SEB113 Problem Solving Task 1

Pharmacokinetics

Semester 1, 2021

|  |  |
| --- | --- |
| Due date | 11:59pm 25 April, 2021 |
| Last name |  |
| First name |  |
| Student number |  |

# About this Problem Solving Task

On completion of this problem solving task you should be able to:

* display numerical and graphical summaries of key features of a data set
* analyse a first-order differential equation used to model a physical system.

Here is a checklist of the steps you need to go through before submitting this online.

* **Individualise your data** by subsetting to keep only the row with your student number in it.
* **Answer the questions** in the relevant areas in this document.
  + For all steps that require you to show your working, give enough detail (and explanatory text where needed) that anyone reading can follow the logic of your solution.
  + Correct answers with no working will not attract full marks.
  + Provide any R code used to solve the problem in your R script file.
* **Interpret the analysis** in the space provided in the Interpretation section
  + Ensure all plots are included at a resolution that makes them readable and that they have either a caption or a title
* **Provide your completed document** by uploading it to Blackboard as either a Microsoft Word file of format .doc or .docx or a PDF file of format .pdf. Pages files will be awarded a mark of 0
* **Provide your R script** file
  + PSTs with no script files will be considered incomplete and awarded a mark of 0.
  + The script file should
    - have file extension .R
    - contain all code required to read in the downloaded data, and
    - perform all the steps of the analysis that require the use of R

Submit your PST and R script file on Blackboard by the due date. Ensure you have attached both files.

**This is an individual piece of assessment. You should not work with others to complete the task, share your work, or ask other students for their work**. Please ensure you are familiar with [QUT’s policy on Academic Integrity](http://www.mopp.qut.edu.au/C/C_05_03.jsp)

# Introduction

Theophylline is an anti-asthmatic drug which was distributed in tablet form (American Society of Health-System Pharmacists Inc. 2018). In the last few decades, research has led to the development of inhalers and nebulizers for delivery of a range of different anti-asthmatic drugs (Shahidi and Fitzgerald 2010). Nonetheless, the investigation of theophylline allows us to understand the uptake of a drug from the stomach into the bloodstream and its clearance via the kidneys.

This problem solving task contains two main objectives. The first is to examine, describe, and visualise experimental data that comes from a study of the pharmokinetics of theophylline in patients’ bloodstreams following an oral administration of the drug. The second is to consider a mathematical model of the system to describe the dynamics (how it changes with time) of theophylline within the bloodstream. You will then use the information you have synthesized from both the experimental data and the mathematical model to answer questions about the behavior of theophylline and the accuracy of the mathematical model.

c\_0 value =200 k\_a value = 0.062 k\_c value = 1.296

# Section A. Experimental Data [30% Total]

## A1 Data Structure

### A1.1 Importing the data (1%)

In this section of the problem solving task, you will be investigating the Theoph data set in R. Note that this is a built-in data set, and to store it in your environment you simply need to run data(Theoph).

**Exercise:** How many observations are in your data set?

**Answer:**

**Exercise:** How many variables are in your data set?

**Answer:**

### A1.2 Data Dictionary (4%)

In this section, you must collect information about the variables in the Theoph data set and use it to build a data dictionary.

A data dictionary typically displays crucial information and summary statistics about the variables in your data set. This includes the name and type of each variable, its units, and its range. Since Theoph is a built-in data set, you can find out the variable names and units by running ?datasets::Theoph.

As for the range, this is something you need to compute by yourself. In terms of presenting the range in the data dictionary table, please observe the following guidance:

* For continuous or count variables, the range is two numbers, the minimum and the maximum values. If is the minimum and the maximum, then you might write the range as or –. It is **not** the difference between the minimum and maximum values.
* For ordinal categorical variables, give the range as usual.
* For nominal categorical variables, simply list the categories.

**Exercise:** Complete the table below by adding a new row for each variable in the Theoph data set. Use descriptive titles for variables rather than the column name in the data set.

**Answer:**

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | Type | Units | Range |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

**Exercise:** Which variable in our data frame represents our outcome/response/dependent variable?

**Answer:**

**Exercise:** Which variables in our data frame represents potential explanatory/independent variables?

**Answer:**

## A2 Analysis

### A2.1 Numerical summaries (10%)

In this section, you will need to calculate summary statistics for the Theoph data set. Where necessary, round to two decimal places and ensure the units are described appropriately.

Ensure your tables have an appropriate number of columns and rows, have horizontal borders in appropriate places and have captions above the table.

Do not simply present screenshots of R output. You are expected to format your responses in Word.

### Summarising total dataset

**Exercise:** Generate a table that shows the min, mean, median, max and standard deviation of the variables weight and dose. Show all results in one table, rounded to two decimal places. (You may need to stitch several tables together.)

**Answer:**

### Summarising within each subject

**Exercise:** Generate a table that shows the minimum, median and maximum concentration for each subject.

**Answer:**

### A2.2 Graphical summaries

In this section, use Tufte’s principles of graphical excellence to guide the creation of ggplot2 figures that help the reader understand the variability in the data. **Ensure all code is included in the R script file you upload.** All plots are to be labelled appropriately and included at a size and resolution such that the plot is legible. There are many different ways to visualise the data, so don’t feel restricted to one particular type of plot. Ensure your plots have meaningful captions (below the figure) and/or titles.

### A2.2.1 Univariate summaries (5%)

**Exercise:** Create a plot that shows the variability in weight.

**Answer:**

**Exercise:** Create a plot that shows the variability in dose **across all the subjects**.

**Answer:**

### A2.2.2 Multivariate summaries (10%)

**Exercise:** Create a plot that shows the variability in concentration **in each subject**.

**Answer:**

**Exercise:** Create a plot that shows how concentration in the blood stream varies with time.

**Answer:**

**Exercise:** Create a plot that shows how the concentration varies with time for each subject.

**Answer:**

**Exercise:** Recreate the plot from the previous activity, but this time add a **smooth** line of best fit to the data.

**Answer:**

# Section B. Mathematical Model [50% Total]

## B1 The System

Download the pst1data.csv data file from Blackboard and individualise it in R by **keeping only the row that contains your student number** using either the subset() or filter() command. The values in this row will be used for visualising the solution.

### B1.1 Conceptual and quantitative model (5%)

The first order compartment model for pharmacokinetics describes the passage of an ingested compound from the stomach into the bloodstream. The ‘compartments’ refer to the stomach and bloodstream as two distinct but connected reservoirs for the compound. In this assignment, we consider the compound theophylline.

Let be the time in hours since a person ingested a quantity of theophylline in mg (milligrams). Let represent the amount of theophylline (mg) in the stomach (the first ‘compartment’) and let represent the amount of theophylline (mg) in the bloodstream (the second ‘compartment’).

We can use differential equations to model and . To this end, let us first consider a model for the amount of theophylline in the stomach, . Once the person ingests the theophylline, it is absorbed from the stomach into their bloodstream. Therefore, there is an initial amount of theophylline in the stomach at time . After that, the amount of theophylline in the stomach is always decreasing. The rate of change of the amount in the stomach is given by the following model:

where is a rate parameter in hr, and the initial amount of theophylline is given by in mg. In other words, is the amount of theophylline that the person initially ingests.

**Exercise:** What is your value of ? What is your value of ? Include units in your answer.

**Answer:**

The rate of change of the amount of theophylline in the bloodstream is driven by the absorption of the drug from the stomach as well as the clearance of the compound from the bloodstream through the kidneys, with rate parameter . The model is

Taken together, these two equations define a pharmacokinetic model for theophylline uptake in the human body.

**Exercise:** What is an appropriate initial condition for the amount of theophylline in the bloodstream (in mg)? [Hint: this does **not** require any mathematical working.]

**Answer:**

## B2. Analysis

### B2.1 Solution in the stomach (10%)

**Exercise:** Show that is the solution to the above differential equation for . [Hint: you do **not** have to solve the differential equation (though this is also fine).]

**Answer:**

### B2.2 Solution in the bloodstream

Substituting into the differential equation for yields

A **test solution** to this differential equation takes the form

where and are constants to be determined.

### B2.2.1 Setting up the test solution (10%)

**Exercise:** Differentiate the test solution above to obtain . Show your working.

**Answer:**

**Exercise:** Substitute the test solution into the right hand side of the differential equation above. Show your working.

**Answer:**

**Exercise:** Set the derivative of the test solution equal to the answer from the previous exercise so that you have an expression involving on both left and right hand sides. You should see appear exactly once.

**Answer:**

### B2.2.2 Solving for the parameters in the test solution (15%)

We now need to obtain the values of and that satisfy the above equation.

**Exercise:** Factorise the above equation by grouping all terms involving together on each side, and all terms involving together on each side.

**Answer:**

Consider the terms multiplying on each side. These terms inside the brackets on each side must be equal in order for the solution to be valid.

**Exercise:** Setting the left hand group with equal to the right hand group with , determine the value of . Show your working.

**Answer:**

Unfortunately, we cannot use the same technique to solve for . We will use our initial condition for to obtain instead.

**Exercise:** Substitute the value of that you determined into the test solution, set and solve for . Show working.

**Answer:**

**Exercise:** Substitute the values of and into the test solution below to obtain .

**Answer:**

**Exercise:** For what value of is the amount in the bloodstream at its maximum? Show your working.

**Answer:**

## B3 Visualisation (10%)

**Exercise:** Copy and paste the below code fragment into your R script file. Replace the ... with your own code in order to make this a function that reads in a value of time, , and a vector of parameters for , and returns .

calculate\_blood\_amount <- function(...){  
   
 c\_0 <- ...  
 k\_a <- ...  
 k\_c <- ...  
   
 return(...)  
   
}

**Exercise:** Using the values of given to you in the pst1data.csv file, plot the amount of the compound in the bloodstream for the first 24 hours since ingestion. Ensure that your visualisation is readable and clearly labelled. Show, on your plot, the time (in hours) at which the maximum concentration occurs (rounded to two decimal places).

**Answer:**

**Exercise:** Create a data frame containing a sequence of times from 0 to 24 hours in fifteen minute increments. Create two columns, Stomach and Bloodstream containing, respectively, the amounts of the compound in the stomach and bloodstream. Create a table showing the concentrations in both the stomach and bloodstream during the first two hours (in fifteen minute increments).

**Answer:**

**Exercise:** Create a visualisation that shows and . Hint: you may want to use the gather() function to prepare your data for plotting.

**Answer:**

# Section C. Interpretation [20% Total]

Write 2-3 sentences for each answer, ensuring that you refer back to your results and/or the scientific context of the problem. Each question here is weighted equally (i.e., **each question is worth 5% of the total assignment grade**).

**Exercise:** What happens to the amounts of compound in each of the bloodstream and stomach as ? Why?

**Answer:**

**Exercise:** What factors about this system might influence the rates at which the compound is absorbed and cleared? What assumptions might we need to change about our model? You should reference the literature appropriately.

**Answer:**

**Exercise:** Consider the context of the problem. Describe why the rate of change of the amount in the blood stream slows from its initial growth before eventually becoming negative.

**Answer:**

**Exercise:** Looking at the plots you have creating in each section, what can you say about the accuracy of the mathematical model for Theophylline in the bloodstream (section B) when compared with the real data (section A)? You may need to produce an additional plot to draw an effective comparison.

**Answer:**

# Finishing up

Ensure you include the completed document and your R script file when uploading to Blackboard. Ensure all R code used to generate solutions is included in your .R file.

# References

American Society of Health-System Pharmacists Inc. 2018. “Theophylline.” Online: <https://medlineplus.gov/druginfo/meds/a681006.html>. 2018.

Shahidi, N., and J. M. Fitzgerald. 2010. “Current Recommendations for the Treatment of Mild Asthma.” *Journal of Asthma and Allergy* 3. <https://doi.org/10.2147/JAA.S14420>.