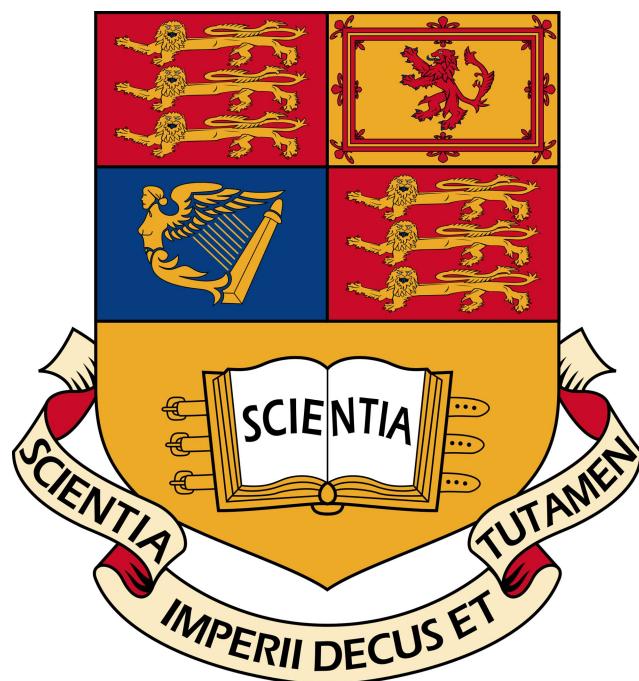


Imperial College London

Department of Electrical and Electronic Engineering

Final Year Project Report 2016

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Project Title: **Improving Antibiotic Dosing In a Hospital Setting**

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## **Abstract**

Antimicrobial resistance is a growing concern today. With the increase in misuse of antimicrobials, the proliferation of antimicrobial resistance has heightened. Firstly, this project concerns the identification of inappropriate dosing of antibiotics amongst a specific group of patients in secondary care. Using the state of the art Pharmacokinetic-Pharmacodynamic (PK-PD) modeling and dosing guidelines provided by the NHS, multiple models were tested to identify the model which best fits the concerned data set. Using patient parameters from the best model, a controller which is capable of altering dosage regimes for these patients was implemented, despite their inherent variability. Single and double compartment models have been used to describe the plasma drug concentration-time profiles within patients for vancomycin. Armed with these results and the desired therapeutic levels of drugs, a PID and an iterative learning controller were implemented. Various factors such as noise in measurements and change in clearance were included in simulations to produce more realistic concentration-time profiles. Multiple performance metrics used in evaluation are also discussed. This project has been able to show the existence of the problem of inappropriate dosing and proved that automated dosing regimens can be designed with the help of PK-PD modeling and a controller.

### **Acknowledgements**

I would like to express my heartfelt gratitude to my project supervisor Dr Pau Herrero-Viñas for his patient guidance and supervision throughout the course of this project. I would also like to thank Dr Timothy M Rawson for his support and constant motivation.

I would like to express my sincere appreciation to my family for understanding and giving me all the necessary support to successfully complete the project.

Last but not least, I would like to thank my friends who have stayed by me and motivated me throughout the project.

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# Nomenclature

<i>AMR</i>	Antimicrobial Resistance	<i>MRSA</i>	Methicillin-Resistant <i>Staphylococcus</i> <i>Aureus</i>
<i>AUC</i>	Area Under Curve	<i>PD</i>	Pharmacodynamic
<i>Cl</i>	Clearance	<i>PID</i>	Proportional-Integral-Derivative
<i>CrCl</i>	Creatinine Clearance	<i>PK</i>	Pharmacokinetic
<i>CrCl</i>	Creatinine Clearance	<i>PK – PD</i>	Pharmacokinetic-Pharmodynamic
<i>ILC</i>	Iterative Learning Control	<i>TDM</i>	Therapeutic Drug Monitoring
<i>IV</i>	Intravenous Infusion	$V_d$	Volume of Distribution

# Chapter 1

## Introduction

### 1.1 Project Motivation

Antimicrobial resistance (AMR) can be defined as the resistance of a micro-organism to an antimicrobial drug that was originally effective for treatment of infections caused by it. AMR is a major threat to patient safety and there is an increasing number of patients who are being affected with bacteria for which there are very few antimicrobials that remain effective today [1].

Antibiotics are a subset of antimicrobials and are used to help combat bacterial infections in particular. Antibiotics have greatly improved the standard and quality of human life since their inception. These drugs combat bacteria by acting on specific targets either on or within the bacteria, killing them or preventing them from multiplying. Though the development of antibiotic resistance is natural, inappropriate use of the drugs accelerates the spread and emergence of new cases. This project is particularly concerned with the rising number of cases of antibiotic resistance.

With an increase in antibiotic resistance, current practices are rendered ineffective in dealing with these resistant strains of bacteria. As a result, more expensive therapies have to be used. This could imply larger doses of drug or the use of more toxic drugs to effectively deal with the infection. With resistant bacteria, the duration of treatment and illness also inevitably increases. This not only increases the strain on medical institutions to deal with these new infections but also increases the risk of worse clinical outcomes and death amongst patients [2].

The misuse of antibiotics remains one of the leading causes of the aggravation of antibiotic resistance. The more pertinent actions of antibiotic misuse are the ones related to the hospital setting include unnecessary prescription of drugs, prescribing excessive inappropriate prescription of broad and narrow-spectrum drugs respectively or even untimely treatment of critically ill patients [3]. About 40% of patients treated with antibiotics for bacterial

infections were given either a drug too broad spectrum compared to the susceptibility of the pathogen or given unnecessary antibiotics [4].

In order to prevent further proliferation of antibiotic resistance, it is imperative to be able to place patients on correct dosing regimes and stop superfluous treatment regimes. There are two primary steps to effective antimicrobial therapy. First the correct antibiotic has to be selected to deal with the infection. Subsequently, the patient should be placed on the right dosing regime. Unfortunately, there is a large volume of data that has to be analysed before an effective dosing strategy can be implemented. Furthermore, as each individual is slightly varied from the other, the problem is made more complex. Junior doctors, with less experience, may find it especially difficult to determine this optimal dosing. Moreover, as AMR can change overtime, doctors are required to adapt the dosing regime constantly during the treatment period. Hence, a point-of-care decision support system may assist doctors to select the right dosing strategy for their patients.

## 1.2 Project Objectives

The Centre for Bio-inspired Technology (CBIT) in Imperial College London in collaboration with the Health Protection Research Unit for Healthcare Associated Infections and Antimicrobial Resistance (HPRU for HCAI & AMR) is developing a decision support system currently. The overarching objective for this project is to develop an antimicrobial dosing module that will be integrated with the support system.

This dosing module will assist doctors design individualised dosing strategies for patients. Patient parameters are bound to change over the course of treatment, especially with critically ill patients. The dosing module will be able to adapt the dose administered accordingly to achieve intended targets based on the changing patient parameters. Typically, these changes are ignored and as a result sub optimal therapy is provided. With the dosing module, accounting for these changes, doctors are able to optimise therapy for multiple patients simultaneously despite consistently changing parameters.

This project looked to first establish the existence of the problem of inappropriate dosing amongst patients in local hospitals. Using Pharmacokinetic-Pharmodynamic (PK-PD) population modeling and existing hospital guidelines, the variation of drug concentration in a patient can be predicted. Different indices can then be used to determine if patients are being dosed appropriately to achieve optimal results.

Next, control theory can be used to design a closed loop system capable of intelligently adapting dosing regimes for different patients. PK-PD modeling principles will be used to design and test the controller. Knowledge of therapeutic levels of the required serum drug concentration for optimal therapy is also integral in implementing an effective feedback system. With this, different controllers can be implemented and adapted to give the most realistic individualised dosing regimes.

## 1.3 Project Scope

Since it is impractical to be able to tackle all the available antibiotics at once, this project will focus on one particular antibiotic. Patient parameters such as weight and serum drug concentration levels during the treatment period are required to develop a robust population model. Drugs under Therapeutic Drug Monitoring (TDM) will have the required information necessary for analysis and modeling. Of the few drugs which are under TDM here in the UK, this project will focus on vancomycin.

The programming language and environment for statistical computing and graphics, R, was selected as the platform to perform PK-PD modeling because it allows the utilisation of Pmetrics. Pmetrics is a package that allows quick implementation and analysis of PK-PD modeling. MATLAB was used for data processing and the implementation of the control systems.

## 1.4 Report Overview

This report has been categorised into 7 different chapters. Chapter 1 provides an introduction to the report in which the scene is set and a high level description of the problem is provided. The aims and objectives of this project are also covered in this chapter. In Chapter 2, the background information required for this project is detailed. Additional insight into the antibiotic resistance is provided before equations related to PK-PD modeling and closed loop controllers are explained. In Chapter 3, the specific requirements for different parts of the project are listed in detail.

Chapter 4 describes the first part of this project, problem analysis. Comparisons between dosing regimes provided and the ideal ones stipulated by hospital guidelines are made in this chapter. In Chapter 5, multiple PK models are tested and evaluated to identify the best model to represent the given data set. Statistical comparisons are made between one and two compartment models and the effects of covariates analysed. Chapter 6 covers the implementation of closed loop controllers. Different input scenarios have been modeled and simulated to obtain realistic representations of the variation of drug concentrations in patients. The results obtained with different PK-PD models are compared and evaluated. The feasibility of using closed loop control to optimise dosing is also analysed here. Finally, Chapter 7 concludes the project and looks at possible areas for future development.

# **Chapter 2**

## **Background**

### **2.1 Antibiotics**

Antibiotics are used to treat or prevent certain types of bacterial infection. They work by killing bacteria or preventing them from reproducing and spreading [5]. Antibiotics which are bactericidal kill the bacteria while those which are bacteriostatic work by preventing further reproduction of bacteria. These drugs are only effective against bacterial infections and ineffective against viral infections such as the common cold.

In general, antibiotics are prescribed when a patient is diagnosed with a bacterial infection that satisfies the following conditions.

1. Infection cannot be cleared by the body's immune system
2. Infection can spread and infect others
3. Will take a long time to recover from infection if not treated
4. If untreated, could result in serious additional complications

Antibiotics can be administered orally, topically or via injections. Oral antibiotics which include pills and capsules, tablets and liquids are usually used in the treatment of mild to moderate infections in the body. Topical antibiotics such as creams, lotions, sprays or drops are usually used to treat skin infections. In more severe cases of infection, injections or infusion through a drip is used to release the antibiotic directly into the blood or muscle [5] as this removes the lag time required for the absorption of the drug.

#### **2.1.1 Classification Of Antibiotics**

Antibiotics can be classified in a number of ways based on type of activity or the bacteria spectrum upon which they work on. However, the most effective and useful classification is based on the chemical composition of the drugs. Using this classification, antibiotics can be segregated into five different main classes. Drugs belonging to a particular class will have

the similar patterns of effectiveness, toxicity and allergic potential [6]. The classes along with their descriptions and the potential side effects are summarised in Table 2.1.1.

Table 2.1: Classification of antibiotics

Class	Description	Drawbacks
Beta-Lactams, Penicillin and Cephalosporins	Hinder the growth of bacteria cell walls	Diarrhoea, nausea, mild stomach cramps
	Used to treat skin, dental, ear, respiratory and urinary tract infections, gonorrhea and pneumonia	Very high doses of penicillin can cause neurotoxicity and hematologic toxicity in some Cephalosporins
Macrolides	Bind with bacterial ribosomes to inhibit protein synthesis	Nausea, vomiting, and diarrhea
	Used to treat respiratory tract, genital, gastrointestinal tract, and skin infections	Should be used with caution for patients with liver dysfunction
Fluoro-quinolones	Stops reproduction by inhibiting bacteria's ability to produce DNA	Vomiting, diarrhea and abdominal pain
	Used to treat skin, urinary tract and respiratory infections like bronchitis and sinusitis	Serious effects include central nervous system abnormalities, phototoxicity, QT interval prolongation, tendinopathy and tendon rupture, and convulsions
Tetracyclines	Inhibit protein synthesis in bacteria and has a chemical structure of 4 rings	Cramps or burning of the stomach, diarrhea, nausea, vomiting, esophageal ulceration, sore mouth or tongue.
	Most commonly used to treat severe rosacea and acne	Should not be used in children under 8 years of age
Aminoglycosides	Stop bacteria from being able to perform protein synthesis	Major irreversible ototoxicity
	Used to treat infections caused by gram-negative bacteria	Nephrotoxicity (kidney damage) when used in high concentrations
Glycopeptides	Hinder the growth of bacteria cell walls	Nephrotoxicity and rarely ototoxicity
	Narrow spectrum affecting only Gram positive bacteria	Red man syndrome with rapid infusion

## 2.2 Antimicrobial and Antibiotic Resistance

Antimicrobial resistance is resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it [2]. Microorganisms include bacteria, fungi, viruses and parasites. Antibiotic resistance refers to a specific subset of antimicrobial resistance as only bacterial infections are dealt with.

Antibiotic resistance occurs when an antibiotic has lost its ability to effectively control or kill bacteria growth [7]. This implies that the bacterial infection continues to worsen even with therapeutic levels of an antibiotic in the bloodstream. This project will focus on antibiotic resistance.

Bacteria can become resistant either by genetic mutation or by acquiring DNA from another bacterium. Genetic mutation occurs spontaneously with or without antibiotics present and different mutations result in the bacteria developing different ways to render antibiotics ineffective. Some mutations prevent antibiotics from reaching within their target cells by closing up entry ports into the cell, while others change the structure of the target cells or entirely eliminate them. At times, enzymes are also produced that are capable of destroying the incoming antibiotic [7]. Hence, when antibiotics are introduced to these bacteria, the susceptible cells are killed off leaving behind the sub-population which is resistant.

Bacteria also release DNA upon death which can then be taken up by suitable bacteria through a process known as transformation. This process results in the genetic alteration of the recipient cell [8]. Any bacteria which acquires resistant genes via spontaneous mutation or genetic exchange has the ability to resist one or more antibiotics [7].

Antibiotic resistance is a major threat because resistance characteristics can spread from one bacterial population to another. New generations of bacteria can inherit these resistance traits which is known as spreading "vertically" or bacteria can share or exchange sections of genetic material with other bacteria known as spreading "horizontally". Since horizontal transfer of genetic material can occur between different bacterial populations, new resistant traits of bacteria may emerge which could be deadly as there is no effective way of dealing with the infections [7].

One very good example to highlight the seriousness of antibiotic resistance is Methicillin-Resistant *Staphylococcus Aureus* (MRSA). 70% – 90% of *Staphylococcus aureus* are resistant to penicillin. MRSA is a type of bacteria that is resistant to a number of widely used antibiotics, making it more difficult to treat than other types of infections. MRSA bacteria is usually transferred by skin-to-skin contact and other contaminated objects. Resident patients in hospitals are more prone to this infection [9]. Patients diagnosed with MRSA are estimated to be 64% more likely to die than people with a non-resistant form of the infection [2].

Though the development of resistance in bacteria is a natural process, the misuse and overuse of antibiotics drastically escalates the process. When antibiotics are given for too short a time or at low doses, not all the bacteria is killed and hence the surviving sub-population pass on the survival traits to more bacteria. This in turn results in stronger infections and even death. On the other hand, excessive use of ineffective and inappropriate antibiotics also cause the bacteria to adapt and become resistant to different antibiotics [10]. Therefore it is integral that the correct type and amount of antibiotic is given to the patient to curb the proliferation of antibiotic resistance.

### 2.3 Effective Antibiotic Dosing

Once the bacterial infection is identified and the appropriate antibiotic needed to deal with the infection has been determined, a suitable dosing strategy is required. Effective antibiotic dosing is a significant contributor to successful clinical outcomes and should not be taken lightly.

There are three primary objectives of antibiotic dosing. Firstly, since antibiotics aim to kill or prevent the spread of bacteria, effective dosing should maximise the rate and extent of bacteria killing or spreading. Even though the most resistant bacteria can be inhibited or killed by a sufficiently high concentrations, due to the toxicity of the drugs, it is not possible to increase the dosage indefinitely. Therefore, the second objective is to minimise the possibility of drug toxicity in patients. Likewise, the patient cannot be given too little of a drug as it results in the bacteria becoming resistant to the antibiotic. This would prevent further treatment with the same drug and stronger, more potent drugs have to be prescribed to deal with the infection. As a result, effective antibiotic dosing should aim to minimise the development of antibiotic resistance.

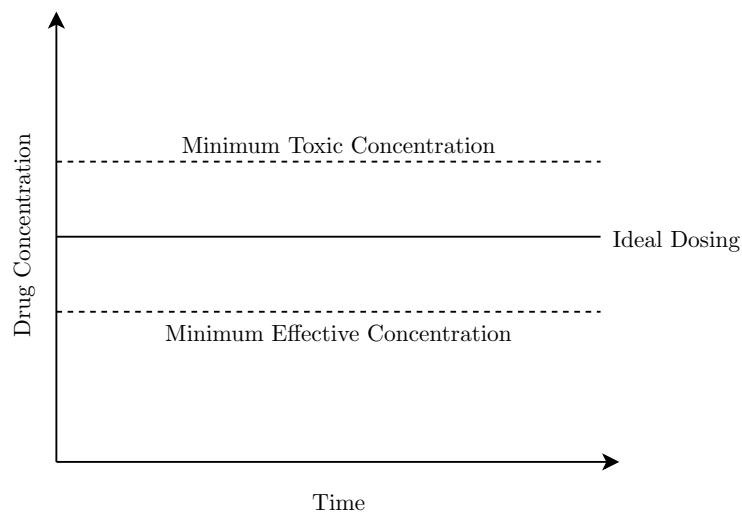


Figure 2.1: Ideal concentration curve for continuous infusion

Figure 2.1 illustrates the range between which the ideal dosing should fall within in order to satisfy the above mentioned objectives for the simplest case of continuous infusion. The upper limit is referred to as the minimum toxic concentration while the lower bound is known as the minimum effective concentration.

In reality, the drug concentrations are not at the ideal dosing levels from the start of treatment as shown in the ideal case. However, in order to achieve the desired concentration as soon as possible, a loading dose is given. A loading dose is either a large initial dose or a series of such doses. Once the loading dose has been administered, the steady state concentration can be maintained at the ideal dosing level with continuous infusion as before. With the incorporation of the loading doses, the concentration time curves can be updated as shown in Figure 2.2.

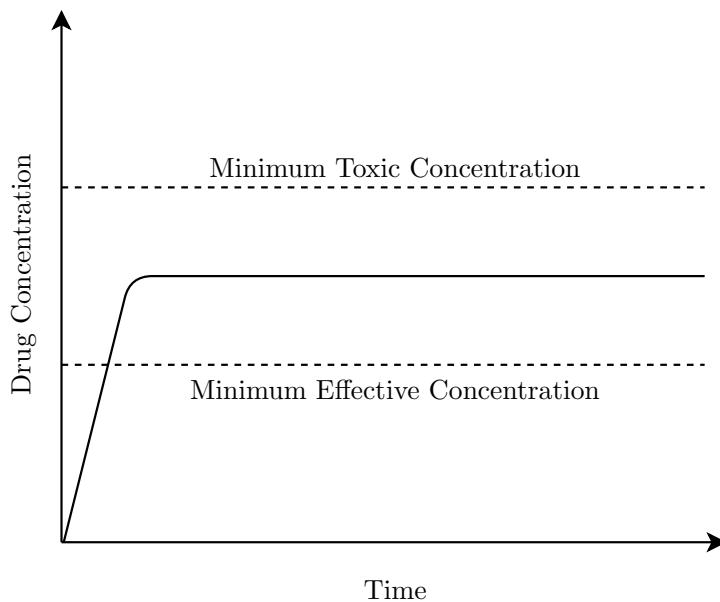


Figure 2.2: Realistic concentration curve for continuous infusion

## 2.4 Pharmacokinetic-Pharmacodynamic(PK-PD) Modeling

Pharmacokinetic-pharmacodynamic (PK-PD) modeling links the dose concentration relationships (PK) and concentration-effect relationships (PD), thereby facilitating the description and prediction of the time course of drug effects resulting from a certain dosing regime [11].

In order to be able to effectively design appropriate dosing recommendations and strategies, it is integral that the pharmacokinetic and pharmacodynamic properties of a drug are fully

understood. Regulatory authorities also do recommend that the PKPD relationships are analysed in different drug development problems to ensure efficacy [12].

Pharmacokinetics (PK) describes the relationship between drug-dosing and the drug concentration-time profile in the body [13]. Drug concentration here refers to the amount of drug determined to be in plasma. In general, PK models show the movement and fate of a drug in a biological system after it has been administered. These models will be further discussed in Section 2.4.1. Knowledge of the pharmacokinetics of a drug will allow drugs to be used rationally and doses tailored to individual patients.

Pharmacodynamics (PD) on the other hand describes the relationship between concentration and both the wanted and unwanted effects on the body [13]. The effect of the drug is measured based on a variable such as blood glucose level or blood pressure. This will be further described in Section 2.4.2.

### 2.4.1 Pharmacokinetics

The general equation which relates drug concentration to various PK parameters is given by:

$$C(t) = F(p) \quad (2.1)$$

where

$C(t)$  = Drug Concentration at time t

$F(p)$  = Function of PK parameters, p

There are several PK parameters that are based on body physiology of the patient. The main parameters are Dose (D), Bioavailability (F), Volume of distribution ( $V_d$ ), Absorption rate constant ( $K_a$ ), Clearance ( $Cl$ ) and Half-life ( $t_{\frac{1}{2}}$ ) of a drug. In order to be able to best determine the ideal dose for a patient, the more important parameters are  $Cl$  and  $V_d$ .

#### Clearance

Clearance ( $Cl$ ) can be considered to be the most important PK parameter. It is defined as the volume of plasma cleared of drug per unit time or a constant which relates the rate of elimination to plasma drug concentration [14]. This process is irreversible. Clearance or also commonly referred to as plasma clearance is primarily a combination of two different processes, namely elimination and metabolism. Elimination is performed by the kidneys while metabolism is due to the liver. Total clearance can therefore be represented as a combination of these two entities and any other types of clearance in the body as given by Equation 2.2.

$$Cl(total) = Cl(renal) + Cl(liver) + Cl(other) \quad (2.2)$$

In order for a drug to be eliminated from the body, the drug needs to be delivered to the respective organs which is due to plasma flow in the body. Hence, the rate of elimination is proportional to the drug concentration in plasma. A higher concentration of drug in the plasma will mean that more drug is delivered to the organs, resulting in larger amounts of drug being eliminated. Hence,

$$\text{Rate of Elimination} \propto \text{Concentration} \quad (2.3)$$

$$\text{Rate of Elimination} = k * \text{Concentration} \quad (2.4)$$

$$\text{Rate of Elimination} = Cl * \text{Concentration} \quad (2.5)$$

From the above equations,  $Cl$  can be seen to be the proportionality constant which relates the rate of elimination from the body to the drug concentration in plasma.  $Cl$  is usually constant for most drugs, for the usual doses dealt with in clinical practice. Drugs with such a characteristic is said to follow first order kinetics. Mathematically, clearance for such drugs can be represented as the product of the first order elimination rate constant and the volume of distribution as given in Equation 2.6.

$$Cl = k_e * V_d \quad (2.6)$$

where

$k_e$  = Elimination rate constant

$V_d$  = Volume of distribution

### Volume of Distribution

Volume of distribution ( $V_d$ ) or used interchangeably with apparent volume of distribution is the volume of plasma required in which the total amount of drug in the body would be required to be dissolved in order to reflect the drug concentration attained in plasma [14].  $V_d$  is calculated based on the ratio of the amount of drug and the plasma concentration of drug in the body, represented by Equation 2.7.

$$V_d = \frac{A}{C} \quad (2.7)$$

where

$A$  = Amount of drug in the body

$C$  = Plasma concentration of drug

The type of drug administered will affect the volume of distribution. Some drugs accumulate in tissues (lipid soluble) tend to have a high  $V_d$  since the plasma concentration of the drug will be low. Likewise, water soluble drugs have a small  $V_d$  since the concentration in plasma will be comparatively higher.

$V_d$  is particularly useful as it allows determining of the loading dose if the ideal dosing concentration is known. Furthermore, if the plasma concentration is known, the remaining amount of drug in the patient can be calculated at any point in time. Lastly, with the help of  $V_d$ , the drugs relative ability to distribute to different body compartments can be analysed and modeled. Since the body is represented by compartments in pharmacokinetics, the  $V_d$  of the drug provides insight into whether the drug will stay primarily in the central compartment (high  $V_d$ ) or if there is penetration into peripheral compartments (low  $V_d$ ).

### One/Single Compartment Model

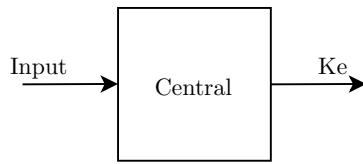


Figure 2.3: Single Compartment Model

The one compartment model, also known as the single compartment model, can be represented by Figure 2.3. For the one compartment model, the entire body is treated as a single compartment shown as the central compartment. The process of absorption and elimination all occur within this compartment. There is no further re-circulation of the drug within the body.

The rate of change of concentration of drug within the central compartment will be dependent on the input and output rates. Since drugs can be administered in different ways, for the same rate of elimination, the variation in concentration will depend on method of administration. Equation 2.8 represents the variation of concentration of drug ( $C$ ) for the simplest case in which administration is a single IV bolus dose.

$$\frac{dC}{dt} = -k_e * C \quad (2.8)$$

The elimination rate constant,  $k_e$ , is first order and hence elimination of the drug will be proportional to the remaining amount of drug in the compartment. Solving the differential equation gives

$$C(t) = C_0 e^{-k_e t} \quad (2.9)$$

From Equation 2.9, the drug concentration can be determined at any time,  $t$ , for a particular initial concentration,  $C_0$ .  $C_0$  is usually approximated to be  $\frac{\text{Dose}}{V}$ . The result is a downward sloping concentration-time curve. Concentration-time curves are also known as PK curves. These two terms will be used interchangeably in this report.

When the drug is administered orally, then the basic differential equation can be modified to be

$$\frac{dC}{dt} = \frac{k_a * A_a}{V} - (k_e * C) \quad (2.10)$$

where  $A_a$  is the absorption depot given by

$$\frac{dA_a}{dt} = -(k_a * A_a) \quad (2.11)$$

Solving this differential equation gives

$$C = \frac{F * Dose * k_a}{V * (k_a - k_e)} (e^{-k_e t} - e^{-k_a t}) \quad (2.12)$$

Since an oral dose enters the human gastrointestinal tract (GI tract), only a fraction of the dose will be absorbed into the circulatory system. This fraction of dose that is available for absorption is represented by  $F$  in Equation 2.12.  $F$  is also known more commonly as Bioavailability.  $k_a$  is the first order absorption rate constant.

Lastly, the drug can be administered via IV. This method of administration is especially common in a hospital setting. Under such cases, the basic differential equation can be altered as follows:

During Infusion:

$$\frac{dC}{dt} = (\frac{k_0}{V}) * (k_e * C) \quad (2.13)$$

After Infusion:

$$\frac{dC}{dt} = -k_e * C \quad (2.14)$$

where  $k_0$  is the rate of infusion.

When integrated, the concentrations can be expressed as

During Infusion:

$$C = \frac{k_0}{k_e * V} (1 - e^{-k_e t}) \quad (2.15)$$

After Infusion:

$$C = \frac{k_0}{k_e * V} (1 - e^{-k_e T}) e^{-k_e (t-T)} \quad (2.16)$$

$T$  in Equation 2.16 represents the total time for infusion. After the infusion is stopped, only elimination is present and hence the concentration of the drug can be expected to decrease in the central compartment. At steady state, the rate of infusion is equal to the

rate of elimination. Hence if infusion is continuous, the concentration of drug at steady state can be obtained from Equation 2.15 when  $t \rightarrow \infty$  giving Equation 2.17.

$$C_{ss} = \frac{k_0}{k_e * V} = \frac{k_0}{CL} \quad (2.17)$$

With the above equations, the appropriate concentration-time relationship of the drug in the central compartment can be analysed for different methods of administration. Therefore, if the therapeutic level of drug required is known, the equations can be used to determine the amount of dose that should be provided at any time instant. However, more often than not, since distribution is not immediate as is assumed in the single compartment model, more complicated models are required to obtain a more realistic representation of the concentration-time effects.

### Two Compartment Model

Multi compartment models are used when the drug concentration in various parts of the body is non-identical. This is due to the dissimilarities in drug affinity to the different tissues [15]. The body is hence, described as one or more interconnected compartments depending on the drug distribution to the different parts of the body. Most drugs can be modeled using either a single or two compartment model which will be the focus of this project.

A two compartment model as the name implies has two compartments, a central and peripheral compartment. The schematic of the model is shown in Figure 2.4.

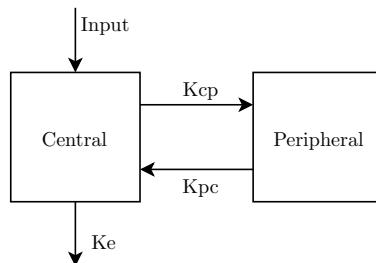


Figure 2.4: Two Compartment Model

There are a few characteristics of the two compartment model which are worth highlighting. When the drug is introduced into the body, it first reaches the central compartment and subsequently moves into the peripheral compartment shown by  $k_{cp}$  in Figure 2.4. The movement of drug between compartments can be represented either with inter-compartmental clearance,  $Q$ , or in terms of transfer rate constants,  $k_{cp}$  and  $k_{pc}$ . The volume of the peripheral compartment is given by

$$V_p = \frac{k_{cp}}{k_{pc}} V_c \quad (2.18)$$

where

$k_{cp}$  = First order transfer rate constant from central to peripheral compartment

$k_{pc}$  = First order transfer rate constant from peripheral to central compartment

$V_p$  = Volume of peripheral compartment

$V_c$  = Volume of central compartment

Inter-compartmental clearance is given by  $Q = k_{cp} * V_c$ . Therefore, the value for Q will be the same in both directions, i.e. to and from the central compartment.

As in the case of the single compartment model, differential equations can be used to explain the drug concentrations in each of the compartments. The rate of change of the drug concentrations in any compartment is equal to the net sum of the rates of drug transfer into the compartment minus the sum of rates of drug transfer out of the compartment. Hence the equations differential equations for the simplest case of a IV bolus administration can be represented as follows:

Central Compartment:

$$\frac{dA_c}{dt} = (k_{pc} * A_p) - (k_{cp} * A_c) - (k_e * A_c) \quad (2.19)$$

Peripheral Compartment:

$$\frac{dA_p}{dt} = (k_{cp} * A_c) - (k_{pc} * A_p) \quad (2.20)$$

where

$A_c$  = Amount of drug in central compartment

$A_p$  = Amount of drug in peripheral compartment

Solving the differential equations give

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} \quad (2.21)$$

where

$$A = \frac{\text{Dose}(\alpha - k_{pc})}{V_c(\alpha - \beta)}$$

$$B = \frac{\text{Dose}(k_{pc} - \beta)}{V_c(\alpha - \beta)}$$

$$\alpha = \frac{1}{2}((\alpha + \beta) + \sqrt{(\alpha + \beta)^2 - 4\alpha\beta})$$

$$\beta = \frac{1}{2}((\alpha - \beta) + \sqrt{(\alpha + \beta)^2 - 4\alpha\beta})$$

Using the substitutions for the sum and product of  $\alpha$  and  $\beta$ ,

$$\alpha + \beta = k_e + k_{cp} + k_{pc} \quad (2.22)$$

$$\alpha\beta = k_e k_{pc} \quad (2.23)$$

Thus  $\alpha$  and  $\beta$  can be determined if the values of  $k_e$ ,  $k_{cp}$  and  $k_{pc}$  are known in the following manner

$$\alpha = \frac{1}{2}((k_e + k_{cp} + k_{pc}) + \sqrt{(k_e + k_{cp} + k_{pc})^2 - 4k_e k_{pc}}) \quad (2.24)$$

$$\beta = \frac{1}{2}((k_e + k_{cp} + k_{pc}) - \sqrt{(k_e + k_{cp} + k_{pc})^2 - 4k_e k_{pc}}) \quad (2.25)$$

If the dose is administered orally for a 2 compartment model, the final concentration equation can be represented as a tri-exponential equation representing absorption, distribution and elimination of the drug in Equation 2.26.

$$C = \frac{DoseF k_a}{V_c} \left( \frac{(k_{pc} - \alpha)e^{-\alpha t}}{(\beta - \alpha)(k_a - \alpha)} + \frac{(k_{pc} - \beta)e^{-\beta t}}{(k_a - \beta)(\alpha - \beta)} + \frac{(k_{pc} - k_a)e^{-k_a t}}{(\alpha - k_a)(\beta - k_a)} \right) \quad (2.26)$$

In the case where the drug is administered via continuous infusion, at steady state, the rate of infusion is equal to the rate of drug elimination. The concentration of drug in the central and peripheral compartments will also be equal at steady state. This is similar to the single compartment model and the steady state concentration is given by Equation 2.27.

$$C_{ss} = \frac{k_0}{Cl} \quad (2.27)$$

When the infusion is not constant, the concentration of drug declines based on a bi-exponential equation after the infusion is stopped as shown in Equation 2.28.  $A'$  and  $B'$  are hybrid coefficients.

$$\frac{dA_c}{dt} = A' e^{-\alpha t} + B' e^{-\beta t} \quad (2.28)$$

Based on the equations which describe the different cases for a 2 compartment model, the PK curve can be derived using computer programs such as MATLAB.

#### 2.4.2 Pharmacodynamics

The effect of drug on a variable such as glucose levels or blood pressure can be described by the following mathematical function:

$$E(t) = E_0 + \frac{E_{Max} * C(t)^\gamma}{EC_{50}^\gamma + C(t)^\gamma} \quad (2.29)$$

where  $E_{Max}$  is the maximum effect that can be achieved by the drug in the investigated system and  $EC_{50}$  is the drug concentration that results in half of the maximum effect.  $\gamma$  is

the Hill or sigmoidicity factor that helps determine the steepness of the relationship between the drug and the concerned variable [13].

Equation 2.29 has its limitations as at high concentrations it is difficult to estimate  $E_{Max}$ . Therefore the equation can be altered to when  $C \ll EC_{50}$  to the following with a constant  $a$ :

$$E(t) = E_0 + a * C(t)^{\gamma} \quad (2.30)$$

$E_0$  in the above equations may not remain constant throughout the study period and could have significant fluctuations. Therefore when a variable such as blood pressure is measured to determine the effect of the drug, the result obtained is usually a sum of the underlying effect variable in the absence of the drug and the influence of the drug on the effect variable [13].

### Parameters for Antibiotics

Pharmacodynamics of antibiotics refers to how the drug affects the bacteria concerned. There are some pharmacodynamic parameters which are commonly used such as the Minimum Inhibitory Concentration (MIC).

MIC is defined as the lowest drug concentration that completely inhibits visible growth of the microorganism [16]. However, measuring this value results in large errors. It is therefore better to combine certain PK indices such as Area under the Curve (AUC) together with MIC to get better understanding of the PD effects of the antibiotics.

There are 3 main PK-PD indices [12] which help in the classification of drugs.

1. AUC/MIC
2.  $C_{Max}/MIC$
3.  $T_{>MIC}$

where  $C_{Max}$  is the highest concentration in the AUC and  $T_{>MIC}$  is the cumulative percentage of a 24 hour period that the concentration is above the MIC.

A drug which is dependent of the first index  $AUC/MIC$  shows that it is independent of the rate at which the drug is administered. This implies that so long as the total AUC is the same, a sharp increase in concentration with rapid elimination will produce the same level of bacterial killing as compared to continuous infusion of the drug. However, a drug represented by the second index  $C_{Max}/MIC$ , shows that the effect of the drug is only dependent on the highest concentration achieved making such drugs very sensitive to infusion lengths. Drugs represented best by  $T_{>MIC}$  show that the antibacterial effect of the drug is at its maximum just above MIC. Thus, no further bacteria killing will occur even by increasing the concentration of the drug in the body.[13]

### 2.4.3 PK-PD Population Modeling

Overall, a population model consists of three entities. First, a structural model describing the typical concentration-time and/or effect variable-time profiles in the population. Second, a statistical model quantifying and separating different types of variability. The third entity is a covariate model[13]. The first structural model refers to the various PK models described above and this gives us the deterministic model.

Statistical models help to account for the unexplainable variability in concentration within the population. Variability by definition refers to the extent to which data points in a statistical distribution or data set diverge from the average or mean value. Variability also refers to the extent to which these data points differ from each other.[17]. Biological variability exists due to various reasons such as body size, disease state and genotype. Each patient is different from the other in some manner and hence there will be differences between them.

Covariate models explain variability predicted by covariates. Covariates are patient specific factors such as weight, age, and gender that might affect the PK or PD of the drug. A covariate is also a secondary variable that can affect the relationship between the dependent variable and other independent variables of primary interest [18]. For example, creatinine clearance ( $CrCl$ ) is a good covariate for  $Cl$  and therefore help reduce the unexplained variability between patients. Incorporating this covariate will allow better dosing as patients with lower  $CrCl$  will be given lower doses due to their limited ability to eliminate the drug.

Once an appropriate model has been identified and model parameters are estimated, software such as Nonlinear Mixed Effects Modeling is used to integrate the available data and models together.

## 2.5 Vancomycin

Vancomycin is a glycopeptide antimicrobial chemotherapeutic agent typically used in the treatment of *Staphylococcus aureus* infections which show a resistance to  $\beta$ -lactams. It is the front line therapy for MRSA but has some serious side effects as as nephrotoxicity, particularly in patients with impaired renal functions if used inappropriately. Since vancomycin has a narrow therapeutic window and there are concerns over its efficacy, it is placed under Therapeutic Drug Monitoring in the United Kingdom.

Therapeutic Drug Monitoring (TDM) encompasses the measurement of serum drug levels and the application of clinical pharmacokinetics to improve patient care [14]. The aim of TDM is to personalise drug therapy to each patient and optimise dosing to avoid concentrations from dropping below or rising above the therapeutic levels and toxic plasma drug concentrations respectively.

There are a couple of reasons why vancomycin has been chosen for this project. Firstly, since the drug has been placed under TDM, there is access to patient parameters and dosing regimes. This data is an integral part of PK-PD modeling.

Secondly, MRSA is becoming an increasing burden in the hospital setting and has emerged as one of the predominant pathogens in health-care associated infections. This in turn results in the increased use of vancomycin in treatment. With this increased use, it is predicted that the outcomes of treatments will worsen in an environment of selection pressure and steadily increasing use. Therefore, it is imperative that strategies should be put in place to deal improve the results of vancomycin therapy.

### 2.5.1 PK-PD modeling of Vancomycin

There are a wide variety of pharmacokinetic variability in vancomycin. Different one and two compartment models have been suggested to effectively model patient variability. These models will be tested and evaluated in subsequent chapters. The best model will be chosen to represent the available data set.

It is accepted that the best pharmacodynamic indicator for vancomycin is the 24 hour AUC to MIC ratio [19]. Studies have suggested that the clinical and bacteriological response to vancomycin therapy was superior in patients with a  $AUC_{24}/MIC$  value of greater than 400 [20]. However, in the UK, most TDM guidelines continue to monitor vancomycin based on peak or trough concentration levels. Such monitoring have however, shown to under achieve acceptable levels in clinical practice [21]. Generally, a trough level higher than 10 mg/L is expected and trough levels are considered more important than the peaks which occur in concentration-time profiles. However, sustained peaks of over 20 mg/L do pose a problem and could lead to toxicity in patients [22].

The MIC value is taken to be 1 for the rest of this report. Hence the pharmacodynamic indicator, AUC:MIC, simply becomes dependent on the 24 hours AUC value. Therefore, in subsequent analysis and evaluation, only the 24 hour AUC values are considered and mentioned.

## 2.6 Closed Loop Controllers

Control systems work on the principle of feedback in which a signal to be controlled is compared to a reference signal and the error between the 2 signals is used to tabulate the corrective action. Controllers help perform this corrective action. There are different types of controllers which can be implemented for a closed loop system. For this project, the Proportional-Integral-Derivative (PID) controller and Iterative Learning Controller will be discussed and implemented.

### 2.6.1 PID Controller

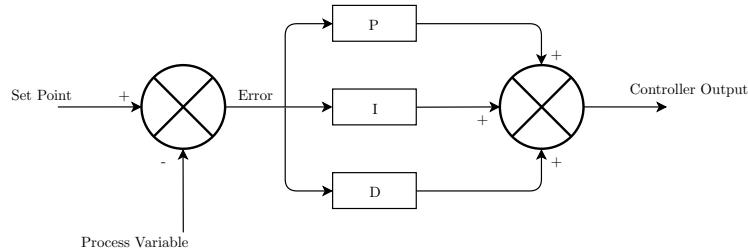


Figure 2.5: PID controller block representation

A PID controller can be represented by Figure 2.5. As seen there are three separate entities involved in determining the correction. The correction can be represented by Equation 2.31.

$$\text{Controller Output} = K_p * \text{Error} + K_d \frac{d\text{Error}}{dt} + K_i * \int \text{Error} \quad (2.31)$$

where

$$\text{Error} = \text{Process Variable} - \text{Set Point}$$

$$K_p = \text{Proportional Factor}$$

$$K_i = \text{Integral Factor}$$

$$K_d = \text{Derivative Factor}$$

The proportional response depends only on the error term. Increasing the proportional gain  $K_p$ , increases the speed of the system response. However, if it is too large, the process variable will begin to oscillate. There is a threshold for  $K_p$ , beyond which the oscillations will be too large leading to instability.

The integral component sums the error over time. Hence a small error term will cause the integral term to increase. Since the integral response will continue to increase so long there is existence of error, the resulting correction is to drive the system towards the steady state value where error will be 0. The steady state error is the difference between the process variable and the set point at  $t \rightarrow \infty$ .

Finally, the derivative term causes the output to decrease if the process variable increases very rapidly. Increasing the magnitude of  $K_d$  causes the controller to react more strongly to changes in the error term and increases the speed of the response on the whole. The derivative term is very sensitive to noise and hence it is practical to have a lower value for  $K_d$ .

The PID controller is a commonly used control system and is simple to implement. The aim here is to control the amount of dose given based on the difference in ideal expected concentration and the outputs of the PK model differential equations.

### 2.6.2 Iterative Learning Control

Iterative Learning Control (ILC) is a methodology that tries to address the problem of transient response performance for systems that operate repetitively [23]. A general ILC scheme can be represented by Figure 2.6.

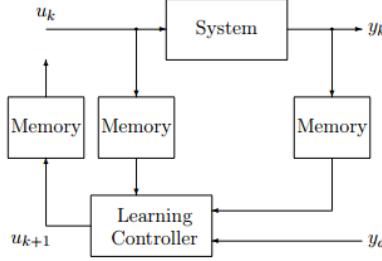


Figure 2.6: ILC Configuration

The main idea behind an ILC algorithm is to minimise the error between actual and desired output. Based on the error during the  $k^{th}$  trial, the ILC algorithm generates a modified input signal  $u_{k+1}(t)$  which is applied the next time the system operates. A typical ILC algorithm has the following form [23]:

$$u_{k+1}(t) = u_k(t) + \gamma e_k(t + 1) \quad (2.32)$$

where

$u_{k+1}$  = Output of Controller

$u_k$  = Input to Controller

$\gamma$  = Proportional Constant

$e_k = u_k - u_{k+1}$

$t$  = Time

A successful ILC algorithm looks to continuously reduce error between the observed and predicted output through multiple iterations. ILC algorithms help preserve information about the effect of the input at each instant during the iteration and use that information to compute corrections to the control signal during the next trial [24]. This means that  $u_{k+1}(t)$  can be determined based on what happened after  $u_k(t)$ .

Since the process of dosing is a iterative process where multiple doses are given, the aim is to use ILC to control the amount of drug given to a patient to achieve a given trough concentration. With the help of PK-PD modeling, Pk profiles of different patients can be predicted. If the ideal trough level is known, the difference between the predicted profile and the ideal trough level will represent the error. With this, the amount of dose given in the next iteration can be modified. The time taken to achieve this ideal concentration will be

dependent on how aggressive the controller is tuned for. The more aggressive the controller, the higher the value of  $\gamma$ .

## 2.7 Existing practices

Some development and research has gone into manipulating dosing regimes for patients diagnosed with HIV. Proposed methods use non liner model predictive control (MPC) to optimise dosing for patients. Usage of periodic MPC coupled with a model incorporating drug PK and PD was shown to be a sufficient way to compute the optimal drug doses for HIV-1 infection therapy in [25]. Therapy involving 2 types of drugs and weights were added to control the amount of each drug administered to the patient. Patient adherence was also included in the model used and the controller could meet the desired specifications for patient adherence of 90%.

[26] shows the feasibility of using mathematical models and MPC to enhance immune responsiveness to HIV through dynamic scheduling of treatment. Tuning of the controller paramaters was done manually via trial and error. Error in the model was also simulated and the results showed the robustness of the controller in still being able to optimise scheduling for HIV.

Lastly, a patent entitled "Closed Loop Control System Interface and Methods" [27] exists. It focuses on diabetes where closed loop therapy systems are used to control insulin delivery based on real time feedback of the patient glucose levels.

These publications do show the possibility of using closed loop control to optimise dosing. However, this area remains relatively unchartered and there are not many details on using such a technique to optimise dosing in a hospital setting.

## Chapter 3

# Requirements Capture

This chapter lists the deliverables of this project in detail. The project is broken down into three distinct parts, each with its own set of distinct aims and objectives. Furthermore, since this project has a real-world relevance, it is important to understand the specific functions of this project.

In the first half of the project, the primary aim is to establish the existence of the problem of misusing antibiotics due to inappropriate dosing regimes in a hospital setting. This establishment is necessary to prove that a solution is required and integral in combating AMR. The aims for this part of the project are as follows:

1. Establish dosing regimes for all patients within data set based on hospital guidelines provided to doctors.
2. Compare dosing regimes derived from guidelines and the actual dosing regimes provided in data set.
3. Determine if guidelines are being followed by clinical staff

In the next part of the project, the primary aim is to find the PK model which best represents the data set available which lead to the following aims:

1. Test and evaluate different PK models using Pmetrics to determine the best model to represent data set.
2. Based on the best model selected, predict PK curves for each patient.
3. Determine the AUC:MIC ratio achieved at steady state and evaluate if therapeutic levels are achieved.

The second part of the project will involve implementing the control system capable of individualising dosage regimes to patients. The aims for this part of the project are as follows:

- i. Identify a controller capable of optimising dose for individual patients with PK models.

- ii. Test controller under different conditions such as error in measurement.
- iii. Test different methods of drug administration.
- iv. Ensure controller is able to achieve intended AUC:MIC ratio at steady state.

The above list of requirement and tests is necessary to ensure that the controller is able to achieve the intended targets. Controllers do have varying parameters and hence, it would be interesting to analyse the potential relationship between the controller parameters and patient demographics. This will allow easy tuning for future patients.

It is also integral to ensure that the PK profiles generated by the controller are realistic. This can be achieved by modeling different scenarios such as varying  $C_l$  of a patient during therapy and testing the controller with such situations. The PK curves obtained would then be a more realistic representation, allowing analysis of the feasibility of using a closed loop system to optimise dosing for patients.

## Chapter 4

# Problem Analysis

In this chapter, the problem of inappropriate dosing for patients in the data set is established and justified. This is done by comparing the actual dosing regimes patients underwent and the ideal dosing regimes that they should have been placed under if the hospital guidelines were followed exactly. The methodology adopted and results of the analysis are discussed before concluding the chapter with an evaluation section.

### 4.1 Data Set

The data used is obtained from non-critically ill patients managed in three hospitals in north west London. Routinely collected data from two prospective audits of vancomycin therapy was interrogated. Identified subjects not on renal replacement therapy had their demographic and TDM data extracted for analysis.

A total of 24 patients were identified and the median age was 56.5 years. The age range is between 21- 87 years. The patient demographics recorded include Height, Weight, Gender, Age and Serum Creatinine. Variation in attributes such as weight and serum creatinine were not recorded throughout the dosing regime. Since a complete set of data is only available for each patient at the onset of treatment, attributes are assumed to stay constant throughout the treatment period.

## 4.2 Design and Objectives

Currently, there are guidelines in place to assist doctors with the prescription of drugs. The Adult Treatment of Infection Policy aims to ensure appropriate empiric choice, dosage and duration of antibiotic therapy in adults, and to provide contact details for specialists who can provide additional advice [28]. The purpose is ultimately, to enable the safe and effective use of antimicrobials at Imperial College Healthcare NHS Trust.

Adherence to the infection policy is mandatory and the policy details different methods and dosage amounts that should be prescribed to patients suffering from different ailments. Such guidelines help doctors especially the junior ones in determining the right amount of dose to administer.

The doses that were administered to each of the 24 patients is available in the data collated. Using the infection policy, the ideal dosing regime for each of these patients can be tabulated. Comparing the infection policy dosing regime and the actual dosing regime which was administered, will help confirm if doctors and nurses are indeed following these hospital guidelines. Therefore, the aim for this part of the project is to identify the number of patients within the data set who have been dosed correctly based on the infection policy.

## 4.3 Methodology

Patients can be given a loading dose which is based on their actual body weight and not the renal function. Subsequently, an initial maintenance dose is given 12 or 24 hours after the loading dose. The amount of dose and dose interval is determined by the patients creatinine clearance. The creatinine clearance can be obtained using the Cockcroft-Gault equation as shown in Equation 4.1.

$$\text{Creatinine Clearance (CrCl)} \text{ (ml/min)} = \frac{140 - \text{age (years)} * \text{weight(kg)} * N}{\text{Cr (micromol/L)}} \quad (4.1)$$

where

$N = 1.23$  for males and  $1.03$  for females

$Cr =$  Serum Creatinine

Weight = Actual body weight or maximum body weight whichever is lower

Based on the calculated value for  $CrCl$ , the corresponding dose interval and maintenance dose can be determined from Table 4.1. For subsequent doses, a pre-dose vancomycin level is taken before administering the dose. Based on the measured vancomycin level, the next dose can be adjusted to reach the intended target level of 10-15 mg/L. This adjustment in dose is done based on Table 4.2.

<b>CrCl (ml/min)</b>	<b>Dose Interval (Hours)</b>	<b>Maintenance Dose (mg)</b>
> 110	12	1500
90-110	12	1250
75-89	12	1000
55-74	12	750
40-54	12	500
30-39	24	750
20-29	24	500

Table 4.1: Initial maintenance dosing table for different levels of  $CrCl$

<b>Target pre-dose vancomycin level</b>	<b>Pre-dose level (mg/L)</b>	<b>Action</b>
10-15	<10	Move up one stage in maintenance dosage regimen
10-15	10-15	Continue current dosing regimen
10-15	>15-20	Move down one level in maintenance dosing regimen
10-15	>20	Stop and restart lower dosing regimen once level <20 mg/L

Table 4.2: Adjustments to dose based on pre-dose vancomycin level

## 4.4 Results

Table 4.3 shows the calculated values for  $CrCl$  for all the patients and the corresponding maintenance dose that should have been given based on the guidelines. The actual maintenance dose given is also included in the table for easy comparison.

Based on the above mentioned methodology, the ideal dosing for the patients can be calculated. Figure 4.1 shows the dosing regimes as determined by the hospital guidelines in blue and the actual dosing administered to the patients in red for all 24 patients in the data set.

Patient ID	CrCL (ml/min)	Expected Initial Maintenance Dose (mg)	Current Initial Maintenance Dose (mg)
1	58.2174	750	750
2	46.0043	500	1000
3	53.9560	500	750
4	55.7221	750	750
5	41.7055	500	500
6	129.1582	1500	750
7	178.3053	1500	750
8	143.3894	1500	1250
9	31.2255	375	500
10	136.8153	1500	1250
11	21.0773	250	750
12	13.5362	250	750
13	32.9797	375	750
14	77.9489	1000	1000
15	31.9402	375	750
16	128.3254	1500	1000
17	80.2027	1000	1000
18	92.9377	1250	1250
19	65.1076	750	500
20	105.9654	1250	1000
21	83.6680	1000	1000
22	33.8934	375	750
23	63.7409	750	750
24	13.5229	250	750

Table 4.3:  $CrCl$ , expected initial maintenance dose and current initial maintenance dose given for all 24 patients in the data set

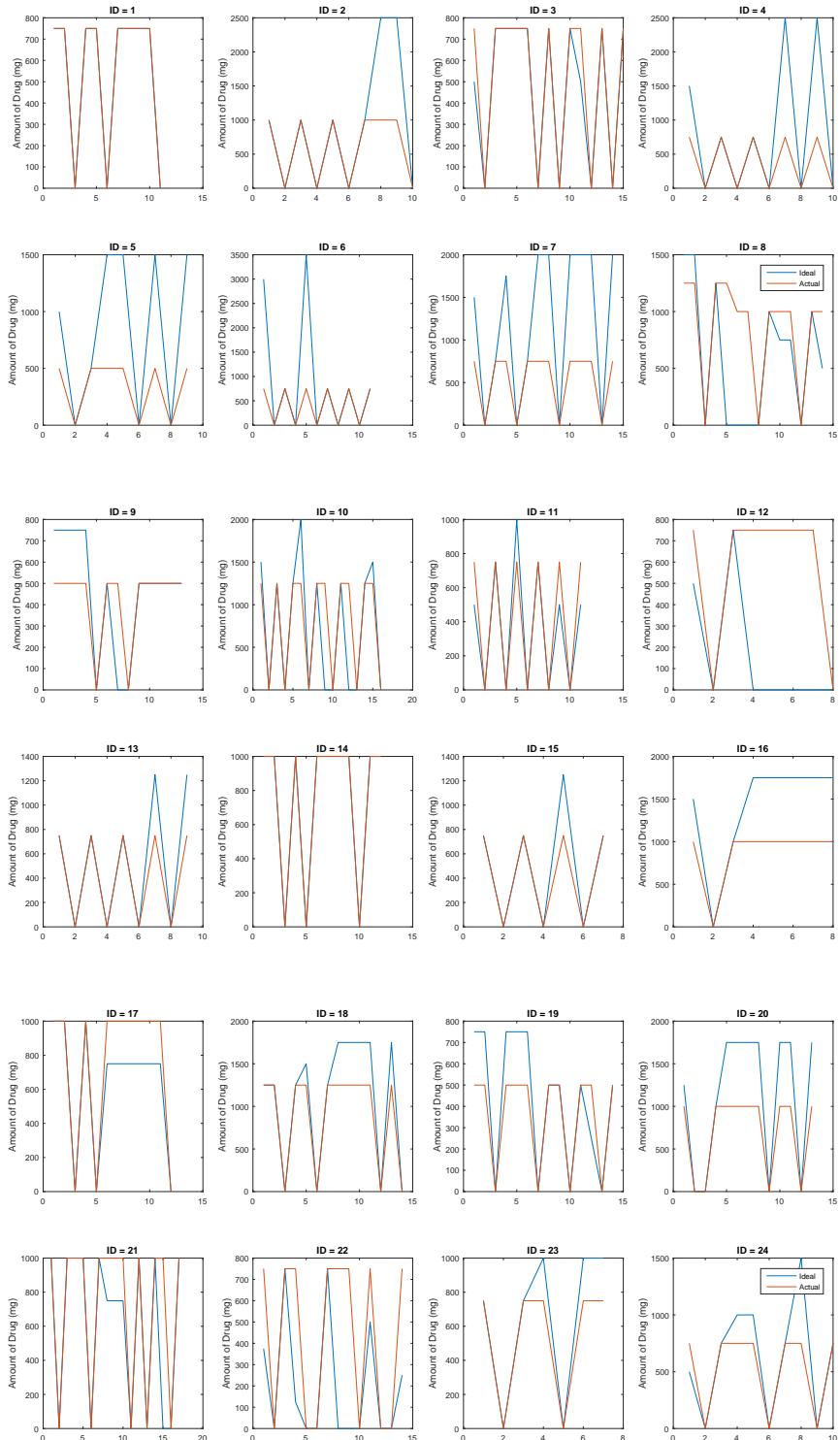


Figure 4.1: Actual dosing regime and ideal regime based on infection policy for all 24 patients

## 4.5 Evaluation

There are a number of assumptions made in this analysis. Firstly, the patients are not given a loading dose and the first dose given at  $t = 0$  is taken to be the initial maintenance dose.

As mentioned previously, in the data provided, readings for the patients weight, height, age, gender and serum creatinine levels are only available at the start of therapy. Though, some of the covariates such as gender and age will not vary within 120 hours, other covariates such as weight and creatinine levels can change over this course of time. The extent of change will depend on the type and seriousness of the diagnosed illness. In this analysis, the second assumption is that all covariates stay constant over the given period of time. This assumption has to be enforced primarily because sufficient data is not available.

The target pre-dose vancomycin will depend on the type of infection. If patients are diagnosed with severe or deep-seated infections caused by *S.aureus* such as staphylococcal, bacteraemia, osteomyelitis, endocarditis, hospital acquired pneumonia, suspected meningitis or if advised by the infection team, the target vancomycin level should be 15-20 mg/L. However, since neither the details of what the different patients are diagnosed with nor the extent of their infections is available, the target pre-dose vancomycin level is assumed to be the standard target level of 10-15 mg/L.

The final assumption relates to the procedure followed when it comes to updating the doses of the patients. Drug concentration levels are measured before a dose is given, usually about 30 minutes before administration of the dose. However, since the time taken to process the blood sample in the laboratory and provide a drug concentration level is typically greater than 30 minutes, doctors and nurses do not have sufficient time to alter the dose based on the reading. Hence, the next dose is given immediately. Changes are made to the dose to reach the target level for the next subsequent dose. As a result, there is a single dose delay for changes to take effect. For example, if a measurement of drug concentration is taken before the second dose and it is below the target level, the same amount of drug as the first dose is given and the third dose is increased to reach the target level.

From the plots in Figure 4.1, it is clear that on the whole there are discrepancies between the actual dosing and those deemed ideal by the hospital guidelines. From Table 4.3, it is already evident that the initial doses given to some of the patients do not match. However, in certain cases such as Patient 1, both regimes match exactly, implying that hospital guidelines were followed exactly. On the contrary, Patient 7, shows that the guidelines have not been followed totally as at every new dose the amount determined by the guidelines is different from the actual administered dose. However, before jumping to conclusions, it is important to consider the assumptions that were made in this analysis. It may be a possibility that additional complications or negative interactions with other drugs in the treatment of the patient prevented increase in the dose. Hence, there are multiple factors at play here when considering whether the hospital guidelines have been followed to the book.

Determining the ideal dosing regime from the data alone also presents its own set of challenges. Patient 2 helps illustrate this difficulty. The patient pre-dose vancoymcin concentration showed that it was 6 mg/L for the first measurement. Due to the assumption stated above, the next dose given at point 3 is the same as point 1. The next dose however, should be a higher one, greater by 250 mg, based on Table 4.2. However, between the 3<sup>rd</sup> and 5<sup>th</sup> dose, another measurement is taken. This gave a result of 6.2 mg/L. Since this is based on the doses given by the hospital, it is difficult to determine the impact that increasing dose has on the next pre-dose concentration. As a result, the previous dosage provided by the hospital has to be taken into account when deciding the future ideal doses. Therefore, the error propagates through the ideal dosing regimes.

Nevertheless, it is still clear that the infection policy is not strictly adhered to. This can be validated by Patient 22. The pre-dose concentration measured was 21.9 mg/L at point 5. This is clearly too high a concentration and the dosing should be reduced to prevent the concentration from reaching toxic levels. Despite this, the dosage was kept constant, illustrating that the guidelines have not been followed.

In addition, there are multiple instances in which the first maintenance dose has been calculated incorrectly. The initial dose involves solving for the  $CrCl$  level and referring to Table 4.1 to determine the dose. The differences between the starting point of the two plots allow the conclusion that the calculations were not made in determining the first dose for some of the patients.

Despite, the assumptions made, it is clear that the policies are not strictly followed based on the above analysis. Often in clinical practice, there are concerns over the accuracy that the trough levels are not taken correctly and other apprehensions about increasing doses due to the toxicity of vancomycin at high concentrations. As a result, the guidelines are often ignored, despite them being there to optimise the dosing for patients. Furthermore, though these policies are available in hard and soft copies, doctors and nurses have to recalculate the new doses manually. A large number of patients will further aggravate the problem. This is already considered simple case as the assumptions made help simplify the calculations by a considerable amount. If other factors were to come into play such as the use of multiple drugs, it would definitely be difficult for the staff to create individualised dosing regimes.

Despite the assumptions and error propagation in the above analysis, it is safe to conclude that the policies have not been followed strictly. Incorporation of these policies into a system such as the dosing unit will assist staff in individualising therapy. It is important to note that these policies essentially serve as a guide for doctors and it is ultimately on the doctors' discernment to determine the right amount of dose. However, recommendations made will clearly be beneficial and improve antibiotic prescribing within the hospital setting, demonstrating the need for the dosing module.

# Chapter 5

## PK-PD Modeling

In this chapter, different PK models are tested evaluated. Based on a specific evaluation criteria, the best model is chosen to represent the data. The predicted PK curves for the different patients is also analysed.

Comparison to the infection policy allowed the establishment of the problem with antibiotic dosing within the hospital setting. However, due to the heavy reliance on the data available, there are considerable limitations to the extent at which the analysis could be performed.

PK-PD modeling helps alleviate this problem by predicting the concentration-time (PK) curves of the patients over the course of study with the given data. Based on the PK profiles of the patients, it is possible to determine if the concentration of vancomycin are at therapeutic levels. In addition, the PD indice Area Under Curve (AUC) can be used to also analyse the effectiveness of the dosing regime.

### 5.1 Methodology

PK-PD modeling was primarily carried out in R with a package known as Pmetrics. Initially, PK models were implemented in MATLAB to gain key insights into development of the models. The results of this implementation can be found in Appendix A. Subsequently, R was used for complex modeling based on actual data.

Pmetrics is a R package developed by the USC Laboratory of Applied Pharmacokinetics (LAPK) for non-parametric and parametric PK-PD population and individual modeling and simulation. It is designed primarily for pharmacometric researchers and has been around for nearly 35 years [29]. Two primary components, the data and model files are required to be able to perform population modeling with Pmetrics. Details of these files can be found in Appendix B.

Vancomycin pharmacokinetics vary widely between patients and hence, a suitable model has to be selected to represent all the patients in the data set. Both single and double

compartment models were experimented with. The best model was determined based on the  $R^2$  value obtained from the observed vs predicted plots. The models which produced the best results are discussed in the following section. In general, a generic model is first tested to establish a base line standard. Modifications are then made by including secondary equations and covariates to be able to better represent the 24 patients.

## 5.2 Results and Discussion

### 5.2.1 Single Compartment Model

With the single compartment, the primary variables estimated by Pmetrics are  $V_d$  and  $Cl$ . Without the use of covariates, the observed vs predicted plots for both individual and population are shown in Figure 5.1. The  $R^2$  value essentially shows how close the predicted individual parameters are to the actual one. Hence, the higher the  $R^2$  value, the better the specified model is at representing the patients. A  $R^2$  value of 82% was achieved for the individual plot. The population predictions are then extrapolated based on the individuals in the data set. The  $R^2$  value for the population plot is 36.6%.

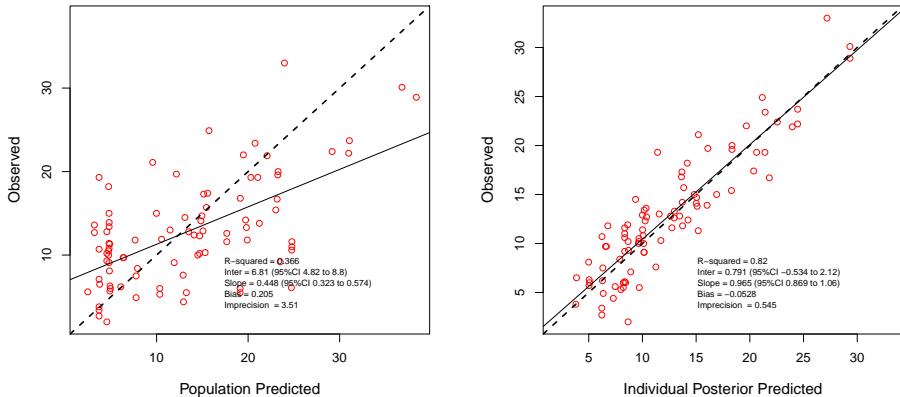


Figure 5.1: Observed vs Predicted Graphs for single compartment model without covariates

With each run, Pmetrics also predicts the concentration-time (PK) curves of the patients over the treatment period. However, due to the sheer number of models tested, not all the plots are not shown in this report. Literature suggests large differences in Vancomycin parameters and multiple relationships were tested. However, the results obtained were consistently worse off than the base case.

$$k_e = \frac{CL}{V} * \frac{Weight}{70} \quad (5.1)$$

Finally, the effect of covariates was analysed. Since the range of weight values for patients in the data set tends to be significant, adding weight in the calculation of  $k_e$  will account for this variability. With the addition of weight,  $k_e$  is calculated as in Equation 5.1. Individual

weight values were normalised using a constant value of 70 which is considered the standard weight. With this modification, a higher  $R^2$  value of 83.8% was achieved for the individual observed-predicted plots as shown in Figure 5.2.

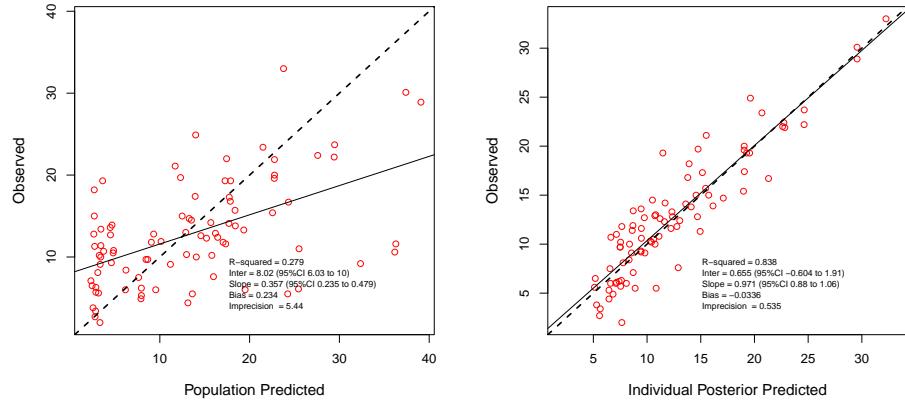


Figure 5.2: Observed vs Predicted Graphs for single compartment model with covariate weight

It is interesting to note that when the weight factor is added to the calculation without the normalising constant of 70, a relatively poor  $R^2$  value of 49.8% is achieved.

### 5.2.2 Two Compartment Model

The two compartment model has been used to represent the variation of Vancomycin in some publications [19]. Since Vancomycin penetrates into most body spaces, there have been results which show that the two compartment model lead to significantly better predictions. Hence, multiple variations of the two compartment model was also tested to determine if it was indeed better.

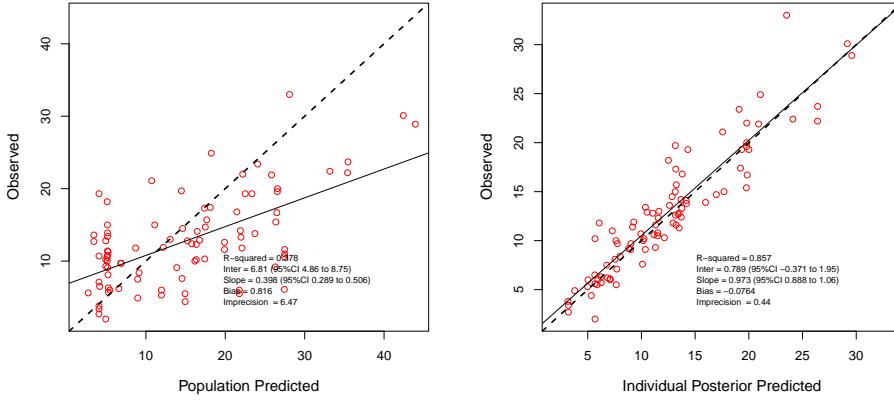


Figure 5.3: Observed vs Predicted Graphs for two compartment model without covariates

In the first test, Pmetrics was used to estimate primary variables  $V_d$ ,  $Cl$ ,  $Q$ , and  $V_p$ . Secondary equations,  $k_e = \frac{CL}{V}$ ,  $k_{cp} = \frac{Q}{V}$  and  $k_{pc} = \frac{Q}{V_p}$  were also specified. The graphs obtained are shown in Figure 5.3. This model produced a significantly higher  $R^2$  value of 85.7%. The PK curves were also plotted to make sure that the model is biologically plausible. Figure 5.4 shows the different concentration-time curves for the first 18 patients in the data set. The concentration variation seem to be reasonable but there is an upward trend as patient id increases. It can be seen that Patients 12 and 18 have very high predicted concentrations which were confirmed by academics to be unreasonable. Hence the models had to be tweaked to force the modeling to be done based on physiologically plausible estimates.

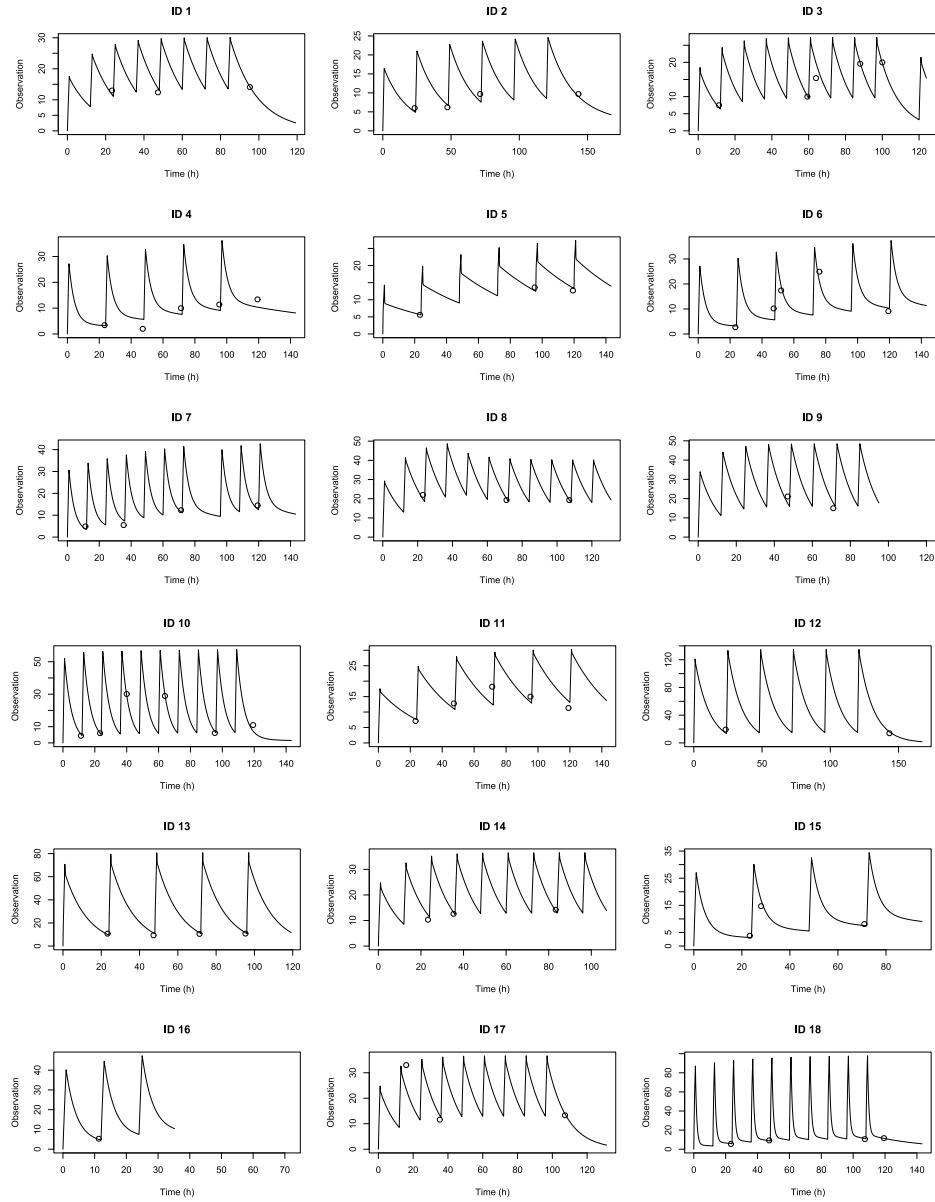


Figure 5.4: Concentration-time curves for the Patients 1 -18 with two compartment model without covarites

Pmetrics can be forced to estimate the primary parameters within a given range of values. Hence narrowing this range to one that is biologically feasible will prevent the irregularities obtained in the PK curves. Restricting  $V_d$  to be between a range of  $15 < V_d < 70$  concluded to produce the best results. The range for  $Cl$  was specified to be  $0.1 < Cl < 8$ . The resulting observation vs prediction plots are shown in Figure 5.5. A higher  $R^2$  value of 85.9% was obtained.

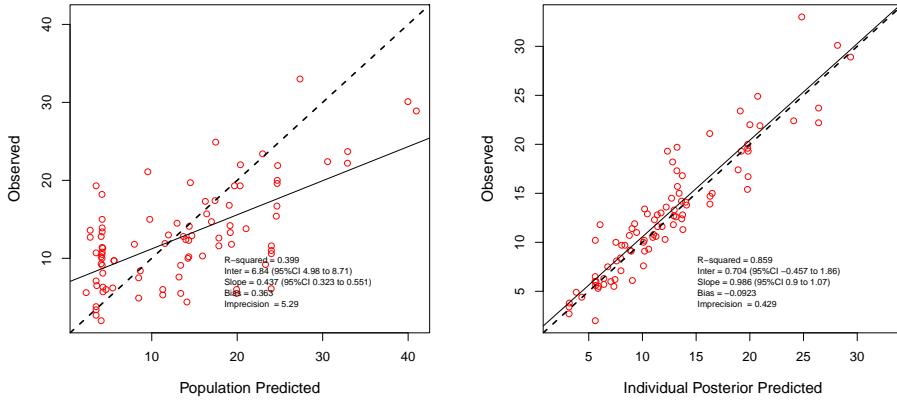


Figure 5.5: Observed vs Predicted Graphs for two compartment model without covariates but with restricted ranges  $15 < V_d < 70$  and  $0.1 < Cl < 8$

During the experimentation process, in deciding the best range of values for  $V_d$  and  $Cl$ , the  $R^2$  value obtained was lower when a minimum value for  $V_d$  was specified. However, since the PK curves obtained are more realistic, this trade off is acceptable. The PK profiles of the Patients 10-18 are no longer unreasonable as seen in Figure 5.6.

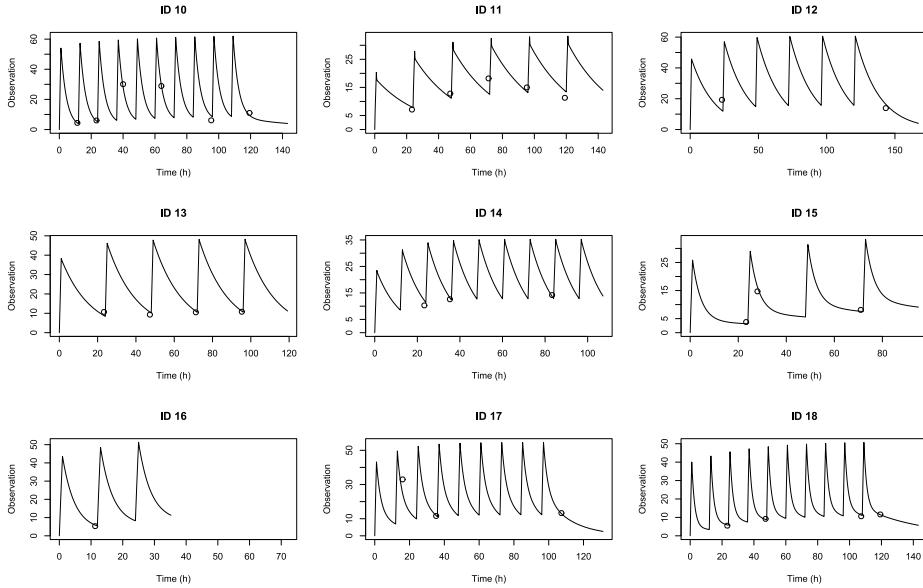


Figure 5.6: Concentration-time curves for Patients 10 - 18 with two compartment model without covariates but with restricted ranges  $15 < V_d < 70$  and  $0.1 < Cl < 8$

The final model tested, involved stripping down the model file to just include the bare minimum required to define a two compartment model for Pmetrics. Furthermore, since adding weight as the covariate, resulted in improved results for the single compartment model, Equation 5.1 was used to calculate  $k_e$  once again. The corresponding results for the observed vs predicted plots are shown in Figure 5.7. From the plots, a relatively high  $R^2$  value of 87.9% is obtained with the two compartment model. Furthermore, the PK profiles of the patients are also consistent and free from any abnormally high concentrations.

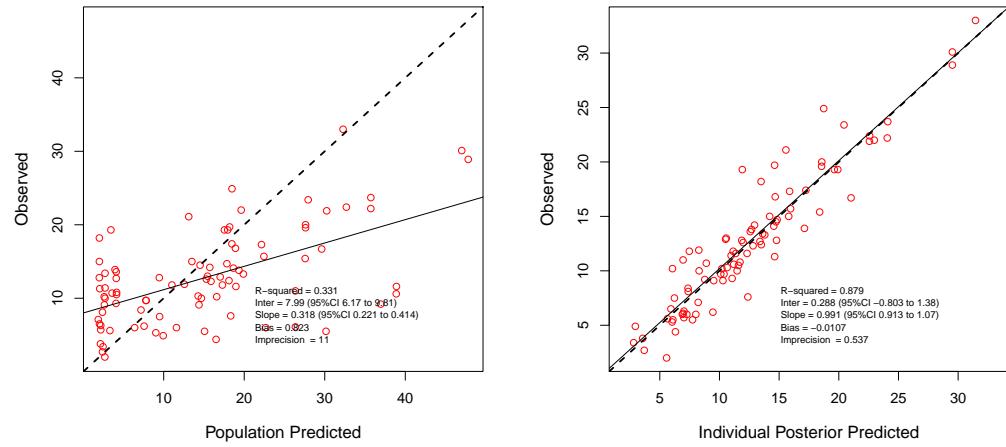


Figure 5.7: Observed vs Predicted Graphs for two compartment model with weight covariate and restricted ranges  $15 < V_d < 70$  and  $0.1 < Cl < 8$

### 5.3 Evaluation

From the above results, the two compartment models in general, have produced consistently higher  $R^2$  values. The best one and two compartment models were compared statistically and the results obtained are shown in Table 5.1.

Model	AIC	-2log likelihood
One Compartment	509.3	503
Two Compartment	494.8	484

Table 5.1: Statistical comparison between the best one and two compartment models

The two compartment model can be seen to be an improvement as the AIC and -2log likelihood values are lower as compared to the one compartment model. Therefore, it can be concluded that the two compartment model offers a better representation for the 24 patients in this data set as compared to the one compartment model.

As mentioned previously, the best pharmacodynamic indicator for vancomycin is the 24 hour AUC:MIC ratio. Taking the MIC to be 1, an AUC of 400 or greater will mean that patients have been treated effectively. In order to calculate the effective AUC at steady state, the concentration time curves of the patients were recorded.

Since the infection policy is also available, an additional dimension can be added to the analysis. Based on the dosing regimes calculated for each individual patient in the previous chapter, Pmetrics can be used to predict the concentration-time curves of the patients if the infection policy was followed. The data file was altered to represent the ideal dosing regimes derived from the hospital guidelines in the previous chapter. The same two compartment model file was run to obtain the PK profiles.

Figure 5.8 shows both the PK profiles based on the actual dosing regimes and the dosing regimes proposed based on the hospital guidelines. The blue plots show the PK profiles based on the original data while the red plots represent the ones derived from the guidelines. The plots show that there differences between the hospital guidelines and the actual dosing regimes.

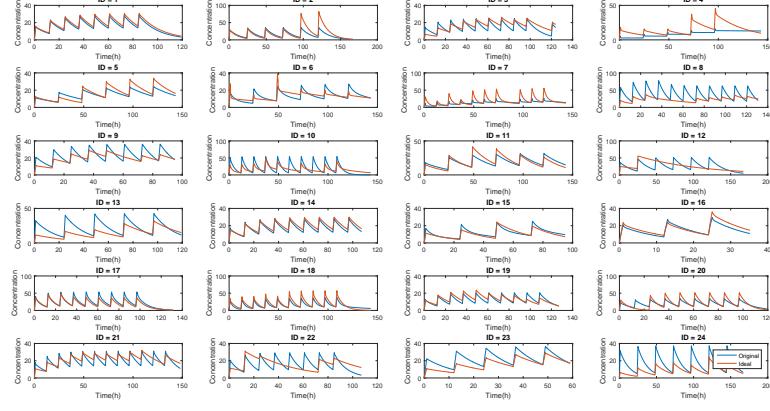


Figure 5.8: PK profiles of all 24 patients predicted by Pmetrics based on initial data and hospital guidelines

Individual patient steady state AUCs were then tabulated. Since the PK profiles are of varying lengths, different steady state values. When profiles only lasted 35 hours, steady state was taken to be between 24 and 35 hours, while steady state was between 48 to 59 hours for patients with profiles that ended at 60. For the rest of the patients, the steady state was taken to be between 72 to 96 hours. Based on these considerations, the AUC values for all the patients are illustrated in Figure 5.9.

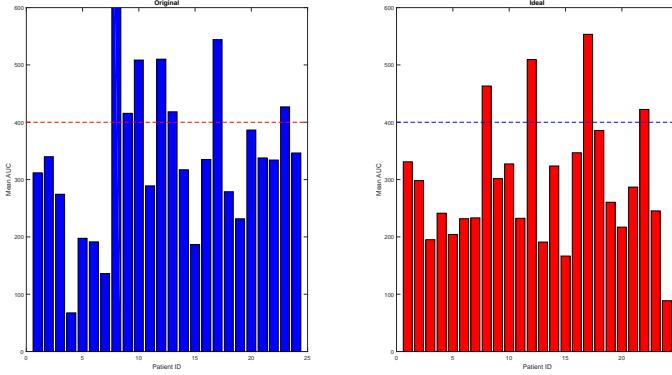


Figure 5.9: AUC values at steady state for all 24 patients

The histogram on the left of Figure 5.9 shows the original data while the one on the right shows the one derived from the hospital guidelines. The dotted lines in both plots show the ideal AUC that should be achieved at steady state. From the plots, it is evident that the dosing regimes applied to the patients fail to achieve the necessary AUC:MIC ratio of 400.

From the original data, Patient 8 has an AUC:MIC ratio of 900. Such high values of AUC:MIC have been associated with increased risk of nephrotoxicity and should clearly

be avoided. Only a total of 7 patients have achieved the necessary targets out of the 24 patients.

It is interesting to note that AUC values achieved by the graphs derived from the hospital guidelines also do not achieve the intended targets. However, AUC values achieved show lower variance between patients and are less drastic as compared to the initial data. Furthermore, extremely high AUC values are also avoided as in the case of Patient 8. Therefore, it is clear that the guidelines do help to standardise therapy and improve consistency in dosing, but the dosing regime achieved may still be sub optimal.

However, these results should be taken in perspective. The errors in using the guidelines discussed in the previous chapter will inevitably propagate through. Furthermore, since the PK profiles vary with time, AUC values achieved will vary with the steady state timings considered.

There are also some limitations with using Pmetrics in this analysis. The number of patients being the biggest concern. PK-PD modeling was performed on a data set of 24 patients. Such a small sample size forces Pmetrics to make broader estimations. Hence a larger data set with rich data will allow for better modeling and the achievement of more accurate predictions. In addition, the model file used requires an error polynomial. These error coefficients are usually provided by the laboratories that record and collate the data. Since there were no error coefficients provided in the data file, these numbers had to be guessed leading to potentially poorer results.

These limitations make PK-PD modeling seem very trial and error based. Multiple iterations with slight changes in the model file results in significant changes in the results obtained. Hence, access to thorough data will make this process significantly easier.

Despite the above limitations, there are some key takeaways from this analysis. Firstly, it can be seen that a two compartment model better representation of our data set based on the  $R^2$  values achieved. Secondly, regardless of whether the hospital guidelines are being followed or not, current dosing strategies are failing to dose patients in the most optimal manner. Therefore, alternate dosing strategies are necessary to achieve ideal drug levels amongst patients.

The use of PK-PD modeling to analyse and quantify the extent of effective therapy based on AUC values is hugely beneficial. Based on these findings detailed in this chapter, an abstract was submitted to the 2016 BIA spring scientific meeting. A presentation was also done at this meeting under the title: Investigating vancomycin therapy across secondary care pathways; are we dosing patients appropriately? A scientific paper is also to follow in the near future.

# Chapter 6

## Controller Implementation

This chapter details the two different controllers that were implemented. The first part of the section covers the PID controller and discusses the results obtained under varying initial conditions. The following part of this chapter goes on to elaborate on ILC. Finally, the feasibility of using closed loop control to optimise dosing is evaluated.

### 6.1 Model Discretisation

Since computer controlled systems are no longer continuous but discrete in nature, it is necessary to perform discretisation. The differential equations describing the one and two compartment models are continuous in nature. These equations have to be discretised to make them suitable for implementation and numerical implementation on digital computers.

The concentration value at each time instant is tabulated from the based on Equation 6.1.

$$C = C + \Delta C \quad (6.1)$$

$$= C + \frac{dC}{dt} T_s \quad (6.2)$$

where

$C$  = Concentration

$T_s$  = Sampling Time

Substituting Equation 2.13 into the above equation yields Equation 6.3 which represents the concentration of drug in the central compartment for a one compartment model with infusion.

$$C = C + \frac{\text{Rate} - Cl * C}{V_d} * T_s \quad (6.3)$$

where

$C$  = Concentration in central compartment

$V_d$  = Volume of distribution

$Rate$  = Infusion Rate

$T_s$  = Sampling time

$Rate$  is the output of the controller and represents the rate of infusion of drug into the body. For the two compartment model, the relation is slightly more complicated as represented by Equation 6.4.

$$C_c = C_c + (Rate - k_{cp}C_c + k_{pc}C_p + k_eC_c) * T_s \quad (6.4)$$

$$C_p = C_p + (k_{cp}C_c - k_{pc}C_p) \quad (6.5)$$

where

$C_c$  = Concentration in central compartment

$C_p$  = Concentration in peripheral compartment

$k_{cp}, k_{pc}$  = Transfer rate constants

$k_e$  = Elimination rate constant

$T_s$  = Sampling time

$Rate$  = Infusion rate

The controllers are implemented based on the above equations. Varying the sample time essentially implies the rate at which serum drug concentrations can be measured and rates updated by the controllers. Sampling times are specified in minutes and a zero-order hold model is used to convert the discrete form back into continuous concentration curves. This means that increasing the sampling time greater than 1 minute will lead to steps in the PK profile as the concentration values are held constant for each sample interval.

## 6.2 Testing Variability

The controllers aim to optimise dosing to achieve a given target of AUC of  $\geq 400$  over 24 hours, for different patients. Since most drugs have a MIC of 1, controllers designed to achieve this target can be used to optimise dosing regimes for multiple drugs and not just vancoymcin.

There are multiple scenarios which can potentially affect dosing strategies. For example, the  $Cl$  value of a patient may vary over 24 hours. The controller should be able to deal with these changes and still eventually produce a concentration-time graph with an AUC of at least 400 at the end of 24 hours. Testing and accounting for such situations is important in not only producing more realistic PK curves but also integral in analysing the effectiveness of using controllers for dose optimisation. Multiple scenarios have been modeled and the results are discussed in the next section.

Though the main determinant of whether therapeutic levels of vancoymcin is achieved in patients is dependent on the AUC value, other constraints are also included to prevent concentrations from reaching toxic levels or dropping below therapeutic levels. The minimum tough concentration achieved should be higher than 10 mg/L and the maximum should not be greater than 20 mg/L for an extended period of time.

Both the one and two compartment models were tested. The effects of patients parameters of the controller coefficients are also analysed. The values for each patients'  $Cl$  and  $V_d$  were obtained from Pmetrics based on the most successful models.

## 6.3 Results and Discussion

### 6.3.1 PID Controller

The parameters of the PID controller,  $K_p$ ,  $K_i$  and  $K_d$ , defined in Equation 2.31 are made to relate to each other based on the following relationships:

$$K_i = \frac{K_p}{T_s}, \quad K_d = K_p * T_i \quad (6.6)$$

$T_s$  represents the sampling time used in the discretisation of the continuous time function and  $T_i$  is an integral constant.

The PID controller is used for continuous infusion. The output will therefore represent the rate of infusion into the central compartment. With continuous infusion, the PK profile will be a straight line where the steady state concentration is reached when rate of infusion is equal to rate of elimination. However, to achieve an AUC of 400 with a straight line profile, concentration should be equal to  $400/24$  mg/L. Therefore the set point is set to 16.667 mg/L.

### Single Compartment Model

The initial concentration in the central compartment is taken to be 0. The plots on the left of Figure 6.1 depict the PK profiles of all 24 different patients. The corresponding dosing vs time plots is shown on the right. Total simulation time is fixed at 24 hours. The parameters used for the tuning of the PID controller are  $K_p = 0.5$ ,  $T_i = 0.1$  and  $T_d = 1$ . These parameters are fixed for the next few cases, unless specified otherwise, for all patients.

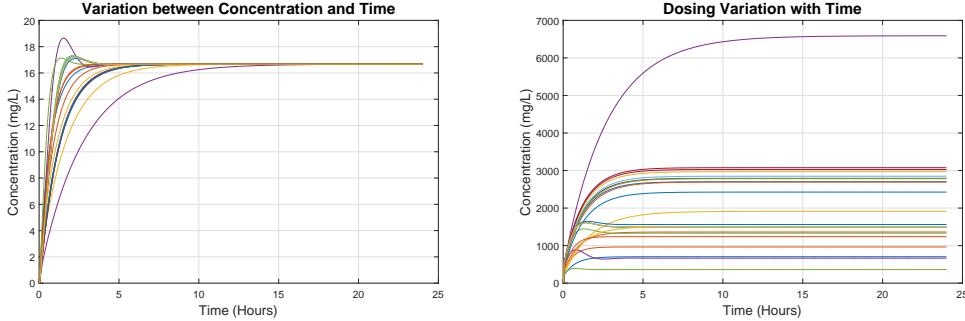


Figure 6.1: PK and dosing curves for patients with fixed PID controller parameter,  $K_p = 0.5$

The above case assumes that the rate of infusion can be changed every minute, resulting in smooth curves which converge to the expected value of 16.667. However, it is impractical and potentially dangerous for the patient to continuously alter the rate of infusion. Hence a more reasonable time frame of 15 minutes is taken. With this change, the following set of graphs are obtained as shown in Figure 6.2. Despite this added complexity, the controller is still able to reach the expected steady state value of 16.667 mg/L but the overshoots have increased.

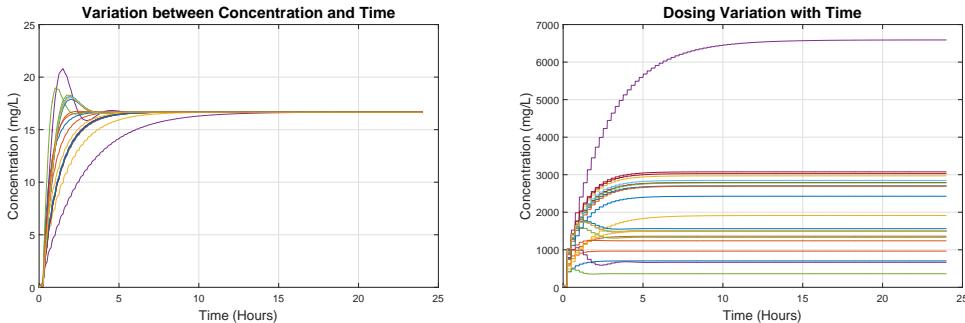


Figure 6.2: PK and dosing curves for infusion rate changed every 15 minutes

The cumulative AUC achieved with time is also plotted to determine if the targets are being reached. Figure 6.3 shows the cumulative AUC for 3 different cases with the same tuning parameters. Infusion rate is set to every minute, every 15 minutes or every 30 minutes. In all 3 cases, the profiles do converge to the steady state value within 5 hours except for the purple plot. As a result, the major differences in AUC occur within the first 5 hours. In addition, it can be seen that the cumulative AUC at 24 hours for all 3 cases failed to reach

the intended value of 400.

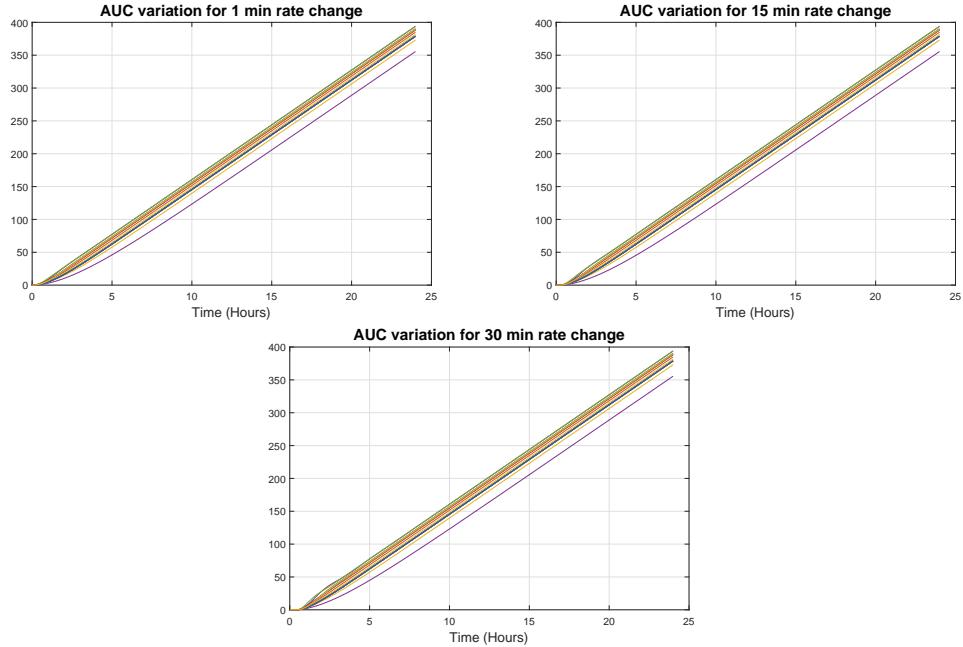


Figure 6.3: Variation in cumulative AUC with infusion rate changes every 1, 15 and 30 minutes

In the above mentioned cases, the targeted AUC is not achieved as the set point has been kept constant. Once the concentration reaches 16.667 mg/L, the error term becomes 0 and there is no more change in the output. However, this does not guarantee that the overall AUC will be 400. In order to resolve this issue and to compensate for the loss of area initially, the set point should be updated accordingly. This adaptive set point PID algorithm can be summarised by the flow chart in Figure 6.4.

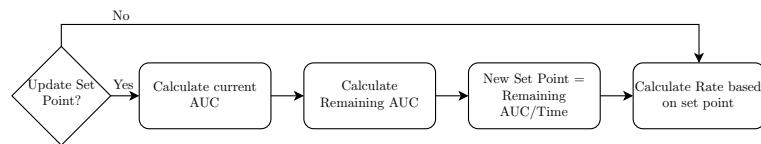


Figure 6.4: Algorithm workflow for PID control

Initially, the PID controller function was adapted to update the set point every 6 hours. Since the total simulation time is 24 hours, 6 hours provide sufficient time for the initial AUC to be updated and changed accordingly. With this updated algorithm, the plots on the left of Figure 6.5 are obtained. From the plots, at every 6 hours, there is a spike when there is a change in the set point. The accumulative AUC graphs shown on the right of Figure 6.5, confirm that overall AUC at the end of 24 hours is approximately 400 for all the patients.

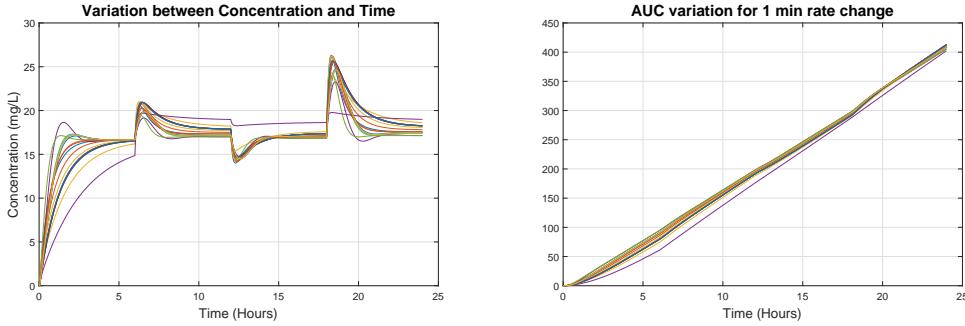


Figure 6.5: PK and cumulative AUC curves for PID with adaptive set point

The overshoot at  $t = 18$  is particularly large for all the patients. However, the maximum peak is still below the toxic levels and only occurs for a short period of time. Clinically, it is still acceptable though large overshoots are not desirable from a control point of view.

During the course of treatment, the infection can potentially cause undesired effects on the body. For example, patients can have varying  $Cl$  during treatment due to impaired renal functions. Variation in  $Cl$  will have an impact on the amount of drug in the system due to the lack of ability to clear it. If doses are not adjusted accordingly, this may cause an accumulation of drug resulting in increased chances of toxicity. The controller should be able to account for variations in  $Cl$  and rectify the doses accordingly to achieve the necessary target AUC.

$$Cl = A * Cl * \sin\left(\frac{2\pi}{SimulationTime * 60} * Time + 2\pi rand\right) \quad (6.7)$$

where

$A$  = Percentage variability

$SimulationTime$  = Total length of dosing in hours

$Time$  = Time vector for period of simulation time

$rand$  = Random generator in MATLAB

$Cl$  can be modeled to vary sinusoidally over 24 hours based on Equation 6.7, obtaining the plot shown in Figure 6.6.  $A$  was set to 0.2 to model a 20% variability in clearance and the value of  $CL$  was changed every 3 hours.

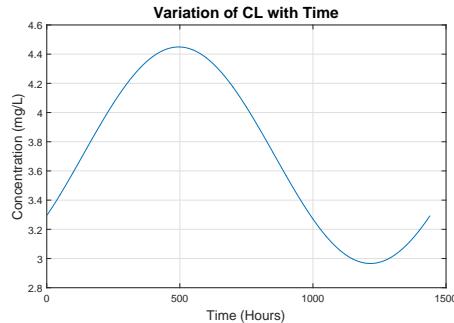


Figure 6.6: Variation of  $Cl$  with time for Patient 1

With this added change, the PK profiles of the different patients was plotted as shown in Figure 6.7. With the addition of variability in  $Cl$ , there are increased oscillations in the PK profiles. A reduction in  $Cl$  corresponded to a decrease in the amount of drug given to the patient. This response is ideal as a lower  $Cl$  value implies the lack of ability to eliminate the drug from the system. With reduced elimination, the amount of drug needed to maintain a constant concentration in plasma should decrease as well. Hence, the response provided by the controller is accurate. The plots for cumulative AUC show that the intended target is still reached for most of the patients for the adaptive set point PID controller, shown in Figure 6.8 but due to the changes in  $Cl$ , the required AUC is not achieved for some patients.

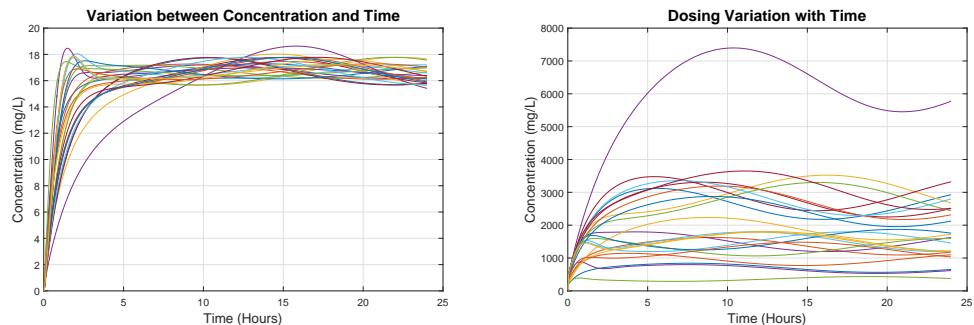


Figure 6.7: PK and dosing curves for PID with  $Cl$  varying every 3 hours

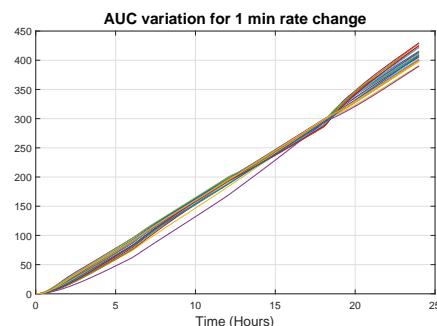


Figure 6.8: Cumulative AUC curves with  $Cl$  varying every 3 hours

Typically, when measurements are taken, there is a possibility of error in the measurement. An error term is introduced into the differential equation to obtain Equation 6.8. In this analysis, error is taken to be a fixed percentage of the measured value.

$$C = C + \frac{Rate - Cl * C * error}{V} * T_s \quad (6.8)$$

where

*Rate* = Output of controller

*C* = Concentration

*error* = Percentage error decrease

*Cl* = Clearance

*V* = Volume of distribution

The plots for the basic PID controller without adaptation of the set point is shown in Figure 6.9. Error was varied between 5% to 50%. The green plots show the original plots while the red ones represent the PK profiles with an error of 5%. Lastly, the blue plots represent an error of 50%. In general, the introduction of error causes the overshoot to increase. The PK profiles do still converge to the expected values. In reality, error in measurement may not be a fixed value but may be dynamic in nature. Nevertheless, this analysis shows the robustness of the controller as convergence is still observed.

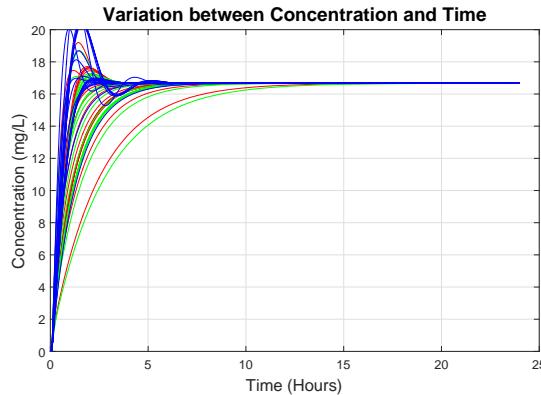


Figure 6.9: PK profiles with 0, 5% and 50% errors

### 6.3.2 Grid Search Algorithm

In all the above simulations and analysis, the value of  $K_p$  has been fixed at 0.5 for all the patients. However, the controller can be tuned to be optimal to each patient. Initially tuning of  $K_p$  was performed manually to reduce any large overshoots and to achieve the fastest time to steady state. Manually tuning the parameters led to the following graphs depicted in Figure 6.10.

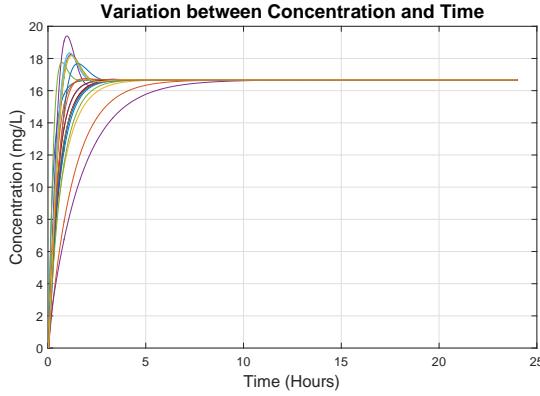


Figure 6.10: PK profiles of all 24 patients with manually tuned  $K_p$  values

A grid search algorithm was then implemented in order to find the optimal parameters for each patient automatically. Ideally, the PK profile of a patient should reach steady state quickly while minimising the percentage overshoot. Hence, percentage overshoot and rise time were used as performance metrics in the tuning. A maximum tolerance for overshoot was set to 10% of the steady state value. The overshoot and rise time were calculated during each iteration while varying  $K_p$  between 0.1 and 2. Results obtained were ranked in descending order for each metric. The ranks were then summed up for each value of  $K_p$ . Weights were added to give more importance to overshoot than the rise time. The value of  $K_p$  which generated the highest rank, 2 being the best, was taken as the optimal  $K_p$  value for that particular patient.

Figure 6.11 shows the PK profiles obtained with  $K_p = 0.5$  in red, manual tuning in blue and automated tuning using grid search algorithm in green. The value of  $T_i$  and  $T_d$  were kept constant and the value of  $K_p$  was varied between 0.1 and 2. The results obtained clearly show the reduction in overshoot and tighter profiles generated with the automated tuning. Therefore this is a clear improvement.

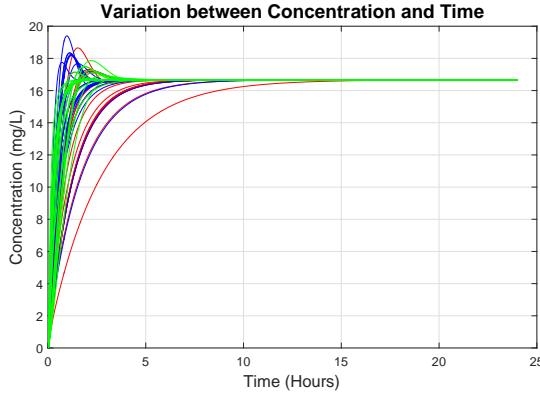


Figure 6.11: PK profiles of all 24 patients with fixed  $K_p$ , manually tuned  $K_p$  and automated tuning

The improvements can be quantified in terms of overshoot, rise time and AUC error at the end of 24 hours. Table 6.1 shows the different values obtained for the 3 different methods of tuning. The rise time is given in minutes. From the table, the values obtained for percentage overshoot is lower for automated tuning than when  $K_p$  is selected manually. The mean values for overshoot, rise time and AUC error for automatic tuning are 0.0131, 116.7083 and 7.2498 while the mean values for manual tuning are 0.0383, 192.9167 and 8.7507 and finally the mean values for fixed  $K_p$  are 0.0157, 364.6250 and 16.7735. Hence the parameters determined by automatic tuning are the best resulting in the least AUC error while minimising overshoot and rise time. There are some cases where the AUC error is higher than the manually tuned like in the case of Patient 4. This is because there is a greater overshoot with the manually tuned  $K_p$ , inevitably leading to a greater AUC. Since the reduction of overshoot is prioritised, this loss is justified.

As the  $K_p$  values have now been individualised to the patients, it may be possible to draw a relationship between the patient parameters and  $K_p$ . Such a relationship, will make future tuning of the controller a lot easier for new patients. The values of  $K_p$  were plotted against different patient parameters such as  $Cl$ ,  $V_d$  and  $Weight$ . The following scatter plots in Figure 6.12 show these comparisons for automatic tuning.

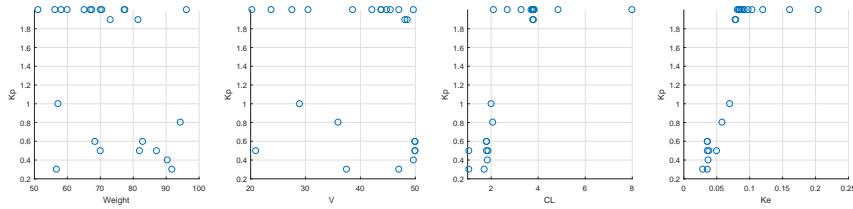


Figure 6.12: Scatter plots of  $K_p$  against weight,  $V_d$ ,  $Cl$  and  $k_e$  with automatic tuning

Patient ID	%Overshoot			Rise Time			AUC error		
	Fixed	Manual Tuning	Automatic	Fixed	Manual	Automatic	Fixed	Manual	Automatic
1	0	0	0	505	248	113	20.7369	10.438	5.2885
2	0	0	0	367	227	68	15.0583	9.4636	3.8689
3	0	0	0	513	187	106	21.225	8.249	5.4106
4	0.0373	0.1097	0.0373	96	45	96	10.1308	4.6808	10.1308
5	0.0414	0.1051	0.0063	90	47	178	9.5852	4.8621	15.8826
6	0.0373	0.1176	0.0534	96	42	79	10.1312	4.3025	8.4659
7	0	0	0	510	226	113	20.9657	9.6057	5.3457
8	0	0	0	297	120	72	11.7574	4.6078	3.0438
9	0	0.0007	0.0022	245	95	76	11.2847	6.3311	5.7119
10	0	0	0	703	340	205	26.9919	12.345	6.8524
11	0.1281	0.1897	0.0748	59	104	92	6.0548	3.0969	9.9986
12	0.0352	0.1004	0.0352	57	26	57	5.9048	2.76	5.9048
13	0.0373	0.1176	0.0534	96	42	79	10.131	4.3024	8.4657
14	0	0	0	508	220	107	21.1258	9.6785	5.6619
15	0.0277	0.0681	0.0277	102	62	102	10.5831	6.6666	10.5831
16	0	0	0	529	529	130	21.4645	21.4645	5.4704
17	0	0	0	470	244	133	18.4096	9.2744	4.7068
18	0	0	0	1128	716	305	44.4137	27.8149	11.2094
19	0	0	0	521	287	122	21.3085	11.8999	5.4314
20	0	0	0	512	189	112	21.0659	8.1879	5.3708
21	0	0	0	511	183	107	21.2399	8.2548	5.6919
22	0	0	0	525	241	135	21.0988	9.6662	5.379
23	0	0.0066	0.0066	213	85	85	11.6281	7.3197	7.3197
24	0.0334	0.1047	0.0169	98	125	129	10.2691	4.7436	12.8016

Table 6.1: Overshoot, rise time and AUC error for fixed  $K_p$ , manually tuned  $K_p$  and automatically tuned  $K_p$  for all 24 patients

The results obtained do not show any significant relationship. The best relationship identified is the saturation of  $K_p$  as  $K_e$  increases. Since the AUC error achieved by manual tuning were not too far off the automatic tuning, manually tuned  $K_p$  values were also used in the identification of a potential relationship. There was a clear relationship between Weight and  $K_p$ . Figure 6.13 shows the scatter plot achieved and the corresponding best fit polynomial. The best fit equation is a cubic expression as given by Equation 6.9.

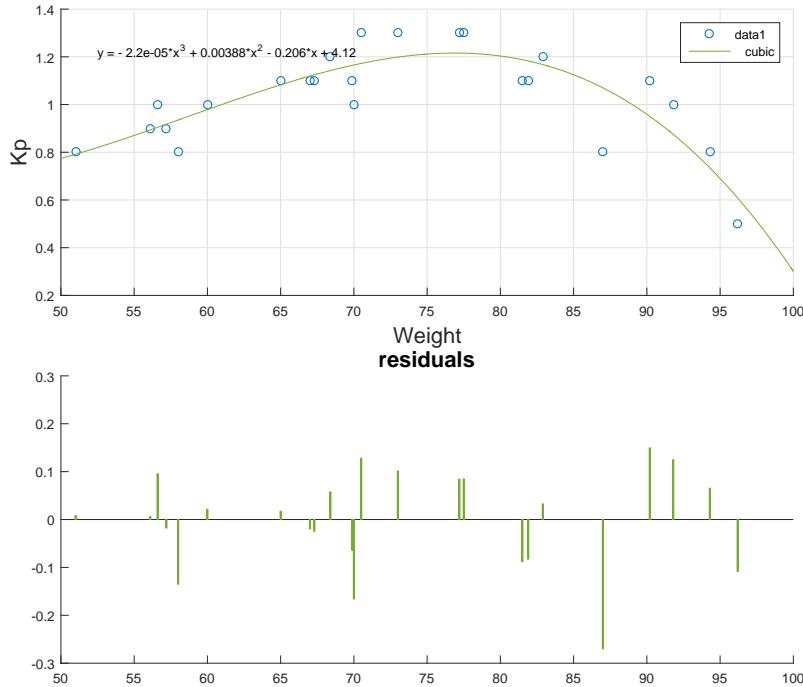


Figure 6.13: Relationship between Weight and  $K_p$  for manual tuning

$$K_p = -2.2 * 10^{-5} * Weight^3 + 0.00388 * Weight^2 - 0.206 * Weight + 4.12 \quad (6.9)$$

### Two Compartment Model

Similar analysis, as detailed above, were carried out with the two compartment model. Sampling frequency was set to  $T_s = 1$  and the patient parameters were obtained from the best two compartment model generated with Pmetrics. With the same relationship shown in Equation 6.6 between  $K_p$ ,  $K_i$  and  $K_d$ ,  $K_p$  was set to 0.1 as keeping it at 0.5 lead to instability. The basic implementation of the PID controller produced the results shown in Figure 6.14. The set point still remains the same at 16.667 mg/L. The PK profiles can be seen to converge to the expected value.

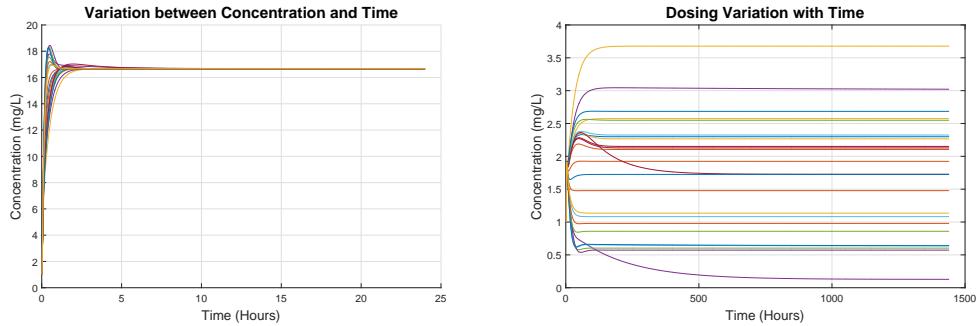


Figure 6.14: PK and dosing profiles of 24 patients with basic two compartment model.  $K_p = 0.1$

As compared to the one compartment model, the rise times for the two compartment model are a lot faster with a mean rise time of 86.6 minutes. The one compartment model had a mean rise time of 131 minutes even with a more aggressive  $K_p$  factor of 0.5. Furthermore, the profiles are also more tightly related to each other as compared to the one compartment model profiles. However, with the constant value of  $K_p$ , some patients can be seen to have significant overshoots.

The grid search algorithm was once again used to individualise the parameters to the patients. The resulting PK profile of can be seen in Figure 6.15.

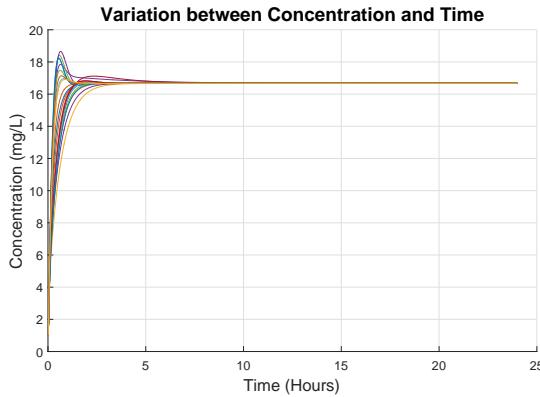


Figure 6.15: PK and dosing profiles of 24 patients with basic two compartment model.  $K_p$  is individualised to patient.

Next, the value of  $Cl$  was made to vary with time like in the single compartment case. The results obtained are shown in Figure 6.16. The profiles of all 24 patients do converge towards the expected steady state value of 16.6667 mg/L. Once again, the oscillations are generated as in the one compartment case. However, the amplitude of the oscillations are reduced considerably.

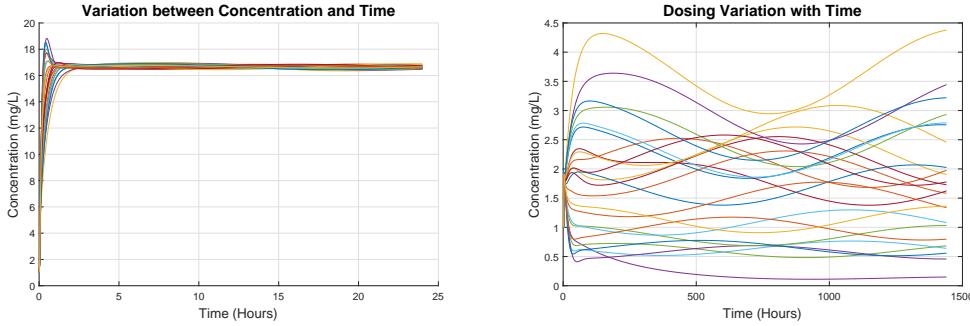


Figure 6.16: Pk and dosing profiles of 24 patients with basic two compartment model.  $Cl$  varies sinusoidally with time.

The cumulative AUC graphs are shown in Figure 6.17 for the simple two compartment model. As expected, without the adaptation of the set point, the target of 400 was once again not achieved. Using the same algorithm for the adaptation of the set point as before, the intended target of 400 was achieved for all 24 patients. The plot on the right of Figure 6.17 confirms this.

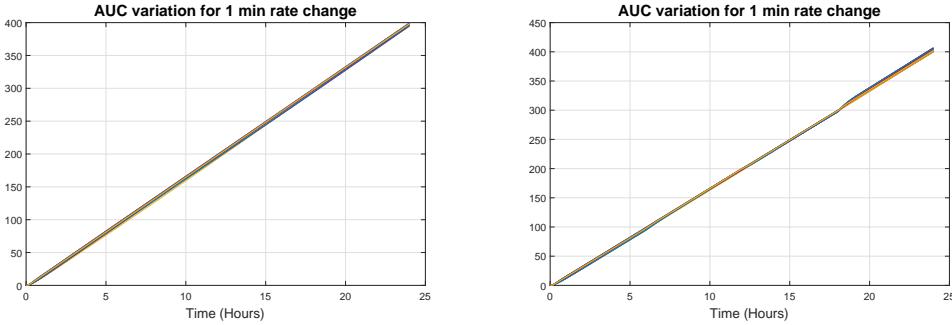


Figure 6.17: Cumulative AUC for two compartment model with and without set point adaptation.

## 6.4 Iterative Learning Control

In ILC, an initial amount of drug is administered first and the concentration time profile is predicted using the differential equation of a single compartment model. Before the next dose is given, the drug concentration is recorded and error is measured. Unlike, the continuous infusion case where the reference PK profile is a straight line, time limited IV and oral dosing do not have reference curves. Hence, a correlation between the trough level and AUC needs to be established before compensation can be performed.

A trough concentration of under 15 mg/mL has been suggested to achieve an AUC greater than 400 if the MIC is less than 1 mg/mL [22]. The set point taken to be the median of the therapeutic range suggested by the hospital guidelines, 10-15 mg/L. A set point of 12.5 is used for the rest of the analysis in this section. The ILC is tested primarily for the limited IV and oral administration cases.

For the limited IV drug administration, the time to complete infusion is taken to be 2 hours. Hence infusion rate will be dependent on the dose that is administered given by *Dose/InfusionTime*. Initial dose was set to 1000 mg for all 24 patients in the data set.

Figure 6.18 show the PK profiles for the 24 patients.  $\gamma$  and total time for simulation was set to 60 and 240 hours respectively. A sufficiently long simulation time was set to ensure that enough time was given for the control algorithm to reach steady state. Subsequently, the steady state AUC values were tabulated for the patients to determine if the targeted value of 400 is achieved.

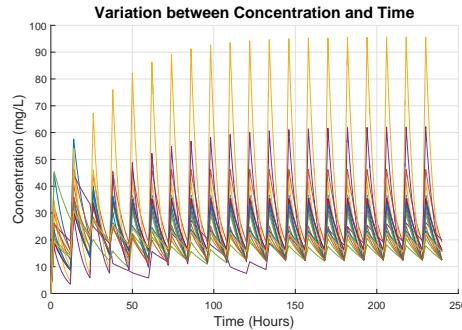


Figure 6.18: PK profiles for all 24 patients with IV administration and ILC. Initial dose = 1000mg.

From the plots, close to the end of the simulation time, all patients have a trough concentration of 12.5 mg/L. This is the intended target and ideally should correspond to an 24 hour AUC of greater than 400. The AUC at steady state (192-216 hours) is tabulated and the results are shown in Figure 6.19.

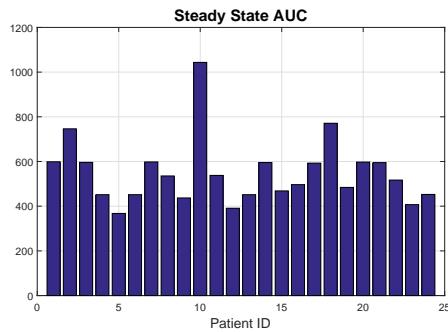


Figure 6.19: Steady state AUC values for all 24 patients for time limited IV. Initial dose = 1000mg, Infusion time = 2h.

From the histogram, not all the patients reach the intended target of 400 at steady state. Two patients did not achieve the ideal target of 400 while two patients had AUC values which were higher than the safe range, namely Patients 10 and 18. The safe upper bound for AUC before chances of toxicity increase is 700.

Infusion time was then changed to 5 hours and the initial amount of drug was kept at 1000 mg for all 24 patients. The PK profiles obtained are shown in Figure 6.20. The PK profiles obtained are shown in Figure 6.20, revealing a considerable decrease in the peaks. Hence, it can be expected that the steady state values for AUC should also decrease. This is confirmed in the histogram shown on the right in Figure 6.20. Though the highest steady state value has now dropped to 742.9 (Patient 10), it is still higher than the safety limit of 700. More patients (8 of 24) are also now below the ideal target of 400.

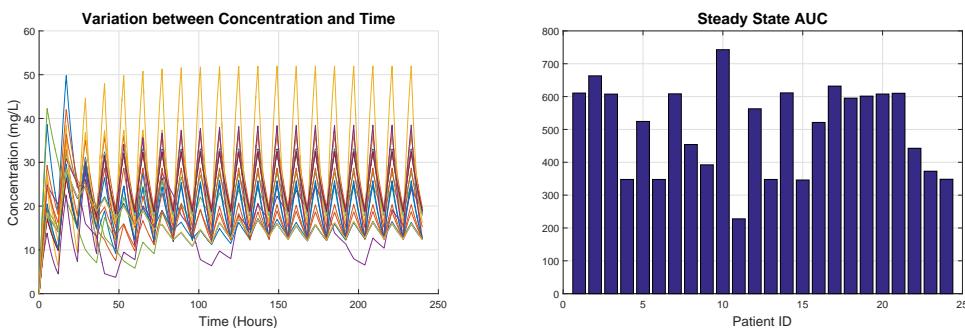


Figure 6.20: PK profiles and steady state AUC values for all 24 patients with IV administration. Initial dose = 1000mg, Infusion time = 5h.

The differential equation which represents oral consumption of a drug is slightly different from the infusion differential equation. The absorption constant,  $k_a$ , is taken to be 0.5. Based on the Equations 2.10 and 2.11, ILC was applied for the 24 patients with the initial dose of 1000 mg. The PK profiles of the patients are shown in Figure 6.21.

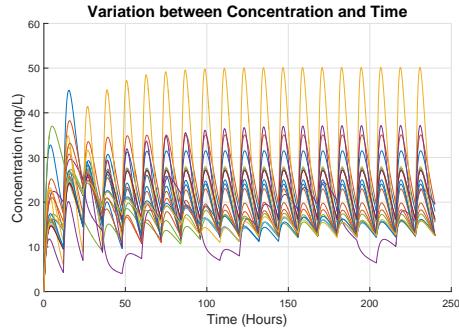


Figure 6.21: PK profiles for all 24 patients with oral administration and ILC. Initial dose = 1000mg.

Next the clearance of the patient was made to vary with time as in the previous section. The effect of varying  $Cl$  was determined for the Patient 1. Figure 6.22 shows the PK profiles of Patient 1 when  $Cl$  is taken to be constant throughout the time period and when it is varying sinusoidally. Both the IV and oral cases are shown on left and right of the figure respectively. The underlying sinusoidal change in CL is evident from the plots.

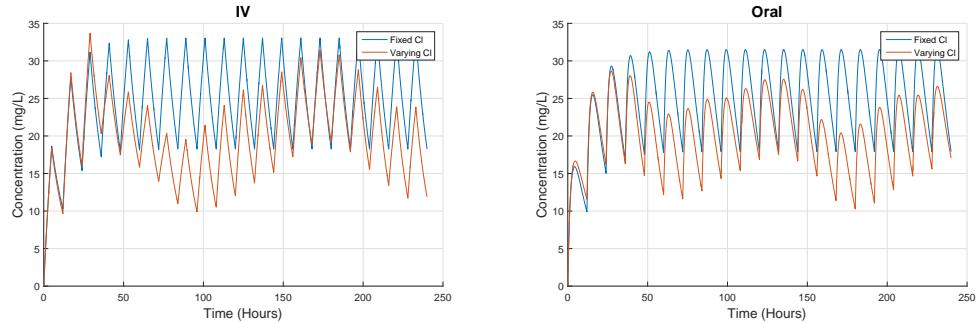


Figure 6.22: PK profiles for Patient 1 with fixed and varying  $Cl$  for IV and oral administration. Initial dose = 1000mg.

## 6.5 Evaluation

For the PID controller, the two compartment model has shown faster convergence (faster rise times) and better stability properties as compared to the one compartment model. With the addition of disturbances in the system, such as introduction of variation in the value of  $Cl$ , there are fewer oscillations for the two compartment model. There is also less variation between patients with the two compartment model in comparison as PK curves are tighter together.

When the PID controller parameters were individualised to the patient parameters, the grid search algorithm produced the best results with the fastest mean rise times, lowest percentage overshoot and lowest AUC error at the end of 24 hours. However, the difference in AUC error between the two methods of tuning was only 1.5009 higher for the manual as compared to automatic.

The grid search algorithm is, however, more robust in determining the parameters as compared to the visual approach. Furthermore, the algorithm allows testing of a wide range of parameters for  $K_p$  which will be extremely time consuming if performed manually. In the above analysis, the weights for the overshoot and rise time were at a ratio 3:2. This ratio can be further manipulated to determine the most ideal parameter. However, due to the limited number of patients available, in the above analysis, it was done based on trial and error.

However, the individualised parameters are not directly transferable between the one and two compartment model as the patient parameters predicted using PK-PD modeling are different for the same patient between models. The same grid search algorithm, however, failed to effectively remove all overshoots greater than 10% for the two compartment model. Closer analysis revealed, some patients, Patient 5 for example, had overshoots for all the tested range of  $K_p$  or had very long rise times for lower values. Hence the weighting used in the previous section results is not ideal in this case resulting in some patients still having overshoots in the personalised values of  $K_p$ . However, the overshoots are within the acceptable clinical range and are acceptable.

Adapting the set point along the dosing regime is also favorable as the expected value of AUC is reached in this case for both the one and two compartment model. It can be seen from the PK profile, when the set point is updated, there is a sharp increase in PK profile which will correspond to a sharp rise in the dosing vs time plot. Though within the acceptable range, it is likely that the issue arises due to the derivative term in the output equation. As established before, the derivative term is calculated by determining the slope of the error over time. When there is a change in the set point, it is comparable to introducing a step function at that point. Therefore, the relative change is enormous and causes the error term to increase greatly. This issue can be potentially resolved by saturating the differential term.

There were some considerations which were made in this analysis. Firstly, readings taken under a hospital setting are definitely prone to errors. There are numerous sources of error involved in measurements. Firstly, there may be errors in measurement when blood samples are taken. Errors could also arise due to the body conditions of the patient when the reading is obtained. Furthermore, the equipment used to measure serum concentrations will inevitably have some form systematic error. In the above analysis, error is taken to be a fixed percentage of the measured value. However, in reality, more often than not, errors tend to be dynamic in nature and have some form of relationship with the previous results. Since the type of equipment or the state of patients is unknown, a fixed error was considered.

Secondly, in the simulations, the measurements of serum concentrations was assumed to be instantaneous. Taking a measurement of serum concentration is analogous to sampling the continuous differential equation. Advances in technology have allowed the processing of blood samples to be quick and efficient. Hence, it is justified to assume that readings are obtained instantaneously when sampled.

The ILC implementation helped to account for different types of drug administration. The above results, performed with a two hour infusion time, showed significant peaks in some of the PK profiles predicted for some of the patients. A single compartment model was used to predict the PK profiles after a dose was given. Due to these peaks, the AUC obtained at steady state is also higher than acceptable levels. In some cases, the trough concentration also drops below 10 mg/L. However, the PK profiles obtained could potentially be better if the proportional constant in ILC,  $\gamma$ , was adapted for each individual patient.

However, the general trends of the profile obtained is accurate. Once the system has been validated, an useful application would be to analyse the effects of varying dosing regimes and doses on the steady state AUC. Doctors will be able to alter dosing patterns and determine if the required AUC will be achieved at steady state. For example, the effect of increasing infusion time was analysed and it could be seen that the peaks of the PK profiles decreased, which in turn affects steady state AUC values. Hence, combinations of dosing strategies and amounts of doses can be analysed which is particularly useful in optimising dosing strategies.

The implementation of oral administration and varying  $Cl$  was done with ILC to show its feasibility. Once again, the added flexibility of being able to use PK-PD modeling to predict the effects of varying conditions will allow the creation of better and more robust dosing strategies which are catered to the individual.

The results obtained above demonstrate the feasibility of using a closed loop system to optimise dosing regimes for patients. In all the cases considered, both the PID controller and the ILC have been able to achieve the required targets in terms of AUC and trough concentrations. The PK profiles obtained are within acceptable ranges and there are no unrealistic estimates present. Furthermore, since the output of the controller represents the rate at which the drug is administered, the individualised dosing profiles can be easily generated for each patient as shown in the previous section.

Using closed loop control to optimise dosing is relatively new with little literature on this topic. The inclusion of different parameters in the simulations allow for better and more accurate representations of real world scenarios. For example, patients who are critically ill may have changing clearances over the duration of therapy. This case was simulated with  $Cl$  varying sinusoidally. Such a scenario is an extreme case and it is unlikely that a patient will have such considerable changes in clearance over a short period of time like 24 hours. Despite this, the controllers have been able to deal with such cases demonstrating the robustness of the design.

From the methodology adopted above, optimising dosing is a two step process. The first is determining the PK model which represents the data best and predicting the patient parameters. These parameters are then used in the design of the controller. The scatter plots showing the PID controller parameters against different patient characteristics, do suggest possible relationships between the two entities.

The cubic relationship obtained in Equation 6.9 with the manually tuned parameters and  $K_p$  is integral in future tuning for patients. Such relationships allow quick tuning such that dosing plans can be obtained quickly and efficiently. However, in the above analysis, the size of the data set used is small and hence there are insufficient points to solidify a strict relationship. While the cubic relationship suggests a possible trend, it is important to carry out more testing and simulation of rich data sets to make the analysis complete and robust.

Nevertheless, the testing has shown that PK-PD modeling and control theory go hand in hand in being able to optimise dosing regimes for patients. Having a poor model to represent the data set will result in inaccurate predictions of  $Cl$  and  $V$ , leading to in poor predictions of the PK profiles.

The data used in the above testing is not robust as mentioned in Chapter 5. From the results and discussions made thus far, the heavy reliance on a rich data set to be able to produce accurate results is evident. Hence, more data is required not only to design the controllers and models but also to validate the results obtained from the controller. On the whole, closed loop control and PK-PD modeling can be used to design and build the dosing module once validation is performed.

## Chapter 7

# Conclusion and Future Work

The aim of this project was to address the rising problem of antimicrobial resistance by tackling misuse of antibiotics in a hospital setting. Particularly, this aim can be fulfilled by developing an antimicrobial dosing module that will be integrated to a decision support system currently being developed. Stemming from this aim, there are three primary objectives to this project. Firstly, the problem of inappropriate dosing had to be identified within a hospital setting. Secondly, drug specific PK-PD population models should be studied and implemented. Finally, a controller capable of automatically adjusting dosing for patients should be implemented.

The project focused in on a single antibiotic, namely vancomycin. Based on the infection policy provided by the NHS for administration of vancomycin, the ideal dosing regimes for patients in the date set were determined. Comparisons were made between these derived dosing regimes and the actual dosing regimes implemented. Discrepancies were found between the two dosing regimes, proving that the guidelines were not followed for all the patients.

Different PK models were tested and evaluated primarily based on the  $R^2$  values obtained in the observed vs predicted plots. The best one and two compartment model were identified and compared against each other. A two compartment model was identified as the best model to represent the data. Covariate modeling was also done and weight was incorporated into the model, resulting in a final  $R^2$  of 87.9%. AUC:MIC ratio was also selected as the PD indice to determine the effectiveness of therapy. Based on the selected model, the PK profiles generated revealed that patients in the data set did not achieve the AUC:MIC ratio of 400 which is analogous with optimal therapy. This finding proved the existence of the problem and satisfied objectives 1 and 2.

The results showed that patients are undergoing sub optimal therapy and there is a need to change current dosing practices in hospitals for patients in secondary care. These results were presented at the 2016 BIA spring scientific meeting under the title: Investigating vancomycin therapy across secondary care pathways; are we dosing patients appropriately?

Finally, successful implementation of a PID controller for continuous infusion and ILC for IV and oral doses, demonstrated that dosing regimes can be optimised for different patients. Based on the patient parameter predictions obtained from PK-PD modeling in Pmetrics, the controllers were designed and tested. The steady state AUC was seen to reach 400 after 24 hours when the set point was updated during the treatment.

In addition to meeting the objectives by producing a working controller, PK curves obtained were also made more realistic by modeling real life situations and incorporating them into the models. The implemented controllers were able to adapt to the different conditions and achieve the intended targets. Furthermore, controller parameters were optimised with the use of a grid search algorithm and a plausible relationship was also established between  $K_p$  and patient weight.

This project can be considered ground breaking as the use of closed loop control to optimise dosing is limited in both literature and practice. Currently, closed loop control has been suggested to optimise dosing and therapy for HIV patients. Hence, by proving the feasibility of using controllers to individualise dosing, this project has presented an innovative method to combat the misuse of antimicrobials in a hospital setting.

## 7.1 Future Work

Throughout this report, the importance of a rich data set and the reliance on it to achieve accurate results has been emphasised numerous times. Though the feasibility and implementation of the controllers have been proven to be possible, the results obtained have to be validated with clinical data. Hence, one area of future work will be to validate the results obtained with clinical data. With access to sufficient data, the relationships established in this report can be further strengthened. A larger number of patients will allow a better relation to be formed between the controller and patient parameter. Equation 6.9 can also be verified using new patients who were not initially included in the data set.

Secondly, additional constraints can be modeled into the controllers and more simulations can be performed to make the controller more robust. For example, time delays can be incorporated into the controller as measurements of serums concentrations may not be instantaneous in all cases. Furthermore, the error dynamic can be modeled and incorporated into the controller. This will involve understanding the sources of error and finding the relationship between different samples.

Lastly, the analysis can be extended to other drugs and not just vancomycin. The decision support system should ideally be able to handle multiple drugs. Hence, if sufficient data is available, the principles established can be extended to other drugs. It would be particularly interesting to establish a relation between the controller parameters and the drug type. The effect of having more than one drug in the regime can also be analysed. In such cases, the differential equations may no longer be linear and more complicated control mechanisms such as Model Predictive Control can be considered.

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## Appendix A

# MATLAB Implementation

PK-PD modeling was primarily performed in both MATLAB and R. Initially with the differential equations discussed in the previous section, different models were implemented in MATLAB to be able to better understand the workings of these models. The results discussed by *Elisabet I. Nielsen and Lena E. Friberg* in [13] were replicated to study the variations in the equations. The differences are due to the variations in methods of dosing, i.e. IV vs Oral.

The main result replicated was that of a single compartment PK model based on Equation 2.8. PK parameters used were given in the paper:  $CL = 7l/h$ ,  $V_c = 20l$ ,  $t_{1/2} = 2h$ ,  $Dose = 500mg$ ,  $K_a = 4/5h^{-1}$ . Two separate values for the absorption constant,  $K_a$  were given for slow and fast absorption respectively. The result to be replicated is shown in Figure A.1.

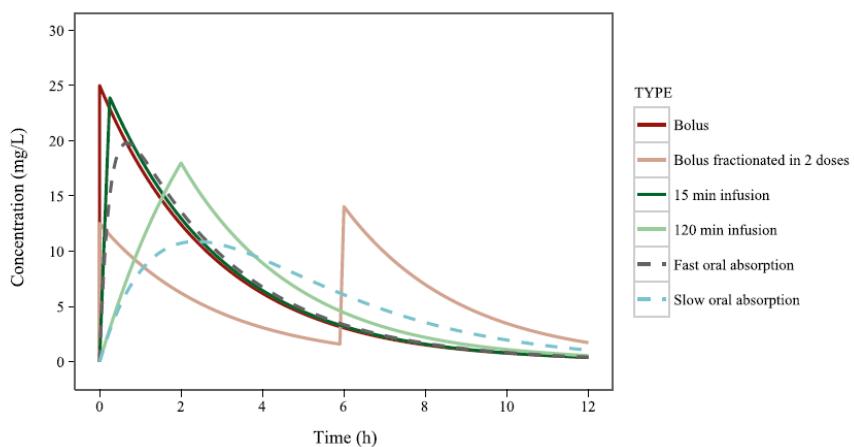


Figure A.1: Research Paper Results

## A.1 Results

With the above data, single compartment differential equations were solved in MATLAB using ODE 45. As seen, the results were replicated exactly showing that the model equations implemented were indeed accurate for all graphs. This verification is integral as subsequent modeling will involve use of these differential equations and this experiment provides sufficient validation on the accuracy of the model.

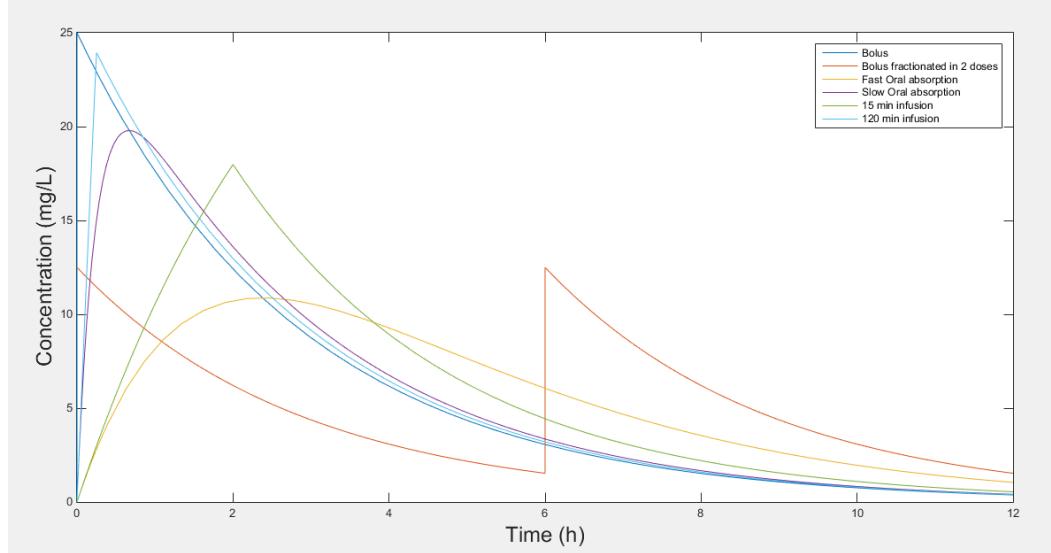


Figure A.2: Results from MATLAB

# Appendix B

## Pmetrics Components

### B.1 Data File

The data file is a comma separated file which contains details of different patients arranged in the following order:

1. ID - Identifies each individual.
2. Event ID - Every row must have an entry with 0 meaning an observation, 1 implying an input such as a dose and 4 representing reset.
3. Time - Shows the elapsed time in decimal hours after the first event.
4. Duration - Duration of infusion in hours. If Event ID is 1, there must be an entry. For a bolus dose, duration is 0.
5. Dose - Dose amount in mg
6. Additional Doses - Number of additional doses to be given in the next interval.
7. Dosing Interval - Interdose interval and is only relevant if Additional Dose is not 0.
8. Input - Defines which input the Dose corresponds to. The Input is defined within the model file.
9. Output - Observation or output value.
10. Output Equation Number - Shows the output equation number that corresponds to the Out value. Output equations are also defined within the model file.
11. C0,C1,C2,C3 - Coefficients of the assay error polynomial for that observation.
12. Covariates - Any number of covariates can be defined from this point.

The format described above is mandatory to be able to operate Pmetrics. For this project, the data was obtained from Queen Mary Hospital. A total of 24 patients were studied who were placed in secondary care. The dosing of the patients were recorded for at least 24 hours and potential covariates such as weight, height and clearance were also recorded. This data set will form the basis for this project and all modeling will be done with regards to these 24 patients.

## B.2 Model File

The model file is the second integral part required for the running of Pmetrics. The model file is a text file which enables users to specify the model that should be used in the analysis. There are 11 main blocks which help effectively describe the relevant model. Though some blocks have to be included to ensure Pmetrics understands the components involved, not all 11 blocks have to be specified for a particular model. These 11 blocks are listed below:

1. Primary Variables - Model parameters that are to be estimated by Pmetrics or are fixed parameters. There must at least be two and at most 32.
2. Covariates - Covariates specified here should match the data file in terms of order and number. In the data file shown above, there are 6 covariates specified and hence the matching model file should contain all the six covariates.
3. Secondary Variables - Defined by combinations of primary, covariates and other secondary variables.
4. Bolus Inputs - Bolus dose administered as in data file and compartment number specified.
5. Initial Conditions - All model compartments have zero concentrations by default. However, this can be changed by specifying it in this block.
6. F(bioavailability) - Bioavailability term if present is specified here
7. Lag Time - Delay after an absorbed dose before observed concentrations
8. Differential Equations - Model can be specified in terms of differential equations here with a maximum of 20.
9. Output - Output equations
10. Error - Two choices for error term which incorporate C0,C1,C2,C3 specified in the data file.
11. Extra - Meant for very complex models to specify subroutines.