concentration profile:

Property	**Value**
Dose	50 (mg)
Elimination Rate	0.033
Volume	30

From Figure 12, we can see that the concentration eventually fulls under the lower bound of 1.0mg/L before the full 24 hour period is up. Say, for demonstration purposes, that we want the concentration to remain somewhere within the desired zone for the full 24 hour period. This is often the case for when we want a long-term therapeutic effect. One way we can achieve this without considering using multiple doses is by increasing the dose given, which increases the initial concentration. Increasing the dose and trying both 60mg and 70mg, we see that:

Figure 13 shows us that the 70mg dose stays within the desired range for the entire 24 hour period, whereas the 60mg dose dips below the minimum in the last few hours. This means we would continue forward using a 70mg dose for single doses.

Say that we are now interested in achieving this therapeutic effect over an extended time period, say 7 days (168 hours). We can of course consider all 3 of

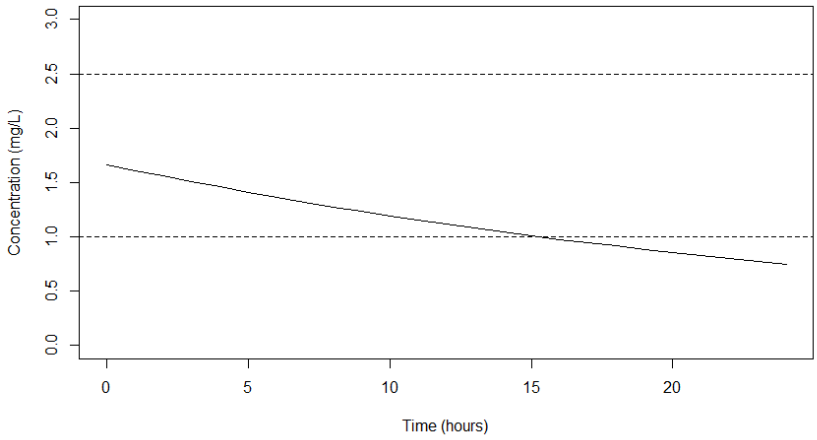

Figure 12: A basic bolus dose concentration profile with desired range between 1.0mg/L and 2.5mg/L

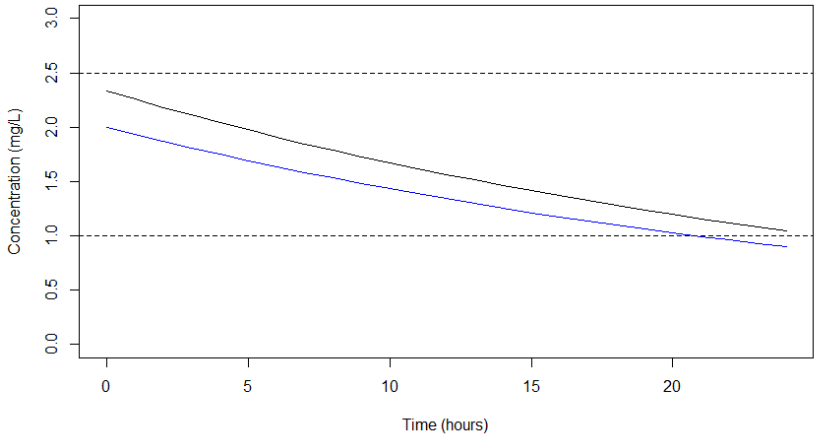

Figure 13: The same subject with a 60mg (blue) and 70mg (black) dose applied.

the 50, 60, and 75mg doses, as long as we chose an appropriate dose interval time such that we stay within the desired range. Again, for demonstration purposes, lets say that a study found the safe range could be extended up to 4.0mg/L before any significant toxic side effects occurred. Starting with an initial dosing interval of 24 hours, for the same subject we achieve the following profile:

From Figure 14, we can see that the 70mg dose has a steady state peak above the desired maximum, and of course the 50mg and 60mg doses do temporarily dip below the minimum. This suggests we should either use the 70mg and increase the dosing interval such that the steady state maxima do not peak above the desired maximum, or we use the lower doses and lower the dosing interval such that they do not trough below the minimum, using the latter suggestion, we can experiment with the following intervals:

Figure 15 shows us that the only regime that just about lies entirely within the

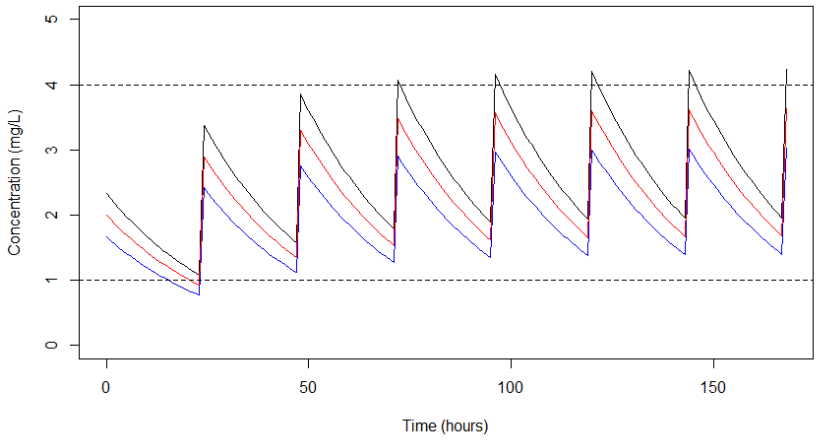

Figure 14: The plasma concentration for this subject over 7 days for 50mg (blue), 60mg (red), and 70mg (black) bolus doses.

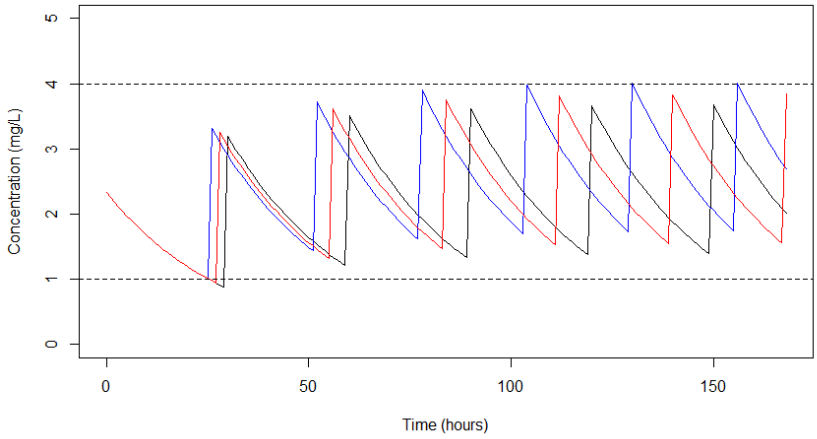

Figure 15: A 70mg dose for the subject with an interval of 26 (blue), 28 (red), and 30 (black) hours.

desired range is the 26 hour interval. Of course, if this was found to be too tedious to implement or otherwise undesirable, the other doses and differing intervals can be considered.

This method of finding a dosing regime is more heuristic in nature and, as seen from Figure 15, more open to interpretation as to whether the maximum and minimum steady state concentrations are acceptable. We are also using a uniform dosing regime rather than varying the dose each time. In the cases where we know V and k_e, as well as the region we want the steady state concentration to fall into, we can manipulate our formulas in order to calculate a suitable dosing regime, a starting dose and a maintenance dose. Assuming $V = 30$ and $k_e = 0.33$, and that we want the concentration to lie within the range 1.0mg/L and 3.0mg/L, we can start by finding τ from:

$$\begin{aligned}
\frac{C_{min}}{C_{max}} &= e^{-k_e\tau} \\
\implies \frac{1}{3} &= e^{-0.33\tau} \\
\implies -log(3) &= -0.33\tau \\
\therefore \tau &= \frac{log(3)}{0.33} = 3.39 \ (2dp)
\end{aligned}$$

Next, we can calculate the starting and maintenance doses by manipulating these same formulas:

$$\begin{aligned}
D_0 &= C_{max} * V = 3 \cdot 30 = 90 \\
D_1 &= C_{max} * V * (1 - e^{-k_e\tau} = 90 \cdot (1 - e^{-0.33 \cdot 3.39}) = 60.59... \approx 61
\end{aligned}$$

so we would start the regime by administering a 90mg dose, and then around every 3.39 hours we would administer a 61mg dose to maintain the concentrations. Here we have used the maximum and minimum concentrations at steady state as the maximum and minimum of the range we want the concentration to lie in, so the concentration will fluctuate between the maximum and minimum, rather than lying safely below or above the maximum or minimum as previously shown.

4.4 Population Bolus Dosing

Now we can look at a similar process but for population modelling. As in the oral dose simulations, we can simulate the random effects by:

$$\begin{aligned}
Cl_i &= \exp(\beta_1 + b_{1,i}) \\
k_{ei} &= \exp(\beta_2 + b_{2,i}) \\
b_{j,i} &\sim \text{MVN}\big(\vec{0}, \Sigma\big)
\end{aligned}$$

with everything defined and distributed as previously. Assuming a safe region of 0.5mg/L to 2.5mg/L, we use the following parameters/population means to gain the also following concentration profile:

Parameter	**Value**
Clearance	3.0
Volume	30
Dose	50 mg
Interval	12
Pop. Size	10
Ω	$\begin{pmatrix} 0.1 & \\ 0.05 & 0.1 \end{pmatrix}$

Figure 16 shows us that some members of the cohort peak above and below the maximum and minimums respectively. Looking at the population mean, it would appear that taking the route of altering the dose or the interval exclusively may not yield the wanted results. After altering either or both, it was clear that each time a

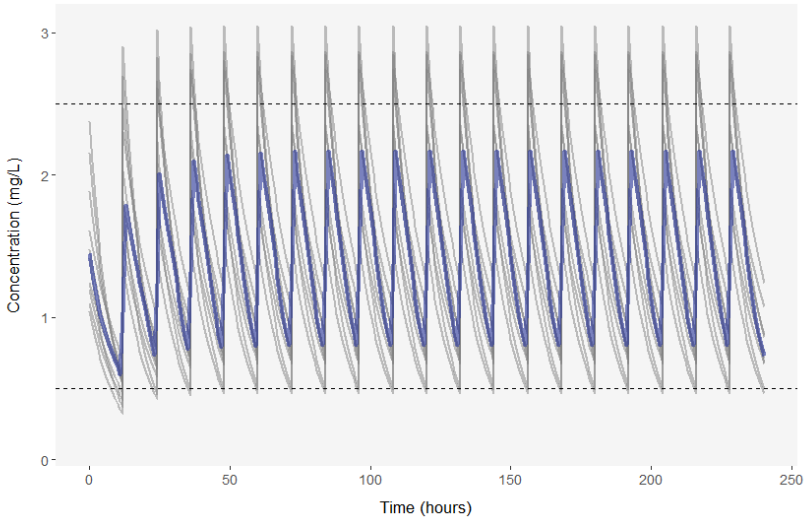

Figure 16: A population simulation for a cohort of n=10 people with the population mean in the bold blue line.

significant proportion of the cohort lay outside of the desired interval for some time periods. In cases like this, it would be wise to either change dosing and method, or to abandon the drug trial altogether in favour of finding a more efficacious one.

As we saw in the single-subject case, we could use the formulae for maximum and minimum steady state concentrations to calculate a suitable dosing regime. This can be done using the population mean values in the same way as the exact values we used previously. The difficulty however comes from allowing for the random effect in these calculations. If we calculated a regime for each individual, we could take averages to find an average suitable dosing regime, and implement that. This could get tedious if we have a large number of subjects, which we would wish to have in order to get a more accurate average.

5 Discussion

When simulating the single-subject case for an oral dosing regime, we eventually saw that the relationship between the log AUC and dose is roughly linear. This is a powerful tool to use when making inferences about the expected total drug exposure for different doses of the same drug on a subject. This idea can of course also be extrapolated to the population analysis case, where a greater number of data points can lead us to a more accurate model to estimate this total exposure from. Furthermore, we can see that the maximum and minimum concentrations in steady state can help us when considering a desired safe zone, as in the population case we can plot an interval of both the maximums and the minimums and use this for inference on whether an individual is likely to stay within the desired safe zones.

When we were simulating the bolus dosing data, we aimed to demonstrate how the plasma concentration profile would aid us in deciding a dosing regime. In the single-subject case, we saw that it was fairly straightforward to alter the regime in order to have the concentration lie in a desired interval. This can be argued to be the case because of our instantaneous uptake, where naturally it would be easier to manipulate the concentration curve to fit in the desired interval due to their being less variables to consider. On top of this, one could argue that it could also be due to the constant term in the concentration equations, as it relies only on the dose given and the volume it is distributed in, rather than on an absorption coefficient or indeed an elimination coefficient, so a change in dose would yield a more drastic change in the concentration curve.

When it came to the population simulations for bolus dosing, we saw a very similar effect from the random simulations as for the oral dosing simulations. This isn't unexpected, as the population randomness isn't relying on the dosing type but rather the biological differences between a population. There is a similar difficulty however in altering a dosing regime for a population using bolus doses. Again, this can be explained by the arbitrary choices and lack of random effects simulated into the maximum and minimum desired levels.

Taking the approach of using the maximum and minimum levels of the safe zone to calculate the necessary values for a dosing regime is efficacious, but as seen can lead to some time intervals and dose amounts that would be tedious to implement. Often, for the dosages one can us a rough amount, say 60mg instead of 61mg, as this is likely to maintain the steady state concentration within the interval, as the maximum and minimum steady state concentrations we are attempting to maintain are the same as the endpoints of the interval. The report '*Dosing Regimen Adjustments In Renal Impairment*' [12] uses this method to adjust dosing regimes for patients with renal impairment, with the extra processes of renal excretion and non-renal excretion being taken into account.

As mentioned, the safe zones chosen for the demonstrations were largely arbitrary and picked due to being able to aid the demonstrations. In reality, when studying a specific drug at this stage, we likely already have an idea from a pre-clinical trial as to the potential toxic and non-therapeutic regions of the drug. For example, a population PK analysis on orally administered Aripiprazole, a drug used to treat Schizophrenia, published by the American College for Clinical Pharmacology [13] used data from 5 separate clinical studies, with 4 of the studies being phase-I trials

with the fifth being a phase-III trial. Furthermore, this study in particular also showed how regular PK analysis can be used alongside other statistical modelling methods such as linear regressions in order to find covariates that play into the pk properties of a drug, such as sex or subject weight.

Throughout the simulations for oral dosing, we assumed a bio-availability of 1. This is highly unlikely, as the drug is likely to get absorbed randomly throughout the body before it passes into the stomach/lungs. When studying specific drugs, the bio-availability is usually calculated as the ratio of the AUC of a non-bolus divided by the dose amount given to that of the AUC of a bolus dose divided by its amount given. The bio-availability, being a constant value below 1, would only scale the concentration profiles we produced in the y-axis, and so largely has no effect for demonstration purposes.

6 Conclusion

The scope of this dissertation focused only on 1-compartment oral and bolus dosing models, for multiple and single doses, but there is a wider range of similar concepts that would make for a great exploration in the next stages. For example, in our models we have assumed there to be a constant absorption and elimination rate, which may not necessarily be mathematically true (or biologically accurate). Elimination and absorption rates can be non-linear in some cases [14], where we can still incorporate random effects in order to account for population differences. On top of this, we could also explore using a different number of compartments in our model, for example 2 compartments, where the derivation for the concentration function would change based on needing to make further assumptions.

The parameters we introduced in the Background section do indeed allow us to describe most properties of drugs in a PK analysis, but this list is not exhaustive nor is it the only approach available. We could also introduce the concept of a 'terminal elimination half-life', which is the time taken for half of the drug to have been excreted from the body. Log-linear regression analysis on the concentration-time curve can be used to calculate the terminal elimination half-life, considering the slop of this regression line as the reciprocal slope for the half-life line [15]. On top of the total exposure to the drug, we can also measure how long a drug is likely to stay inside the body. When considering individual molecules of the drug, this is known as the Mean Residence Time (MRT), and makes use of the first moment of the concentration equations and the areas under curve of this first moment as well as the regular concentration [16].

More methods of statistical analysis can be employed to aid PK analysis than were used here. For example, the just mentioned linear regression analysis is used for the terminal elimination half-life, and can be also used to find how covariates such as weight or sex effect the PK properties of a drug. Furthermore, when we have a non-simulated data set and we fit a model to that data, we can use measures of accuracy, such as bias and root mean square error (RMSE) to test the accuracy of our fitted model. This can open up the world of Pharmacological Research to that of Machine Learning [17], where various machine learning methods such as Monte Carlo simulation [18] and maximum a posteriori Bayesian estimation (MAP-BE).

Theoretically, a Bayesian approach rather than a frequentist approach is perfectly viable for PK analysis [19]. Markov chain Monte Carlo (MCMC) methods allow for posterior inference on arbitrarily complex models, so we can make predictions into pk properties accounting for the right uncertainties.

The computations executed here were done exclusively using R, and the packages *clinPK* and *PKPDsim*. The packages are based on the same mathematical formulae defined and derived here, with slight variations when it comes to picking whether to use clearance or volume, for example. How these packages were implemented specifically is of course detailed in the R Code Appendix. Another software language, SAS, could also have been used in the place of R. SAS is a statistical programming software, and has many specialisations when it comes to simulating and modelling clinical data, such as in pharmacokinetics [20]. Indeed, many papers on and teaching materials for pharmacokinetics uses SAS, due to its high specialisation and ease of use in this case. It is, however, less accessible than R, and so R was chosen for

the computations. Of course Python, or indeed another other language adept at statistical computations, could have been used, but these require far more work to gain the same results for a project of less complexity, such as this one.

References

[1] C. A. Umscheid, D. J. Margolis, and C. E. Grossman, "Key concepts of clinical trials: a narrative review," *Postgraduate medicine*, 2011.

[2] J. J. L. Lertora and K. M. Vanevski, *Introduction to pharmacokinetics and pharmacodynamics*, p. 35–54. Cambridge University Press, 2010.

[3] R. J. Flanagan, M. Rupah, T. J. Meredith, and J. D. Ramsey, "An introduction to the clinical toxicology of volatile substances," *Drug Safety*, 2010.

[4] M. P. Doogue and T. M. Polasek, "The ABCD of clinical pharmacokinetics," *Therapuetic advances in drug safety*, 2013.

[5] K. Wolff, *Basic Pharmacokinetics of Substance Misuse*, pp. 37–56. 01 2017.

[6] A. Rescigno, "Compartmental analysis and its manifold applications to pharmacokinetics," *The AAPS Journal*, vol. 1, 2010.

[7] D. A. Spyker, R. J. Rugloski, R. L. Vann, and W. M. O'Brien, "Pharmacokinetics of amoxicillin: Dose dependence after intraveneous, oral, and intramuscular administration," *Antimicrobial Agents and Chemotherapy*, pp. 132–141, 1977.

[8] A. A. Alhadab and R. C. Brundage, "Population pharmacokinetics of sertraline in healthy subjects: a model-based meta-analysis," *The AAPS Journal*, 2020.

[9] K. E. Atkinson, *An introduction to numerical analysis*. John Wiley & Sons, 2nd ed., 1989.

[10] R. Keizer, J. Hughes, D. Tong, and K. Woo. https://cran.r-project.org/web/packages/clinPK/clinPK.pdf. Accessed: 03-06-22.

[11] R. Keizer, J. Hughes, D. Tong, and K. Woo. https://cran.r-project.org/web/packages/PKPDsim/PKPDsim.pdf. Accessed: 03-06-22.

[12] D. L. Giusti and W. L. Hayton, "Dosing regimen adjustments in renal impairment," *Annals of Pharmacotherapy*, p. 382 to 387, 1973.

[13] X. Wang, A. Raoufinia, S. Bihorel, J. Passarell, S. Mallikaarjun, and L. Phillips, "Population pharmacokinetic modeling and exposure-response analysis for aripiprazole once monthly in subjects with schizophrenia," *Clinical Pharmacology in Drug Development*, p. 150 to 164, 2022.

[14] A. M. Stein and L. A. Pelentier, "Predicting the onset of nonlinear pharmacokinetics," *CPT: Pharmacometrics & Systems Pharmacology*, p. 670 to 677, 2018.

[15] K. C. Lasseter, A. G. Porras, A. Denker, A. Santhanagopal, and A. Daifotis, "Pharmacokinetic considerations in determining the terminal elimination half-lives of bisphosphonates," *Clinical Drug Investigation*, p. 107 to 114, 2005.

[16] H. Y. Cheng and W. J. Jusko, "Mean residence time concepts for pharmacokinetic systems with nonlinear drug elimination described by the michaelis-menten equation," *Pharmaceutical Research*, p. 156 to 164, 1988.

[17] J.-B. Woillard, M. Labriffe, A. Pr´emaud, and P. Marquet, "Estimation of drug exposure by machine learning based on simulations from published pharmacokinetic models: The example of tacrolimus,"

[18] J. Menčík, *Monte Carlo Simulation Method*. 04 2016.

[19] D. J. Lunn, N. Best, A. Thomas, J. Wakefield, and D. Spiegelhalter, "Bayesian analysis of population pk/pd models: General concepts and software," *Journal of Pharmacokinetics and Pharmacodynamics*, 2002.

[20] G. S. Klonick. https://support.sas.com/resources/papers/proceedings-archive/SEUGI1991/Pharmacokinetic%20Analysis%20with%20the%20SAS%20System.pdf. Accessed: 03-06-22.

Single-Subject Oral Code

```
library('clinPK')
library('tidyverse')
library('PKPDmodels')
library("data.table")


funcEst_auc_inf = function(f, end, num_ints){
  h = end / num_ints
  x_val = c(seq(from = 0, to=end, by = h))
  composite = 0
  for(i in 2:(end-1)){
    composite = composite + f(v_val[i])
  }
  sum = (2 * composite) + f(x_val[1]) + f(x_val[end])
  estimate = 0.5 * h * sum
  return(estimate)
}

#one person set parameters
total_time1 = c(0:120)#such that we have 10 doses
thhth = length(total_time1)
dose1 = 50
tau1 = 12
KA1 = 0.5
CL1 = 1
V1 = 30
F1 = 1


model1 = pk_1cmt_oral(t = total_time1, dose = dose1,
tau = tau1, KA = KA1, CL = CL1, V = V1, F = F1)
names(model1)[1] <- "time"
names(model1)[2] <- "concentration"
plot(model1, type = "l")
#lines(please, col="red")

max_conc = function(D, KA, CL, V, tau){
  KE = CL / V
  tpk = (log( (KA * (1-exp(-KE * tau)))/ (KE *
  (1-exp(-KA * tau)))))/ (KA - KE)
  const = (D*KA)/(V*(KA-KE))
  elim = exp(-KE*tpk)/(1-exp(-KE*tau))
  abs = exp(-KA*tpk)/(1-exp(-KA*tau))
  maxconc = const * (elim - abs)
  return(maxconc)
```

```
}

min_conc = function(D, KA, CL, V, tau){
  KE = CL / V
  const = (D*KA)/(V*(KA-KE))
  elim = exp(-KE*tau)/(1-exp(-KE*tau))
  abs = exp(-KA*tau)/(1-exp(-KA*tau))
  minconc = const * (elim - abs)
  return(minconc)
}

conc_max_m1 = max_conc(dose1, KA1, CL1, V1, tau1)
conc_min_m1 = min_conc(dose1, KA1, CL1, V1, tau1)
plot(model1, type = "l")
abline(h=conc_max_m1, col="red")
abline(h=conc_min_m1, col="red")

model1_ext = pk_1cmt_oral(t = c(0:240), dose = dose1,
tau = tau1, KA = KA1, CL = CL1, V = V1, F = F1)
plot(model1_ext, type = "l")
abline(h=conc_max_m1, col="red")
abline(h=conc_min_m1, col="red")

model2 = pk_1cmt_oral(t = c(0:240),dose = 50,
tau = 6,KA = 0.5,CL = 1.5,V = 30,F = 1)
model2_max = max_conc(50, 0.5, 1.5, 30, 6)
model2_min = min_conc(50, 0.5, 1.5, 30, 6)

model3 = pk_1cmt_oral(t = c(0:240),dose = 50,
tau = 24,KA = 0.5,CL = 1.5,V = 30,F = 1)
model3_max = max_conc(50, 0.5, 1.5, 30, 24)
model3_min = min_conc(50, 0.5, 1.5, 30, 24)

plot(model2, type = "l")
lines(model1_ext, col="red")
lines(model3, col="blue")
abline(h=conc_max_m1, col="red", lty=2)
abline(h=conc_min_m1, col="red", lty=2)
abline(h=model2_max, col="black", lty=2)
abline(h=model2_min, col="black", lty=2)
abline(h=model3_max, col="blue", lty=2)
abline(h=model3_min, col="blue", lty=2)

dataEst_auc_inf = function(data){
  intervals = nrow(data) - 1
  height = nrow(data) / intervals
  composite = 0
```

```
  for(i in 2:(nrow(data)-1)){
    composite = composite + data[i, 2]
  }
  sum = (2 * composite) + data[nrow(data), 2]
  estimate = 0.5 * height * sum
  return(estimate)
}

defInt_auc = function(dose, v, cl, ka, n, tau, t1, t2){
  ke = cl / v
  const = (dose/v) * (ka/(ka-ke))
  part1 = ((exp(tau*ka*n)-1)*(exp(ke*t2-(ke+ka)*t2)))
  /(ka*(exp(tau*ka)-1))
  part2 = ((exp(tau*ke*n)-1)*(exp(ka*t2-(ke+ka)*t2)))
  /(ke*(exp(tau*ke)-1))
  part3 = ((exp(tau*ka*n)-1)*(exp(ke*t1-(ke+ka)*t1)))
  /(ka*(exp(tau*ka)-1))
  part4 = ((exp(tau*ke*n)-1)*(exp(ka*t1-(ke+ka)*t1)))
  /(ke*(exp(tau*ke)-1))
  integral = const*((part1 - part2) - (part3 - part4))
  return(integral)
}

five_mg_model = pk_1cmt_oral(t = c(0:240),dose = 5,tau = 12,
KA = 0.5,CL = 1.5,V = 30,F = 1)
ten_mg_model = pk_1cmt_oral(t = c(0:240),dose = 10,tau = 12,
KA = 0.5,CL = 1.5,V = 30,F = 1)#
twofive_mg_model = pk_1cmt_oral(t = c(0:240),dose = 25,
tau = 12, KA = 0.5,CL = 1.5,V = 30,F = 1)
sevenfive_mg_model = pk_1cmt_oral(t = c(0:240),dose = 75,
tau = 12, KA = 0.5,CL = 1.5,V = 30,F = 1)
hundred_mg_model = pk_1cmt_oral(t = c(0:240),dose = 100,
tau = 12,KA = 0.5,CL = 1.5,V = 30,F = 1)

plot(hundred_mg_model, type="l")
lines(sevenfive_mg_model)
lines(model1_ext)
lines(twofive_mg_model)
lines(ten_mg_model)
lines(five_mg_model)

five_auc = dataEst_auc_inf(five_mg_model)
ten_auc = dataEst_auc_inf(ten_mg_model)
twofive_auc = dataEst_auc_inf(twofive_mg_model)
fifty_auc = dataEst_auc_inf(model1_ext)
sevenfive_auc = dataEst_auc_inf(sevenfive_mg_model)
hundred_auc = dataEst_auc_inf(hundred_mg_model)
```

```
aucs = c(five_auc, ten_auc, twofive_auc, fifty_auc,
sevenfive_auc, hundred_auc)
logaucs = log(aucs)
doses = c(5, 10, 25, 50, 75, 100)
plot(doses, logaucs, xlab="Dose (mg)", ylab="log(AUC)")
abline(lm(logaucs ~ doses), col="red")
```

Multiple Subject Oral Code

```
library('clinPK')
library('tidyverse')
library('PKPDsim')
library('PKPDplot')
library("data.table")

dataEst_auc_inf = function(data){
  intervals = nrow(data) - 1
  height = nrow(data) / intervals
  composite = 0
  for(i in 2:(nrow(data)-1)){
    composite = composite + data[i, 2]
  }
  sum = (2 * composite) + data[nrow(data), 2]
  estimate = 0.5 * height * sum
  return(estimate)
}


p = list(CL = 3.0, V= 30, KA = 0.5)
rands = c(0.1,
          0.05, 0.1)
r = new_regimen(amt = 50, interval = 12, n = 20)

size = 10
popmod = new_ode_model(model="pk_1cmt_oral")
multimod = sim(ode = popmod,
               parameters = p,
               regimen = r,
               n = size,
               omega = rands,
               only_obs = TRUE
)
results = data.table(multimod$t, multimod$y)
plot(multimod)
```

```
model_1 = multimod
plot = plot(model_1)
plot + geom_hline(yintercept = 0.5, linetype="dashed",
    color ="black") + geom_hline(yintercept = 2.5,
    linetype="dashed", color ="black")

regimen_2 = new_regimen(amt = 50, interval = 10, n = 20)
multimod_2 = sim(ode = popmod,
                 parameters = p,
                 regimen = regimen_2,
                 n = size,
                 omega = rands,
                 only_obs = TRUE
)
#results = data.table(multimod$_t, multimod$y)
plot(multimod_2) + geom_hline(yintercept = 0.5,
    linetype="dashed", color ="black") +
    geom_hline(yintercept = 2.5, linetype="dashed",
    color ="black")

model_2 = multimod_2 %>% filter(!id == 6)
plot_2 = plot(model_2, ylim=c(0,3))
plot_2 + geom_hline(yintercept = 0.5, linetype="dashed",
    color ="black") + geom_hline(yintercept = 2.5,
    linetype="dashed", color ="black")

model_2_n1 = model_2[model_2$id == 1,]
model_2_n1 = data.frame(model_2_n1$t ,model_2_n1$y)
auc_n1 = dataEst_auc_inf(model_2_n1)

model_2_n2 = model_2[model_2$id == 2,]
model_2_n2 = data.frame(model_2_n2$t ,model_2_n2$y)
auc_n2 = dataEst_auc_inf(model_2_n2)

model_2_n3 = model_2[model_2$id == 3,]
model_2_n3 = data.frame(model_2_n3$t ,model_2_n3$y)
auc_n3 = dataEst_auc_inf(model_2_n3)
```

Bolus Dose Code

```
library('clinPK')
library('tidyverse')
library('PKPDsim')
library('PKPDplot')
library("data.table")
library("ggplot2")
```

```
model_1 = pk_1cmt_bolus(t=c(0:24), dose=50, tau=25,
    CL = 1.0, V=30)
plot(model_1, type="l", ylim=range(0:3), xlab="Time (hours)",
    ylab="Concentration (mg/L)")
abline(b=1, h=1, lty=2)
abline(b=1, h=2.5, lty=2)

model_2 = pk_1cmt_bolus(t=c(0:24), dose=60, tau=25,
    CL = 1.0, V=30)
model_3 = pk_1cmt_bolus(t=c(0:24), dose=70, tau=25,
    CL = 1.0, V=30)

plot(model_3, type="l", ylim=range(0:3), xlab="Time (hours)",
    ylab="Concentration (mg/L)")
lines(model_2, col="blue")
abline(b=1, h=1, lty=2)
abline(b=1, h=2.5, lty=2)


model_4 = pk_1cmt_bolus(t=c(0:168), dose=50, tau=24,
    CL = 1.0, V=30)
model_5 = pk_1cmt_bolus(t=c(0:168), dose=60, tau=24,
    CL = 1.0, V=30)
model_6 = pk_1cmt_bolus(t=c(0:168), dose=70, tau=24,
    CL = 1.0, V=30)
plot(model_6, type="l", ylim=range(0:5), xlab="Time (hours)",
    ylab="Concentration (mg/L)")
lines(model_4, col="blue")
lines(model_5, col="red")
abline(b=1, h=1, lty=2)
abline(b=1, h=4, lty=2)

model_7 = pk_1cmt_bolus(t=c(0:168), dose=70, tau=26,
    CL = 1.0, V=30)
model_8 = pk_1cmt_bolus(t=c(0:168), dose=70, tau=28,
    CL = 1.0, V=30)
model_9 = pk_1cmt_bolus(t=c(0:168), dose=70, tau=30,
    CL = 1.0, V=30)
plot(model_9, type="l", ylim=range(0:5), xlab="Time (hours)",
    ylab="Concentration (mg/L)")
lines(model_7, col="blue")
lines(model_8, col="red")
abline(b=1, h=1, lty=2)
abline(b=1, h=4, lty=2)
```

```
bolus_mod = new_ode_model("pk_1cmt_iv")
p = list(CL = 3.0, V= 30)
rands = c(0.1,
          0.05, 0.1)
r = new_regimen(amt = 50, interval = 12, n = 20)
size = 10
pop_bolus_mod = sim(ode = bolus_mod,
                    parameters = p,
                    regimen = r,
                    n = size,
                    omega = rands,
                    only_obs = TRUE
)
plot(pop_bolus_mod) + geom_hline(yintercept = 0.5,
linetype="dashed", color ="black") +
  geom_hline(yintercept = 2.5, linetype="dashed",
  color ="black")


alt_reg = new_regimen(amt = 60, interval = 12, n = 20)
alt_bolus_mod = sim(ode = bolus_mod,
                        parameters = p,
                        regimen = alt_reg,
                        n = size,
                        omega = rands,
                        only_obs = TRUE
)
plot(alt_bolus_mod) + geom_hline(yintercept = 0.5,
linetype="dashed", color ="black") +
  geom_hline(yintercept = 2.5, linetype="dashed",
  color ="black")
```