SEB113 Problem Solving Task 1

Pharmacokinetics

Semester 1, 2019

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| --- | --- |
| Due date | 11:59pm 7 April 2019 |
| 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 for ingestion orally (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 (N. 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, after 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.

# Section A. Experimental Data [30% Total]

## A1 Data Structure (5%)

### A1.1 Importing the data

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

**Exercise:** How many observations are contained within your data set?

**Answer:**

**Exercise:** How many variables are contained within your data set?

**Answer:**

### A1.2 Data Dictionary

Describe the variables contained within the Theoph data. Since this is a built-in dataset, you can access information on it by running ?datasets::Theoph. While the range of the data is a summary statistic, it is customary to include the range of the variables in the data dictionary. For categorical variables, you are only required to give a range if the variable is ordinal, otherwise, use the range column in the table below to describe the nominal categories. Use descriptive titles for variables rather than the column name in the data set. You may use R for to help you with your data summary.

**Exercise:** Given the above instructions, complete the table below by adding a new row for each variable in the Theoph data set.

**Answer:**

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

**Exercise:** Which variable in our data frame represents our outcome/response/dependant 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 that help the reader understand the data without needing to look at the entire dataset.

Ensure your tables have an appropriate number of columns and rows, have horizontal borders in appropriate places and have captions above the table (select the entire table, right click on it and select “Insert Caption” in Microsoft Word).

Where necessary, round to two decimal places and ensure the units are described appropriately.

### 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 (15%)

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

**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:**

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

**Answer:**

### A2.2.2 Multivariate summaries

**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 by time and 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 retaining the row that contains your student number. The values in this row will be used for solving and visualising the solution.

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

The first order compartment model for pharmacokinetics describes the passage of an ingested compound, such as theophylline, from the stomach into the bloodstream. Over the course of a few hours, the amount in the stomach, $y\_{1}(t)$, and bloodstream, $y\_{2}(t)$, vary from their initial values.

The compound is absorbed from the stomach into the bloodstream, such that the rate of change of the amount in the stomach is given by the following model:

$$\frac{dy\_{1}}{dt}=-k\_{a}y\_{1} (1)$$

with initial amount $y\_{1}(0)=c\_{0}$ having units mg (milligrams).

**Exercise:** Given the information about the units of $y\_{1}$ and $t$, state the value of $k\_{a}$ with appropriate units. Show your working/explain your reasoning.

**Answer:**

The rate of change of the amount in the bloodstream is driven by the absorption from the stomach as well as the clearance of the compound from the bloodstream through the kidneys, with rate parameter $k\_{c}$. The model is

$$\frac{dy\_{2}}{dt}=k\_{a}y\_{1}-k\_{c}y\_{2} (2)$$

**Exercise:** What is an appropriate initial condition for the amount of the compound in the bloodstream? State it with appropriate units.

**Answer:**

**Exercise:** Given the information about the units of $y\_{1},y\_{2},k\_{a}$ and $t$, state the value of $k\_{c}$ with appropriate units. Show your working/explain your reasoning.

**Answer:**

## B2. Analysis

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

**Exercise:** Show that $y\_{1}(t)=c\_{0}e^{-k\_{a}t}$ is the solution to the above differential equation for $y\_{1}\left(t\right)$ (equation (1)).

**Answer:**

### B2.2 Solution in the bloodstream

Substituting $y\_{1}(t)=c\_{0}e^{-k\_{a}t}$ into the differential equation for $y\_{2}(t)$ (equation (2)) we obtain

$$\frac{dy\_{2}}{dt}=k\_{a}c\_{0}e^{-k\_{a}t}-k\_{c}y\_{2} (3)$$

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

$$y\_{2}\left(t\right)=Ae^{-k\_{a}t}+Be^{-k\_{c}t} (4)$$

where $A$ and $B$ are constants to be determined.

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

**Exercise:** Differentiate the test solution above (4) to obtain $\frac{dy\_{2}}{dt}$ and call this (5). Show your working.

**Answer:**

**Exercise:** Substitute the test solution (4) into the right hand side of the differential equation above (3). Show your working.

**Answer:**

**Exercise:** Set the derivative of the test solution (5) equal to the answer from the previous exercise so that you have an expression involving $A,B,e^{-k\_{a}t},e^{-k\_{c}t}$ on both left and right hand sides. You should see $c\_{0}$ appear exactly once.

**Answer:**

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

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

**Exercise:** Factorise the above equation by grouping all terms involving $e^{-k\_{a}t}$ together on each side, and all terms involving $e^{-k\_{c}t}$ together on each side.

**Answer:**

Consider the terms multiplying $e^{-k\_{a}t}$ 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 $e^{-k\_{a}t}$ equal to the right hand group with $e^{-k\_{a}t}$, determine the value of $A$. Show your working.

**Answer:**

We cannot use the same technique to solve for $B$, unfortunately. We will use our initial condition for $y\_{2}(t)$ to obtain $B$ instead.

**Exercise:** Substitute the value of $A$ that you determined into the test solution, set $t=0$ and solve for $B$. Show working.

**Answer:**

**Exercise:** Substitute the values of $A$ and $B$ into the test solution below to obtain $y\_{2}(t)$.

**Answer:**

**Exercise:** For what value of $t$ 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 and complete it to be a function that reads in a value of time, $t$, and a vector of parameters for $c\_{0},k\_{a},k\_{c}$, and returns $y\_{2}(t)$.

calculate\_blood\_amount <- function(){

 c\_0 <-
 k\_a <-
 k\_c <-

 return()

}

**Exercise:** Using the values of $c\_{0},k\_{a},k\_{c}$ 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 $y\_{1}(t)$ and $y\_{2}(t)$. 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.

**Exercise:** What happens to the amounts of compound in each of the bloodstream and stomach as $t\rightarrow \infty $? 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?

**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)?

**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>.

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