Drugs in the Body

Project 2

MATH 3MB3 - Introduction to Modelling

Group 35

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1 | Introduction

The administration and metabolism of drugs within the human body plays a vital role within the medical and pharmacological domain, while emphasizing the importance of the patient's well-being. When it comes to drugs, it's a very critical process when calculating the administration dosages in terms of each patient's body. You must ensure effectiveness while equally making sure to avoid any risks of overdosing. Drugs can be administered into the body through many ways such as intravenously, orally, sublingually, etc (Le, 2022). All these methods determine the way the drug will behave within the human body. A drug's absorption and effectiveness can be influenced by a number of factors, including the drug's design, chemical and physical qualities, the physiologic characteristics of the consumer, and more (Le, 2022). In addition, metabolic pathways are important because they determine how the body breaks down and gets rid of the pharmaceuticals that are taken (Mohsin et al., 2024).

The objective of this study is to better understand the combined effects of drug delivery techniques and metabolic processes on a patient's dosage routine over time by exploring their intricate interplay. Understanding the interconnected process of drug administration and metabolism, is a very crucial process in clinical relevance. Researchers who are interested in this process are able to create and tailor drugs with specific requirements so that it fits each of the individual patients' needs through the analysis of the variables which ultimately influence medication dosage. Furthermore, knowledge of different metabolic pathways and drug delivery methods may contribute to the development of safer and more effective treatments, which will enhance patient outcomes and ensure the reduction of the risk of negative drug reactions.

In this report, you will find that we investigate how the delivery of different medication and metabolic pathways affects each patient's dosage plan and the effects on their body. The research question guiding our work is, "How do different models predict the amount of a drug circulating in the body?". Using mathematical modeling tools, particularly differential equations, it will help you understand the complex effects of various drug delivery strategies and metabolic pathways on the body's spatial distribution of drug concentrations. From this report, we hope to model and offer insights on what the best methods of administration may be through the computational analysis. Through the solution of important issues regarding the kinetics of drug delivery and metabolism, we believe our work will help clear the way for future pharmacology and personalized medicine research.

2 | Model

2.1 | Base Model

There are two base models that are considered, which differ by the method of administering the drug - either intravenously (base case 1) or by an oral pill (base case 2). In either case, the main assumption is that 100% of the drug that is administered is available either instantly (for intravenous) or gradually (for orally). This means any drug loss during administration is omitted.

There are three state variables that are involved, but only two independent ones.

- $A(t)$: the amount of drug in the body in milligrams, after t hours.
- $D(t)$: the dosing rate; how many milligrams enter circulation per hour, after t hours.
- $P(A)$: the processing rate; how many milligrams leave circulation per hour.

For all cases, the model follows this general form, where the rate of change of drug in the body is equal to the inlet rate minus the outlet rate.

$$\frac{dA}{dt} = D(t) - P(A) \tag{1}$$

For the base models, the processing rate is assumed to happen linearly, and is proportional to the amount of drug currently in circulation. In this equation, c is the clearance rate in inverse hours.

$$P(A) = cA \tag{2}$$

For intravenous administration, the drug is delivered continuously at a constant rate of r mg/hour for h hours, after which no more drug is administered. The dosing rate is modeled as a piecewise function, as follows.

$$D(t) = \begin{cases} r & \forall\ 0 \le t \le h \\ 0 & \forall\ t > h \end{cases} \tag{3}$$

For oral administration, the maximum dosing rate (release) is denoted as D_{max} mg/hour and h is the number of hours taken to have a dosing rate that is 37% of the maximum dosing rate.

$$D(t) = D_{max} e^{-t/h} \tag{4}$$

For all cases, c is kept constant at 0.5 h^{-1}. For the first base case, h is fixed at 5 hours, while r takes on either 1, 2, or 4 mg/h. For the second base case, h is fixed at 50 hours, while D_{max} takes on either 1, 2 or 4 mg/h. These values are chosen to evaluate the robustness of the model.

2.2 | Analysis of Base Model

When considering the equilibria of the two base models, it can be seen that the amount of drug in the body will eventually go to zero. Intuitively, the drug is only administered for a fixed dose, whilst the body continuously clears the drug. So eventually, the drug amount will go to zero. Mathematically, as $t \to \infty, A(t) \to 0$.

For the intravenous case, after h hours, the total amount administered is simply $r \times h$ mg. For the oral case, integration is required, as shown below. For the time period of [0, h], the total amount of drug released by the pill is $0.63D_{max}h$. In other words, the average rate of release is only 63% of the maximum at h.

$$\int_0^h (D_{max}e^{-t/h})dt = D_{max}[-he^{-t/h}]_0^h = D_{max}(-he^{-1} + he^0) = D_{max}h(1 - 1/e) = 0.63D_{max}h$$

The base case simulations are shown in **Figure 1** for the intravenous case and in **Figure 2** for the oral case. The `ode` function was used in R to solve the system of differential equations. As expected with enough time, the amount of drug in the body goes to zero for all cases.

For the intravenous case, the simulation shows that a higher rate of administration leads to greater amounts of drug, with a higher peak and a longer time to go to zero.

For the oral pill case, the plot is smoother, since administration is not abruptly cut off (non-piecewise). Similarly, with higher maximum release/dosing rates, there are greater amounts in the body, with a higher peak and a longer time to go to zero. Initially, the inlet/dosing rate is greater than the outlet/clearance rate, leading to an increase in drug amount, but then after some time, the clearance rate becomes greater than the dosing rate. Interestingly, this critical time point seems to be roughly constant across different values of D_{max}.

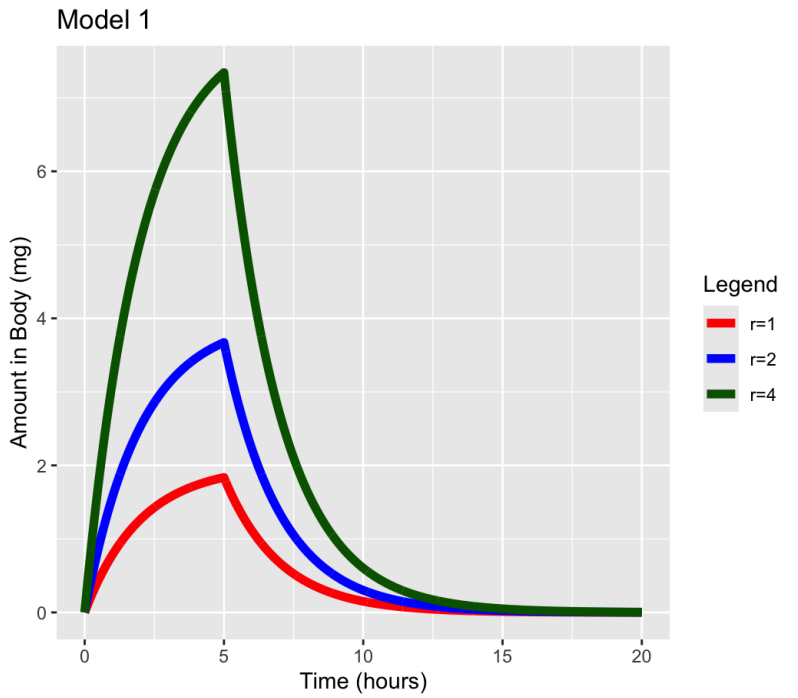

Figure 1. Numerical simulation of base model 1 after 20 hours.

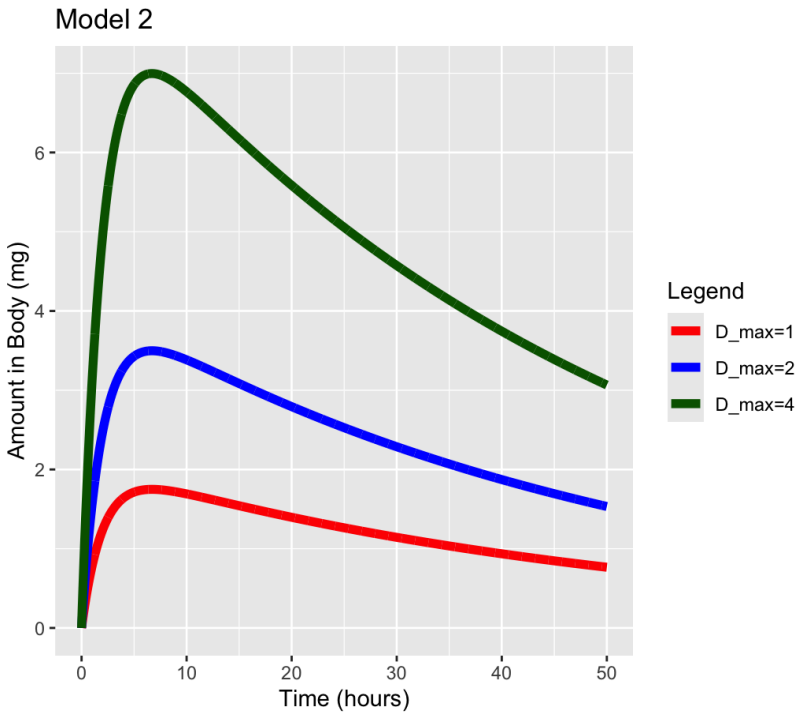

Figure 2. Numerical simulation of base model 2 after 50 hours.

2.3 | Model Extension

Starting with the intravenous base case, this extension looks at modifying the processing rate. Instead of modeling the clearance as exponential drug clearance, it is now assumed that the drug is cleared logistically, according to the following equation. The rest of the model remains the same.

$$P(A) = cA(1 - A/K) \tag{5}$$

This equation differs by including a new parameter, K milligrams. This parameter can be thought of as the "carrying capacity" of the body's metabolism for the particular drug. Instead of being metabolized at a linear rate of the amount in the body, the drug is now metabolized at a *fraction* of this maximum rate.

This extension is more realistic since the body cannot clear a drug faster and faster with greater amounts of the drug - there has to be a limit. In other words, the body cannot process unlimited amounts of the drug. By approaching this limit logistically, it better models real life (Korzekwa & Nagar, 2023).

For this extension, the dosing rate is the same as in the intravenous case, with the constant parameters $r = 1$ mg/hour and $h = 5$ hours. The clearance rate is kept constant as before at $c = 0.5$ h^{-1}. The K parameter is investigated at 5, 10, and 30 mg.

3 | Results

The research question guiding this project focuses on understanding how different models predict the amount of drug circulating in the body. For this extension model, the main interest lies in understanding the logistic drug metabolism, which is centered around K.

Instead of the processing rate being a linear function of the drug amount, it is now a *fraction* of this maximum rate. As evident by the modeling equation and the graph in **Figure 3**, as the amount of the drug approaches K, this fraction decreases, until it reaches zero at exactly K. Any amount beyond K, the body is unable to process and this makes the processing rate negative. This suggests that instead of clearing the drug, more drug is being added into circulation, in addition to the dosing rate. This is a limitation of this model, which leads to an unrealistic assumption. However, as long as the carrying capacity is greater than the amount of drug in the body at any given point in time, the model works appropriately.

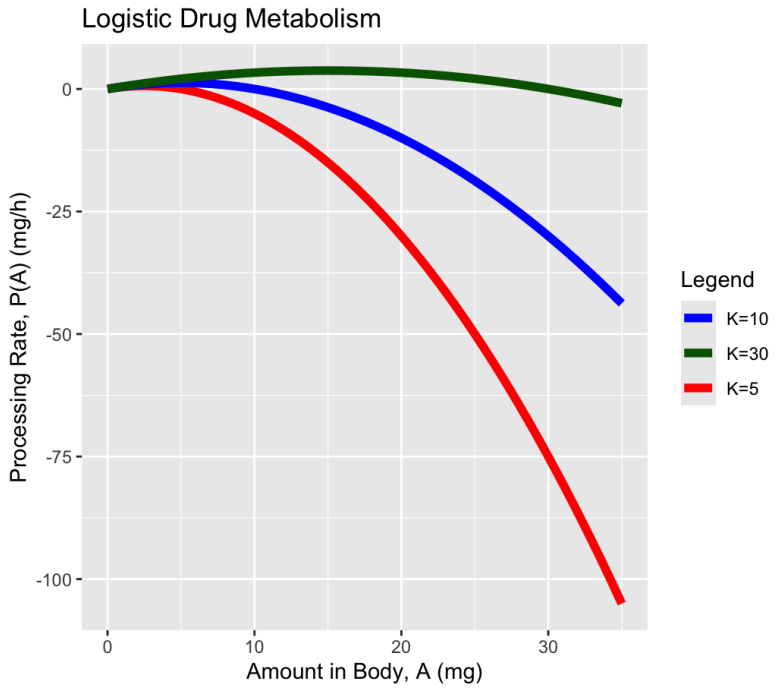

Figure 3. The effect of K on the logistic drug processing rate.

As the plot in **Figure 4** shows, for the parameters chosen (as defined above), with greater carrying capacities, the peak is lower, but still happens at h. Metabolism happens faster with greater carrying capacities, as expected. Ultimately, in the cases considered, the amount of drug eventually reaches zero.

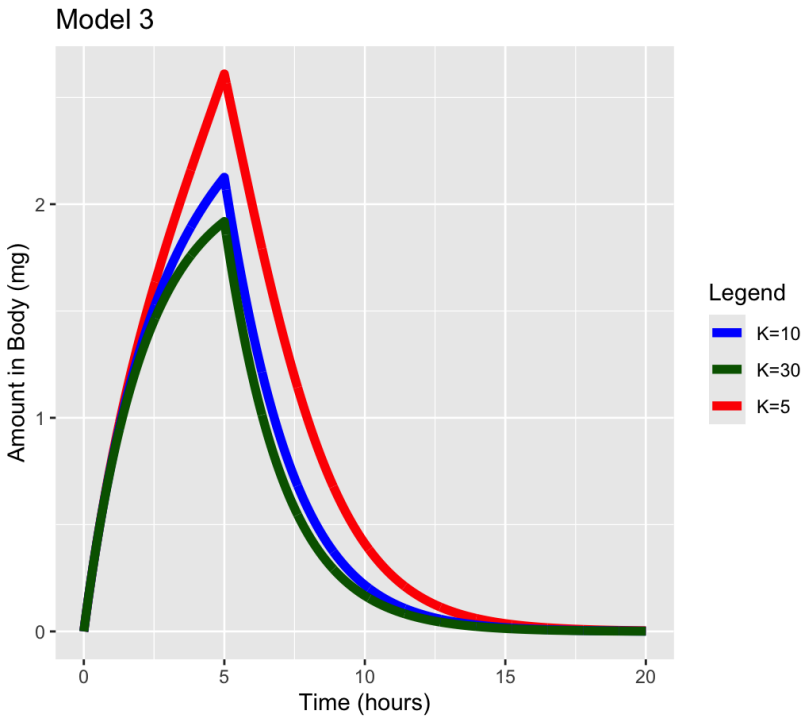

Figure 4. Numerical simulation of extension model after 20 hours.

4 | Discussion

The results reported in the previous section shed light on the dynamics of drug metabolism in the context of the logistic processing rate model, with an emphasis on the carrying capacity (K) parameter. Various simulations revealed that when carrying capacity increased, the peak drug concentration declined while metabolic rate increased. Regardless of the carrying capacity, the drug concentration eventually became zero. These findings directly address the research topic by showing how various models predict the amount of drug circulating in the body, with a particular emphasis on logistic drug metabolism.

Putting these findings into perspective with real-world settings has several implications. To begin, the model's ability to reflect the impacts of carrying capacity on drug metabolism is consistent with physiological understanding, which holds that the body's capacity to metabolize a drug is finite. This emphasizes the need of including realistic considerations into pharmacokinetic models to ensure accurate predictions. Furthermore, the observed drop in peak concentration with larger carrying capacities has implications for dosage strategies, implying that people with higher metabolic capabilities may need higher beginning doses to achieve therapeutic levels.

However, it is crucial to acknowledge the limits of this approach. One notable disadvantage is the assumption of a set dose rate and duration, which may not completely account for real-world scenarios in which dosage patterns vary depending on individual characteristics and treatment protocols. Furthermore, the model's simplicity may have overlooked other factors impacting drug metabolism, such as genetic variants, co-administered drugs, and physiological circumstances, which could have an impact on the accuracy of the projections.

Moving forward, one path for future study could be to incorporate more complexities into the model to improve its predictive skills. For example, including genetic information to personalize drug metabolism predictions or taking into account the effects of concurrent drugs on clearance rates could lead to a more complete understanding of drug dynamics. Furthermore, studying the effects of various dosing strategies, such as continuous infusion or variable dosing regimens, may provide insights on optimizing drug administration protocols for better therapeutic outcomes.

A relevant study by Smith et al. (2020) investigated the impact of genetic polymorphisms on drug metabolism and highlighted the importance of personalized dosing strategies in optimizing therapeutic efficacy while minimizing adverse effects. By integrating such findings into pharmacokinetic models,

future research could further advance our understanding of drug metabolism dynamics and inform clinical practice.

In conclusion, the results presented in this study contribute to our understanding of drug metabolism dynamics under the logistic processing rate model. While acknowledging its limitations, the findings underscore the importance of realistic modeling approaches in pharmacokinetics. Moving forward, incorporating additional complexities and personalization factors into models could enhance their utility in guiding clinical decision-making and optimizing drug therapy.

5 | References

Korzekwa, K. & Nagar, S. (2023, January 9). *Process and System Clearances in Pharmacokinetic Models: Our Basic Clearance Concepts Are Correct*. Drug Metab Dispos 51, 4. https://doi.org/10.1124/dmd.122.001060

Le, J. (2022, June 22). *Drug administration - drugs*. Merck Manual Consumer Version. https://www.merckmanuals.com/en-ca/home/drugs/administration-and-kinetics-of-drugs/drug-administration

Mohsin, N. ul A., Farrukh, M., Shahzadi, S., & Irfan, M. (2024, February 14). *Drug metabolism: Phase I and phase II metabolic pathways*. IntechOpen. https://www.intechopen.com/chapters/88053

Smith, R.L., O'Connell, K., Athanasiu, L. et al. (2020, June 19). *Identification of a novel polymorphism associated with reduced clozapine concentration in schizophrenia patients—a genome-wide association study adjusting for smoking habits*. Transl Psychiatry 10, 198. https://doi.org/10.1038/s41398-020-00888-1

Appendix A | R Code

```
# MATH 3MB3 PROJECT #

library(deSolve)
library(ggplot2)

# MODEL 1 #

h = 5

# r = 1 mg/h

# for t between 0 and h:
params <- c(r = 1, c = 0.5)
states <- c(A = 0)
model <- function(t, states, params) {
  with(as.list(c(states, params)), {
    dA <- r - c*A
    list(c(dA))
  })
}
times <- seq(0, h, by = 0.01)
soln <- ode(y = states, times = times, func = model, parms = params)
y1 <- soln[,2]
x1 <- soln[,1]

# for t greater than h
params <- c(r = 0, c = 0.5)
states <- c(A = tail(y1,n=1))
model <- function(t, states, params) {
  with(as.list(c(states, params)), {
    dA <- r - c*A
    list(c(dA))
  })
}
times <- seq(h, 20, by = 0.01)
soln <- ode(y = states, times = times, func = model, parms = params)
y2 <- soln[,2]
x2 <- soln[,1]

# solutions:
A_val1 <- c(y1,y2)
```

```
t_val1 <- c(x1,x2)

# r = 2 mg/h

# for t between 0 and h:
params <- c(r = 2, c = 0.5)
states <- c(A = 0)
model <- function(t, states, params) {
  with(as.list(c(states, params)), {
    dA <- r - c*A
    list(c(dA))
  })
}
times <- seq(0, h, by = 0.01)
soln <- ode(y = states, times = times, func = model, parms = params)
y1 <- soln[,2]
x1 <- soln[,1]

# for t greater than h
params <- c(r = 0, c = 0.5)
states <- c(A = tail(y1,n=1))
model <- function(t, states, params) {
  with(as.list(c(states, params)), {
    dA <- r - c*A
    list(c(dA))
  })
}
times <- seq(h, 20, by = 0.01)
soln <- ode(y = states, times = times, func = model, parms = params)
y2 <- soln[,2]
x2 <- soln[,1]

# solutions:
A_val2 <- c(y1,y2)
t_val2 <- c(x1,x2)

# r = 4 mg/h

# for t between 0 and h:
params <- c(r = 4, c = 0.5)
states <- c(A = 0)
model <- function(t, states, params) {
  with(as.list(c(states, params)), {
    dA <- r - c*A
    list(c(dA))
```

```
  })
}
times <- seq(0, h, by = 0.01)
soln <- ode(y = states, times = times, func = model, parms = params)
y1 <- soln[,2]
x1 <- soln[,1]

# for t greater than h
params <- c(r = 0, c = 0.5)
states <- c(A = tail(y1,n=1))
model <- function(t, states, params) {
  with(as.list(c(states, params)), {
    dA <- r - c*A
    list(c(dA))
  })
}
times <- seq(h, 20, by = 0.01)
soln <- ode(y = states, times = times, func = model, parms = params)
y2 <- soln[,2]
x2 <- soln[,1]

# solutions:
A_val3 <- c(y1,y2)
t_val3 <- c(x1,x2)

# Making the plot for Model 1
soln <- data.frame(time=t_val1, r1=A_val1, r2=A_val2, r3=A_val3)
colours <- c("r=1"="red","r=2"="blue","r=4"="darkgreen")

ggplot(soln)+
  geom_line(mapping=aes(x=time,y=r1,colour="r=1"), lwd=2)+
  geom_line(mapping=aes(x=time,y=r2,colour="r=2"), lwd=2)+
  geom_line(mapping=aes(x=time,y=r3,colour="r=4"), lwd=2)+
  labs(x='Time (hours)', y="Amount in Body (mg)", title="Model 1",
colour="Legend")+
  scale_colour_manual(values=colours)

# MODEL 2 #
h=50
# Dmax = 1 mg/h

params <- c(D_max = 1, c = 0.5, h=50)
states <- c(A = 0)
model <- function(t, states, params) {
  with(as.list(c(states, params)), {
```

```
    dA <- D_max*exp(-t/h) - c*A
    list(c(dA))
  })
}
times <- seq(0, h, by = 0.01)
soln <- ode(y = states, times = times, func = model, parms = params)
A_val1 <- soln[,2]
t_val1 <- soln[,1]

# Dmax = 2 mg/h

params <- c(D_max = 2, c = 0.5, h=50)
states <- c(A = 0)
model <- function(t, states, params) {
  with(as.list(c(states, params)), {
    dA <- D_max*exp(-t/h) - c*A
    list(c(dA))
  })
}
times <- seq(0, h, by = 0.01)
soln <- ode(y = states, times = times, func = model, parms = params)
A_val2 <- soln[,2]
t_val2 <- soln[,1]

# Dmax = 4 mg/h

params <- c(D_max = 4, c = 0.5, h=50)
states <- c(A = 0)
model <- function(t, states, params) {
  with(as.list(c(states, params)), {
    dA <- D_max*exp(-t/h) - c*A
    list(c(dA))
  })
}
times <- seq(0, h, by = 0.01)
soln <- ode(y = states, times = times, func = model, parms = params)
A_val3 <- soln[,2]
t_val3 <- soln[,1]

# Making the plot for Model 2
soln <- data.frame(time=t_val1, D1=A_val1, D2=A_val2, D3=A_val3)
colours <- c("D_max=1"="red","D_max=2"="blue","D_max=4"="darkgreen")

ggplot(soln)+
  geom_line(mapping=aes(x=time,y=D1,colour="D_max=1"), lwd=2)+
```

```
  geom_line(mapping=aes(x=time,y=D2,colour="D_max=2"), lwd=2)+
  geom_line(mapping=aes(x=time,y=D3,colour="D_max=4"), lwd=2)+
  labs(x='Time (hours)', y="Amount in Body (mg)", title="Model 2",
colour="Legend")+
  scale_colour_manual(values=colours)

# MODEL 3 #

h = 5

# K = 5 mg

# for t between 0 and h:
params <- c(r = 1, c = 0.5, K = 5)
states <- c(A = 0)
model <- function(t, states, params) {
  with(as.list(c(states, params)), {
    dA <- r - c*A*(1-A/K)
    list(c(dA))
  })
}
times <- seq(0, h, by = 0.01)
soln <- ode(y = states, times = times, func = model, parms = params)
y1 <- soln[,2]
x1 <- soln[,1]

# for t greater than h
params <- c(r = 0, c = 0.5, K=5)
states <- c(A = tail(y1,n=1))
model <- function(t, states, params) {
  with(as.list(c(states, params)), {
    dA <- r - c*A*(1-A/K)
    list(c(dA))
  })
}
times <- seq(h, 20, by = 0.01)
soln <- ode(y = states, times = times, func = model, parms = params)
y2 <- soln[,2]
x2 <- soln[,1]

# solutions:
A_val1 <- c(y1,y2)
t_val1 <- c(x1,x2)

# K = 10 mg
```

```
# for t between 0 and h:
params <- c(r = 1, c = 0.5, K = 10)
states <- c(A = 0)
model <- function(t, states, params) {
  with(as.list(c(states, params)), {
    dA <- r - c*A*(1-A/K)
    list(c(dA))
  })
}
times <- seq(0, h, by = 0.01)
soln <- ode(y = states, times = times, func = model, parms = params)
y1 <- soln[,2]
x1 <- soln[,1]

# for t greater than h
params <- c(r = 0, c = 0.5, K=10)
states <- c(A = tail(y1,n=1))
model <- function(t, states, params) {
  with(as.list(c(states, params)), {
    dA <- r - c*A*(1-A/K)
    list(c(dA))
  })
}
times <- seq(h, 20, by = 0.01)
soln <- ode(y = states, times = times, func = model, parms = params)
y2 <- soln[,2]
x2 <- soln[,1]

# solutions:
A_val2 <- c(y1,y2)
t_val2 <- c(x1,x2)

# K = 30 mg

# for t between 0 and h:
params <- c(r = 1, c = 0.5, K = 30)
states <- c(A = 0)
model <- function(t, states, params) {
  with(as.list(c(states, params)), {
    dA <- r - c*A*(1-A/K)
    list(c(dA))
  })
}
times <- seq(0, h, by = 0.01)
```

```
soln <- ode(y = states, times = times, func = model, parms = params)
y1 <- soln[,2]
x1 <- soln[,1]

# for t greater than h
params <- c(r = 0, c = 0.5, K=30)
states <- c(A = tail(y1,n=1))
model <- function(t, states, params) {
  with(as.list(c(states, params)), {
    dA <- r - c*A*(1-A/K)
    list(c(dA))
  })
}
times <- seq(h, 20, by = 0.01)
soln <- ode(y = states, times = times, func = model, parms = params)
y2 <- soln[,2]
x2 <- soln[,1]

# solutions:
A_val3 <- c(y1,y2)
t_val3 <- c(x1,x2)

# Making the plot for Model 3
soln <- data.frame(time=t_val1, K1=A_val1, K2=A_val2, K3=A_val3)
colours <- c("K=5"="red","K=10"="blue","K=30"="darkgreen")

ggplot(soln)+
  geom_line(mapping=aes(x=time,y=K1,colour="K=5"), lwd=2)+
  geom_line(mapping=aes(x=time,y=K2,colour="K=10"), lwd=2)+
  geom_line(mapping=aes(x=time,y=K3,colour="K=30"), lwd=2)+
  labs(x='Time (hours)', y="Amount in Body (mg)", title="Model 3",
colour="Legend")+
  scale_colour_manual(values=colours)

# Exploring the K Parameter

A <- seq(0,35,by=0.5)
c <- 0.5

P1 <- c*A*(1-A/5)
P2 <- c*A*(1-A/10)
P3 <- c*A*(1-A/30)

soln <- data.frame(X=A, Y1=P1, Y2=P2, Y3=P3)
colours <- c("K=5"="red","K=10"="blue","K=30"="darkgreen")
```

```
ggplot(soln)+
  geom_line(mapping=aes(x=X,y=Y1,colour="K=5"), lwd=2)+
  geom_line(mapping=aes(x=X,y=Y2,colour="K=10"), lwd=2)+
  geom_line(mapping=aes(x=X,y=Y3,colour="K=30"), lwd=2)+
  labs(x='Amount in Body, A (mg)', y="Processing Rate, P(A) (mg/h)",
title="Logistic Drug Metabolism", colour="Legend")+
  scale_colour_manual(values=colours)
```

Appendix B | Individual Contributions

Anum Amin	• Completed the Introduction for the report.
Riyadh Baksh	• Created project R script. • Created presentation slide. • Completed Model and Results sections of report.
Avan Mamende	• Completed the Discussion section of the report.
Dhuha Mashaleh	• Completed the Discussion section of the report.