STOCHASTIC CONTROL METHODS TO INDIVIDUALISE DRUG THERAPY BY INCORPORATING PHARMACOKINETIC, PHARMACODYNAMIC AND ADVERSE EVENT DATA.

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by

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There are a number of methods available to clinicians for determining an individualised dosage regimen for a patient. However, often these methods are non-adaptive to the patient’s requirements and do not allow for changing clinical targets throughout the course of therapy. The drug dose algorithm constructed in this thesis, using stochastic control methods, harnesses information on the variability of the patient’s response to the drug thus ensuring the algorithm is adapting to the needs of the patient.

Novel research is undertaken to include process noise in the Pharmacokinetic/Pharmacodynamic (PK/PD) response prediction to better simulate the patient response to the dose by allowing values sampled from the individual PK/PD parameter distributions to vary over time. The Kalman filter is then adapted to use these predictions alongside measurements, feeding information back into the algorithm in order to better ascertain the current PK/PD response of the patient. From this a dosage regimen is estimated to induce desired future PK/PD response via an appropriately formulated cost function. Further novel work explores different formulations of this cost function by considering probabilities from a Markov model.

In applied examples, previous methodology is adapted to allow control of patients that have missing covariate information to be appropriately dosed in warfarin therapy. Then using the introduced methodology in the thesis, the drug dose algorithm is shown to be adaptive to patient needs for imatinib and simvastatin therapy. The differences, between standard dosing and estimated dosage regimens using the methodologies developed, are wide ranging as some patients require no dose alterations whereas other required a substantial change in dosing to meet the PK/PD targets.

The outdated paradigm of ‘one size fits all’ dosing is subject to debate and the research in this thesis adds to the evidence and also provides an algorithm for a better approach to the challenge of individualising drug therapy to treat the patient more effectively. The drug dose algorithm developed is applicable to many different drug therapy scenarios due to the enhancements made to the formulation of the cost functions. With this in mind, application of the drug dose algorithm in a wide range of clinical dosing decisions is possible.
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“At present you need to live the question. Perhaps you will gradually, without even noticing it, find yourself experiencing the answer, some distant day.”

Rainer Maria Rilke, Letters to a Young Poet.

I am sure my words lack ability to express the full extent of a rewarding experience that the research herein has provided, however, please accept this statistician’s attempt. My two supervisors Dr. Steven Lane and Dr. Andrea Jorgensen have been continual sources of motivation and support, I am sure that a better pair of mentors would be difficult to come by. I express my sincere gratitude to Professor Paula Williamson and Professor Munir Pirmohamed who both provided funding that allowed my studies to be possible. To Dr. Andrea Davies, Dr. Martin Smith and the members of the Laboratory of Applied Pharmacokinetics I express my thankfulness for your respective contributions to the research in this thesis.

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1 INTRODUCTION

The following chapter contains background information on the motivation for the research conducted in this thesis. Particular attention is given to introducing individualised drug therapy and then explaining why it is important in healthcare.

In order to better treat the patient the stages of data collation to enable individualisation of drug therapy are explained. Following this, an explanation overviews the impact and reception of individualised drug dosing, highlighting the current level of research activity and with subsequent reasoning for this level.

1.1 Introduction to Individualised Drug Therapy

The care of a patient involves effective diagnosis and treatment; during the treatment of a condition or disease the clinician will often prescribe some form of drug therapy. This drug treatment will aim to treat the ailment directly or indirectly by relieving one or all of the symptoms that are presented by the patient.

The list of drugs in healthcare used to treat various conditions and diseases is vast with new drugs added every year. Many drugs cause adverse events which are dose dependent, consequently there is a need to identify the correct dose for each specific patient, maximising the efficacy of the drug whilst minimising their risk of experiencing an adverse drug reaction (ADR).

The identification of the optimum dose begins in an extensive multi-phase testing process for all new drugs. However, as a drug is often intended for wide spread use,
the main objective of testing is to show an acceptable level of safety and efficacy in the general population. Most dose identification will be optimal for the ‘average patient’ and this is estimated from statistical analysis of the population using summary statistics such as the mean drug response.

The recent focus towards personalised medicine has highlighted this issue in drug dosing; the administration of the dose that is appropriate for the average patient will lead to a hugely variable response over the entire population. Identifying and measuring these sources of variability leads to drug dose algorithms which personalise drug therapy for the patient. The benefits of drug dose algorithms include more optimal treatment for the patient and the potential reduction in treatment costs from minimising the occurrence of adverse events.

1.2 The Variability of Drug Response in the Population

The objective of a drug dose algorithm, to find the optimum dose, is complicated by the inter-individual variability in the response of each individual patient to a specific drug. Inter-individual variability is inherently biological due to each patient’s PK, what the body does to a drug, being unique. In a population of highly variable, in drug response, patients, patterns of variability must be identified.

Patterns that exist between individual patient PKs are often referred to as sources of inter-individual variability. A diagram showing sources of variability and the interaction between them is shown in Figure 1-1 presented originally in Jamei et al. (2009) [1]. The interplay of these various sources of variability means that each
patient has PK different from other patients; the modelling of this interplay is explained in Chapter 2 of this thesis.

Figure 1-1: Relationships of Sources of Variability Affecting the PKs of the Patient (Jamei et al., 2009).

The various relationships shown in Figure 1-1 and their effect on patient response will be more consequential for some drugs and nullified in others, for example, renal function will impact on clearance of all renally excreted drugs [2] whereas brain volume is only considered when drug molecules are small enough to enter the brain [3].

Due to inter-individual variability, prescribing a single dose of a drug for all patients does not induce efficacy in the majority of patients and can be potentially dangerous. Therefore, each drug that is to be prescribed to a patient represents a new challenge to the clinician in the determination of the optimal dosage regimen for the patient. Considering this challenge, various statistical methods have been
applied to the individualisation of a dosage regimen to aid clinicians in drug therapy decisions. Examples include linear regression methods in warfarin therapy [4], maximum a posteriori (MAP) Bayesian methods also in warfarin therapy [5] and stochastic control methods in digoxin [6].

Overall, the information for individualising a dosage regimen comes from many different sources. Identifying and measuring the variability that these sources cause in PK/PD response is important so that statistical methods can predict future PK/PD response of various patients in a population that require individualised dosage regimen to reach therapeutic targets. Often sources of variability are identified from specialised studies, such as clinical trials looking at the pharmacogenetics, the study of how genetic differences affect drug response. Gaining this information on variability from specialised studies means collaboration across disciplines is needed to incorporate the information effectively.

1.3 The Stages Involved in Individualising Drug Therapy

Intra-individual variability is the difference in patient response over time. This is due to changes in bodily processes such as drug absorption and metabolism [7]. Causes of these intra-individual changes include diet and fluctuating co-morbidity [8, 9]. Due to intra-individual variability a patient may require different amounts of drug over the course of therapy. Estimating when these changes in dosage requirements occur is another challenge to the clinician. Most current statistical methods do not consider this aspect of individualised drug therapy, for example, linear regression methods estimate an individualised dose by accounting for the average effect of covariates on patient response [10].
Often both sources of variability do not act in a linear way or act together to produce an enhanced effect on patient response to a drug. Understanding the magnitude of effect from the sources of variability is a requirement to facilitate individualise drug therapy. However, this understanding involves many different fields of medicine, which also relies upon effective collaboration. For example, to understand the effects of a patient’s genetics on drug response the expertise of a pharmacogenetic researcher is required, however, to then relay this expertise into a PK/PD model a pharmacometric researcher would be needed.

This multi-disciplinary need of the personalised medicine approach means not only that differing types of research are needed but also that there are overlaps of research and requirements of information from one discipline to another discipline in order to continue research into individualising a dosage to prescribe a patient. Due to research occurring at different stages, the personalised medicine approach incurs a natural timeline, shown in Figure 1-2. The understanding of this time line in reference to when proposed research is best conducted is crucial.
Figure 1-2: Flow Diagram of the Individualisation of Dosing.

The main focus of this thesis, the development of a drug dose algorithm, requires research into the magnitude of the variability caused by patient characteristics. Therefore the ability to estimate an individualised dose for a specific patient, currently, is only possible relatively late after a new drug is developed.

Figure 1-3 is taken from a publication highlighting the importance of genomically derived biomarkers by Meyer et al. (2002) [11]. Within the circle of Figure 1-3 there are phases of research that reveal sources of variability to individualise drug therapy. Moreover, Figure 1-3 shows research is conducted into the clinical targets for drug therapy, this research is a particular requirement to allow statistical methods to be utilised to individualise dosage regimens. For example, targeted studies confirm clinical PK/PD response targets that are used directly in algorithms as a mechanism to ‘judge’ dosage prospective dosage regimens; this will be explained further in Chapter 4.
Figure 1-3: Personalised medicine — integrating drug discovery and development through molecular medicine. Genomically derived biomarkers are being identified throughout the drug discovery and clinical development process. They will not only support personalized medicine, but will also enhance drug discovery and clinical development by generating new targets, validating targets and identifying patients that will benefit from novel therapeutics. ADMET, absorption, distribution, metabolism, elimination, toxicity [11].

The research in personalised medicine is shown in this section to be a connected network of various disciplines and areas of science. This research network seeks to improve the care of the individual patient by continual investigation of both intra- and inter-individual variability in patient response to drug therapy. This variability is then considered in statistical methodology to individualise dosage regimens that seek to bring a patient to therapeutic response.

1.4 The Types of Individualised Drug Therapy

Perceived variability in drug response can be used to indicate where individualised drug dosing will be particularly beneficial. The impact of individualised drug therapy is particularly clear in drug therapies that incur a large amount of variability in drug response, for example, individualised dosing of vancomycin has been researched previously [12]. However, the different levels of variability seen in the response to a drug often determine the type of dose individualisation methodology required.
Holford and Buclin (2012) [13] considered different levels of perceived variability of drug response and dosing methods available to create a criterion for dose individualisation. The different dosing types were population dosing (single dose for all patients), group dosing (different doses based on covariates) and target concentration intervention (doses estimated through monitoring measured drug responses) depending on the predictable and unpredictable variability seen in the drug response of the population. This thesis focuses on using stochastic control to achieve the latter type of individualised dosing.

Target concentration intervention is used alongside prediction-based learning of a patient’s drug response utilised with certain methodologies, e.g. stochastic control. The dose-exposure-response relationship is derived which allows estimation of a patient’s dosage regimen [14]. By making a prediction about the patient’s response based on the known pharmacological information the process of individualised therapy is begun before any response data is collected from the patient. This also means that if response data is collected it can be reconciled with predictions (bottom-up) with actual measurements (top-down) to reduce variability in the system [15, 16]. This is in contrast to the current process of determining dosage regimen that relies solely on detecting pattern recognition in plasma concentrations (or other PK/PD responses) measured through blood sampling. The PK/PD models required to perform the bottom-up approach will be elaborated upon in Chapter 2 of this thesis, whilst the reconciliation of the top-down measurements from a patient will be researched in Chapter 4.
Overall, when perceived variability complicates the estimation of an individualised dosage regimen stochastic control methodology has been used to guide a patient to therapeutic response. Firstly the system is individualised by predicting the response of the patient to different dosage amounts. Secondly, the vast information and research assimilated to aid the decision of individual dose is continually updated. And finally, when measurements are taken they are reconciled with the predictions made by the dose-exposure-response model to ensure variability around the patient response is reduced.

1.5 The Reception of New Research into the Individualisation of Drug Therapy

The uptake of sophisticated methods to achieve the goal of individualising drug therapy, such as stochastic control, has been limited despite their long time availability. To name but one, the Laboratory of Applied Pharmacokinetics (LAPK) has produced research based on stochastic control methods for over 20 years [17].

As highlighted in this chapter, research in this area has been limited by the need for collaboration between disciplines. The fusion of clinical expertise and statistical methodology needed for sources of variability to be correctly integrated into a drug dose algorithm is hard to attain. For large scale uptake of drug dose algorithms to occur collaborations need to be assembled internationally.

Single disciplinary approaches in the area of individualised drug therapy have led to research which is one dimensional in application. In one extreme, entirely clinically relevant research is conducted but lacks the statistical methodology to optimise therapy; a case study of this is given in Chapter 3. However, on the other hand,
methodological research is undertaken that would appropriately harness the variability in pharmacology yet applicability is not fully considered; explained more in Chapter 4.

With these issues in consideration the reasons for the lack of drug dose algorithms being used in standard clinical practice is understandable. Yet, the advancements that could be achieved with further research must not be overlooked; already benefits have been shown such as in Jelliffe et al. (2012) [6] where an explanation is provided as to how digoxin therapy has been optimised for patients since the 1980s. To improve individualised drug therapy by better estimating the patient response and incorporating more clinical opinion, further research into applying stochastic control theory to individualising dosage regimens is presented in this thesis. In Chapters 5, 6, and 7 of this thesis examples will be given that demonstrate the applied methodology of the stochastic control approach explained in Chapter 4.

Chapter 5 will concentrate on estimating dosage regimens to induce a PK target. Initial applications will explain the stochastic control approach and introduce novel methodological research presented in this thesis. The final example of chapter, section 5.3, utilises the full stochastic control methodology proposed in section 4.3. The research of section 5.3 has been presented previously at the Drug Information Association 2012 conference and the Population Approach Group Europe 2012 conference and subsequently published as abstracts [18, 19].

Chapter 6 introduces new methodology for individualised dosage regimen estimation by discrete outcome variables. Initial sections 6.2 and 6.3 focus on post-dosage regimen estimation diagnostics that show the clinician the probabilities of
therapeutic effect and an adverse event occurring. Section 6.4 explains the new methodology of incorporating a Markov model within the cost function to consider probabilities in dosage regimen estimation. The methodology is then applied to the imatinib example again to enable comparison of the dosage regimens estimated in section 6.5.

Chapter 7 details an example of stochastic control applied to a PD target. The example consists of a simulated control trial for simvastatin therapy. This is the first use of simulation in stochastic control guided drug therapy. A main intention of the research in Chapter 7 is to enable uptake of the methodology by providing evidence to suggest individualised dosing is effective.
Chapter 1 introduced the paradigm of individualising dosage regimens prescribed to the patient. The PK/PD of a patient can be represented in a mathematical model, the study of pharmacometrics. From this model the response of the patient can be predicted and estimated for different dosage regimens.

This chapter begins with a brief explanation of the science that the PK/PD model is to represent, as well as an introduction to the objective of PK/PD models in translational medicine. With this background, the pharmacometric model is laid out including an explanation of the parameters within the model. Finally, approaches used in current software packages that calculate PK/PD parameters are explored.

### 2.1 Background Science and Basis of Translational Objective

#### 2.1.1 What is Pharmacokinetics?

PK is an umbrella term for many areas of research into the mechanisms of absorption and distribution of an administered drug, the chemical changes of the substance in the body and the effects and routes of elimination of the drug from the body. Overall, PK is the study of how the body affects an administered drug. The research areas in PK are condensed into the acronym ‘LADME’ that stands for:

\[
\text{Liberation} \ 	ext{A} \ 	ext{B} \ 	ext{S} \ 	ext{D} \ 	ext{M} \ 	ext{E} \ 	ext{I} \ 	ext{L} \ 	ext{I} \ 	ext{M} \ 	ext{I} \ 	ext{N} \ 	ext{A} \ 	ext{T} 
\]

\[
\text{Liberation} \ 	ext{Absorption} \ 	ext{Distribution} \ 	ext{Metabolism} \ 	ext{Elimination}. 
\]
In each area, there can be significant intra and inter-individual variability, due to this variability, the study of PKs is crucial in the determination of the appropriate dosing of a drug to a particular patient. To appropriately mimic patient PK, mathematical models are required that include parameters representative of the PK processes in the body. PK studies are necessary to determine by how much or why parameters vary between individuals.

PK is often studied along with PD, which is the study of how the drug affects the body. Both areas provide valuable information when investigating a drug’s possible effect both on a population of patients and/or an individual patient and as a consequence can inform individual dosage regimens, with the aim of increasing efficacy and reducing the risk of adverse events.

### 2.1.2 What is Pharmacodynamics?

The study of what the drug does to the body is called PD. Examples of PD outputs include the intensity and duration of a drug’s therapeutic effect or an adverse drug reaction. The biology in PK refers to how much of a drug is at a site of effect in the body. PD studies investigate the effect that this amount of drug is generating by being at the site of effect, therefore PK is tandem to PD. PK/PD models will model the complete process from dose to drug effect (see section 2.2.5).

In some situations whilst the drug may be abundant at a site of effect the subsequent effect of the drug on the body may not be therapeutic. This means that some drugs are not dosed according to PK targets but rather according to a PD target. For instance in the case of the anticoagulant drug warfarin [20], a PK
dependent variable (plasma concentration or clearance) of the drug in the body is not indicative of therapeutic effect [21], and thus warfarins PD response, measured in terms of the International Normalised Ratio (INR), is referred to instead to indicate a therapeutic effect.

### 2.1.3 The Use of Mathematical Models in Pharmacokinetics and Pharmacodynamics

The application of mathematical modelling to PK/PD, called pharmacometrics, allows models to be constructed to derive an estimate for PK/PD responses over a continuous time frame, such as the concentration of a drug in the plasma of the blood after an IV infusion. Pharmacometrics uses statistical techniques to estimate parameter values. The relationship between these parameters, the model, describes the time profile of a PK/PD response. The PK/PD model facilitates the ability to compare, evaluate and predict future PK/PD response.

Pharmacometrics is best applied assuming a stochastic framework. This implies that the parameters are random in the sense that their values cannot be expressed as a single value such as in deterministic models. Parameters in stochastic models are presented as a distribution which is a statistical technique for describing the range of values that are permissible for the parameter. The values in this range will have probabilities attached to them meaning that the higher the probability the more likely that the parameter will be that value at any time point. If it was possible to measure the value of a parameter from a stochastic model repeatedly and plot a histogram of the measurements, the histogram would resemble the probability distribution of the parameter.
To construct a combined PK/PD model the relationship between the concentration of drug in the body/plasma (the PK measurement) and the magnitude of the drug effect (the PD measurement) must be established. This link between the PK and PD varies in mathematical complexity, as will be explained in section 2.2.

### 2.1.4 Data in Pharmacokinetics

PK data is variable in quantity; datasets can be sparsely or densely sampled. Densely sampled data tends to be difficult to obtain, this is due to the processes needed to measure the PK response. Sampling is normally done by taking blood through IV bolus or cannula and due to the invasive nature patients are often reluctant to consent to frequent sampling, hence sparse sampling is often undertaken. However, with fewer samples from a single patient often intra-individual patient variability is hard to quantify and this impacts on the certainty of subsequent parameter estimates of patient PK/PD.

Sparse sampling is often used when data is required from specialist populations leading to paediatric, elderly and at risk patients being included as the amount of blood required over a dose interval is significantly reduced. For these reasons it has become more common to develop models using sparse data and PK/PD analyses are often conducted on as little as one sample per patient. Analytical techniques will be explained in section 2.3 with a discussion of the strands of the modelling methodologies and their respective strengths and weaknesses. However the focus of this following section is on how to model a patient PK/PD.
2.2 Formulating the Pharmacometric Model

2.2.1 Modelling Methodologies

When applying statistics to biological systems there is need to make assumptions to allow the construction of mathematical models that appropriately represent collected data. The assumptions are necessary because statistical models are more simplistic than biological systems that exist in our bodies [1]. However, although these models are more simplistic, the discrepancy between statistical models and actual biological systems need not be an issue when assumptions are properly handled.

For the construction of the models there are a number of mathematical techniques used to model PK/PD processes including, in order of diminishing complexity, physiology based, compartmental and non-compartmental models.

Predominantly physiology based modelling has only been used in PK application, physiologically-based PK (PBPK). For this modelling technique, anatomical and chemical pathways in the body are both considered individually in the model. For example, the anatomical pathway of blood flow between the spleen and portal vein [1].

This is in contrast to compartmental modelling where several PK processes are simplified, such as the gut being represented as a single compartment. This approach is the most commonly utilised due to the wealth of methodology accumulated from its long term use in PK/PD modelling.
Thirdly, non-compartmental models consider the concentration profile of a patient without time. Using this approach the concentration is not constrained to follow assumptions that are made in compartmental modelling.

The pharmacometrician must be aware of the trade-off between simplified and complex modelling. Simplified modelling will bring benefits such as easier comprehension, less computational requirements and reduced mathematical complexity whereas more complex modelling may lead to greater accuracy in predicting a PK process [1, 22].

To allow the methodology to be explained thoroughly, in this thesis, compartmental modelling will be utilised. Compartmental modelling is preferable as it has been the standard modelling technique in pharmacometrics for over forty years [23]. Further, compartmental modelling involves significantly less mathematical formulae than PBPK modelling; this allows for more complex control methods, explained later in the thesis. With concentration-time sensitive responses being considered this thesis, such as an adverse event caused by a drug concentration above a certain value in time, non-compartmental modelling would not be appropriate as time is not considered in these models.

### 2.2.2 Compartmental Modelling

In a crude sense, compartmental modelling reduces the PK/PD system of the body to the drug moving between ‘boxes’. Consider a box that is wholly sealed apart from flows of a liquid into and/or out of the box. A system of differently sized boxes and variable flow speeds into and/or out of the boxes can be used to cause the
liquid to flow differently. This system of boxes provides a crude parallel with the body’s PK/PD system as a drug moves across tissue membranes within the body.

Each box represents a different aspect of the body’s pharmacology; an area commonly represented in PK applications is the central plasma compartment where the concentration of the drug in the plasma of blood (the ‘plasma concentration’) at the site of drug action is considered.

The flow rates between boxes describe the drug concentration being distributed around the body or excreted out of the body. The flow rate can be as simple as a unit amount of drug per hour up to more complex systems like those described by Michaelis-Menten kinetics [24]. More boxes and complex absorption rates lead to more PK/PD parameters to estimate, shown in section 2.2.4.

Compartmental modelling seeks to describe the PK/PDs of the body in a more simplistic way to the actual bodily processes. Due to this, PK/PD data from different studies of the same drug may be modelled differently; in two publications regarding the PK of warfarin by Hamberg et al. (2007 & 2010) [21, 25] two different models were used. This difference in models can occur due to a number of factors including different sampling frequencies in the data, assay errors of measurements and the different inter-individual variabilities seen in the two derivation cohorts.

The PD of a drug in compartmental modelling is described by compartments in tandem from the central plasma compartment of the PK model. This can range from a simple extra compartment attached to the PK model through to complex
multi-chain compartments designed to model various phases of drug effect. PD models will be discussed further in section 2.2.5.

### 2.2.3 Commonly-used PK Parameters

Although compartmental modelling is a simplification of the biological processes seen in the body, the parameters used in modelling can still be interpreted physiologically. This is important as patient characteristics can be drawn from specific parameter values, for example, lower than normal parameter values for a patient’s elimination of a drug could indicate deteriorating condition. Parameter values can be calculated for either a population (population mean) or an individual patient (patient-specific mean) along with their respective variances.

The PK parameters for absorption can range from a single constant to more complex absorption rates involving several parameters. For oral dosing, the standard modelling technique is to use an absorption compartment which acts to gradually release the drug into the blood, this mimics the gastrointestinal tract [26]. Whereas with intravenous infusion the release is considered instantaneous as the drug immediately enters the blood stream [27]. In the simple case for oral dosing the PK parameter, the rate constant of absorption, denoted $k_a$ is used. The rate constant of absorption describes the rate the drug enters the apparent site of interest, e.g. plasma concentration of a drug in the plasma of the blood.

To model the distribution of the drug around the body the parameter, volume of distribution denoted $V_d$ is used. Similar to absorption, the number of parameters used to model the distribution of the drug in the body will be from one upwards
depending on the complexity of the distribution model. The parameter is theoretical in the sense that the volume of distribution is the amount of volume that the drug would have to equilibrate over in order to derive similar concentrations of drug in the plasma. Whilst the name suggests a quantity of space, the parameter considers elements such as solubility and size of the drug molecules. Drugs that have a larger molecule size will have a smaller volume of distribution to the drugs with smaller molecule size due to distribution across different tissue membranes [28]. The drug in the blood is assumed to instantaneously mix over the entire volume of a compartment, for example, it would be assumed that blood samples from two different areas of a compartment would contain the same concentration of the drug.

Elimination is the rate the drug is excreted from the body over time. In the simplest case, three parameters contribute to this phase of PK, the volume of distribution, $V_d$, the clearance denoted $Cl$, and the constant of elimination denoted $k_e$. The clearance is the amount of blood that has drug extracted from it over time. These elimination parameters are proportional through the volume of distribution with a linear relationship described as such,

$$k_e = \frac{Cl}{V_d}$$  \hspace{1cm} 2.1

These parameters are used in models to construct a relationship that derives the concentration, $C_t$, of a drug in a compartment or compartments. The different ways they can be used to model various drugs will now be investigated.
2.2.4 Commonly-used Compartmental Models

Different drugs will have different systems of PK parameters as the body processes the drugs in different ways. PK/PD models can parallel bodily processes sufficiently to generate acceptable predictions that coincide with measurements taken from a patient, such as, plasma concentrations of a drug measured from blood samples. The predictive power of a model is determined by how close estimations are to measurements.

Pathways of administration are drug formulation specific. Different pathways of administration include constant intravascular (IV) infusion over a certain duration of time, IV bolus and oral dosing. Each pathway of administration needs to be treated differently when modelling. With IV routes of administration it is assumed that the drug is instantaneously absorbed into systemic circulation [29]; whereas with oral dosing the absorption process is not instantaneous and so there is a need to calculate the appropriate absorption PK parameters.

Figure 2-1 describes the effect that different routes of administration have on the plasma concentration of a drug in the central plasma compartment of the body. All three graphs in the diagram are generated from a model where the administered drug enters a single compartment which then has only one outflow (representing the excretion of the drug).
Figure 2-1: Concentration-Time Plots for Different Routes of Drug Administration in a One Compartment PK Model.

The biggest difference in the curves comes from the oral dosing route of administration. The curve generated arcs up and then down compared to the instantaneous decline of plasma concentration after administrations of IV infusion
and IV bolus doses. This is due to the drug being gradually released into the central plasma compartment through gradual absorption. To model this gradual absorption an extra compartment is needed; in this extra compartment the oral dose instantaneously appears and is released at the desired rate into the central plasma compartment. With IV infusion and IV bolus routes it is assumed that the drug instantaneously enters the central compartment thus the concentration curves are declining once the drug enters the compartment.

The three curves in Figure 2-1 are derived from a one compartment PK model. A one compartment model assumes that the entire area of distribution in the body is one rapidly mixed compartment where the drug flows around constantly and is not subject to different rates of flow. This model is applied to various drugs [30, 31].

![Figure 2-2: Graphical Representation of the One Compartment Model.](image)

The one compartment PK models for IV infusion (equation 2.2), IV bolus (equation 2.3) and oral dose (equation 2.4) are parameterised as

\[
C_t = \frac{IV_{dur}}{k_e V_d} (1 - e^{-k_e t})
\]  

2.2
\[ C_t = \frac{IVb_0}{V_d}.(e^{-k_et}) \]  \hspace{1cm} (2.3)

\[ C_t = \frac{u_0k_d}{(k_e - k_a).V_d}.(e^{-k_et} - e^{-k_at}) \]  \hspace{1cm} (2.4)

where \( IV_{dur} \) is the infusion rate given during the time interval \((0, dur)\), \( IVb_t \) is an IV bolus dose given at time \( t \), \( u_t \) is an oral dose given at time \( t \).

Some drugs, such as vancomycin [32], are better modelled with a two compartment PK model. The concentration time curve will display a two stage elimination when the drug has to travel through different mediums of tissue in the body leading to some of the drug being distributed quickly and the remainder distributing more slowly [33]. To model the different phases of elimination, an extra compartment is added to the model, the ‘peripheral compartment’ which has two pathways one in and one out of the central compartment.

Figure 2-3 describes the plasma concentration time curves derived from three different routes of administration and the two compartment PK model. The axis ranges are the same as in Figure 2-1 to allow comparison of the concentration values over time. The two stage elimination can be seen in these concentration time plots.
Figure 2-3: Concentration-Time Plots for Different Routes of Drug Administration in a Two Compartment PK Model.
The two compartment PK models for IV infusion (equation 2.5), IV bolus (equation 2.6) and oral dose (equation 2.7) are described mathematically as:

\[ C_t = \frac{IV_t}{V_1(\alpha - \beta)} \left( \frac{\beta - k_{21}}{\beta} \right) \cdot (1 - e^{\beta t}) e^{-\beta t} \]

\[ + \left( \frac{k_{21} - \alpha}{\alpha} \right) \cdot (1 - e^{\alpha t}) e^{-\alpha t} \] \hspace{1cm} 2.5

\[ C_t = \frac{IV b_0}{V_1(\alpha - \beta)} \left( (\alpha - k_{21}) e^{-\alpha t} + (k_{21} - \beta) e^{-\beta t} \right) \] \hspace{1cm} 2.6
\[ C_t = \frac{u_0 \cdot k_a}{V_1} \left( \frac{(k_{21} - k_a)}{(\alpha - k_a)(\beta - k_a)} e^{-k_a t} \right. \]
\[ \left. + \frac{(k_{21} - \alpha)}{(k_a - \alpha)(\beta - \alpha)} e^{-\alpha t} \right. \]
\[ \left. + \frac{(k_{21} - \beta)}{(k_a - \beta)(\alpha - \beta)} e^{-\beta t} \right) \]

where \( \alpha, \beta = \frac{1}{2} \left( k_{12} + k_{21} + k_e \right) \pm \sqrt{\left( k_{12} + k_{21} + k_e \right)^2 - 4 \cdot k_{21} \cdot k_e} \) formulated in Metzler et al. (1971) [34] includes parameters \( k_{12} \) and \( k_{21} \) that represent the flow rates into and out of the central plasma compartment, \( C_t \).

Models can be extended to more than the one and two compartmental models discussed above by adding compartments to describe different PK processes until the model represents the complete physiology of the patient; this is the methodology of PBPK modelling [1]. With PBPK intricate and precise processes will be mathematically described leading to individual pathways and organs being described with their own flow rates and compartments.

### 2.2.5 Pharmacodynamic Modelling

Modelling pharmacodynamics (PD) means deriving the relationship between drug concentration and drug response. As shown in the previous sections, modelling PK allows patient absorption, distribution, metabolism and excretion to be investigated. The subsequent relationship between these concentrations and the response to the drug can also be modelled leading to a PD model. A model that has both PK and PD aspects has the acronym PK/PD model.
The process of linking the PK of a drug to the PD in modelling begins by interpreting the concentration of the drug in the central compartment as a magnitude of effect that then occurs as a consequence. For instance, a model for warfarin would link the concentration in the plasma to the consequential anticoagulation effect of the drug. Often, there is a delay in a patient experiencing a therapeutic drug effect after a target drug exposure is attained [35]; this delay is modelled by adding one or more compartments to the PK model. The Hill equation is one of several models used to interpret the concentration of the drug in the central compartment as a value of drug effect [36].

\[ EFF_t = E_{base} + \frac{C_t \cdot E_{\max}}{C_t + EC_{50}} \]  

where \( EFF_t \) is the effect of a drug at time \( t \). \( E_{base} \) is the baseline effect on the body in absence of the drug, for example an INR value of 1 before warfarin is prescribed [21]. If there is no baseline effect level in the body in the absence of a drug then \( E_{base} \) is equal to zero, this occurs in drugs that cause effects that naturally the body wouldn’t exhibit, for example, muscle relaxation and altered central nervous system function [37, 38]. The maximal effect that the drug can cause to the body is described by the parameter \( E_{\max} \). The parameter \( EC_{50} \) is the concentration that is required to produce 50% of the maximal effect of the drug.
The effect of the drug at time $t$, $EFF_t$, is the amount in the effect compartment connected to the central compartment. Figure 2-5 graphically describes a two compartment PK model with an effect compartment. The additional mathematical

\[
\frac{dEFF_t}{dt} = k_{1e} \left( E_{base} + \frac{C_t \cdot E_{max}}{C_t + E_{C50}} \right) - k_{e0} EFF_t \quad 2.9
\]
equation to describe the effect compartment is given in equation 2.9. To describe the entire model in Figure 2-5 mathematically equations 2.6, 2.7 and 2.9 are used.

The PD model described in this section can be used to describe various drug effects. For example, later in this thesis, the PD effects of imatinib and simvastatin will be considered with the above model. Imatinib is a drug used to treat leukaemia by encouraging cytogenetic and molecular effects in the body [39], whilst simvastatin is dosed to reduce a patient’s cholesterol levels in a desired target [40].

### 2.3 Software Packages for Pharmacometric Analysis

As shown in section 2.2, PK/PD model consist of parameters that describe internal processes, e.g. the absorption of a drug from the gut. Due to the multiple parameters involved in PK/PD model particular software is required to analyse data. PK/PD data is analysed to estimate values of parameters however different methods and assumptions are used by software packages. One particular difference in methodology regarding the estimation of individual parameters is important due to the derived distributions. The different methodologies parametric and non-parametric are discussed briefly in the next two sections.

### 2.3.1 Parametric Approach Software

The main software package associated with parametric modelling is ‘NONMEM’ which is an acronym for non-linear mixed effects modelling. NONMEM was developed at the University of California at San Francisco by Lewis Sheiner and Stuart Beal [41].
The NONMEM software is a program that performs regression analysis and in particular is able to perform non-linear regression. As parameters within PK/PD models are random variables, distributions of these random variables require particular estimation methods. The parameter estimation methods included in NONMEM, such as conditional likelihood and Laplace transforms, mean parametric distributions can be calculated for parameters.

NONMEM includes fixed effects in models as population values of parameters then random effects represent the between subject variability. Both of these values are assumed to be represented by a parametric distribution. The combination of these two effects into a mixed-effect model allows individual parameter distributions for each patient. For example an individual’s clearance is expressed as

\[
Cl = \theta_{Cl} \cdot e^{\tilde{\eta}}
\]

where \(\theta_{Cl}\) is the typical (population) value, \(\tilde{\eta}\) is a random effect quantity for an individual. This relationship leads to a \(\theta\) being a log-normally distributed individual parameter distribution which is appropriate as pharmacometric parameters tend to follow this behaviour [42] and a property of the distribution is restriction to non-negative values. This is important as PK parameters are assumed non-negative biological values.

2.3.2 Non-Parametric Approach Software

An example of non-parametric modelling software is Pmetrics [43]. Importantly, it should be noted recent iterations of NONMEM and Pmetrics [41, 43] allow both to
perform parametric and non-parametric analysis however both packages retain their respective main approaches of parametric and non-parametric analysis.

With a non-parametric approach, the models for a patient’s PK/PD remain however the parameters in the models are not assumed to follow a distribution such as log-normal. The basic intention is to allow the data to determine the shape of the distribution. As the distribution is purely determined from empirical data and not altered by a parametric assumption the statistical property of consistency is assured. As more data is collected the distribution of the parameters will approach the true distribution of the parameters.

The strength of this non-parametric approach is that outliers and sub-populations are more likely to be included in the parameter distributions. For example, in the parametric approach slow- and ultra-metabolisers of a drug might only be included in the tails of distributions meaning they are ‘highly unlikely’ patients however a non-parametric approach will be more sensitive to these sub-populations and appropriate probabilities will be attached to the sub-populations. Figure 2-6 presents a graph from the Neely et al. (2012) showing a comparison between a non-parametric approach and a parametric approach. In the graph two parameters volume of distribution, \( V_d \), and constant of elimination, \( Kel \) (denoted in this thesis by \( k_e \)) have been estimated.
Figure 2-6: The Comparison of Non-Parametric and Parametric Analyses (Neely et al. (2012)).

“A, Results of the NPAG fit. True parameter values from the simulated population are shown as black squares, with NPAG support points shown as circles whose size is an approximate multiple of the size of 1 square, proportionally increased according to the probability of each NPAG point.

B, Results of the IT2B fit. True parameter values are shown as white squares. Note the outlier in the upper right corner. The bivariate normal parameter distribution estimated by IT2B is depicted as ellipses of fading colour corresponding to the percentile of the distribution. The white cross at the centre is the mean.”

In the top right of A and B in Figure 2-6 there is an outlying set of parameters, it is clear that whilst the non-parametric analysis (A) attributes probability to this point, the parametric approach (B) does not do so. Secondly, the parametric approach used in B, has the ability to define a bimodal distribution. A bimodal distribution would potentially be more appropriate for this data but analysis does not conclude a bi-modal distribution, rather the two ‘strands’ of parameter sets are combined into a unimodal distribution in B.

The grey circles in Figure 2-6 A represent support points and their respective probabilities based on the size of the circle. In a population sense, each grey circle is a set of parameters with their prevalence observed in the current data expressed as a probability. Currently in Pmetrics individual posterior distributions are formed by reweighting the support points based on subsequent individual data. If data is similar to that already in the population model then this distribution will be entirely
appropriate however when data from a new patient indicates a parameter set that is in between support points the posterior is less precise. The impact of this approach to deriving individual parameter estimate will be discussed in section 4.3.
Drug dose algorithms are effective when they capture a high amount of inter-individual variability in the population. However, often a large amount of data is needed to identify sources of variability but the required data can be hard to obtain.

In view of this challenge, a large amount of research has been conducted that does not require invasive data such as plasma concentrations. In this chapter, methodology outside the main focus of this thesis, stochastic control methods, is presented. A commonly utilised method, the linear regression algorithm, is presented as a worked case study in warfarin. In comparison to other methods the application of a linear regression algorithm requires reduced computational demand and data which is easier to obtain, such as the demographic factor, age.

In light of these positive aspects and the popularity of linear regression algorithms, the purpose of this chapter is to clarify the limitations of such an approach when pharmacometric models are not utilised and discern requirements for a drug dose algorithm to be fully effective.
3.1 A Review of A Priori Regression Models for Warfarin Maintenance Dose Prediction

3.1.1 Introduction

Warfarin is the most commonly used anticoagulant in the UK, with an estimated 1% of the population currently undergoing warfarin therapy [44]. The aim of warfarin therapy is to bring INR, a measure of the patient’s clotting capability, within a therapeutic range, and to maintain it within that range. Although warfarin is an effective anticoagulant, determining the dose required to achieve a stable therapeutic INR (the ‘stable maintenance dose’) is difficult due to the large inter-individual variability in maintenance dose requirements, and warfarin’s narrow therapeutic index.

The therapeutic INR range is typically 2 to 3 for warfarin patients, and outside this range adverse events are more likely to occur [45]. If the concentration of warfarin in the body is too low then the drug will not provide desired therapeutic effects, leading to a risk of thrombosis. Conversely, if the amount of warfarin in the body is too high there is an increased risk of the most critical adverse event associated with warfarin therapy, severe haemorrhage [44]. In a recent large study of reasons for hospital admissions in the Merseyside, England, warfarin was shown to be the third highest cause of an ADR, being responsible for just over 10% of all hospital admissions for adverse drug reactions [46].

Due to the difficulties in determining the required stable maintenance dose for a given patient, several different regression models for dose prediction have been proposed worldwide. These models vary in terms of the predictive factors they
include, with some including only patient demographics such as age, weight, height and co-morbidities, others including details of initial INR measurements and loading doses and others including details of co-medication with drugs known to alter the effect of warfarin. Models comprising only demographic, loading dose or co-medication details use information that is readily available to the clinician and a few recent studies have derived such algorithms [47, 48].

More recently, to explain more variability in individual maintenance dose requirements, dosing algorithms have also included genetic factors [4, 49-52], in particular variants in the VKORC1 and CYP2C9 genes. These genes have been identified in pharmacogenetic studies to be consequential in dosing requirements due to their effects on PK/PD [53]. However, the benefit of including genetic information in dose prediction remains to be shown in practice [54, 55] despite the science being conclusive that a patient’s genetics alter their warfarin dose requirements [44, 53].

When developing dose prediction regression models, the outcome of interest is stable maintenance dose; therefore it is necessary to identify, for each patient included in the dataset used to derive the model (the ‘derivation dataset’), the dose at which stable, in-range INR has been achieved. However, since INR is sensitive to many factors, including dietary changes [56] and alcohol intake [51], measurements often fluctuate out of range even after an initial period of stability has been achieved.

Figure 3-1 shows three different patients all receiving standard care and, in all but one patient, INR measurements do not continuously stay within therapeutic range
(INR 2-3). Thus, defining what constitutes a patient’s stable maintenance dose is difficult and importantly this dose may change over time.

Figure 3-1: INR-Time profiles of three patients receiving standard warfarin therapy.
The top graph for patient 1 demonstrates an example of a patient with highly fluctuating INR level. At some points the dosage amount of 6mg appears to induce an in-range INR value however at other times it is not sufficient for efficacious effect. For patients such as this constant monitoring and appropriate dosage regimen adjustment is recommended to ensure maximal warfarin therapy. Unfortunately, linear regression methods are non-adaptive to patient response and such dosage adjustment is only possible if particular covariates are included. For example, if an INR measurement on a certain day after therapy initiation was included as a covariate.

The middle graph shows patient 4 on a constant dose who remains within the therapeutic range for the duration of the study. With a drug such as warfarin this is a rare occurrence; however the patient’s INR curve does move very close to the minimum and maximum target INR values on two occasions. These small divergences could be due to demographic changes such as weight fluctuations, dietary factors or co-medications that cause only slight effects on the efficacy of warfarin. Linear regression methodology does not permit effective modelling of small divergences as parameters are assumed constant.

In the bottom diagram patient 26 through a combination of frequent dose modification and apparent warfarin resistance did not achieve steady state dosing. The INR curve appears to be less subject to high fluctuations despite the frequent dose changes. Assuming full compliance, the patient appears to have an underlying resistance to warfarin.
Patient 26 is a clear example of variability that maintenance dosing algorithms do not incorporate as the patient has not been induced to a constant in-range INR level. Linear regression methods use a process of patient selection through steady state criteria to build a dataset for dose algorithm derivation. This process could be seen as a ‘cherry picking’ process where patients whose dosage regimen does not cause a constant in-range INR, potentially entire outlying populations of patients, are excluded from the dataset. These outlier patients are exactly those who require accurate dosage regimen estimation the most.

Despite the number of published dose prediction regression models, they have rarely been integrated into standard clinical practice [54]. This, in part, is due to the fact that most of these algorithms have not been externally validated in an independent dataset and if they have then replication has been poor [10, 57, 58]. With a view to assessing how well previously published models predicted dose in a dataset outside the derivation dataset, their predictive ability was tested in an independent patient cohort. This also allowed the performance of the models to be compared against each other. Further, it allowed the evaluation of how suitable linear regression, the most commonly utilized method for deriving warfarin dosing algorithms, is to estimate maintenance dosing; particularly in light of the fact that the stable dose for a patient can change with time.

### 3.1.2 Methods

Patients included in the validation cohort were a subset of those previously included in a prospective study of warfarin pharmacogenetics (the ‘Liverpool study’) [20]. Patients were recruited from the Royal Liverpool and Broadgreen
University Hospitals Trust and University Hospital Aintree between November 2004 and March 2006. Patients were required to be initiating warfarin therapy and able to provide informed consent to participate in the study. Since the study was of an observational nature, patients received customary clinical care and dosing was in line with standard protocol within the recruiting hospitals. At the patient’s index visit demographics and baseline INR were recorded, and a blood sample was taken for genotyping. Three further fixed study visits were scheduled for 1, 8 and 26 weeks after initiation onto warfarin. All INR values measured and dose changes made during the follow-up period were recorded. Three patients fitted with mechanical prosthetic heart values, who therefore had a recommended INR range of 3-4, were excluded from the current study, leaving a total of 997 patients. Full information on the procedure for the genotyping of patients is presented in the original paper on the Liverpool study [20]. A summary of patient demographics, clinical information and pharmacogenetics is given in Table 3-1.
Table 3-1: Demographic, Clinical and Pharmacogenetic Information of Patients in the Validation Cohort.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>508</td>
</tr>
<tr>
<td>Age</td>
<td>Mean 68 (SD 13)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male: 280 (55%) Female: 228 (45%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82 (SD 19)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169 (SD 11)</td>
</tr>
<tr>
<td>Therapeutic dose (mg)</td>
<td>4.19 (SD 2.05)</td>
</tr>
<tr>
<td>On Amiodarone Co-medication</td>
<td>Yes- 46 (9%) No- 462 (91%)</td>
</tr>
<tr>
<td>CYP 2C9</td>
<td>\</td>
</tr>
<tr>
<td></td>
<td>*1 313</td>
</tr>
<tr>
<td></td>
<td>*2 98</td>
</tr>
<tr>
<td></td>
<td>*3 43</td>
</tr>
<tr>
<td>VKORC1</td>
<td>GG 206</td>
</tr>
<tr>
<td></td>
<td>GA 224</td>
</tr>
<tr>
<td></td>
<td>AA 77</td>
</tr>
</tbody>
</table>

SD: Standard Deviation

In the Liverpool study, a stable maintenance dose was defined as the daily dose required to achieve three consecutive INR measurements within the individual’s target range (2-3 unless patient required a different therapeutic range). A stable maintenance dose was identified on the assumption that patients fully complied with their dosing regimens and that the only reason for dose modification was recorded clinical practice. After applying this definition of stable maintenance dose, of the initial 997 patients, 508 patients were found to have achieved stability during follow-up and they formed the subset of patients included in the ‘validation cohort’.

The intention was to obtain a set of dose prediction regression models that were relatively recent, sufficiently diverse from each other, applicable to our validation cohort and had high performance in their original derivation dataset. Models were
not considered from publications over ten years old which meant that the majority incorporated pharmacogenetic information [53]. Variables included in the models included a unique combination of any of the following types demographic, clinical, pharmacogenetic, and dose response and co-morbidity information. Applicability to the validation cohort was mandatory; this meant models selected would need to consist of covariates measured in the Liverpool study. The models’ initial performance in the derivation dataset was also highly important, on the basis that algorithms tend to predict less of the variability in validation datasets [10, 58]. The search for dose regression models was conducted on the 20th of December 2011.

3.1.2.1 Statistical analysis

To determine the ability of the regression models to explain variability in dose requirements in the validation cohort the warfarin dose predicted by the regression model was plotted against the actual warfarin dose and then a linear regression line fitted. The accuracy of the algorithms was judged using the R-squared statistic (unadjusted and adjusted), mean absolute error (MAE), mean percentage absolute error, and the slope and intercept of the regression line.

The R-squared statistic is a measure of the amount of variability explained in a dataset. However, the R-squared statistic is not affected by a constant error in dose prediction; for example, if an algorithm in this study was altered by adding 100mg to each dose prediction, the R-squared statistic would remain the same even though the dose predictions would now be severely over estimated.
The mean absolute error (MAE) statistic measures how close the predictions are to the actual values across all patients in a dataset, and therefore is important when considering which model has the best predictive capability. However, the clinically desired value of this statistic varies. For example, in an opinion publication Kimmel [59] recommended a MAE of 1mg/day because ‘a change in warfarin dose from a baseline of 5mg is sufficient to change the INR by 0.5’.

The slope and intercept of the R-squared line are also measures of a model’s accuracy, a slope of one and an intercept of zero indicate that there is no proportional or constant error respectively. If the slope coefficient is different from one there will be either over or under prediction in some, if not all estimated doses. The intercept term gives an insight into how well the model is predicting at low doses. These statistics should all be used together to appropriately judge a model as each statistic can appropriately assess a different aspect of the model’s predictive ability.

3.1.3 Results

The selection process (the four questions given in section 3.1.2) found six dosing models which meet the criteria specified in the Methods section of this manuscript, these are detailed in Table 3-2.
Table 3-2: List of dose prediction models [4, 47-50, 60].

<table>
<thead>
<tr>
<th>Paper</th>
<th>Dosing Equation</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le Gal et al.</td>
<td>ln(Dose) = 2.5 + 0.1*(Total first week dose) – INR at day 8 + 1.5*(INR at day 5 &lt; 2.0)</td>
<td>2009</td>
<td>Y</td>
<td>Y</td>
<td>0.88</td>
</tr>
<tr>
<td>Solomon et al.</td>
<td>Dose = 3.26 – 0.31*(amiodarone) – 0.032*(age) + 0.28*(Loading Dose/end of load INR)</td>
<td>2004</td>
<td>Y</td>
<td>Y</td>
<td>0.80</td>
</tr>
<tr>
<td>Anderson et al.</td>
<td>Weekly Dose = 1.64 + exp[3.984 – 0.197*(1<em>2) – 0.360</em>(1<em>3) – 0.947</em>(2<em>3) – 0.265</em>(2<em>2) – 1.892</em>(3<em>3) – 0.304</em>(VKORC1 CT) – 0.569*(VKORC1 TT) – 0.009*(age) + 0.094*(gender) + 0.003*(weight)] (25% dose reduction for those on amiodarone)</td>
<td>2007</td>
<td>Y</td>
<td>Y</td>
<td>U*</td>
</tr>
<tr>
<td>Wadelius et al.</td>
<td>(\sqrt{\text{Weekly Dose}} = 9.46832 – 0.90112*(\text{VKORC1 AG}) – 2.01863*(\text{VKORC1 AA}) – 0.50836*(\text{CYP2C9 <em>1</em>2}) – 0.97546*(\text{CYP2C9 <em>1</em>3}) – 1.10204*(\text{CYP2C9 <em>2</em>2}) – 1.74761*(\text{CYP2C9 <em>2</em>3}) – 3.40061*(\text{CYP2C9 <em>3</em>3}) – 0.036868*(\text{age}) – 0.27698*(\text{female}) – 0.06992*(\text{# of drugs which increase INR}))</td>
<td>2008</td>
<td>Y</td>
<td>Y</td>
<td>0.59</td>
</tr>
<tr>
<td>Sconce et al.</td>
<td>(\sqrt{\text{Dose}} = 0.628 – 0.0135*(\text{age}) – 0.240*(\text{CYP<em>2}) – 0.370</em>(\text{CYP<em>3}) – 0.241</em>(\text{VKOR}) + 0.0162*(\text{height}))</td>
<td>2005</td>
<td>Y</td>
<td>Y</td>
<td>0.54</td>
</tr>
<tr>
<td>Zhu et al.</td>
<td>ln(Dose) = 1.35 – 0.008*(\text{age}) + 0.116*(\text{gender}) + 0.004*(\text{weight}) – 0.376*(\text{VKORC1-AA}) – 0.318*(\text{2C9_3}) + 0.271*(\text{VKORC1-GG}) – 0.307*(\text{2C9_2}))</td>
<td>2007</td>
<td>N</td>
<td>Y</td>
<td>0.61</td>
</tr>
</tbody>
</table>

1. Was the paper published after 2002?
2. Does the model contain more than two different covariates than another dose prediction regression model already selected? (Although, where relevant novelty existed similar dose prediction regression models were compared and this novelty explained.)
3. Does the model include only covariates measured in the Liverpool study?
4. As R-squared is the most frequently reported statistic to judge model performance in the reviewed papers, is the value of this statistic above 0.5?

*R-squared statistic from derivation dataset not reported.

#Reason for inclusion explained in manuscript.

The model presented by Le Gal et al [48] includes only clinical covariates, including INR measurements on day 5 and day 8 and the total dose of warfarin taken during the first week. The second model, proposed by Solomon et al [47] includes...
information on total loading dose, INR at the end of the loading phase, age and the use of the co-medication amiodarone. The drug amiodarone inhibits the clearance of warfarin meaning that patients taking it should be prescribed a reduced dose of warfarin. These two models do not include any information on genotypes and, as a consequence, may have an advantage in that they are based on data readily available to the clinician, so can be used without having to attain a patient’s genotype information.

Four of the included models include genotypes for variants in CYP2C9 and VKORC1. The models proposed by Anderson et al. (2007) [4] and Wadelius et al. (2009) [60] assume that CYP2C9 alleles are non-proportional, thus including a separate covariate for each possible genotype, whereas the models proposed by Sconce and Zhu assume an additive effect of the variant allele.

The models proposed by Anderson et al. (2007) [4] and Wadelius et al. (2009) [60] calculate a total weekly dose of warfarin; consequently clinicians would have to divide the recommended weekly dose into seven daily doses as they consider appropriate.

Anderson et al.’s (2007) model [4] includes demographic, genotype, and co-medication covariates. The model was applied in the randomized control trial and information on the model’s R-squared in the derivation cohort is not supplied. However, the performance of a model used in a randomized control trial is of interest in this study. The model from Wadelius et al. (2009) [60], contains the largest number of covariates incorporating demographic, genotype and co-medication information.
The model proposed by Sconce et al. (2004) [47] included fewer covariates than most of the other pharmacogenetic models, with demographic information only on age and height being included along with information on the genotypes. Similar in composition, but including weight instead of height, the model derived by Zhu et al. (2007) [49] has already been externally validated once in the recent study by Linder et al. (2009) [58], and was found to explain slightly less variability in the validation dataset than in the derivation dataset. The reason for the inclusion of two similar dosing equations was to assess whether the model developed by Sconce et al. (2005) [50] derived at the University of Newcastle, United Kingdom has an advantage over models derived in other countries in explaining variability in the Liverpool-based validation cohort. Similarities could be evident in, for example, demographics and the ethnical constitutions of the two cohorts. The strength of these two models in particular was that they contain a small number of covariates yet explain a large amount of variability in their respective derivation datasets.

### 3.1.3.1 Dose Prediction Model Performance

Predicted versus actual stable maintenance dose for each validated model are shown in Figure 3-2 and Figure 3-3. Further summary statistics are presented in Table 3-3 and provide a deeper insight into the ability of the models to correctly estimate the required maintenance dose.
Figure 3-2: Graphs of clinically guided predicted dose and actual warfarin dose.

Figure 3-3: Graphs of pharmacogenetics guided predicted dose and actual warfarin dose.
Table 3-3: Table showing summary statistics about the performance of the six dose prediction models.

<table>
<thead>
<tr>
<th>Model</th>
<th>Absolute Error</th>
<th>R-squared (%)</th>
<th>Intercept</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Error) Mean ± SD</td>
<td>(Percentage) Mean ± SD</td>
<td>Coefficient of Determination</td>
<td>Adjusted</td>
</tr>
<tr>
<td>Solomon</td>
<td>1.21 ± 1.23</td>
<td>36.3 ± 60.0</td>
<td>34.9</td>
<td>34.0</td>
</tr>
<tr>
<td>Le Gal</td>
<td>1.20 ± 1.31</td>
<td>39.3 ± 73.4</td>
<td>39.2</td>
<td>38.8</td>
</tr>
<tr>
<td>Anderson</td>
<td>1.16 ± 0.99</td>
<td>39.5 ± 68.6</td>
<td>41.4</td>
<td>40.6</td>
</tr>
<tr>
<td>Zhu</td>
<td>1.29 ± 1.34</td>
<td>32.6 ± 46.0</td>
<td>38.8</td>
<td>38.1</td>
</tr>
<tr>
<td>Sconce</td>
<td>1.28 ± 1.28</td>
<td>38.1 ± 64.5</td>
<td>29.5</td>
<td>28.8</td>
</tr>
<tr>
<td>Wadelius</td>
<td>1.46 ± 1.28</td>
<td>51.0 ± 88.5</td>
<td>35.6</td>
<td>35.0</td>
</tr>
</tbody>
</table>

From Figure 3-2 it can be seen that the Le Gal et al. (2010) model has predicted negative doses for some of the study participants. The reason why these patients were estimated as requiring a negative warfarin maintenance dose was a high INR or low dosages during the first week of treatment. The model does not have the ability to deal with these events and consequently the predicted doses for these patients are not applicable. To further investigate the model’s ability all negative warfarin dose estimations were set to zero, with this change the percentage of variability explained improved to 46.2%.

### 3.1.4 Discussion

The concept of individualized warfarin dosing is desirable for the patient, clinicians and wider health organisations, due to warfarin’s narrow therapeutic index and large inter-individual variability in dose requirements. The patient can be reassured that the drug dose is tailored towards their needs and the clinician can make medical decisions based on a dose algorithm which seeks to bring the patient within
a therapeutic INR range. Further, if clinical endpoints are improved this often means the cost of therapy reduces [20, 61].

There is little doubt that pharmacogenetics can greatly inform warfarin treatment and this has been recognised with the updated recommendations on warfarin packaging by the United States Food and Drug Administration [62]. Further, a recent paper by Schwab et al. (2011) [63] declared the goals to achieve optimal complex, patient-dependent dosing regimens was to inform clinicians of pharmacogenetic principles and to build up health care teams.

Several warfarin dosing algorithms have been published, many including pharmacogenetic information, and the majority are in the form of linear regression models. In this chapter, six different dose prediction linear regression models were compared using an independent cohort of patients to test their predictive ability outside their original derivation cohorts. This was done by re-fitting each model in turn to the validation dataset and assessing the variability explained (R²), as well as comparing the predicted stable dose against actual stable dose. Acknowledgement is required that, unlike randomized control trials, this method of validation does not allow for dose prediction models to be assessed by clinical endpoints, for example time spent within therapeutic range as patients are not prescribed the dose predicted.

At the time of writing there have been six randomised trials of different warfarin dosing algorithms to standard therapy [54, 64-66]; with the exception of Caraco et al. (2007), which concluded a significant improvement in both primary clinical endpoints, these trials did not report significant differences in primary clinical
endpoints. However, several large, well powered trials are currently underway to investigate clinical endpoints further [67-69].

Unsurprisingly, the performance of all six models was worse in the validation cohort as compared to the derivation cohort [10, 58]. Although the diminished performance could be explained by several factors, this poor replication has also been observed previously [10, 51], leads us to hypothesise that regression modelling may not be the most optimal approach for developing a warfarin dosing algorithm.

A key reason for this is the fact that developing a regression model necessitates each patient’s stable maintenance dose to be determined in accordance with a particular definition of stable dose. Choosing this definition in itself is difficult as evidenced by the many different definitions given in the literature (see Section S2, Supplementary Appendix 1 [70]), and stable dose of a patient under one definition may well be different to the patient’s stable dose under another. Further, depending on the definition used, some patients are excluded from analysis on the basis that their dosing history never meets the criteria specified in the definition.

For example, in the validation cohort stable dose was defined as three consecutive INR measurements within the individual’s target range, at the same daily dose. Due to frequent fluctuations in and out of range, and corresponding dose changes, the dosing history of 492 patients did not meet this criterion and therefore they had to be excluded from analysis. Not only is this a significant loss of information, but more importantly it might lead to important sources of variability being missed since the least stable patients are necessarily excluded from analysis. Therefore,
dose prediction regression models can overlook information needed to appropriately recommend doses for the least stable patients – exactly the patients who need individualized dosing.

All six dose prediction regression models, including two non-pharmacogenetic models, have performed at similar levels in this chapter. Based on these findings, it is stipulated that linear regression models may not be able to fully draw on the variability that pharmacogenetics can explain.

The need to exclude non-stable patients, the lower than clinically desired performance and apparent low ability to incorporate pharmacogenetic information [54, 59, 65, 66] of the linear regression dose prediction models validated here suggest that more advanced methods may be required for dose estimation. Methods such as those implemented in Hamberg et al. (2010) [21] and Perlstein et al. (2011) [71] incorporate non-stable patients into the analysis as well as looking at PK/PD parameters.

Research has been undertaken to explain the variability in PK/PD parameters for warfarin [21, 25, 50, 58, 72, 73]. PK/PD modelling along with the study of the variability in PK/PD parameters endeavour to explain the non-linear relationship between warfarin dose and response [21, 25]. Deriving information on patients PK/PD parameters allows for more adaptive models which in turn may improve the individualisation of warfarin therapy for patients. Adaptive models would ideally provide initial dose recommendations, based on demographics, genotype and other readily attainable information and response could then be fed back into the model regularly, with the model then providing updated dose predictions.
It must be noted, however, that models used to represent PK/PD are complex and therefore their implementation into clinical practice involve a large degree of collaboration. Dosing algorithms must be convenient and applicable to a practising clinician. In consideration of this, potential presentation solutions have been constructed, for example, the dose advisor made available through the internet (www.warfarindosing.org), an Excel spreadsheet warfarin dose calculator [52, 70], however this calculator’s algorithm are based on linear regression models. Alternatively, a table of recommended doses given in Hamberg et al. (2010) [21] generated by simulation from a PK/PD model. The potential solutions given are effective as initial dose recommendations, however if the patient does not respond to the recommended dose they offer no adaptive solutions.

In summary, validation in an independent dataset is paramount for any warfarin dose prediction regression model and, as demonstrated in this chapter, the predictive ability of a model diminishes in an independent dataset compared to a derivation dataset. Even for the best performing model investigated here, over half of the variability in stable maintenance dose requirements remains unexplained. Further, a significant proportion of patients are excluded from the datasets used to derive dose prediction models since the criteria set out in the definition of stable dose precludes them. This can have a detrimental effect on model performance since it means that information needed to appropriately recommend doses for the least stable patients – exactly the patients who need individualized dosing – may be overlooked. In light of these issues, more advanced methods of developing dosing algorithms should be explored. In particular, these methods should not assume a
single value of stable dose for a patient, but rather allow dose requirements to adapt with time, to reflect the sensitivity of INR to variation such as dietary changes, alcohol intake and co-medications.
In Chapter 2, a PK/PD model was explained that allows prediction and estimation of future patient drug response. However, in Chapter 3 an alternative approach to the individualisation of a dosage regimen was explored which does not require a PK/PD model. PK/PD models involve a higher level of computation and statistical methodology; however, their merits include better prediction and estimation of patient drug response.

The linear regression methods of Chapter 3 also demonstrate a lack of adaptability to the patient. This is caused by two factors; firstly, the parameters used to inform the linear regression algorithms are deterministic, meaning that the full possibilities of patient response are not considered. Secondly, further measurements from the patient cannot be used to individualise a dosage regimen if the patient’s current drug therapy is not efficacious.

In this chapter, the methodology of stochastic control is explained which allows an adaptability to a drug dose algorithm in order to better treat the patient. Initial sections introduce the stochastic control methodology and provide a history of the approach. Then the novel innovations to the methodology are introduced alongside a description of mathematical notation and formulae.
4.1 What is Stochastic Control?

Stochastic control is implemented on systems that characteristically contain random deviations, for example, aircraft navigation systems [74] and financial markets [75]. The goal is to control the system such that system’s deviation from an intended course is minimised. In contrast to systems of deterministic parameters, where the true value of the parameter is estimated given certain information, the basic element of stochastic control is that a system’s parameters are assumed to be random variables thus containing uncertainty.

Random parameters are often analysed using a number of summary statistics such as measures of average (means, medians, etc.) and measures of variability and deviation (standard deviation and variance). When predictions of future system behaviour are made using summary statistics, rather than the entire distribution of the parameter, the full range of possible outcomes from the system are not considered. This is the issue when random parameters exist in the system; whilst measures of average describe a ‘general tendency’ of a parameter there is a need to control in respect of entire distributions and evolving parameter values.

As discussed in Chapters 1 and 2 a random parameter may be generated naturally or by human interaction. The controller must attempt to measure these random parameters and input statistics from these measurements into a model. The model can then be used to make estimates as to how the system will perform over a period of time in the future. From this the system inputs are controlled to attain maximised rewards from the system, for example an in-range value of INR after warfarin therapy.
In section 3.1 the estimation of an efficacious warfarin dosage regimen was considered using linear regression methodology which does not allow the merits given above of stochastic control. The ability to deal with stochastic parameters leads to stochastic control presenting a superior method for the estimation of dosage regimens. Over the course of this chapter the way in which stochastic control is applied to dosage regimen estimation will be explained. The highlights of the stochastic control method are given including the consideration of noise within patient PK/PD parameters, the use of prior information, the use of a cost function and feedback of future measurements to individualise the dosage regimen.

4.2 A Brief History of Control Methodologies in Drug Therapy

The search for control literature that contained applications in medicine generated a selection of publications from a number of years beginning around the latter nineteen-seventies with the initial publication of Sawchuk et al. (1977) [76]. This section highlights different approaches to control that have been developed by a number of different research groups around the world; the technical details of the stochastic control approaches will be discussed later in this thesis.

The initial paper by Sawchuk et al. (1977) used what is commonly referred to as the Sawchuk-Zaske method, which derives individual PK parameters that are then used to predict a future steady-state concentration trough or peak. These equations were then optimised by which dosage amount induced the desired steady state concentration.
The assumption of steady state concentration was relaxed in the methodology presented by Sheiner et al. (1979) [77] and Peck et al. (1980) [78]. These papers prompted the beginning of maximum a posteriori (MAP) Bayesian methods in drug therapy; where previous information on parameters is combined with current data to derive individual estimates of PK parameters that would then be used to calculate an individualised dosage regimen. MAP Bayesian methods estimate point estimates of PK parameters therefore uncertainty around the patient’s PK/PD response is not considered in this approach. To ensure the entire possibilities of PK/PD response are considered parameters in pharmacometric models must be described with a distribution and not as fixed values. In section 4.5.2 the effect of stochastic parameters on the range of estimated PK output is shown.

Based on the MAP Bayesian approach many software packages have been developed including TCI Works [79], OPT [80, 81], MWPharm [82] and Abbottbase [83].

In certain areas of medicine where near constant feedback of patient response is possible, for example, anaesthesia, the proportional-integral-derivative (PID) controller has been applied. PID controllers utilise a linear approximation of non-linear processes and are unable to predict future measurements, individualisation occurs by adjusting the drug input based on the observed error between system prediction and past measurements from the patient [84] [85] [86] and Slate et al. (1982) [87]. With most drug therapies the level of measurement feedback that is required to utilise PID controllers is not possible due to the invasive nature of sample collection, i.e. from blood samples.
Stochastic control methodology that considers the uncertainty of patient PK parameters has been utilised to individualise drug therapy. In Schumitzky et al. (1986) [88] a stochastic control approach is considered alongside non-parametric methods of estimating patient PK parameters. The methodology of Schumitzky et al. (1986) [88] was developed into the multiple model (MM) approach. The MM approach is first presented in the 1994 publication by Bayard et al. (1994) [89] along with an application in lidocaine therapy (this application will be presented as an example later in this thesis). The MM approach links together the non-parametric approach, explained in section 2.3.2, to population PK parameters [17] with measurement feedback impacting on parameter model probabilities [90].

Based on a PK population non-compartmental model derived using parametric methods, Lago (1992) [91] presents an open loop stochastic control method. To individualise drug therapy to the patient the approach reduces the normally distributed population model to a number of equally spaced discrete points, which are then assigned probabilities meaning the approach is similar to the MM approach. Two applications are presented, the first without discrete point probabilities (appropriate for dosing a population) and the second with model probabilities (more individualised to the patient).

Katz et al. (1986) [92] was the first publication from another group; in their research they perform a control with PK parameters in a compartmental approach and a parametric population PK model. Further publications from this group include publications detailing stochastic control application in PD processes [93, 94] using maximum likelihood techniques. With maximum likelihood techniques the dose is
chosen that maximises the likelihood that the probability distribution of the PK/PD response is in a desired therapeutic interval.

In the stochastic control methodologies presented in this section, distributions are presented as a series of discrete points. Each discrete point is treated as a possible parameter value for a patient and the probability is distributed around these points. Possible parameter values not given a point are considered to have zero probability of occurring; this can lead to a parameter with a range of values that are difficult to interpret. For example, a discrete parameter distribution could have points for the parameter to take the value of 0.1 and 0.2 whilst values of any small amount either side such as 0.11, 0.09, 0.19 or 0.21 are determined to have zero probability of occurring. This property of discrete distributions does not appear to fit the individual patient well as intra-individual variability is best considered as a continuous distribution [1, 95, 96]. In section 4.5.2 the impact of continuously distributed parameters on the PK/PD output will be considered further.

The work of the Laboratory of Applied Pharmacokinetics (LAPK), some of which was explained in section 2.3.2, has led to a software package MM-USC*PACK [97] being developed as well as Pmetrics [43] that runs in the R statistical package [98]. MM-USC*PACK and Pmetrics provide interfaces, primarily for clinicians, to personalise a dosage regimen to a patient’s individual needs.

Control methods where alternatives to PK/PD models inform patient response predictions have been published. For example, in Arnsparer (1983) [99] parameters were recalculated by a recursive least-squared estimator; the parameter were linear regression coefficients that related the dose to the desired
outcome, blood pressure. To understand further about the patient’s individual response to a drug the focus must be to investigate and formulate a model that provides a prediction based on PK/PD parameters. As Chapter 2 explained, PK/PD compartmental models are not entirely paralleled with the true PK/PD of a patient. However, the merits of formulating the PK/PD models allow some physiological meaning to parameters (see section 2.2.3).

This brief history is intended to reinforce that control methods are variable in their approaches to individualising a dosage regimen. However, the control problem can be generalised as will be explained in section 4.4 of this chapter. The next section is an introduction to a new approach presented in this thesis for individualising a dosage regimen using stochastic control.

### 4.3 A New Approach in the Application of Stochastic Control Theory in PK/PD

Based on the literature review of the previous section, broadly speaking, control approaches perceive individual PK parameters in two ways. Firstly, as MAP Bayesian estimates with no variance attached, this assumes the patient’s pharmacokinetics are known to be that value and are without uncertainty. In taking this approach, the information given about the variance from PK analysis is either not analysed or discarded reducing the precision of predictions from the model, which is paramount for optimal control of a PK/PD response.

Secondly, population distributions of parameters are weighted to produce a posterior distribution for the patient (see section 2.3.2). The MM approach taken by the LAPK group perceives an individual’s parameters in such a way alongside non-
parametric methods of deriving the population distribution. The weighting increases the probability of points of the population distribution that are derived as more likely to describe the patient’s true PK parameters. Consequently, the weighting reduces the probability at points where the parameter values are less likely to describe the patient’s true PK parameters.

Assuming statistical consistency, with more samples the posterior distribution will tend to the true distribution of the individual’s PK parameters. To achieve this, if a patient is between points, meaning that their derived PK parameter set does not have a point in the population distribution then a grid of new points is added to the posterior based around a point estimate of the patient’s PK parameter set, however these points do not remain in the distribution [90]. Overall, the effect of less likely PK parameter sets, to represent the individual, only tend to zero probability with patient samples rather than simply and appropriately being discarded.

A new perspective on the individual PK/PD parameter set is proposed in this thesis and applied in latter examples of the next chapter. The approach needs to consider the entire distribution of the individual’s PK/PD parameters and further focus upon the individual’s PK/PD behaviour (intra-individual variability). Synthesising these two approaches leads to each individual having their own PK/PD parameter distribution. For example, a patient’s volume of distribution would have a distribution indicating a range of values that have been derived as plausible for the parameter value at any given time.

The range of values applicable to the parameter can be derived parametrically or non-parametrically, explained in section 2.3. In the absence of individual data such
as plasma samples, the individual PK/PD parameter distribution should be based on parameter-covariate relationships quantified in population PK analysis. The impact of this new approach will be shown in examples presented in Chapters 5-7 of this thesis.

4.4 Considerations for Application to Pharmacokinetics

4.4.1 Preliminaries for Stochastic Control Application

The PK/PD of a drug act over a continuous time frame, as shown in previous chapter diagrams. For example, in section 2.2.4, the plasma concentration in the central compartment is considered to have a value at every given time. In general stochastic control methodology, the subject of control, such as the plasma concentration or other PK/PD response, is referred to as the state, $x$, of the system. The set of all possible states, $X$, can be continuous or discrete but the system always occupies a state $x \in X$.

The action of control, $u$, is an intervention performed to alter the state to a desired value. The dosage regimen (often in mg/h for infusion or mg for dose) is the action of control that is taken to induce certain PK/PD responses. The clinician will decide from a range of efficacious dosage regimens, $u$, within a set of all possible dosage regimens, $U$, e.g. doses cannot be negative. At state $x$, the set of possible actions given that the patient is in this state is $U_x \in U$ e.g. doses above a certain amount may be known to induce adverse events based on toxicology data.
Decisions to alter dosage regimens can be made when a clinical event causes the need for action, such as an adverse drug reaction, or at clinician designated times. Therefore, the action of control occurs at the discrete time steps,

\[ T \equiv (1, 2, \ldots, N) \quad 4.1 \]

where \( N \leq \infty \). When \( N \) is a finite number, the control is a finite horizon problem, and in the infinite case an infinite horizon problem. In a finite horizon case, at time \( N \) no action is implemented as the system has reached a pre-designated conclusion.

### 4.4.2 The Mechanism of Stochastic Control in Pharmacokinetics

Assume a time point \( t \in T \), and a dosage regimen, \( u_t \), required for a patient that induces them to a desired PK/PD response at the next discrete time point \( t + 1 \), \( x_{t+1} \). To calculate the value of \( x_{t+1} \) a function is required - the state function. In a PK/PD application, state functions and parameter values will be derived using the methods explained in sections 2.2 and 2.3. The state function is:

\[ x_{t+1} = f_t(x_t, u_t, \omega_t, \theta) \quad 4.2 \]

where \( f_t \) is a known function at time \( t \) and \( \theta \) is a set of pharmacokinetic parameters. The state function consists of information the previous PK/PD response \( x_t \), the dosage regimen, \( u_t \), noise of the system and parameters being included in the system. Process noise, \( \omega_t \), can be an error in drug administration, dose timing or model inaccuracies and will be discussed further later in section 4.5.2.
Dosage regimen information, $u_t$, is expressed as:

$$u_t = k_t(x_{t+1}, y_t)$$ \hspace{1cm} 4.3

where $k_t$ is a known function at time $t$ and $y_t$ is the value of a measured PK/PD output at time $t$. This dosage regimen information is paralleled to the decision process of a clinician in drug therapy; a dosage regimen prescribed will be based on the predicted current PK/PD response of the patient, $x_t$, and the available measurements of PK/PD responses, $y_t$.

The measurements of a PK/PD response, $y_t$, e.g. plasma concentration, can be taken via procedures such as blood samples. Whilst they are a direct measurement of the PK/PD response, as opposed to predictions from the state function, measurements are still subject to variability from separate sources. The precision of the measurement can be impaired by aspects such as assay error and time record errors [17, 100]. $y_t$ is expressed:

$$y_t = h_t(u_t, v_t)$$ \hspace{1cm} 4.4

where $h_t$ is a known function at time $t$ and $v_t$ is the measurement variance that indicates the precision of a measurement.

The information provided on current PK/PD response, current dosage regimen and measurements (equations 4.2, 4.3 and 4.4 respectively) is collated to make a
decision about the next dosage regimen to prescribe a patient. This decision is done with the aid of a cost function which considers all current information alongside future prediction of patient PK/PD response and derives an optimal dosage regimen for a given therapeutic target. Without the cost function the estimation of the dosage regimen to cause the given therapeutic effect in the patient is subject to bias as subjective decisions would replace the objective cost [101-103]. In PK/PD application, a control function is formulated to penalise deviations outside the therapeutic range caused by different dosage regimens; the least penalised dosage regimen is then recommended for prescription.

The cost function of the system, \( J(U) \), occupying a state, \( x_{t+1} \), after the dosage regimen \( u_t \), between \( t \) and \( t + 1 \) is:

\[
J(U) = \mathbb{E}(g(x_{t+1}, u_t))
\]  \hspace{1cm} 4.5

where \( g \) is a known function linking a certain PK/PD response and dosage regimen to a cost. The cost is considered a random quantity as it is conditional on future PK/PD response, \( x_{t+1} \), derived from random PK/PD parameters, \( \theta \) (explained further in section 4.5.2). The entire set of possible actions of control, \( U \), is considered in order to estimate the maximal dosage regimen for the patient.

Extending the cost function of equation 4.5 to multiple future time steps,
The cost function considered over multiple time steps allows greater control of the PK/PD response. In PK/PD applications this means that a dosage regimen can be estimated based on predictions about the patient’s PK/PD response further into the future. An issue in past studies into individualising dosing is that the future PK/PD response of the patient only is considered over a short time [102-104]. Often, dosage regimens are required that provide an initial loading dose and then a reduced maintenance dose, such as in warfarin therapy. Estimating the PK/PD responses of the patient throughout this process of dosage adjustment is important to maximise the therapeutic effect of a drug.

In light of this, the cost function is to be formulated drug specifically to enable determination of an appropriate dosage regimen for the patient. An example of a cost function is one that penalises for distance away from a desired therapeutic point:

$$J(U) = \sum_{i=t+1}^{N} E(g(x_i, u_{i-1}))$$

where $\alpha_i$ is a nonnegative multiplicative constant which reflects the importance of control at time $i$ and $\hat{x}_i$ is the estimated PK/PD response. $\beta_i$ is the target state which the system is to be altered to by using a specific dosage regimen, $u_{i-1}$. In this case, a dosage regimen would be estimated by minimising the cost function (the
expected value of the mean squared error between the predicted PK/PD response and the target PK/PD response). This cost function is best used for drugs that cause a therapeutic effect at specific plasma concentrations.

The overview in this section of the mathematics required to individualise dosage regimens reveals the objective mechanism, the cost function, central to stochastic control. However, whilst the cost function is objective it is not at the expense of important clinical expertise. For example the target PK/PD response, $\beta$, is identified using clinical expertise.

As explained before, the cost function is a random quantity as the variables used to calculate its value are random parameters. The distribution of the cost function is the subject of the next section (section 4.5), with particular reference to prior distributions of the parameters required in calculation, the consideration of noise in PK/PD applications and the ability to consider the cost function over time.

To ensure greater control, measurements of PK/PD responses can be fed-back to the system at time points to allow an interactive aspect to the stochastic control. In section 4.6, the extra mathematics and explanation required to perform this feedback will be given.

### 4.5 Derivation of the Cost Function Distribution

#### 4.5.1 Prior Distributions

The distribution of control function value, $J(U)$, is derived from random parameters. Each random parameter requires known prior distributions to attribute
probabilities to their range of values. The following prior distributions are assumed known:

\[
\begin{align*}
\text{a) } p(x_t|\theta), & \quad \text{b) } p(\omega_{t+1}|x_t, u_t, \theta), \\
\text{c) } p(v_t|y_t), & \quad \text{d) } p(\theta)
\end{align*}
\]

Equation 4.8a is the probability distribution for the initial state and can often be derived exactly; however, it can also be interpreted from prior PK/PD response information. \(p(x_0|\theta)\) is required to start the ‘domino’ process of PK/PD response determination as subsequent distributions of the PK/PD response, \(x_{t+1}\), will be estimated using equation 4.2.

Secondly, equation 4.8b is the probability density function for process noise given the current PK/PD response, dosage regimen and parameters. This distribution will be explored further in section 4.5.2.

The measurement variance density, equation 4.8c, is constructed by parameterising the error of the assay used to measure PK/PD responses. The assay error of PK measurements is a subject of debate [17], different models consider that the error is a constant percentage of the actual value and that there is a lower limit where measurements are unquantifiable below this concentration [105]. Whereas other models represent the assay errors as finite values for all concentrations and develop an assay error polynomial to represent this knowledge [17].

Finally the distribution of the pharmacometric model parameters (see section 2.2) is specified in equation 4.8d. The specific process needed to calculate this
distribution was explained in section 2.3. For a population wide dosage regimen the population PK/PD parameter distributions could be used to estimate the dosage regimen that, on average, induces over the population some specified therapeutic effect. This technique offers little individualisation of dosage for patients because the dose will be tailored to treat the ‘average’ patient and variability in the population will cause this approach to be sub-optimal. Therefore this distribution of PK/PD parameters needs to be individualised towards the patient.

The distributions shown in equation 4.8 are all used to derive the probability distribution of $x_{t+1}$,

$$p(x_{t+1} | x_t, \omega_t, u_t, v_t, \theta)$$  \hspace{1cm} 4.9

The many inputs into this distribution indicate just how intricate the system is able to be. This intricacy is important and necessary in PK/PD application as different sources of variability affect an output. Previously, the effect of noise, $\omega$, has not been considered in the state function in PK/PD application. The next section will consider the impact of different parameterisations of noise on the prediction of the future PK/PD response.

### 4.5.2 The Distribution of Predicted Plasma Concentration

In this thesis, each patient is considered to have their own individual distribution of parameters. However, individual PK/PD parameter distributions are not routinely calculated in practice. Software packages, such as NONMEM or Pmetrics, have the ability to calculate individual PK/PD parameters however either variance is not
calculated (point estimates) [106] or not representative of intra-individual variability due to calculation from reweighted population PK/PD distributions [43]. The effects of different implementations of process noise on the predicted PK/PD response are considered in this section. The simulations of this section are informed by the PK parameters, \( p(\theta(\text{units})) \), expressed as,

\[
\begin{align*}
p(k_a (1/h)) & \sim \ln N(\ln(0.4) , 0.7), \\
p(V_d (l)) & \sim \ln N(\ln(250) , 0.03), \\
p(Cl (l/h)) & \sim \ln N(\ln(12.5) , 0.2)
\end{align*}
\]

where \( k_a = \frac{Cl}{V_d} \). A simulation consists of the plasma concentration time profile of a patient, with a starting plasma concentration distribution, \( p(\hat{C}_0 | \theta) \sim N(1000,50) \), after administration of a single oral dose, \( u_0 \), of 400mg. \( \hat{C}_0 = \hat{x}_0 \), indicating that the starting concentration is assumed to be normally distributed around 1000ng/ml, this could be from a blood sample taken at the time or a derived estimation.

Firstly, a one compartment PK oral dosing model (see section 2.2.4) is assumed without noise included in the system, hence \( p(\omega_t | x_t, u_t, \theta) = 0 \), described mathematically as,

\[
\frac{dCA_t}{dt} = -k_a CA_t, \quad \frac{dC_t}{dt} = \frac{k_a CA_t}{V_d} - k_d C_t.
\]

The simulation described above was repeated 10,000 times and the final plasma concentration values from those repetitions, \( p(\hat{C}_{24} | \hat{C}_0, \omega_0, u_0, v_0, \theta) \), are
presented in Figure 4-1 by a histogram. MATLAB (The MathWorks Inc., Natick, MA, version 2011a) was used to perform this simulation by running equation 4.11 through an ordinary differential equation solver.

![No Noise Histogram](image)

**Figure 4-1: Histogram of Predicted Plasma Concentration from a Model Not Including Noise.**

Whilst the data appears to have a near to central peak, the Jarque-Bera test for normality provides evidence to suggest that the distribution is not normal by rejecting the null hypothesis that the values come from a normal distribution (p-value=0.003). Whilst the plasma concentration doesn’t have to obey a specific distribution there are considerations when the estimated plasma concentration is distributed other than normally.

Noise is now introduced into the ordinary differential equations thus formulating stochastic differential equations. Using the current methodology for introducing
noise to the estimation of individualised dosage regimens [88] noise was added.

Accordingly, the model for plasma concentration was changed to,

\[
\frac{dC_A}{dt} = -k_a C_A \\
\frac{dC_t}{dt} = \left( \frac{k_a C_A}{V_d} - k_e C_t \right) dt + d\rho_t \quad 4.12
\]

where the noise is parameterized as \( p(\omega_t | x_t, u_t, \theta) = \rho_t \), \( \rho_t \) is Brownian motion [107] such that process noise, \( W_t = \frac{d\rho_t}{dt} \) and \( W_t \sim N(0,50) \). The histogram of 10,000 simulations \( p(\hat{C}_{24} | \hat{C}_0, \omega_0, u_0, v_0, \theta) \) generated from the 4.12 model is shown in Figure 4-2. The data fails to pass the same test of normality (P-value=0.0001).

![Brownian Noise Histogram](image)

**Figure 4-2**: Histogram of Predicted Plasma Concentration from a Model with Brownian Noise.

To truly represent intra-individual variability, PK/PD parameters must be allowed to vary over time [108]. Changing parameter systems have been considered before
with the Interacting Multiple Model (IMM) [109] however the approach considered the entire patient’s parameter distribution to change only at points of measurement or when a new dose of a drug is given. The main application of the IMM approach was for patients deteriorating in condition or with known time dependent effects that impact on parameter values. The IMM approach has been applied to the individualisation of gentamicin and vancomycin to patient undergoing cardiothoracic surgery [12]. In Macdonald et al. (2008) [12] the IMM method performed optimally by setting a 3% chance of PK parameter change.

The intention of the process noise to be used in this thesis is different from the IMM approach [108]; the formulation considers at every time step, not just at dose changes and PK/PD response measurements, that the patient PK/PD parameters could have changed to different values rather than have changed to a new parameter value. In this approach the individual's PK/PD parameter distribution is not altered at each time step but rather explored further to discover the full range of the patient’s possible PK/PD response. Factors such as diet [110] and fluctuating co-morbidity [111] are best modelled in this way as they cause small unpredictable changes to PK/PD parameters [112].

To implement the new method of process noise the model was changed back to equation 4.11, however, the parameters values were allowed to change randomly within their distributions, kept at the same values as in the simulations of the other histograms of this section, once every minute leading to 1,440 time steps.
The histogram of $p(\hat{C}_{24}|\hat{C}_0,\omega_0,\nu_0,\theta)$, generated by 10,000 equation 4.13, is presented in Figure 4-3 appears to be normally distributed (P-value=0.29).

\[
\frac{dCA_t}{dt} = -k_dCA_t \quad \frac{dC_t}{dt} = \frac{k_dCA_t}{V_d} - k_eC_t
\]

\[p(\theta_t|\omega_t) \sim \lnN(\mu, \sigma^2)\]

The Jarque-Bera test of normality used in this example, as well as other tests of normality, is highly powered with large samples sizes such as 10,000. This means that for most sets of 10,000 data points the test would reject the hypothesis that the data is normally distributed. Therefore, the rejection of the null hypothesis may not necessarily lead to the conclusion that the data is not normally distributed.
4.5.3 Using the Cost Function to Determine the Optimal Dosage Regimen

Now a future PK/PD response value can be computed with process noise included, the cost function can be utilised to estimate the best dosage regimen for the patient given the intra-variability perceived in their PK/PD parameters.

In equation 4.6, the cost function value, $J(U)$, consists of determining the PK/PD response value at future points $T$, subject to actions of control, $u$. The example of a cost function in equation 4.7 seeks to find the maximal state value, $x_i^*$, which is closest to $\beta_i$. This is done by considering the entire set of actions of control, $U$, and determining the optimal dosage regimen, $u_{i-1}^*$, at all the time points in $T$ to cause this maximal PK/PD response value, $x_i^*$ consistently. For equation 4.7 this process is mathematically presented as:

$$u_{i-1}^* = \arg\min_{x_i} \left( E \left( \sum_{i=t+1}^{N} \alpha_i \left( x_i^* - \beta_i \right)^2 \right) \right)$$

The determination of this optimal dosage regimen can be done in different ways, generalised into the backwards and forwards approach. Working backwards would mean a target is specified and then dosage regimens are chosen to minimise the cost function given this target [113].

For instance, differential equations of a pharmacokinetic system can be solved by specifying the final concentration value needed and rearranging to find the dosage regimen which gives that solution. This approach incurs the problem of dimensionality and is not simple to solve when across several decision epochs due to the solutions being hard to optimise. In a high-dimensional space (each PK/PD
parameter in the predictive model has a range of values as well as a number of possible dosage regimens) this means a large number of possible paths are considered and often several paths meet the objective of this approach.

Forward methods in stochastic control start with, in the PK application, dose-concentration trajectories. The general idea is to guide these trajectories to the desired PK/PD response at one or more time points. An example of the forward method is when different dosage regimens, \( u \), are simulated through the process explained in section 4.5.2. Doses that cause a therapeutic PK/PD response in simulation, such as the target response \( \beta_t \) in equation 4.8, are the optimal dosage regimens.

A similar level of computation is required for forward and backwards methods in determining the dosage regimen to prescribe to the patient. However, forward methods begin at the current time and often from a point where the PK/PD response has been measured either at that time or recently rather than a theoretical point such as in backwards methods.

In past applications cost function values have been calculated only at discrete time points \([89][113]\) and this is the standard methodology currently being used \([114]\). To ensure the control is not separated from potential activity between decision epochs, in this thesis, the approach of complete simulation over the entire time horizon of the problem is considered.

For example, in section 4.5.2 histograms were presented for the predicted plasma concentration at the end of twenty-four hours, however, in this thesis, the
predicted plasma concentration will be considered throughout the twenty-four hours. This allows research to extend into incorporating control of the entire system process.

4.6 Enabling Feedback to the System

4.6.1 Open-Loop and Closed-Loop Control

A dosage regimen can be estimated purely by predicting future patient PK/PD response based on current information [89, 103, 104, 115]. As explained in the previous section 4.5.3, this involves the use of a PK/PD model and process noise to estimate the predicted distribution of the PK/PD response at given times in the future. This predicted distribution of future PK/PD response is then used in a cost function.

This process is called open-loop control as a dosage regimen is derived solely by the prediction of the model [100]. When the PK/PD model is appropriately predictive of the individual patient then open-loop control is appropriate. However, in PK/PD applications the parameters are virtually always subject to very high levels of uncertainty to be assured of this appropriateness.

The issue with open-loop control in individualized therapy is that parameter values are drawn from distributions with a wide range of values. Equation 4.3 indicates that a measurement of the PK/PD response, $y_t$, is considered alongside a prediction of the PK/PD response, $x_{t+1}$, when estimating a dosage regimen, $u_t$, for a patient. Without these measurements the range of the patient’s estimated PK/PD response is not considered with up to date feedback.
Therefore, methodology where measurements are taken into account is needed to ensure optimal drug therapy; meaning that a dosage regimen is informed by measurements from the patient as well as predictions from PK/PD models so as to then reach a desired future PK/PD response or therapeutic response.

Any control that can react to measurements taken is considered a closed-loop control. Closed-loop control allows reduction of the uncertainty in the system by comparing model predictions with measurements from the patient [100]. This is done by the system predicting future PK/PD responses and then, when a measurement of a PK/PD response is made, attempting to reconcile the evidence of both the prediction and the measurement.

A simple diagram of a closed-loop system is shown in Figure 4-4,

![Figure 4-4: A Graphical Representation of a Closed-Loop System](image)

Measurements, $y$, are fed back into the system for the controller’s use at the next decision point in $T$. The clinician can re-evaluate clinical targets for PK/PD responses and the cost function will derive the best dosage regimen to meet these targets.
Essentially the system reinitialises with new initial conditions, such as the prior distributions in equation 4.8, are now dependant on data obtained. If the $y$ loop is removed from the diagram then an open-loop control is represented instead.

The merit of closed loop systems is that the methodology leads to reduced uncertainty of the patient’s PK/PD response, which is used to better individualise a dosage regimen for a patient. However, PK/PD responses are often sparsely sampled leading to limited measurements being available for feedback. As an alternative, if surrogate measures of patient response exist and their relationship to the PK/PD response can be expressed in a function then these too can be fed back into the system.

In this thesis the update of both PK (e.g. plasma concentrations) and PD (e.g. cholesterol levels) outcomes is considered. However, Chapter 8 includes a discussion of the future work required to include appropriate consideration of intra-individual variability in the methodology of parameter re-estimation.

### 4.6.2 Example of a System that Updates with Measurements

The process of feeding back measurements to the system can be done by a number of mathematical algorithms; these are collectively known as filters. Examples of filters are the Gaussian Sum, the MM, Particle and Kalman [116-119]. Filters are effective in the PK/PD application as they account for the variability around a measurement, the assay error. Failure to account for the assay error means measurements are treated as entirely accurate and therefore estimations are not as
reliable due to unconsidered variability. Despite this, there are examples in literature where filters are not utilised [103, 104, 120-122].

In order to update the system with measurements the Kalman filter is utilised in this thesis. The Kalman filter is used to generate an reconciled estimate of PK/PD response based on a measurement and respective PK/PD model prediction [123]. The Kalman filter has been used successfully in both space and military technology before being applied to pharmacokinetics and dose estimation [124].

The system diagram shown in Figure 4-5 demonstrates the general idea of a Kalman filter system. Firstly, the PK/PD responses in the body, $\hat{x}$, are calculated to provide an *a priori* prediction of PK/PD response. This prediction is weighted with a noisy measurement of the PK/PD response, often taken through a blood sample. This weighting produces an *a posteriori* PK/PD response, $\tilde{x}$, estimate with reduced uncertainty.

![Diagram showing a generalisation of the Kalman filter](image)

*Figure 4-5: Diagram Showing a Generalisation of the Kalman filter*

The Kalman filter seeks to manage the various sources of noise and variability in the PK/PD system. Sources of variability are modelled through process noise, $\omega$,
included in the state function (see section 4.5.2). These sources need to be controlled as optimally as possible; therefore, the filter reconciles this process noise in the system to provide an \textit{a posteriori} estimate of PK/PD response that accounts for several types of noise and variability.

The Kalman filter will derive this \textit{a posteriori} estimate with all information described above informing the value. Therefore, the system has no need to retain any other information than the \textit{a posteriori} estimate for the subsequent measurement in time (where it will become the \textit{a priori} estimate). The Kalman filter therefore is a recursive filter requiring only the last estimate for future derivations.

Overall, the Kalman filter enables an interactive aspect to the estimation of the dosage regimens by calculating more certain estimates of PK/PD response based on measurements. This means that the dosage regimens will be able to respond to measurements when they are taken and provide updated estimates of the required dosage regimen. This will be important in applications, such as warfarin dosing, where large numbers of patients never reach stable dosing and must be monitored regularly.

The following sub-sections offer a description of the mathematics involved in the Kalman filter.

\subsection*{4.6.2.1 Prediction}

The standard Kalman filter is described in the following sub-sections, which is applicable in this thesis because of the normally distributed PK/PD response shown
in section 4.5.2 [16]. There are several stages to the Kalman filter beginning with prediction. The prediction of the PK/PD response, $\hat{x}_t$, is found by

$$\hat{x}_t = f(\hat{x}_{t-1}, u_t) \tag{4.15}$$

which is calculated from the mean value of methods shown in section 4.5.2 in absence of process noise. The variance of $\hat{x}_t$ is derived from the following equation:

$$\hat{P}_t = F_t\hat{P}_{t-1}F_t^T + Q_t \tag{4.16}$$

where $F_t$ is the state transition model, which is used to derive how the system covariance is changing over time, and $Q_t$ is the variance of the process noise, $\omega_t$, in the system. Importantly, the covariance is a product of the previous covariance ‘evolved’ by $F_t$ with the addition of $Q_t$ which is used to introduce noise caused by small parameter changes or model misspecification. Utilisation of the previous system covariance in this way preserves the recursive nature of the Kalman filter.

Based on the work in section 4.5.2, an alteration will be made to the calculation of $\hat{x}_t$ and $\hat{P}_t$, this will be shown in section 4.6.2.5 as the rest of the methodology for the Kalman filter is best explained before the novel alteration.

The two equations 4.15 and 4.16 form the prediction part of the Kalman filter. The filter will compare the predicted value, $\hat{x}_t$, and variance attached, $\hat{P}_t$, to the measurement, $y_t$, taken in order to calculate an $a posteriori$ PK/PD response, $\tilde{x}_t$ estimate and covariance, $\tilde{P}_t$. 
4.6.2.2 Update

For an update to occur first a measurement $y_t$ is taken at any time $t$, then the measurement residual is given by

$$e_t = y_t - H_t \hat{x}_t$$  \hspace{1cm} 4.17

where $H_t$ is a known value which relates the predicted state to the measurement. $H_t = 1$ when the measurement is of the predicted PK/PD response. $H_t \neq 1$ when, for example, predicting plasma concentration and creatinine clearance is used as a surrogate measure and the relationship of the surrogate measure to the plasma concentration is required.

The covariance of this residual is derived by

$$S_t = H_t \hat{P}_t H_t^T + R_t$$  \hspace{1cm} 4.18

Where the measurement relationship model, $H_t$, similar to $F_t$ in equation 4.16, ‘evolves’ $\hat{P}_t$ to be comparable with $R_t$, which is the variance of the measurement, e.g. assay error. Notice this function is the scaled current system covariance plus measurement variance. In the case where $H_t = 1$ and $S_t = \hat{P}_t + R_t$.

4.6.2.3 Adjustment of State Value

To complete the process some formulae are introduced that take the residual, $e_t$, and residual covariance, $S_t$, values and reconcile them with the predicted PK/PD response value, $\hat{x}_t$, and covariance, $\hat{P}_t$. Firstly, the Kalman gain is calculated by
\[ K_t = \hat{P}_t H_t^T S_t^{-1}. \] \hspace{1cm} 4.19

This value is how the Kalman filter determines the ‘weight’ of the residual in the next formula to derive the new \textit{a posteriori} PK/PD response estimate. The case where \( H_t = 1 \) and \( S_t = \hat{P}_t + R_t \) leads to \( K_k = \hat{P}_t(\hat{P}_t + R_k)^{-1} \) showing the Kalman Filter is a ratio between system covariance in the absence of and including measurement variance. The new estimate of PK/PD response, \( \tilde{x}_t \), reconciling prediction with measurement, is given by

\[ \tilde{x}_t = \hat{x}_t + K_t e_t. \] \hspace{1cm} 4.20

The residual error can be positive or negative which leads to an appropriate, as per the ratio seen in equation 4.19, addition or subtraction from the \textit{a priori} prediction to the \textit{a posteriori} estimate. The \textit{a posteriori} covariance, \( \tilde{P}_t \), is calculated by

\[ \tilde{P}_t = (1 - K_t H_t)\hat{P}_t \] \hspace{1cm} 4.21

These formulae take us on one ‘loop’ and now equations 4.20 and 4.21 will be taken into consideration at the next loop when another measurement is taken. By using these equations the drug dose algorithm becomes a closed-loop controller.

\subsection*{4.6.2.4 Cases of Values Tending to Zero in the Kalman Filter}

The ability of the Kalman filter to derive an \textit{a posteriori} PK/PD response estimate based on the relative variability in the system is shown when \( \hat{P}_t \) and \( S_t \) tend
towards zero. So in the first case where $\hat{P}_t$ tends to zero, this would be when the prediction from the PK/PD model becomes completely accurate. If

$$\hat{P}_t \to 0$$

$$\Rightarrow S_t \to R_t$$

$$\Rightarrow K_t \to 0$$

$$\Rightarrow \hat{x}_t \to \hat{x}_t$$

$$\Rightarrow \hat{P}_t \to \hat{P}_t \to 0$$

As can be seen, despite any value of measurement the Kalman filter will recognise if the process noise is tending to zero and gradually increase the magnitude of the a priori prediction in the a posteriori estimate.

Now in the case of $R_k$ tending towards zero, which would occur when the measurements are entirely accurate indicators of the true PK/PD response,

$$S_t \to H_t \hat{P}_t H_t^T$$

$$\Rightarrow K_t \to H_t^{-1}$$

$$\Rightarrow \hat{x}_t \to \hat{x}_t + H_t^{-1} e_t = \hat{x}_t + H_t^{-1}(y_k - H_t \hat{x}_t) = H_t^{-1} y_t$$

$$\Rightarrow \hat{P}_t \to (1 - H_t^{-1} H_t) \hat{P}_t = 0$$
This shows that when the measurement variance tends to zero the \textit{a posteriori} estimate will tend to the measurement value divided by the measurement relationship model used to translate indirect measurements to that of the primary PK/PD response, an example of this is given just after equation 4.17.

### 4.6.2.5 Considerations for the Estimation of State and State Covariance in the Kalman Filter

The description of the formulae in the Kalman filter, gave equations 4.15 and 4.16 as the estimates of PK/PD response, $\hat{x}_t$, and PK/PD response covariance, $\hat{P}_t$, respectively. In equation 4.16 of the Kalman Filter methodology, the prediction of the PK/PD response covariance is done by taking the covariance at the previous measurement and prediction reconciliation, $\hat{P}_{t-1}$, and using the Kalman filter to evolve the covariance value to a current prediction of PK/PD response covariance, $F_t\hat{P}_tF_t^T$. The $Q_{t-1}$ term added in equation 4.16 to allow classification of perceived noise into the PK/PD response covariance. Overall, the method of the Kalman Filter is to use analytical functions to derive the distribution of the predicted PK/PD response.

Earlier in section 4.5.2 an example was given that generated a distribution of the predicted plasma concentration through repeated simulation. The simulated distribution derived gives a prediction of the PK/PD response value, $\hat{x}_t$, and the PK/PD response covariance, $\hat{P}_t$. Therefore the information that the Kalman filter requires about the PK/PD response estimate and covariance are provided without the need to determine $F_t$. The simulated sample variance will replace the $F_t\hat{P}_tF_t^T$ term from equation 4.16. This use of a simulated distribution contrasts to the
analytical method of the Kalman Filter. With the noise of the parameters now included in the PK/PD response covariance, \( \hat{P}_t \), the additive term \( Q_t \) seen in equation 4.16 will represent model misspecification in this thesis. This classification of the different sources of noise within the system means the system can be analysed more effectively rather than pooling all sources of noise into one value, \( Q_t \).

The distribution of the predicted plasma concentration given by equation 4.13 was generated from 10,000 samples and was deemed to be normally distributed. A reduced amount of samples from \( p(C_{t+1}|C_0, \omega_t, u_t, v_t, \theta) \) will be considered in the following chapters. The mean and variance of the reduced number of samples will be the predicted PK/PD response value \( (\hat{x}_{k|k-1}) \) and the predicted PK/PD response covariance \( (\hat{P}_{k|k-1}) \) respectively. If the plasma concentration samples were not normally distributed then the Extended Kalman Filter would have to be utilised instead of the standard Kalman Filter [16]. The Extended Kalman Filter handles non-normally distributed state distributions by forming a normal approximation of the distribution [119].

### 4.6.3 Application of the Kalman filter for the dosing of lopinavir

#### 4.6.3.1 Introduction

The main interest of this section is to demonstrate an application of the Kalman filter. Individualised dosage regimens are not considered which allowed the focus to be on explaining how measurements can be fed back into the drug dose algorithm to enable a closed-loop control.
The Kalman filter, explained in the previous sections, allows feedback of PK/PD response to be reconciled with predictions generated from a PK/PD model. In doing this a closed-loop system is formed. An example of a closed-loop system is shown in this section for patients receiving the antiretroviral drug lopinavir.

Lopinavir is used to treat HIV-infected patients and is given as an oral dose at, most often, a daily interval. To reduce pill burden the drug is often given in combination with ritonavir, since the mechanism of action of the two drugs produces a desired antiretroviral effect.

4.6.3.2 Method

The dataset of patients used in this example of a closed-loop system had been used in a population PK/PD analysis by Dickinson et al. (2011) [125]. For the following example, a dataset of healthy volunteers from two London based hospitals was used. The doses of lopinavir and ritonavir given to the sixteen patients in the original study were 400/100mg and then 800/200mg; eighteen plasma concentration samples at both dose amounts were taken over a 72 hour period post-doses. The dataset studied in thesis comprised of patient ID, sampling times, dosage amounts (mg), and the area under the plasma concentration curve of ritonavir (mg.h/l). Further detailed information on the data can be found in Boffito et al. (2008) [126] and Dickinson et al. (2011) [125].

The data was inputted into MATLAB (The MathWorks Inc., Natick, MA, version 2011a). MATLAB is a software package for mathematical computation, visualization,
and programming. Therefore the language of the programme allowed the description of Kalman filter and the pharmacometric model in differential equation and analytical form. The filter utilised the predictions ($\hat{x}_t$) given by the model in the original paper and the plasma concentration samples as measurements ($y_t$).

The model used for lopinavir was a one compartment PK model for the concentration of the drug in the plasma, $C_t$, with an extra equation used to mimic the absorption of the oral dose into the central plasma compartment is,

$$\frac{dCA_t}{dt} = -k_a CA_t \quad \frac{dC_t}{dt} = \frac{k_a CA_t}{V_d} - k_e C_t. \quad 4.24$$

To enable individualisation in the lopinavir clearance parameter a power relationship was derived with the area under the curve (AUC) of Ritonavir [125], which is expressed as

$$Cl_i = \theta_1 \cdot (AUC_i/4.57)^{\theta_2} \quad 4.25$$

where $Cl_i$ is the apparent oral clearance of Lopinavir of the $i$th patient, $\theta_1$ is the population estimate of the apparent oral clearance, $AUC_i$ is the AUC of Ritonavir of the $i$th individual of which 4.57 is the median value and finally $\theta_2$ is the scaling power of the effect of $AUC_i$ on $Cl_i$. This is a method of modelling the effect of co-medications on PK parameters of drugs. The population mean PK parameter values were taken from Dickinson et al. (2011) [125], expressed as,
where \( k_e = \frac{c_l}{V_d} \). The effect of not individualising these parameters was investigated by comparing predictions of PK response to measurements taken from the patient.

The outputs of this study were the estimates of plasma concentration over time and the error attached to these estimates. To represent the time-dependent error of predictions made by the model of lopinavir an equation was introduced to model this variance in the system,

\[
\hat{p}_t = 0.1 * t. 
\]

This variance was plotted alongside the mean value of plasma concentration over time.

### 4.6.3.3 Results

Data from sixteen patients was used in the Kalman filter. The dataset include 10 male and 6 female patients; the median age was 42 years (range 25-55 years); and the median weight was about 85 kg (range 53-115 kg).

The concentration-time graphs for the 72 hours of sampling are shown for 4 patients in Figure 4-6 to Figure 4-9. As the population PK parameters were used to derive predictions of the plasma concentration this will mean that the predictions will be for the ‘average’ patient in the population. In Figure 4-6 and Figure 4-7 the

\[
k_a (1/h) = 0.26, \\
V_d (l) = 14.9
\]
predictions tended to be similar to the measurements taken, whereas Figure 4-8 and Figure 4-9 show predictions further away from the measurements taken.

**Figure 4-6:** Plasma Concentration-Time Profile of Patient 1 Receiving a 400mg Dose of lopinavir.

**Figure 4-7:** Plasma Concentration-Time Profile of Patient 7 Receiving a 400mg Dose of lopinavir.
Figure 4-8: Plasma Concentration-Time Profile of Patient 3 Receiving a 400mg Dose of lopinavir.

Figure 4-9: Plasma Concentration-Time Profile of Patient 5 Receiving an 800mg Dose of lopinavir.
The variance attached to the estimated plasma concentration is represented in the figures by a block around the mean estimate, the black line. When a measurement is fed back the variance is reduced to equal or less than the measurement assay error. Then the variance around the patient plasma concentration increases from the value at time of measurement; this is due to the system relying on the prediction from the pharmacometric model, which is less certain than a measurement from a blood sample.

4.6.3.4 Conclusion

When a measurement is taken the Kalman filter reconciles the measurement with the predicted value. Unless the measurements and the predictions are the same values, curves that are not smooth will always be expected. Figure 4-6 and Figure 4-7 are examples where because the predictions and the measurements taken are similar to the estimate of PK/PD response, the blue line, tends to be smoother.

Figure 4-8 and Figure 4-9 shows what happens when predictions and measurements are further apart. The PK/PD response estimate line has more breaks as the prediction, derived from population pharmacokinetic parameters, is not directly comparing with the more accurate measurements, taken from the patient at discrete time points.

In this case where the prediction is less accurate, from the proof given in equation 4.23 as the assay error of the PK/PD response measurement reduces, the new PK/PD response estimate tends to the measured value. Shown in both Figure 4-8 and Figure 4-9 the PK/PD response moves most of the way towards the
measurement taken however it finally settles just short due to the prediction form
the PK/PD model still providing some information to the estimate.

In this example, population PK parameters were used to provide prediction of an
individual’s plasma concentration level of lopinavir. The inaccuracies of the
individual plasma concentration predictions were less consequential on overall
PK/PD response estimation as frequent plasma samples taken kept the system
informed of the current plasma concentration of the drug. When fewer blood
samples are taken over the dose interval the system is provided with less feedback
and therefore relies more on the predictive capabilities of the PK model.
Consideration to maximise the accuracy in both the predictions made and
measurements taken is needed to ensure optimal performance of the Kalman filter.

4.7 Discussion

The methodology of stochastic control was introduced in section 4.1 with a brief
history of publications applying the method in the medical setting given in 4.2. In
order to apply stochastic control methods effectively, whether it is to individualise a
dosage regimen or otherwise, the application must be considered mathematically.
Due to this, section 4.4 detailed the mathematical formulae required to perform a
stochastic control.

Over the course of this chapter, a stochastic control system has been constructed,
proposed in section 4.3, consisting of attributes that enable individualisation of
dosing for the patient. A diagram of the overall drug dose algorithm is shown in
Figure 4-10.
The control presented considers entire distributions and thus is stochastic; this attribute means the dosage regimen derived in respect of all possible individual PK/PD responses and not merely the average patient response. Most current dosage individualisation methodology is centred on using MAP Bayesian estimates;
with large uncertainty around the patient response it is important to consider what variability there could be around a point estimate.

An alternative methodology in the individualisation of dosage regimens is to reweight the population distribution according to point estimates. This approach derives an estimate of variability in a patient’s PK/PD parameters to allow dosage regimens to be estimated considering the perceived range of a patient’s PK/PD response; a stochastic control approach. However, in this approach an assumption is made, the amount of inter-individual variability in the population PK/PD parameters is representative of the amount in an individual’s PK/PD parameters. This assumption of equivalency of inter-individual variability to intra-individual variability has not been justified. Considering that the variabilities are of different values [112], research is recommended into identifying not only the quantity of intra-individual variability in PK/PD but further just how this intra-individual variability impacts on PK/PD response over time.

Three ways to consider how intra-individual variability in PK/PD response impacts over time were explained in section 4.5. To explore a new implementation to process noise in this thesis, the prediction of the PK/PD response in the drug dose algorithm will be done according to research by Delattre et al. (2011) [108] that is more biologically relevant than previous implementations. The consideration of the entire patient parameter distribution in this way leads to more informed distribution of the PK/PD response. Further the assumption of equivalency of the intra and inter individual variability is not relaxed.
To allow reconciliation of PK/PD model prediction to measurements sampled from the patient, current methodology in using the Kalman filter was reviewed. The implementation of process noise used in this thesis required the mathematics of the Kalman filter to be reconsidered. Currently variance around the mean patient PK/PD response is calculated by the Kalman filter, whereas, in this thesis the variance is to be estimated from separate simulations. This allows the standard Kalman filter to be used in non-linear PK/PD models rather than the extended Kalman filter that requires approximations of the PK/PD models in order to estimate variance [16, 119].

Overall the system proposed is a stochastic closed-loop control that considers noise within the dynamics. To demonstrate the different parts of this system the next chapter will present examples highlighting certain aspects of the drug dose algorithm (sections 5.1 and 5.2) before using the full proposed system in the final example (section 5.3).
The following chapter applies the stochastic control method explained in Chapter 4 to a set of individual dosage regimen estimation problems. To allow deeper understanding of the stochastic control approach the examples will be applied with different aspects of the methodology. This chapter provides examples of drug therapies that can be individualised by PK targets.

The first example for lidocaine therapy is primarily intended to introduce the handling of stochastic parameters within control theory. The second example with warfarin explains an alteration in current methodology in order to deal with patients who have missing covariates, as well as also introducing noise into the PK response estimation. Finally, the full stochastic control methodology explained in Chapter 4 is applied to imatinib therapy showing the robust and adaptive abilities of the approach.

5.1 Example of Obtaining an Optimal IV Infusion Regimen without Feedback

5.1.1 Introduction

The following example from Bayard et al. (1994) [89] is an introduction to the control of dosage regimens. The example considers a single patient requiring a dosage regimen of changeable continuous IV infusion. The drug to be controlled is the local anaesthetic and antiarrhythmic lidocaine.
The individualised dosing of lidocaine had been considered several times before Bayard et al. (1994) by Vozeh et al. (1984, 1985 & 1987) \cite{127-130}. In Vozeh et al.’s applications individual PK/PD parameters were calculated by adjusting population PK/PD parameters by patient factors, i.e. weight, heart failure. Beach et al. (1988) \cite{131} also reported a dose individualisation study, based on the same methodology as Vozeh et al.’s applications.

The key difference between Bayard et al. (1994) and similar studies into individualised lidocaine dosing at that time was the parameterisation of the population PK/PD distributions. In Bayard et al. (1994) a distribution of discrete points was used to describe population PK/PD parameters, the probability of the points are reweighted accordingly for individual patient PK/PD. In previous applications, the population PK/PD log normal distributions appear to be individualised by shifting the distribution according to the mean estimates of individual PK/PD parameters.

In this section, the discrete distribution of an individual’s PK/PD parameters is investigated. Considering how appropriate the method of reweighting a population distribution is for individualised drug therapy.

5.1.2 Method

The individual’s PK parameter distribution in Bayard et al. (1994), shown in Table 5-1, is derived from a non-parametric population PK distribution (using software similar to the current Pmetrics programme \cite{43}). The derivation of the individual’s PK parameter distribution is done by assigning each discrete support point in the
population PK distribution a probability corresponding to the probability that the patient has that specific parameter value.

Table 5-1: Table of PK Parameters and their Respective Probabilities

<table>
<thead>
<tr>
<th>$k_{10}$ (1/min)</th>
<th>prob</th>
<th>$k_{12}$ (1/min)</th>
<th>prob</th>
<th>$k_{21}$ (1/min)</th>
<th>prob</th>
<th>$V_d$ (L)</th>
<th>prob</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0180</td>
<td>0.3085</td>
<td>0.0330</td>
<td>0.4013</td>
<td>0.0190</td>
<td>0.401</td>
<td>13.7</td>
<td>0.401</td>
</tr>
<tr>
<td>0.0225</td>
<td>0.383</td>
<td>0.0660</td>
<td>0.440</td>
<td>0.0380</td>
<td>0.440</td>
<td>27.4</td>
<td>0.440</td>
</tr>
<tr>
<td>0.0270</td>
<td>0.3085</td>
<td>0.132</td>
<td>0.159</td>
<td>0.0760</td>
<td>0.159</td>
<td>54.9</td>
<td>0.159</td>
</tr>
</tbody>
</table>

As lidocaine displays ‘two-stage’ elimination on its concentration time curve it is assumed that a two compartment PK model best fits the data. Extending equation 2.5 to multiple infusions, the concentration time equation for the central compartment is:

\[
C_t = \sum_{k=1}^{n} \frac{IV_{T_s^k}}{V_d} \left( \frac{k_{21} - \beta}{\beta} \right) \left( 1 - e^{\beta(T_f^k - T_s^k)} \right) e^{-\beta(t - T_s^k)} - \left( \frac{k_{21} - \alpha}{\alpha} \right) \left( 1 - e^{\alpha(T_f^k - T_s^k)} \right) e^{-\alpha(t - T_s^k)}
\]  

5.1

where $\alpha, \beta = \frac{1}{2} \left( (k_{12} + k_{21} + k_e) \pm \sqrt{(k_{12} + k_{21} + k_e)^2 - 4(k_{21} - k_e)} \right)$ formulated in Metzler et al. (1971) [34]. The IV infusion of lidocaine will be changeable at seven time points given in minutes; $T_s^n$ with $n = 1, ..., 7$ represents the start of each level of infusion with $T_s^f$ corresponding to the end of the level of infusion. The time points are closer together at the start of treatment to allow the drug to accumulate to a desirable level in the central compartment. To extend equation 5.1 to changing infusion rates the two sets of time points $T_s^n$ and $T_f^n$ are:
For example, applying these time points at the second infusion change point, the plasma concentration at this time is calculated as,

\[ C_{20} = \frac{IV_0}{V_d(\alpha - \beta)} \left( \frac{k_{21} - \beta}{\beta} \right) \left( 1 - e^{\beta(5-0)} \right) e^{-\beta(20-0)} \]

\[ - \left( \frac{k_{21} - \alpha}{\alpha} \right) \left( 1 - e^{\alpha(5-0)} \right) e^{-\alpha(20-0)} \]

\[ + \frac{IV_5}{V_d(\alpha - \beta)} \left( \frac{k_{21} - \beta}{\beta} \right) \left( 1 - e^{\beta(20-5)} \right) e^{-\beta(20-5)} \]

\[ - \left( \frac{k_{21} - \alpha}{\alpha} \right) \left( 1 - e^{\alpha(20-5)} \right) e^{-\alpha(20-5)} \]

Each parameter \((k_\alpha, k_{12}, k_{21} \text{ and } V_d)\) can take one of three values, shown in Table 5-1 all of which are assumed statistically independent. All possible models of the combination of the four parameters with three possible values are considered therefore there are \(3^4\) eighty-one models in total. This is to be seen as eighty-one different PK parameter sets with varying probabilities of appropriately describing the patient’s individual PKs.

The probabilities of the eighty-one parameter sets are calculated by multiplying the single parameter probabilities, given in Table 5-1 together. This leads to some parameter sets being more likely than others, the lowest probability of a parameter set being 0.3085*0.1587*0.1587*0.1587=0.0012 and the highest probability is 0.383*0.44*0.44*0.44=0.033 (almost 3 times as likely to be the patient’s PK parameter values than the lowest probability).
With the pharmacometric model the plasma concentration of an individual patient can be calculated at infusion change points. To guide the plasma concentration to the desired therapeutic target, the cost function to be minimised is:

\[
IV^*_S (\mu g/min) = \arg\min_{IV_5} \sum_{n=1}^{7} \sum_{l=1}^{81} (C_l - 3)^2 \cdot p(\theta_l)
\]

where \( IV_5 = (IV_0, IV_5, IV_{20}, IV_{50}, IV_{110}, IV_{170}, IV_{230}) \) and \( l \) is the number of the parameter set. Notably equation 5.4 contains the probabilities of the individual parameter sets, which give a weighted average of all possible model outputs. The target lidocaine concentration of 3\( \mu \)g/ml in the central plasma compartment was chosen by Bayard et al. (1994) [89] and the therapeutic range is suggested as 1.5-6\( \mu \)g/ml.

To find the optimal regimen to treat all the eighty-one possible models the ‘Solver’ algorithm was used in Microsoft Excel 2007. The algorithm works by inputting different dose regimens until the minimum of the cost function is found [132]. Whilst the algorithm works by trial and error, successive trials are educated ‘leaps’ to another dosage regimen rather than incremental steps.

### 5.1.3 Results

Applying the algorithm, the maximal regimen, \( IV_5 \), was found to be:

\[
IV_5 = (12.5, 3.03, 1.99, 1.39, 1.24, 1.19, 1.18)
\]
These values, given to 3SF, are identical to those reported in Bayard et al. (1994). A concentration time plot of all eighty-one parameter sets is shown in Figure 5-1, the values are simulated based on giving the dosage regimen. None of the parameter sets produce a concentration higher than 6µg/ml, at any infusion change point, as required. However just over 40% of the observations are below the minimum required concentration of 1.5µg/ml demonstrating that the control is tending to favour low concentrations. The target concentration of 3µg/ml is closer to the lower bound of the therapeutic range so this will encourage concentrations to be lower than if the bound was set in the middle of the therapeutic window.

If the target concentration was changed to 3.75µg/ml, the maximal regimen was found to be:

\[ IV_s = (15.6, 3.79, 2.49, 1.74, 1.55, 1.49, 1.48) \]

The new target concentration causes an expected increase in the recommended infusion rates to meet the target. However, still around 35% of the observations are outside the therapeutic range of 1.5-6µg/ml with 17 observations now above 6µg/ml. Additionally, there is still a tendency for the majority of observations to be grouped at the lower concentrations.
Figure 5-1: Concentration time plots from the 81 parameter sets given dosage regimens in equations 5.5 and 5.6 to target 3 and 3.75µg/ml respectively.

The probabilities are multiplied against the squared distance away from the therapeutic target in the cost function, as shown in equation 5.4. This means higher probabilities will be higher multipliers; minimisation will be best achieved when the highest probabilities are multiplied by the lowest squared distances. This leads to the dosage regimen derived being correctly favourable to minimising the distance away from therapeutic target in the highest probability parameter sets. Reducing the left plot of Figure 5-1 to the ten highest probability parameter sets is of interest to demonstrate that the control has performed in this intended way.

As can be seen from Figure 5-2 apart from two time points the dosage regimen has caused the concentrations from two respective parameter sets to reach and stay within the desired therapeutic range of lidocaine. This demonstrates, firstly, that the cost function has worked to encourage the dosage regimen by controlling the parameter sets that have higher probabilities of occurring. However, the range of
responses is not constant due to the discrete non-parametric individual parameter distribution. A constant range could potentially better describe patient response as biological pathways tend to produce a continuous range of output [133].

**Figure 5-2**: Concentration time plots from the ten highest probability parameter sets given the equation 5.5 dosage regimen.

Comparing Figure 5-2 to Figure 5-3, the concentration time plot of the ten lowest probability parameter sets, Figure 5-3 contains mostly observations below the therapeutic range. The dosage regimen of equation 5.5 is less appropriate for the lowest probability parameter sets; this is due to the cost function incurring less cost for these concentration points being outside the target range.
Figure 5-3: Concentration time plots from the ten lowest probability parameter sets given the equation 5.5 dosage regimen.

### 5.1.4 Conclusion

The way a stochastic control algorithm considers the entire distribution is demonstrated in this example. The eighty-one parameter sets, of the PK parameter density, represented all the different possible parameter combinations of the patient’s PKs. Uncertainty involved in a PK system is represented as any one of the eighty-one models could feasibly describe the patient.

In Bayard et al. (1994) a subsequent control is applied where the eighty-one models are reduced a MAP estimate [89]. This singular MAP is the average of all the parameter sets and therefore the dosage regimen that is derived using this method is for the ‘average’ patient PK/PD response. The dosage regimen for the MAP
estimate is then given in simulation to the eighty-one parameter sets the variability of the plasma concentration increases, with observations ranging from 0.9-9µg/ml. This increased range of potential concentrations highlights the risk in assuming that the patient’s PKs are best described by the ‘average’ of potential values. However, even in the stochastic control approach, studied in this section, the estimated optimal infusion rates caused 40% of the predicted plasma concentrations to fall outside the therapeutic range of lidocaine.

One potential reason for this high amount of out of range predictions could be due to the nature of the control utilised. In Bayard et al. (1994) an open-loop control was used; however, the MM approach can perform closed-loop control when measurements of PK response become available. When measurements from the patient are fed back, the MM approach probabilities are re-calculated through finding how close the prediction from the PK parameter sets is to the measurement and reweighting according to proximity [90]. The parameter sets that generate predictions closer to the measurement are derived as a higher probability than those that are further away with their predictions. This process is repeated for every PK measurement taken.

With increasing measurements the derived PK distribution will tend towards describing the patient’s true PK. However, this reliance on feedback suggests a potential concern in regards to the adaptability of the MM approach. This study, in particular, raises questions as to whether the MM approach is appropriate for patients with limited or no measurements.
For example, the majority of out of range concentrations were from parameter sets that have a volume of distribution value 54.9L. This is where the PK parameter distribution is to be analysed as to whether it is appropriate to the individual patient. If the value of 54.9L is not appropriate to describe an individual patient’s volume of distribution, the parameter sets that include 54.9L, even with low probabilities, contribute to altering the dose away from that which is beneficial for the patient.

In contrast, if the patient’s volume of distribution is appropriately described by 54.9L and the control is run including only parameter sets (27 of the 81 parameter sets) with a volume of distribution of 54.9L the individualised dosage regimens are nearly four times the amount of drug compared to those given in equation 5.5. If the patient’s true PK parameters are of this sub-group of parameter sets then they would benefit from a more individualised dosage regimen to bring them within therapeutic range.

This issue suggests that quick identification of whether a patient is in this subgroup is important. With various factors affecting volume of distribution such as body weight [127], genetics [134], even hydration level [135], it is possible to weight patient probabilities more towards subgroups of the volume of distribution and then, if concentration time data becomes available for the patient, update the weighting. This enhanced method of weighting parameter sets can potentially mean adaptability is enhanced.
In light of the conclusions from this study, in the next example, the MM approach is used in an altered way to allow a stochastic control based on covariates affecting PK parameters.

5.2 **Example of Obtaining an Optimal Oral Dosage Regimen with Noise Introduced and an Altered Multiple Model Approach**

5.2.1 **Introduction**

The drug of interest in this example is the anticoagulant warfarin; current dosing algorithms for warfarin, derived by linear regression methods, were explored in the Chapter 3. The difficulties of deciding upon an appropriate maintenance dose for a patient are complicated by high inter-patient variability caused by, for example, pharmacogenetic factors and warfarin being sensitive to dietary intake [44]. When initiated on warfarin therapy the patient is given loading doses before dosing is refined to a daily maintenance dose.

In the previous example of individualising Lidocaine using a MM approach, the adaptability of the methodology was entirely reliant on attaining concentration time measurements. To reduce this reliance on measurements, information on covariates that affect PK parameters can be used in conjunction with the MM approach. To adjust the MM methodology to this new approach, probabilities of parameter sets correspond to the prevalence of covariates that cause variability in PK parameters.

Assuming concentration targets can be created for warfarin therapy then the drug dose algorithm can estimate a dosage regimen to reach these targets. However,
warfarin is not dosed according to plasma concentrations; the INR measurement
informs most dosing decisions with many different nomograms available for use in
the maintenance dosing phase [10]. In the study of this section, concentration
targets are derived from Hamberg et al. (2010) [21].

5.2.2 Method

This example assumes that the loading dose is fixed for each patient, often the
‘10mg, 10mg, 5mg’ regimen is used in the United Kingdom, with the focus being on
a dosage regimen that provides maintenance dosing after this period of loading. To
model the PK of warfarin, a one compartment model with full bio-available oral
dosing is appropriate [21]. The following equations were used to describe how the
plasma concentration of warfarin changes with time:

\[
\frac{dC_A}{dt} = -k_a C_A \tag{5.7}
\]

\[
\frac{dC_t}{dt} = \left( \frac{k_a C_A}{V_d} - k_a C_t \right) dt + d\rho_t \tag{5.8}
\]

To find values for the parameters in equation 5.7 and 5.8 literature on warfarin PK
parameters was searched and in the study by Hamberg et al. (2010) values have
been derived for warfarin S-clearance in differently genotyped CYP2C9 patients of
various ages.
\[ Cl_{s,71} = \begin{cases} 
0.174 \text{ per } 1 \text{ allele} \\
0.0879 \text{ per } 2 \text{ allele} \\
0.0422 \text{ per } 3 \text{ allele} 
\end{cases} \]

5.9

\[ Cl_{s,\text{age}} = Cl_{s,71} + Cl_{s,71}(71 - \text{age})(1 - 0.0571) \]

5.10

where \( Cl_{s,71}, Cl_{s,\text{age}} \) in \( ml/min \) are CYP2C9 and age dependent values for \( S \)-warfarin clearance respectively, age is given in years, and \( CYP2C9_{1,2,3} \) are genotypes known to affect clearance [73]. Two PK parameters were fixed at the population values reported in Hamberg et al. (2010) [21], \( k_a(1/min) = 0.0267 \), \( V_d(L) = 14.3 \), and \( k_e = \frac{Cl}{V_d} \).

Several values for the clearance of warfarin can be achieved by inputting a range of ages along with different genotypes into the equations 5.9 and 5.10. Using the age range of eighteen to ninety-nine and all possible CYP2C9 genotypes led to \( 81 \times 3 = 243 \) possible parameter sets. This density resembles the previous lidocaine density, Table 5-1, in composition; a density of discrete PK parameter points. However, whereas in the lidocaine example the probabilities had been derived in Bayard et al. (1994) from a measurement of PK response (the MM approach); in this warfarin example patients without PK parameters who require individualised dosing are considered in a new altered MM approach by weighting by prevalence of covariates in the population. Prevalence of different covariates were documented in a recent large warfarin study by the International Warfarin Pharmacogenetics Consortium (IWPC) [70] and these informed the probabilities for all 243 parameter sets.
All 243 possible parameter sets would only apply to patients of whom there was no covariate information but some demographic information, such as age, is easy to obtain. In this altered MM approach, when there are covariates that require further diagnostic tests, such as genotyping, whilst the value of the covariate is being determined, dose estimates can still be obtained for the patient based on the prevalence of the covariate.

If another demographic variable that affected the clearance of warfarin was unknown, such as another genotype, the prevalence could be found for the various variants of that genotype and the 243 parameter sets possible for a new patient would grow accordingly.

To demonstrate the altered MM approach, parameter sets for a 20-year old and a 71-year old patient with unknown genotype were considered. Overall, the dose regimen tends towards the most likely parameter sets; however, less likely, but still probable, sets would not be discarded until the covariate is determined. When the value of the covariate is determined the number of parameter sets that are attributable to the patient would be reduced accordingly until eventually only a single parameter distribution is attributed to the patient.

The objective is to find the optimal dosage regimen in this system using the cost function given by,

\[
 u_t^* = \arg\min_{(u_t)} \sum_{t=1}^{4} \sum_{n=1}^{N} (C_t - \beta_t)^2 \cdot p(\theta|I_t) + \gamma_t(u_t) \quad \text{5.11} 
\]
where $u_t$ is an oral dose given at time $t$, $N$ is the number of parameter sets applicable to the patient, $\beta_t$ is the plasma concentration target at time $t$, $p(\theta|\ell)$ is the prevalence of the parameter set $\theta$ in the population and $w_t$ is a weighting that penalised higher doses. The optimisation problem was set to minimise equation 5.11.

The algorithm was applied to two different scenarios; firstly, when dosing to the parameter sets of a 71 year-old with unknown CYP2C9 genotype and secondly, when dosing to the parameter sets of a 20 year-old also with unknown CYP2C9 genotype. There will be three concentration targets of 0.4, 0.3 and 0.2 mg/l; these represent the three concentrations that lead to an INR value of 2.5 for the three different VKORC1 genotypes G/G, G/A and A/A respectively [21]. The results will present an individualised approach to dosing based on previous information.

To find the optimal regimen to treat the six possible models for each patient, the models were inputted into Microsoft Excel 2007 and the dosage regimens calculated via the Solver algorithm [132] minimising the cost function.

### 5.2.3 Results

The dose recommendations for a 71-year old patient are given in Table 5-2. After the three loading doses the control derives a ‘refinement’ dose before the next three doses, which are of similar amounts; from Figure 5-4, Figure 5-5 and Figure 5-6 it can seen that this is due to the loading doses having caused the concentrations from the parameter sets to rise above or dip below the
concentration target. The concentrations for genotypes that are less prevalent in the population appear to be diverging away from the target concentration.

Table 5-2: Dose Recommendations for a 71-year old Patient with Unknown CYP2C9 Genotype.

<table>
<thead>
<tr>
<th>Target (β₁)</th>
<th>Loading 1</th>
<th>Loading 2</th>
<th>Loading 3</th>
<th>Dose Day 4</th>
<th>Dose Day 5</th>
<th>Dose Day 6</th>
<th>Dose Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>(mg/l)</td>
<td>(mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.4</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>9.42</td>
<td>7.32</td>
<td>7.43</td>
<td>7.62</td>
</tr>
<tr>
<td>0.3</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>4.79</td>
<td>5.45</td>
<td>5.55</td>
<td>5.71</td>
</tr>
<tr>
<td>0.2</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>0.16</td>
<td>3.59</td>
<td>3.67</td>
<td>3.79</td>
</tr>
</tbody>
</table>

Figure 5-4: Dose Derivation in for the VKORC1 G/G Target Concentration: 71-year old patient with unknown CYP2C9.
Figure 5-5: Dose Derivation in for the VKORC1 G/A Target Concentration: 71-year old patient with unknown CYP2C9.

Figure 5-6: Dose Derivation in for the VKORC1 A/A Target Concentration: 71-year old patient with unknown CYP2C9.
From equation 5.10 clearance of S-warfarin is shown to decrease with age therefore, due to the PKs, for the same concentration targets the doses recommended will be higher for a 20-year old compared to a 71-year old, this is shown in Table 5-3. A similar pattern, compared to Table 5-2, of dose loading, single refinement and then converging maintenance doses is seen in Table 5-3. Again, lower probability parameter sets appear to be diverging away from the target concentration in Figure 5-7, Figure 5-8 and Figure 5-9, however, in this case the divergence occurs with more acceleration.

Table 5-3: Dose Recommendations for a 20-year old Patient with Unknown CYP2C9 Genotype.

<table>
<thead>
<tr>
<th>Target ( (\beta_t) )</th>
<th>Loading 1 (mg/l)</th>
<th>Loading 2 (mg/l)</th>
<th>Loading 3 (mg/l)</th>
<th>Dose Day 4 (mg)</th>
<th>Dose Day 5 (mg)</th>
<th>Dose Day 6 (mg)</th>
<th>Dose Day 7 (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>13.95</td>
<td>9.96</td>
<td>10.13</td>
<td>10.47</td>
</tr>
<tr>
<td>0.3</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>8.67</td>
<td>7.42</td>
<td>7.57</td>
<td>7.84</td>
</tr>
<tr>
<td>0.2</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>3.39</td>
<td>4.88</td>
<td>5.01</td>
<td>5.21</td>
</tr>
</tbody>
</table>
Figure 5-7: Dose Derivation in for the VKORC1 G/G Target Concentration: 20-year old patient with unknown CYP2C9.

Figure 5-8: Dose Derivation in for the VKORC1 G/A Target Concentration: 20-year old patient with unknown CYP2C9.

Figure 5-9: Dose Derivation in for the VKORC1 A/A Target Concentration: 20-year old patient with unknown CYP2C9.
In Table 5-2 a common complication of optimisation is presented. For the lowest target concentration of 0.2mg/l the dose recommended on day 4 is below the lowest dose that a clinician is currently able to prescribe. With this particular output from the drug dose algorithm the clinician would decide whether to not give the patient a dose of warfarin that day or to give them the lowest possible dose. Other dose recommendations shown in Table 5-2 and Table 5-3 are able to be rounded to doses that can be prescribed.

5.2.4 Conclusion

This study suggests the benefit of including covariates that affect PK parameters in an altered MM approach. Currently, the MM approach does not consider covariate information [136] however the alteration performed in this study suggests a methodology to incorporate such data.

This inclusion of covariate information is one form of closed loop feedback as it causes the system to update parameter information. In clinical practice basic demographics like age are recorded routinely and are readily available to the clinician. Whereas some covariates will require extra testing to determine, for example, genotyping tests often take time to be completed and as a result will not be directly available to be included in initial dosing decisions. The drug dose algorithm of this section considered weighted probabilities to estimate dosage regimens, in absence of genotype covariate information.

Considerations in using the altered MM approach would the requirement of sufficient data for particular covariates to be investigated. Even when the
parameter distributions are generated from larger datasets, such as in this example, assumptions still have to be made. In the example above, a linear relationship was assumed for age however more data could suggest the relationship between age and a clearance to be more complex.

In addition to linear regression methods, MAP Bayesian control has also been used to individualise warfarin dosing [5, 79]. The control approach used in this study can be used alongside this current methodology; the relevant parameter-covariate sets for a patient can be used as prior information when plasma concentrations are sampled. If the covariate that affects the PK parameter is determined, the posterior results of MAP Bayesian control can be used to inform the respective parameter set for that covariate. For example if there are measurements taken from a patient before they are identified to have CYP2C9 *1*3 genotype then the information from the measurements along with other CYP2C9 *1*3 patient measurements will be used to inform the CYP2C9 *1*3 parameter set in a subpopulation PK analysis. This informed CYP2C9 *1*3 model will then be available in dosage recommendation for future patients.

Further work to make this example of stochastic control more robust would have been to feedback measured concentration values. This process ‘checks’ the prediction of the pharmacometric model against the measurement and reconciles the two to reduce the uncertainty around the true concentration of warfarin in the body. This reconciliation will be done in the next example using the Kalman Filter, explained in section 4.6. This feedback is considered in the subsequent example of this chapter. Further, the plasma concentration over continuous time, rather than
at dosage changes, will be estimated to ensure the patient is dosed after considering the entirety of predicted future outcomes.

Secondly, the noise introduced to the plasma concentration predictions was done by adding a random value onto the prediction, see equation 5.7. As discussed in 4.6.2.5 this process of inputting noise does not lead to a distribution of predicted patient response that is reconcilable using the Kalman filter. In the next example, noise through varying the parameters of the PK model within their distributions by the process explained in 4.5.2 is implemented.

This example has shown that covariate-parameter relationships can be used to inform dosing for a new patient. The parameter values for the example were taken from literature and therefore represent an approach in which data is compounded from other sources rather than concentration-time data. Thus reducing the need for measured patient samples, which require analysis using pharmacometric software incurring extra time and resources.

5.3 Example of Obtaining an Optimal Oral Regimen with Parameter Noise Introduced and Measurements Used to Update the System

5.3.1 Introduction

Imatinib, used in the treatment of leukaemia [137], has an established standard of care however patient PK/PD response is ranging largely due to the inter-individual variability in the population [138]. Imatinib is usually administered as a 400mg dose regardless of patient dosing needs with 800mg doses prescribed if there is an apparent resistance to the drug. Recent publications suggest that the drug be dosed
to maintain an individual trough plasma concentration of around 1000ng/ml [39, 137], this is to ensure that the plasma concentration of the drug stays high enough to inhibit proliferation of Philadelphia positive (Ph+) metaphases [138].

Instead of the MM approach, used in the previous lidocaine and warfarin examples, patient PK parameters point estimates were calculated from the data and a distribution of intra-individual variability was constructed around these point estimates. The measured plasma concentrations were then fed back into the system to reduce uncertainty around the plasma concentration of imatinib.

### 5.3.2 Method

Serial blood samples were collected from a sample of twelve patients attending routine clinic visits at The Royal Liverpool University Hospital between April 2006 and August 2011. The patients were taking imatinib as treatment for chronic myeloid leukaemia. The dataset extract for this study includes patient ID number, time interval since last dose taken (hours), last dose taken (mg) and plasma concentration measurements (ng/ml). The twelve patients in the dataset had their plasma concentrations of imatinib measured six to eight times in a twenty-four hour period post-dose.

Peripheral blood was collected in EDTA coated Monovettes® (Starstedt, Germany) and stored at 4°C until processing. The blood was spun at 500 rcf (relative centrifugal force) and the plasma collected was stored at -80°C until analysed. Imatinib plasma levels were determined by simple UV-HPLC analysis as described by Davies et al. (2009) [139].
The plasma concentration over time is appropriately modelled by a one compartment PK model with full bio-available oral dosing [39, 137]. The following equations describe how the concentration changes with time:

\[
\frac{dCA_t}{dt} = -k_a CA_t \quad 5.12
\]
\[
\frac{dC_t}{dt} = \left(\frac{k_a CA_t}{V_d} - k_e C_t\right) \quad 5.13
\]

where \( k_a, k_e \sim lnN(\mu, \sigma^2) \) are stochastic variables that change randomly every time step (see section 4.5.2).

The estimated individual parameters are shown in Table 5-4 calculated using NONMEM (Version 7.2) in a previous study by Lane et al. (2011) (unpublished work). NONMEM produces point Bayes estimates of individual parameters therefore the values of Table 5-4 formed the mean (\( \mu \)) of the PK parameter distribution. Since distributions indicating intra-individual variability were required for this imatinib example, literature was searched to find estimates of intra-individual variability previously seen in patients taking imatinib. Haouala et al. (2009) [140] indicate that imatinib has a low intra-individual variability however the referenced paper by Picard et al. (2006) [39] does not provide a value for intra-individual variability. Widmer et al. (2006) [141] reported intra-individual variability of 31% in the plasma concentrations of imatinib patients however the paper is unclear as to whether the assay error was included in this amount.
The following methods were performed in MATLAB and a code is provided in Appendix: I of this thesis. To allow an amount of intra-individual variability in the PK response to be studied two parameters, $k_a$ and $k_e$ were selected to vary within their distributions with respect to time. Due to the relationships between all the parameters, varying these two variables caused the entire patient PK to vary with time. In absence of intra-individual variability indication in literature, the lognormal distributions of $k_a$ and $k_e$ were described by $\ln N(\ln(\text{para}), \text{para})$ where $\text{para}$ is the value of the respective parameters in Table 5-4. Due to noise being introduced to the system five simulations were used for each dosage regimen to predict a distribution of plasma concentration.

Table 5-4: Individual PK parameter Bayes estimates.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>$k_a$ (1/h)</th>
<th>$k_e$ (1/h)</th>
<th>$V_a$ (l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>0.436</td>
<td>0.0613</td>
<td>232</td>
</tr>
<tr>
<td>54</td>
<td>0.703</td>
<td>0.0459</td>
<td>313</td>
</tr>
<tr>
<td>56</td>
<td>0.727</td>
<td>0.0523</td>
<td>312</td>
</tr>
<tr>
<td>78</td>
<td>0.617</td>
<td>0.0594</td>
<td>275</td>
</tr>
<tr>
<td>91</td>
<td>0.494</td>
<td>0.0285</td>
<td>297</td>
</tr>
<tr>
<td>101</td>
<td>0.307</td>
<td>0.0632</td>
<td>295</td>
</tr>
<tr>
<td>118</td>
<td>0.684</td>
<td>0.0583</td>
<td>287</td>
</tr>
<tr>
<td>119</td>
<td>0.454</td>
<td>0.0617</td>
<td>280</td>
</tr>
<tr>
<td>122</td>
<td>0.317</td>
<td>0.0437</td>
<td>353</td>
</tr>
<tr>
<td>124</td>
<td>0.722</td>
<td>0.0578</td>
<td>193</td>
</tr>
<tr>
<td>244</td>
<td>0.674</td>
<td>0.0396</td>
<td>271</td>
</tr>
<tr>
<td>328</td>
<td>0.190</td>
<td>0.0361</td>
<td>335</td>
</tr>
</tbody>
</table>

At every measurement time point the Kalman filter [142] is utilised to reconcile the prediction from the differential equations given in equation 5.12 and the measurement. After the measurements were feedback, dosage regimens for seven
twenty-four hour periods were required. A dosing period of seven days allowed patients who may have trough concentrations below or above the desired trough concentration to be prescribed doses to bring them closer to the target concentration before the system derives the appropriate maintenance dosing of imatinib.

The dosing period of a week was assumed long enough for therapeutic trough plasma concentration of imatinib to be achieved and then maintained with the final estimated dose. The drug dose algorithm was only allowed to derive doses in multiples of 100mg as these are the smallest available tablet sizes of imatinib [143] and therefore the dosage regimens that were estimated can be prescribed to the patient.

Given the metrics of the dose requirements and the target trough concentration of 1000ng/ml, the cost function is expressed as:

$$u^*_t = \arg \min_{(u_t)} \sum_{t=1}^{7} \sum_{k=1}^{5} (C_t - 1000)^2$$

$k = 1, ..., 5$ is the number of simulation chains used.

To show the effect of the adjusted dosage regimen derived by the drug dose algorithm each individual patient’s trough concentration over seven days given two dosage regimens were simulated; the dose they were receiving at the time of sampling and the recommended doses estimated by the system. The difference between the trough concentration values achieved and the target trough plasma
concentration of 1000ng/ml [39, 137] is an indicator of the performance of the control.

5.3.3 Results

The dosage regimes derived from the set of twelve patients included in this study are shown in Table 5-5. Results show that the drug dosing algorithm derived new dosage regimens for all but three patients. Of those identified as requiring a different dosage regimen none of the derived dosage regimens recommend a return to the original dose of imatinib after seven days of revised therapy. This suggests that the standard 400mg dose of imatinib does not bring the majority of patients to the TTL of 1000ng/ml. Further in the cases of patients 119 and 122 who were on a dose of 800mg daily when blood samples were taken, only the dosage regimen of patient 119 suggests this was an adequate adjustment to meet the trough plasma concentration target.
Table 5-5: Comparison of the Performance of Current and Revised Dosage Regimens for Each Patient.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Current Daily Dose (mg)</th>
<th>Average Deviance from TTL (ng/ml)</th>
<th>Seven Day Dosage Regimen (mg)</th>
<th>Revised Daily Dose (mg)</th>
<th>Average Deviance from TTL (ng/ml)</th>
<th>Revised Mean Dosage Difference (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>400</td>
<td>-400</td>
<td>800, 700, 700, 700, 700, 700, 700.</td>
<td>400</td>
<td>-314</td>
<td>30</td>
</tr>
<tr>
<td>54</td>
<td>400</td>
<td>-328</td>
<td>700, 600, 600, 600, 600, 600, 600, 600.</td>
<td>328</td>
<td>-214</td>
<td>13</td>
</tr>
<tr>
<td>56</td>
<td>400</td>
<td>-442</td>
<td>800, 700, 700, 700, 700, 700, 700, 700.</td>
<td>442</td>
<td>-314</td>
<td>-43</td>
</tr>
<tr>
<td>78</td>
<td>400</td>
<td>-489</td>
<td>800, 800, 800, 800, 800, 800, 800, 800, 800.</td>
<td>489</td>
<td>-400</td>
<td>0</td>
</tr>
<tr>
<td>91</td>
<td>400</td>
<td>453</td>
<td>200, 200, 300, 300, 300, 300, 300, 200.</td>
<td>53</td>
<td>129</td>
<td>47</td>
</tr>
<tr>
<td>101</td>
<td>400</td>
<td>-512</td>
<td>800, 800, 800, 800, 800, 800, 800, 800, 800.</td>
<td>512</td>
<td>-400</td>
<td>-54</td>
</tr>
<tr>
<td>118</td>
<td>400</td>
<td>-504</td>
<td>800, 800, 800, 800, 800, 800, 800, 800, 800.</td>
<td>504</td>
<td>-400</td>
<td>-29</td>
</tr>
<tr>
<td>119</td>
<td>800</td>
<td>-13</td>
<td>No revision needed</td>
<td>13</td>
<td>143</td>
<td>9</td>
</tr>
<tr>
<td>122</td>
<td>800</td>
<td>432</td>
<td>400, 500, 600, 600, 600, 600, 600, 600.</td>
<td>328</td>
<td>No revision needed</td>
<td>9</td>
</tr>
<tr>
<td>124</td>
<td>400</td>
<td>-244</td>
<td>600, 500, 500, 500, 500, 500, 500, 500, 500.</td>
<td>244</td>
<td>No revision needed</td>
<td>-50</td>
</tr>
<tr>
<td>244</td>
<td>400</td>
<td>-13</td>
<td>No revision needed</td>
<td>13</td>
<td>114</td>
<td>9</td>
</tr>
</tbody>
</table>

Also shown in Table 5-5 are the average deviances from the TTL, which is an indicator of the accuracy of the dosage regimens derived by the system. As the drug dosage algorithm is restricted to estimating feasible doses of 100mg multiples the TTL may not be exactly met even with the revised dosage regimens. If the patients who are advised onto revised dosage regimens were to stay on their standard daily doses then the patient will be up to 48.9% away from the TTL which would lead to doubts as to whether the drug is indeed providing sufficient enzyme inhibition [39]. The concentration-time curves for firstly, the dash dot line, if the patient continued receiving the same dose as at the time of sampling and then secondly, the double dash line, if they were prescribed the derived dosage regimen are shown in Figure 5-10 to Figure 5-18.
Figure 5-10: Plasma Concentration time profile of Patient 28 receiving imatinib.

Figure 5-11: Plasma Concentration time profile of Patient 54 receiving imatinib.
Figure 5-12: Plasma Concentration time profile of Patient 56 receiving imatinib.

Figure 5-13: Plasma Concentration time profile of Patient 78 receiving imatinib.
Figure 5-14: Plasma Concentration time profile of Patient 91 receiving imatinib.

Figure 5-15: Plasma Concentration time profile of Patient 101 receiving imatinib.
Figure 5-16: Plasma Concentration time profile of Patient 118 receiving imatinib.

Figure 5-17: Plasma Concentration time profile of Patient 122 receiving imatinib.
5.3.4 Conclusion

Research into individualising imatinib therapy is available in literature. One particular area of research is in identifying a plasma concentration target that leads to therapeutic response in patients. Based on studies by Picard et al. (2007) [39] and Larson et al. (2008) [137] a target of 1000ng/ml was utilised in this study. However, further research into the individualisation of plasma concentration targets would be recommended, Gotta et al. (2012) [144] reported that variable therapeutic plasma concentration targets had been derived in different population studies. Variable therapeutic plasma concentration targets in different populations would suggest that targets could be individualised based on covariates such as race or pharmacogenetics. Studies where individualised dosage regimens are estimated do not appear in literature. This study suggests that individualised imatinib dosing is preferable to standard dosing in bringing a patient to TTL.
Of the revised dosage regimens the largest average deviation is 5.4% below TTL, which shows the drug dose algorithm is attempting to bring the patient to TTL. Especially encouraging is that patient 78, who was shown in simulation to experience the largest deviation of 48.9% from TTL if they continued to receive standard dosing, would greatly benefit from the therapeutic effect of the revised dosage regimen, which causes no departure from TTL, shown in Table 5-5 and Figure 5-13.

Further, all of the revised dosage regimens show large reductions on the deviations for TTL, as shown in Table 5-5. The drug dosage algorithm is restricted to estimating feasible doses of 100mg multiples the TTL may not be exactly met even with the revised dosage regimens. If the patients who are advised onto revised dosage regimens were to stay on their standard daily doses then they will be up to 48.9% away from the TTL, further seven of the ten patients will be an estimated between 24.4-48.9% below the TTL, which would lead to doubts as to whether the drug is indeed providing sufficient enzyme inhibition.

For some patients a constant dosing level does not appear suitable to maintain them at the desired TTL. This is apparent with patients 91 and 122, see Figure 5-14 and Figure 5-17 respectively, as their doses never converge to one constant daily amount unlike the other patients in the study. These patients would benefit from the drug dose algorithm outlined in this study as the algorithm will derive the best possible doses to reach therapeutic targets whereas in practice only constant daily doses of 400/600/800mg are prescribed.
The approach utilised in this section used parameter densities that represented the intra-individual variability of each patient. This ties into a wider philosophy presented in this thesis that each patient has their own unique parameter density that describes their intra-individual variability by central tendencies and uncertainty. This is in contrast to the previous lidocaine study, in this thesis, where an optimal infusion rate was determined by the MM approach [89], which uses probabilities attached to a reweighted population parameter density to individualise the control to the patient.

The comparison between MM approach and the new methodology applied in this imatinib dosing study is that the intra-individual variability is not assumed to take the value ranges of the inter-individual variability seen in the population. Further, with the intra-individual distributions in this study dosage regimens were estimated that considered the potential for patient PK parameters to change over time. This is in contrast to current individualised dosage regimen control approaches that either assume PK parameters remain fixed throughout studies [145] or can only change value when measurements are taken [109].

The Kalman filter was used to estimate the plasma concentration of patients when measurements were taken. This particular feedback can be thought of as a ‘soft reset’ for the system as only the output parameter, the plasma concentration in this example, is being adjusted. If any future measurements are taken, after a new dosage regimen has been prescribed, the drug dose algorithm can loop these measurements in as well and then derive any further revisions of the drug dose regimen that are required. Further research into identifying the intra-individual
variability seen in PK parameters is required to improve the feedback approach in this study. A potential area would be the development of methodology that calculates the likelihood of PK parameters given the data however does not assume that parameters are time-homogenous.

In conclusion, the drug dose algorithm described in this study provides an effective method to estimate individualised dosage regimens for patients receiving imatinib therapy. The drug dosage algorithm used the Kalman filter to process feedback from plasma concentration samples and predictions from the PK model. The predictions from the PK model were derived from PK parameters allowed to vary within their distributions that represented intra-individual variability. Dosage regimens were calculated by a control function that seek to bring a patient to the reported therapeutic target of imatinib. The system is able to be updated at any point when a measurement from a patient becomes available and a new dosage regimen for any length of treatment can be derived to meet changing therapeutic targets.
The cost function was explained previously in Chapter 4 as a mathematical equation that determines the optimal dosage regimen from a set of all possible dosage regimens. The particular example of a cost function considered in the examples of Chapter 5 determined the optimal dosage regimen by minimising the distance of the predicted PK/PD response from the target value.

The stochastic control of discrete outcome probabilities is presented in this chapter, which requires new formulations of the cost function. The first four sections explain the different ways to utilise discrete outcome probabilities in the individualisation of drug therapy ranging from a post-estimation diagnostic to merging Markov modelling into the cost function of the stochastic control method.

Another example of applying the drug dose algorithm in imatinib therapy is presented where the control function is formulated to control multiple targets, which include probabilistic targets of PD outcome. The results of the approach are compared to the results of section 5.3, the imatinib therapy example.

### 6.1 Examples of Discrete Outcomes in Pharmacometrics Application

#### 6.1.1 Adverse Drug Reactions

The individualisation of a dosage regimen to a specific patient is undertaken to determine the optimised therapy given clinical targets. One such target is a desired
plasma concentration and in previous chapters of this thesis the methodology of using stochastic control to derive a dosage regimen that achieves target PK concentrations is discussed and demonstrated.

Another clinical target, which also affects dosing decisions, is the risk of adverse drug reactions. Dose-dependent adverse drug reactions account for the majority of adverse events; in many cases, higher doses lead to a heightened risk of an adverse drug reaction [146]. However, higher doses can also be required to induce a required therapeutic plasma concentration. This trade-off complicates dosing decisions; with some drug therapies achieving the plasma concentration target may be paramount and an increased risk of adverse drug reactions is an unfortunate consequence in the need for a definite treatment effect. This is often the trade-off between efficacy and the risk of an ADR required in cancer therapy as curing or preventing the spread of cancer is the main priority due to the high death rate from the disease.

However, other drugs can cause severe ADRs, in this case, reducing the risk of occurrence is seen as more important. For example, in warfarin therapy, whilst there are long term health risks with thrombosis, if a higher dose is causing severe side effects then the clinician may consider lowering the dose of warfarin.

ADRs can be predicted by generating models based on data collected from patient response and use of these models is possible in individualised drug dosing [147]. One way to predict the chance of an adverse event is incidence rate monitoring, which is demonstrated later this in chapter.
**6.1.2 Therapeutic Outcomes**

The relationship between drug dose and therapeutic effect on the body is often non-linear. Often the non-linear relationship is modelled by the Hill equation \([148]\). As the Hill equation is a logistic function, at the lowest and highest possible concentrations the effect of the drug on the body will be the two polar extremes of patient response; between these points the range of concentrations will cause gradually increasing magnitudes of drug effect. However, when the relationship between the drug and patient response is not fully established dosing decisions are more complicated. In this situation a probabilistic approach is recommend. In this chapter, probabilities of patient response will be derived and their use in the drug dose algorithm discussed.

Discrete patient responses (DPRs) are set of particular patient responses rather than a continuous scale of patient response. An example of a DPR is the level of therapeutic outcome; e.g. low, moderate or high pain relief. Often a link can be hypothesised between a PK target and a PD effect but the mechanism between the two is not modelled due to issues such as complexity of the mechanism or the inability to measure components of the mechanism.

The incorporation of probabilistic ADRs or DPRs (‘discrete events’) into the estimation of a dosage regimen using stochastic control theory has not been explored previously. In this chapter, methodologies for analysing data to derive probabilities of future ADRs or DPRs are explained, beginning with utilising population data and then progressing to a more mathematical approach of Markov
modelling. Similar to pharmacometric data, reporting can be varied in quantity and quality, the effect of this variability will be discussed in the next section.

### 6.2 Discrete Event Reporting

Discrete event reporting is required in many areas of research including pharmacovigilance, hospital operations and recently the emerging field of health economics. Health economics research utilises discrete event data to ascertain the costs of treatments. Therefore, the main requirement of the discrete event data in health economics is the information on the occurrence and around consequence and treatment.

For discrete event data to be incorporated into the stochastic control algorithms, information is required on why the discrete event occurred. If the discrete event is dependent on the PK response of a patient the ideal source of data would be a PK response measurement at the time of the event. In practice this is not routinely collected and, in the absence of individualised data, other techniques are used, such as the event concentrations from a few sampled patients being extrapolated across the entire population. When PK sampling is not possible in patients, event rates can be presented in respect of dosage amounts. Whilst some dosages of a drug could be linked to event rates over a population, on an individual level this approach ignores the variability in the PK/PD between patients.

For example, consider a population of two patients, one with a low rate of drug clearance and the other with a high clearance, a dose of any amount would cause different plasma concentrations at time points post-dose. If the low drug clearance
patient was to experience an event then the event rate for that given dose would be 50%. Now if this information was utilised to individualise a dose for a new patient, regardless of whether a patient’s rate of drug clearance was known, all dosing at that given dose would have to be considered as incurring a 50% chance of an event. If the plasma concentration of the patient experiencing the event had been measured then there would be the opportunity to introduce individualisation as the event rate is no longer associated with the dose (the input to the PK/PD system) but rather the plasma concentration.

To enhance the ability of the drug dose algorithm presented in this thesis, which estimates individualised dosage regimens to induce therapeutic targets, this chapter will explore probabilities of discrete outcomes. This builds on the research presented in previous chapters, a stochastic control system constructed in Chapter 4 to estimate dosage regimens that induce a certain plasma concentration, examples of which are given in Chapter 5. The enhancement will be the methodology of how to derive and incorporate the information from probabilities into the drug dose algorithm. The following examples will discuss the use of discrete event data within stochastic control algorithms. The first example will discuss a post-control application with subsequent examples incorporating the data into the control function.

### 6.3 Post-Control Determination of Discrete Event Probability

#### 6.3.1 Use of Discrete Event Data Stratified by Dose

In this approach the dosage regimen estimated using stochastic control is subject to post-control assessment with criteria determined by adverse event data. As the
adverse event data is used post control it does not affect the dosage regimen estimation but does provide a probability that the dosage regimen will cause an adverse event in the average patient.

As an example of this approach data presented in literature from a study investigating the safety of topiramate, a drug used in the treatment of epilepsy [149], is applied. In the publication, a table explaining the adverse events at different dosages is presented. If a stochastic controller for topiramate was constructed then dosage regimens derived from the controller could be assessed for their adverse event rates. To demonstrate this assessment, ten ascending dosage regimens were considered, these dosage regimens range from the lowest possible dose to the highest possible dose.

Table 6-1: Table of Probabilities of Adverse Events Occurring at Different Dosages

<table>
<thead>
<tr>
<th>Dosage Regimen</th>
<th>Probability of Developing the Adverse Event ‘Confusion’ During the Dosage Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>200, 200, 200, 200, 200, 200, 200</td>
<td>0.09 * (1) = 0.09 as probability is constant throughout</td>
</tr>
<tr>
<td>200, 200, 200, 400, 400, 400, 400</td>
<td>0.09 * (3/7) + 0.15 * (4/7) = 0.12</td>
</tr>
<tr>
<td>400, 400, 400, 400, 400, 400, 400</td>
<td>0.15</td>
</tr>
<tr>
<td>400, 400, 400, 600, 600, 600, 600</td>
<td>0.17</td>
</tr>
<tr>
<td>600, 600, 600, 600, 600, 600, 600</td>
<td>0.18</td>
</tr>
<tr>
<td>600, 600, 600, 800, 800, 800, 800</td>
<td>0.16</td>
</tr>
<tr>
<td>800, 800, 800, 800, 800, 800, 800</td>
<td>0.15</td>
</tr>
<tr>
<td>800, 800, 800, 1000, 1000, 1000, 1000</td>
<td>0.24</td>
</tr>
<tr>
<td>1000, 1000, 1000, 1000, 1000, 1000, 1000</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Table 6-1 shows the different probabilities for respective dosage regimens, the clinician would be able to see the probability that different dosage regimens have
of causing adverse events over the population. If the probability of adverse event was considered too high in the clinician’s opinion, they could adjust the dosage regimen accordingly. This process allows important clinical judgement to be introduced at another stage of the drug dosing algorithm.

This method serves as a diagnostic on already derived dosage regimens; the next examples will explore how to incorporate the information into the control.

### 6.3.2 Use of Discrete Event Data Stratified by PK response

If a certain plasma concentration was known to induce discrete events then to perform a post-control evaluation of an estimated dosage regimen, firstly, information on the plasma concentration at which the events have occurred would be pooled. This is similar to identifying an appropriate concentration level for therapeutic effect, for instance the 1000ng/ml target used in the imatinib example from section 5.3.

Consider a drug X that is dosed according to a therapeutic trough plasma concentration of 800ng/ml whilst a trough plasma concentration in excess of 1500ng/ml is linked with an ADR. To calculate the probability that the patient will experience the ADR the predicted trough plasma concentration distribution will be estimated and the probability to the right of 1500ng/ml will be the probability of experiencing an ADR on the given dosage regimen.

For example, consider the probability distribution shown in Figure 6-1. The distribution in the grey shaded area is the probability of an ADR occurring at any
time, $t$, on the derived dosage regimen. Each individual dose in the dosage regimen would have a probability distribution attached.

![Diagram](image)

Figure 6-1: Post-Control Discrete Event Probability Determination at Time $t$.

6.3.3 Considerations of Post-Control Discrete Event Probability Derivation

The above examples are sub-optimal for use in individualising drug dosage regimens as the data are not used in the derivation of the regimen but rather as a diagnostic. With this methodology important clinical data is separated from the derivation of the dosing regimen. This separation means the dosage regimen cannot be declared optimal as the discrete data was not incorporated into the control and therefore whilst dosage regimens could induce plasma concentrations
to reach the required therapeutic targets they may also induce plasma concentrations that increase the risk of a discrete event, such as, ADRs.

However, there are advantages to post-control diagnostics of a dosage regimen. In particular, the example in section 6.3.1 was based on event rates being stratified by dose, is a simple application of event data that does not require any data not routinely recorded in clinical practice. However, the approach does not contribute to individualising a dosage regimen as it is population based and a single dose can cause different effects between patients.

Due to these considerations, a drug dose algorithm that uses discrete event probabilities within the control is more appropriate. To enable the drug dose algorithm to derive dosage regimens with discrete event probabilities within the control an adjustment of the system is required. The current system diagram of the drug dose algorithm is shown in Figure 4-10. The next step is to incorporate discrete event probabilities into the controller, shown in the ‘Dose Estimation’ section; this step is shown in Figure 6-2.
Figure 6-2: System Diagram of the Stochastic Controller.
6.4 Intra-Control Determination of Discrete Event Probability

A clinical decision about dosing involves many considerations regarding the different factors that will affect the drug therapy for the individual patient. Often many of these factors are weighted by a clinician’s experience, for instance, with a drug that is treating a very serious disease the importance of ensuring the concentration of the drug in the body is high enough to obtain a therapeutic effect may be paramount compared to the risk of an adverse events occurring. In some drug therapy situations the importance is vice versa, such as when the treatment is long term.

This process of weighting multiple outcomes of therapy is important in this application of stochastic control. Due to the mechanistic nature of the controller the weightings must be interpreted numerically. This numericalisation is complicated by subjectivity, as often weightings are established from a clinician’s experience, which can be highly variable. The issue of weightings is discussed by Ji et al. (2007) [150] where the authors suggest the ranking of different concentrations and their respective effectiveness and toxicity responses in patients. The most desirable outcome, the combination of a highest possible effectiveness with a lowest possible toxicity is given an indifference probability of 1 and then the remaining outcomes, in order of depreciating desirability, are ranked in proportion to the most desirable outcome until the least desirable outcome, which has an indifference probability of 0.

For example, the most desirable outcome is assigned an indifference probability of 1, if there is another outcome that is only slightly less desirable then an indifference
probability of 0.95, or similar high indifference probability, might be assigned to that outcome. The example in Ji et al. (2007) has 5 possible outcomes with indifference probabilities of 1, 0.9, 0.6, 0.2 and 0 respectively. Unfortunately, subjectivity is still introduced by the process of choosing indifference probabilities. When expert clinical opinion is utilised this may not be a major issue, however if subjectivity can be compounded and reinforced with statistical methodology then this is the optimal solution.

### 6.4.1 Development of Discrete Event Control

To generate probabilities of discrete events occurring dependent on therapy a Markov model is a recommended. A standard decision tree model could be used to describe the probabilities [151] where probabilities are derived by considering the frequency of different outcomes after a certain therapy. In contrast to standard decision tree models, Markov models allow probabilities to be time-dependent [152] as well as the ability to consider the patient returning to a previous discrete event [37]. Both of these aspects of Markov modelling are required to perform the novel methodology step of this section; the integration of Markov model probabilities within the stochastic control cost function.

Currently Markov models are used in the cost-effectiveness evaluation of drugs. By considering probabilities of future events alongside the cost of future events, a predicted cost of a therapy can be calculated. As Markov models describe how a random process can evolve over time, this means that different outcomes of therapy, and their cost-effectiveness implications, can be considered by repeated simulation.
For instance, one simulation may consider a situation where the patient will respond very well to therapy, experiencing no adverse events, and therefore the costs of treating the adverse events are not incurred. However, another simulation can consider a situation where the patient experiences multiple adverse events that incur costs to treat. The overall distribution of these simulations presents the possibilities of cost incurred by a therapy and decisions about the therapy can be made based on this distribution.

In a publication by Zingmark et al. (2005) [37] Markov mixed-effect modelling was used to generate time-dependent probabilities. The focus of the publication was to derive probabilities of experiencing different levels of side-effects rather than the cost-effectiveness of the therapy. Accordingly, changes in a side effect response to a drug were recorded for twelve patients every three minutes. Infusion rates of the drug were individualised to achieve the same concentration of the drug in each patient. The model constructed included three states 0, 1 and 2 for when the patient experienced no side effects, mild side effects and moderate to high side effects respectively. The Markovian approach to the problem of predicting discrete events is effective but requires extra data to derive parameter estimates.

The model for the drug used to demonstrate the methodology in the publication was a two-compartment model with constant intravenous administration. The model needed to be linked with the discrete side effect data (0, 1 or 2) collected. In this application the risk of transitioning to a different state of side effect is interpreted from the PK model. The model presented in the appendix code of the
publication formulates the effect compartment amount as shown in equation 2.8 with $E_{base} = 0$.

To begin the estimation of probabilities of side effect state the logistic transform is used,

$$P(s_f|s_c) = \frac{e^{l_x}}{1 + e^{l_x}}$$  \hspace{1cm} (6.1)

with the following logits,

$$l_x = \begin{cases} 
    b_1 + EFF_t & \text{for } s_f \geq 1 | s_c = 0 \\
    b_1 + b_2 + EFF_t & \text{for } s_f = 2 | s_c = 0 \\
    b_3 + EFF_t & \text{for } s_f \geq 1 | s_c = 1 \\
    b_3 + b_4 + EFF_t & \text{for } s_f = 2 | s_c = 1 \\
    b_5 + EFF_t & \text{for } s_f \geq 1 | s_c = 2 \\
    b_5 + b_6 + EFF_t & \text{for } s_f = 2 | s_c = 2
\end{cases}$$  \hspace{1cm} (6.2)

where $b_1 \ldots b_6$ are baseline fixed-effect parameters, $s_f$ is the future state and $s_c$ is the current state of the patient’s adverse events. Based on the logistic transform and respective logits the probability tree shown in Figure 6-3 can be constructed. As the dose effect changes over time this means that the probabilities of $s_f|s_c$ will change over time. Despite these changing probabilities of the future adverse event state, the summation of the probabilities given any current state, $P(s_f = 0,1,2|s_c)$, will always be equal to one. This is an essential characteristic of probability in the Markovian model as $s_f = 0,1,2$ represent the entirety of future outcomes regardless of the current state occupied.
Figure 6-3: Probability Tree of Adverse Event States.

The diagram of the different states and the probabilities are shown in Figure 6-4 to provide a visual representation of the three state Markov model. Each arrow represents a probability and each direction the transition occurring, for example, an arrow going from 1 to 2 represents the probability $P(s_f = 2|s_c = 1)$. 

For each state $s_c$:

- **$s_c = 0$**
  - $P(s_f = 0|s_c = 0) = 1 - \frac{e^{b_1 + \text{EFF}_t}}{1 + e^{b_1 + \text{EFF}_t}}$
  - $P(s_f = 1|s_c = 0) = \frac{e^{b_1 + \text{EFF}_t}}{1 + e^{b_1 + \text{EFF}_t}} - \frac{e^{b_1 + b_2 + \text{EFF}_t}}{1 + e^{b_1 + b_2 + \text{EFF}_t}}$
  - $P(s_f = 2|s_c = 0) = \frac{e^{b_1 + b_2 + \text{EFF}_t}}{1 + e^{b_1 + b_2 + \text{EFF}_t}}$

- **$s_c = 1$**
  - $P(s_f = 0|s_c = 1) = 1 - \frac{e^{b_3 + \text{EFF}_t}}{1 + e^{b_3 + \text{EFF}_t}}$
  - $P(s_f = 1|s_c = 1) = \frac{e^{b_3 + \text{EFF}_t}}{1 + e^{b_3 + \text{EFF}_t}} - \frac{e^{b_3 + b_4 + \text{EFF}_t}}{1 + e^{b_3 + b_4 + \text{EFF}_t}}$
  - $P(s_f = 2|s_c = 1) = \frac{e^{b_3 + b_4 + \text{EFF}_t}}{1 + e^{b_3 + b_4 + \text{EFF}_t}}$

- **$s_c = 2$**
  - $P(s_f = 0|s_c = 2) = 1 - \frac{e^{b_5 + \text{EFF}_t}}{1 + e^{b_5 + \text{EFF}_t}}$
  - $P(s_f = 1|s_c = 2) = \frac{e^{b_5 + \text{EFF}_t}}{1 + e^{b_5 + \text{EFF}_t}} - \frac{e^{b_5 + b_6 + \text{EFF}_t}}{1 + e^{b_5 + b_6 + \text{EFF}_t}}$
  - $P(s_f = 2|s_c = 2) = \frac{e^{b_5 + b_6 + \text{EFF}_t}}{1 + e^{b_5 + b_6 + \text{EFF}_t}}$
The probabilities generated can be implemented in a control function, which can be generalised as,

$$J(U) = \sum_{i=t+1}^{\tau} \left( \alpha_{0i} P(s_f = 0|s_c) + \alpha_{1i} P(s_f = 1|s_c) + \alpha_{2i} P(s_f = 2|s_c) \right)$$

6.3

where $\alpha_{0i}, ..., \alpha_{2i}$ are the weightings given to their respective multipliers. Depending on whether the multiplier is perceived as beneficial or harmful to the patient’s condition the weightings will be negative or positive respectively. For example, the probability of the future adverse event state of the patient being “no adverse events occurring”, $P(s_f = 0|s_c)$, is beneficial to the patient therefore will be assigned a negative weighting to subtract from the cost function. The values of
the weights are subject to clinical opinion however as discussed earlier in this chapter there exists methodology to translate the clinical opinion into weighting values. Other terms such as those included in previous cost functions used in this thesis (equations 5.4, 5.11 and 5.14) would be used alongside these probabilities if they are appropriate to control the drug that required estimation of dosage regimens.

### 6.5 An Example of Discrete Patient Response Control in Imatinib Dosing

#### 6.5.1 Introduction

The drug dose algorithm was applied to imatinib dosage regimen estimation earlier in this thesis (section 5.3) where the required therapeutic target was a trough plasma concentration of 1000ng/ml. This target is PK with the intention that it will induce a desired PD effect. In this example, the dosage regimen estimation will be based on actual targets of those desired PD response thus enhancing the control of imatinib. The DPR effects of imatinib used in this example are the PD responses, cytogenetic [153] and molecular [154].

Cytogenetic response is determined by the amount of Ph+ metaphase cells [155]. In this example, the patient is considered to have a cytogenetic response when there are no longer any Ph+ metaphase cells; this is the definition of a complete cytogenetic response in Bacarrani et al. (2009) [155]. The Ph+ metaphase cell count is an indicator for the diagnosis of chronic myeloid leukaemia as the presence of Ph+ chromosomes is highly correlated to the onset of the disease [156]. Major molecular response is defined as, a ratio of BCR-ABL (a particular gene sequence
associated with leukaemia) less than 0.1% [155]. The DPRs from the patient in this study, ascending in therapeutic effect, are no response, then cytogenetic response and then the combined cytogenetic and molecular response. The highest DPR is a dual effect as molecular response only occurs when the effects of the cytogenetic response have begun [157].

As the methodology explained in the previous section is applicable to all discrete data the PD effects in this example can be modelled as such. The aim of the example will be to use the developed model of discrete treatment data inside the cost function of the drug dose algorithm to derive new dosage regimens for imatinib patients, which consider both PK and discrete PD effect.

### 6.5.2 Method

The dataset consisted of plasma concentration measurements from the twelve patients from the earlier example and an additional seventy-seven sparsely sampled chronic myeloid leukaemia patients receiving imatinib therapy. The patient samples were all collected at routine clinic visits to The Royal Liverpool University Hospital between April 2006 and August 2011. The further blood samples were collected and processed in the same manner as described in section 5.3.2.

The dataset extract for this study includes patient ID number, time interval since last dose taken (hours), last dose taken (mg) and plasma concentration measurements (ng/ml). Additionally, the dataset for this example included whether patients were experiencing molecular and/or cytogenetic response when sampled. PD treatment responses were coded as 0: no PD response, 1: cytogenetic response,
and 2: cytogenetic and molecular response. In the data there were entries for every
different transition (0 to 1, 0 to 2, 1 to 0, 1 to 2, 2 to 0, 2 to 1) as well as entries for
the patient exhibiting the same PD response as before (0 to 0, 1 to 1, 2 to 2).

The PK model for imatinib, a one compartment oral dose model, was given
previously in equations 5.12 and 5.13. To translate concentration in the plasma
compartment into the PD effect of imatinib the following relationship was used.

\[ EFF_t = \frac{E_{max_s_c} \cdot C_t}{C_t + EC50} \]  

For each \( s_c = 0, 1, 2 \) there is a separate value of \( E_{max} \) calculated by NONMEM,
these are shown in equation 6.5

\[ E_{max_{s_c}} = \begin{cases} 
4.80 \text{ when } s_c = 0 \\
5.21 \text{ when } s_c = 1 \\
3.00 \text{ when } s_c = 2 
\end{cases} \]  

The EC50 value was set as 1000ng/ml as, in lieu of prior information on the
parameter, the value is linked to inducing cytogenetic and molecular responses in
therapy and EC50 was derived as a trough plasma concentration of 281ng/ml,
however the clinical outcome of the model, the patient’s reduction in white blood
cell count, differs to the clinical outcome of this example, the molecular and/or
cytogenetic response of the patient.
Equation 6.1 is the logit transform that uses the amount of the effect compartment, $E_{FF_t}$, alongside the logit parameters $b_1, ..., b_6$. To calculate the logit parameters NONMEM$^1$ (Version 7.2) was adjusted to analyse the ordered discrete data. The mean parameters values $b_1, ..., b_6$ and their standard errors calculated by NONMEM are shown in equation 6.6

$$ b_n = \begin{cases} 
  b_1 = -1.21 \pm 0.22 \\
  b_2 = -2.35 \pm 0.54 \\
  b_3 = 2.33 \pm 0.34 \\
  b_4 = -2.60 \pm 0.34 \\
  b_5 = 3 \pm 0.27 \\
  b_6 = -2 
\end{cases} \tag{6.6} $$

The $b_6$ parameter was fixed based on information in Picard et al. (2007) to allow parameter values $b_1, ..., b_5$ to be calculated from the sparsely sampled data.

The control function for the first imatinib example is given in Equation 5.14. With the probabilities of PD effect now being included, in this study the cost function was expressed as:

---

$^1$ The NONMEM control file for the logit parameter calculation is presented in Appendix II.
where \( \alpha PK_c, \alpha 0_c, \alpha 1_c, \alpha 2_c, \alpha D_c \) are weightings for each state, which allow the control to focus on the PK target, the PD target or penalise for distance from current dose. The values of the weightings were different for each current state the patient was in and were derived using the weighting methodology explained in section 6.3.3 [150].

For example, if the patient is currently in a state of no response \((s_c = 0)\), the cost function will need to be more weighted towards the PK target and the PDR probabilities as the current dose is not generating a response. However, if the patient is in a state of full cytogenetic and molecular response the PK target becomes less important as the desired output is already in progress; therefore the weightings are orientated to maintaining a high probability that the patient remains in full response but also taking into account the current dose is inducing the full response.
The plasma concentration measurements used in the example of section 5.3 will provide feedback to the drug dose algorithm ran in MATLAB\(^2\). In addition to the PK measurements the PD response of the patient at the time of measurement will also be included in the drug dose algorithm. This allows the appropriate probabilities of future PD response to be used in the estimation of an optimal dosage regimen for the patient. The required dosage metrics remained as a seven day dosage regimen with daily oral doses.

### 6.5.3 Results

The dosage regimes estimated for the set of twelve patients included in the study are shown in Table 6-2. New dosage regimens are now estimated for all but two patients. Of interest is that the dosage regimens estimated are different to those estimated by the example in Section 5.3, which suggests that the new terms in the cost function have caused adjustment of the dosages due to the new therapeutic considerations. Overall, these results imply that no patient is to be given the standard daily 400mg dose of imatinib to reach the PK and PD targets.

---

\(^2\) The MATLAB for the drug dose algorithm is presented in Appendix II
Table 6-2: Dosage Regimens for each Patient.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Current Daily Dose (mg)</th>
<th>Revised Seven Day Dosage Regimen (mg)</th>
<th>Mean Dosage Difference (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>400</td>
<td>700, 600, 600, 600, 600, 600, 600, 600.</td>
<td>214</td>
</tr>
<tr>
<td>54</td>
<td>400</td>
<td>600, 600, 600, 600, 600, 600, 600.</td>
<td>200</td>
</tr>
<tr>
<td>56</td>
<td>400</td>
<td>600, 700, 600, 600, 700, 700, 600.</td>
<td>243</td>
</tr>
<tr>
<td>78</td>
<td>400</td>
<td>600, 600, 600, 700, 600, 600, 600.</td>
<td>214</td>
</tr>
<tr>
<td>91</td>
<td>400</td>
<td>500, 500, 600, 500, 400, 500, 500.</td>
<td>100</td>
</tr>
<tr>
<td>101</td>
<td>400</td>
<td>700, 600, 700, 600, 700, 700, 600.</td>
<td>257</td>
</tr>
<tr>
<td>118</td>
<td>400</td>
<td>700, 600, 600, 600, 600, 600, 700.</td>
<td>229</td>
</tr>
<tr>
<td>119</td>
<td>800</td>
<td>No revision needed.</td>
<td></td>
</tr>
<tr>
<td>122</td>
<td>800</td>
<td>No revision needed.</td>
<td></td>
</tr>
<tr>
<td>124</td>
<td>400</td>
<td>800, 800, 700, 700, 700, 700, 700.</td>
<td>329</td>
</tr>
<tr>
<td>244</td>
<td>400</td>
<td>700, 600, 600, 600, 600, 600, 600.</td>
<td>214</td>
</tr>
<tr>
<td>328</td>
<td>400</td>
<td>800, 600, 500, 600, 600, 500, 600.</td>
<td>200</td>
</tr>
</tbody>
</table>

Table 6-3 shows the DPR the patients were in at time of blood sampling and the probabilities of transitioning to a different DPR simulated for the dosage they were receiving at the time and the estimated dosage regimen. Overall, the probabilities of transitioning to or remaining at the highest level of response were improved upon by the estimated dosage regimen compared to the dosage the patient was currently prescribed.
Table 6-3: Comparison of the Percentages of Patient Response After Receiving Current and Revised Dosage Regimens.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Current Dosage Regimen</th>
<th>Revised Dosage Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>State</td>
<td>$s_f = 0</td>
</tr>
<tr>
<td>28</td>
<td>2</td>
<td>1.1±0.3</td>
</tr>
<tr>
<td>54</td>
<td>2</td>
<td>1.1±0.3</td>
</tr>
<tr>
<td>56</td>
<td>2</td>
<td>1.2±0.3</td>
</tr>
<tr>
<td>78</td>
<td>2</td>
<td>1.2±0.3</td>
</tr>
<tr>
<td>91</td>
<td>2</td>
<td>0.7±0.2</td>
</tr>
<tr>
<td>101</td>
<td>2</td>
<td>1.3±0.4</td>
</tr>
<tr>
<td>118</td>
<td>2</td>
<td>1.2±0.3</td>
</tr>
<tr>
<td>119</td>
<td>1</td>
<td>0.4±0.1</td>
</tr>
<tr>
<td>122</td>
<td>2</td>
<td>0.7±0.2</td>
</tr>
<tr>
<td>124</td>
<td>0</td>
<td>18.0±3.2</td>
</tr>
<tr>
<td>244</td>
<td>0</td>
<td>16.5±3.0</td>
</tr>
<tr>
<td>328</td>
<td>0</td>
<td>18.9±3.4</td>
</tr>
</tbody>
</table>

The probabilities over the time course of the dosage regimen are shown in Figure 6-6 and every other figure until Figure 6-24. The following legend is applicable to all even numbered graphs between Figure 6-6 to Figure 6-24:
Figure 6-5: Plasma Concentration time profile of Patient 28 receiving imatinib.

Figure 6-6: Markov Model Probabilities of Patient 28 receiving imatinib.
**Figure 6-7:** Plasma Concentration time profile of Patient 54 receiving imatinib.

**Figure 6-8:** Markov Model Probabilities of Patient 54 receiving imatinib.
Figure 6-9: Plasma Concentration time profile of Patient 56 receiving imatinib.

Figure 6-10: Markov Model Probabilities of Patient 56 receiving imatinib.
Figure 6-11: Plasma Concentration time profile of Patient 78 receiving imatinib.

Figure 6-12: Markov Model Probabilities of Patient 78 receiving imatinib.
Figure 6-13: Plasma Concentration time profile of Patient 91 receiving imatinib (Desired Trough Plasma Concentration = x-axis).

Figure 6-14: Markov Model Probabilities of Patient 91 receiving imatinib.
Figure 6-15: Plasma Concentration time profile of Patient 101 receiving imatinib.

Figure 6-16: Markov Model Probabilities of Patient 101 receiving imatinib.
Figure 6-17: Plasma Concentration time profile of Patient 118 receiving imatinib.

Figure 6-18: Markov Model Probabilities of Patient 118 receiving imatinib.
Figure 6-19: Plasma Concentration time profile of Patient 124 receiving imatinib.

Figure 6-20: Markov Model Probabilities of Patient 124 receiving imatinib.
Figure 6-21: Plasma Concentration time profile of Patient 244 receiving imatinib.

Figure 6-22: Markov Model Probabilities of Patient 244 receiving imatinib.
Figure 6-23: Plasma Concentration time profile of Patient 328 receiving imatinib.

Figure 6-24: Markov Model Probabilities of Patient 328 receiving imatinib.
From Table 6-3 and the figures, the results suggest that patients who are already experiencing some form of response (in state 1 or 2) are highly probable to either improve this response to state 2 or continue in state 2. The dosage adjustments made by the drug dose algorithm do cause slight improvements in probabilities however the dosage adjustments are large compared to the return in improved clinical response probability.

The dosage regimens estimated will cause higher than target trough plasma concentrations in some patients, this can be seen in Figure 6-11 and Figure 6-15. This demonstrates that dosage regimens for patients in a state of response do not require, based on probabilities of transitioning to a lower or no response, to be solely targeted to a trough plasma concentration.

The three patients (124, 244 and 328) in the dataset who were in a state of no response at the time of blood sampling had differing sets of probabilities. All three patients require higher dosing to increase the probabilities of transitioning to a cytogenetic or/and a molecular response. In the imatinib example of section 5.3 patient 244 and patient 328 did not require dosage adjustment (see Table 5-5). However, both patients require dosage adjustment to improve their probabilities of response. Figure 6-21 and Figure 6-23 show that the dosage adjustments take the patient’s trough plasma concentrations to above 1000ng/ml. This result will be discussed further in the conclusion as the PK response target does not seem to coincide with a high probability of response in some patients.
6.5.4 Conclusion

Overall with the addition of imatinib PDR probabilities control theory can be formulated more towards clinical decision making. The current methodology of individualised dosage regimen control considers cost functions with singular PK/PD outcomes. An extension on the current methodology is applied in this study of individualised imatinib therapy. In comparison, imatinib therapy was optimised previously by estimating a dosage regimen that bought the patient’s plasma concentration of the drug to 1000ng/ml [18, 19].

Novel work in this study included the derivation of a Markov model for imatinib molecular and cytogenetic response; previously a linked PK/PD model has been derived by Peng et al. (2004) [138] however this considered the white blood cell count as the patient response. Further, the cost function of this study, given in equation 6.7, was able to discern between doses based on multiple clinical outcomes, using the derived Markov model, leading to dosage regimen that was more informed and as a consequence improved the patient response to imatinib.

In all patients the desired outcome of dosage adjustment was to reduce the probability of the dosage regimen not causing a PD effect thus increasing the chances of cytogenetic and molecular response, the highest PDR response. Consequently, the combination of cytogenetic and molecular response was given the highest negative coefficient in the cost function. This was done to greatly minimise the cost of dosage regimens that induced a high probability of the highest level of response ensuring the most efficacious dosage regimens were estimated.
This extra adaptability of the algorithm to appropriately dose patients at different PD response levels was reflected in revised dose recommendation for the same twelve patients from the previous example in section 5.3. Only two patients, 119 and 122, were not recommended new dosage regimens, shown in Table 6-3.

Patients who were already at a state of full response are likely to gain only small increases to an already high probability of staying at that level of response per each 100mg dose increase. For these patients, if the cost function was based solely on the probabilities of response the drug dose algorithm will always minimise the cost function by giving the highest dose possible as this coincides with the highest probability possible. This situation of diminishing but unlimited returns is an issue with imatinib as it can cause toxic effects at high doses [158]. A possible solution might have been possible if toxicity data was available in this set of patients; this could be incorporated into the model to provide a ‘cost’ in the cost function for doses that were too high.

Without toxicity data, the final term in the cost function of equation 6.7 was formulated to penalise the distance away from a fully responsive patient’s current dosage regimen. This meant that the dosage regimens estimated would learn from previous dose information that the patient is responding however would still make sure the probability of continued response was of an acceptable level.

The cost function used in this example estimated, for patients who were in molecular and/or cytogenetic response, slightly higher doses than their current regimen. In the example of section 5.3, the dosage regimens contained doses that were far higher than the current dosage regimen. Based on these results, the
enhanced cost function of this example is more appropriate for patients responding to imatinib therapy with a PD response compared to the technique of dosing according to the singular PK target, seen in current methodology [90, 145]. The enhanced cost function of this study is suggested to be more appropriate for these patients as it takes into account previous dosages that have caused a PD effect and uses probabilities of future PD effect to ensure the effect continues.

Patients who were not presenting a molecular and/or cytogenetic response at the time of blood sampling required dosage recommendations based on different multiple targets. To derive the optimal dosage regimen for these patients the cost function contained the probabilities of the three levels of response and also the PK target from the previous example. In this situation the patient’s current dosing had not induced a molecular and/or cytogenetic response therefore the cost function was set to not learn from dosing history. Instead, the dosage regimen was to induce the patient to the therapeutic trough plasma concentration of 1000ng/ml as well as a higher probability of PD response to imatinib.

The three patients who were not responding at time of dosing produced different probabilities of PD effect, shown in Figure 6-20, Figure 6-22 and Figure 6-24 to responsive patients. If these non-responding patients remained on their previous dosage regimen, the standard of care, the most probable transition would be to cytogenetic response. However, when the patient is on the estimated dosage regimen, the most likely transition alternates between cytogenetic and the dual response of cytogenetic and molecular response. The effect of considering the patient’s trough plasma concentration of imatinib with the corresponding
probabilities means that the dosage regimen will guide the patient to the desired PD effect more effectively than standard clinical practice.

Overall, this example demonstrates new approaches in control theory by extending current methodology to include Markov model probabilities of discrete event within a cost function. This novel methodology can be applied to individualise drug therapies where probabilities are an appropriate indicator of clinical targets.
This chapter presents an example of the stochastic control method explained in Chapter 4 applied to simvastatin therapy. The pharmacometric model is extended to predict both PK and PD responses. As simvastatin is dosed to PD targets the cost function is formulated accordingly.

The drug dose algorithm of this thesis is compared to the current guidelines of individualisation in simvastatin therapy. To carry out this comparison a randomised control trial (RCT) was simulated. Clinical outcomes are investigated to conclude whether the stochastic control of dosage regimens improves simvastatin therapy compared to current dosing guidelines.

7.1 Example of Estimating an Optimal Dosage Regimen to Control a Pharmacodynamic Response

7.1.1 Introduction

So far in this thesis examples of stochastic control have been applied to PK targets and discrete probabilistic events. The discrete event application in imatinib dosage regimen estimation (section 6.5) demonstrated how stochastic control is used in systems where the link between a drug’s PK and PD is either unsure or too complex. In this chapter, an application is considered where the PK/PD link is identified by a compartmental model.

To demonstrate the applicability of the stochastic control algorithm beyond PK applications, the methodology will be applied to estimate an optimal dose for the
cholesterol lowering drug simvastatin used to treat hypercholesterolemia [159]. Simvastatin is prescribed to outpatients and low-density lipoprotein cholesterol (LDL-C) is measured at subsequent clinic visits at least four weeks apart. Therefore, in this application there were large periods between dose adjustments; which means that convergence to a stable maintenance dose will, potentially, be harder to achieve.

Deviations from standard simvastatin therapy have been researched previously, in particular Ara et al. (2009) [161] evaluated the cost-effectiveness of prescribing high doses of statins early in therapy to avoid cardiac events. The meta-analysis included in that study revealed that the highest dose recommended of simvastatin, 80 mg, caused a 45% LDL-C reduction compared to standard care dosing, 40 mg, that caused a 37% reduction in LDL-C. A clear indication of the duration of early high-dose therapy was not reported in the paper. Due to the duration of high-dose simvastatin therapy not being clear, the meta-analysis reporting of a consequential increase in adverse event rate is difficult to translate into dosage recommendations.

Mostly dosage recommendations are derived from studies where simvastatin is compared with other statins at fixed dose levels to identify the superior intervention for various indications, for example Pedersen et al. (2005) [162] studies the comparison of effects that high-dose atorvastatin with usual-dose simvastatin had on reducing myocardial infarction.

The minimal amount of studies into individualised simvastatin therapy motivated this study. Potentially using a stochastic control approach in simvastatin therapy
could improve the magnitude of LDL-C reduction across the population. This suggests that previous studies into simvastatin therapy comparison at fixed dose levels produce a limited view of the efficacy of simvastatin.

### 7.1.2 Method

In the absence of data on patient response in simvastatin therapy, previous results presented in a publication were used in this example; ten virtual patients were generated from distributions described in previous literature on simvastatin PK/PD [40]. From these virtual patients, responses to dosing were be simulated. To investigate the performance of the stochastic control algorithm for simvastatin dosage regimen estimation against standard care there will be two therapy arms in the simulation; the standard care arm and the stochastic control dosing arm, which will be explained further in the methods section. Primary endpoints from these simulations are percentage reduction in LDL-C levels after 3 months, percentage of patients achieving the LDL-C target after 3 months and also average time to stable maintenance dose. In this example stochastic control methods are applied with the simvastatin PK/PD model from Kim et al. (2011) [40] described below:

\[
\frac{dC_A}{dt} = -k_d C_A \\
\frac{dC}{dt} = \frac{k_a}{V_C} C_C - k_e C_t
\]  

7.1 7.2
\[
\frac{dCP_t}{dt} = \frac{0.3 \cdot k_e \cdot V_C}{V_{CP}} C_t - k_1 CP_t \tag{7.3}
\]

\[
\frac{dLDLC_t}{dt} = k_{in} \left( 1 - \frac{E_{max} \cdot CP_t}{EC_{50} + CP_t} \right) - k_{out} LDLC_t \tag{7.4}
\]

where the first two equations, 7.1 and 7.2, describe the PK of simvastatin administered as an oral dose, which is identical to the PKs model used in the imatinib example (section 5.3.2, equations 5.12 and 5.13). The concentration of the metabolite of simvastatin, simvastatin acid (\(CP_t\)), is described by equation 7.3. The simvastatin in the plasma is converted into simvastatin acid producing an active metabolite, \(\beta\)-hydroxyacid [40]. The PD of simvastatin is described by equation 7.4 where the amount of simvastatin acid present in the body is related to the reduction of LDL-C over time. This indirect response model was used in the Kim et al. (2011) publication to represent the delay between plasma concentrations reaching steady state within the patient and the eventual reduction of LDL-C concentrations. The graphical representation of this model is shown in Figure 7-1.
To reduce the computing time in this study, high throughput computing was utilised. The Advanced Research Computing Condor Pool (Condor) is available at the University of Liverpool for computer analyses that would incur an impractically large computing time performed on a single computer. To reduce computational burden, large computer analyses are split into smaller jobs and sent to the Condor to be performed by multiple computers. There were three Condor stages in this study, the MATLAB initialisation, MATLAB product and MATLAB collection.

The MATLAB initialisation stage generated the ten patient mean PK/PD parameter sets. Shown in Table 7-1, the parameter sets were selected by a discrete uniform random number generator\(^3\) applied to the Kim et al. (2011) [40] population parameter distribution ranges. The initial level of LDL-C for each patient was uniform randomly selected from the interval 130-170mg/dl by MATLAB. This initial

---

\(^3\) MATLAB initialisation code provided in Appendix IV
level is chosen to simulate patients who range from borderline high LDL-C levels to definite familial hypercholesterolemia [163].

Table 7-1: Mean PK/PD Parameters for Ten Simulated Simvastatin Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Initial LDL-C (mg/dl)</th>
<th>$k_a$ (1/h)</th>
<th>$V_C$ (l)</th>
<th>$k_e$ (1/h)</th>
<th>$V_{CP}$ (l)</th>
<th>$k_1$ (1/h)</th>
<th>$k_{in}$ (1/h)</th>
<th>$E_{max}$</th>
<th>EC$_{50}$ (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>167</td>
<td>3.03</td>
<td>9030</td>
<td>0.179</td>
<td>1250</td>
<td>0.318</td>
<td>13.4</td>
<td>0.628</td>
<td>1.86e-04</td>
</tr>
<tr>
<td>2</td>
<td>132</td>
<td>2.42</td>
<td>9157</td>
<td>0.185</td>
<td>1387</td>
<td>0.276</td>
<td>12.3</td>
<td>0.491</td>
<td>1.41e-04</td>
</tr>
<tr>
<td>3</td>
<td>159</td>
<td>3.98</td>
<td>8139</td>
<td>0.203</td>
<td>915</td>
<td>0.355</td>
<td>9.54</td>
<td>0.440</td>
<td>8.23e-05</td>
</tr>
<tr>
<td>4</td>
<td>151</td>
<td>4.52</td>
<td>10169</td>
<td>0.156</td>
<td>1397</td>
<td>0.247</td>
<td>12.0</td>
<td>0.530</td>
<td>1.03e-05</td>
</tr>
<tr>
<td>5</td>
<td>164</td>
<td>2.76</td>
<td>8844</td>
<td>0.228</td>
<td>999</td>
<td>0.370</td>
<td>9.93</td>
<td>0.443</td>
<td>8.78e-05</td>
</tr>
<tr>
<td>6</td>
<td>142</td>
<td>4.42</td>
<td>8548</td>
<td>0.195</td>
<td>1513</td>
<td>0.276</td>
<td>9.09</td>
<td>0.475</td>
<td>2.04e-04</td>
</tr>
<tr>
<td>7</td>
<td>160</td>
<td>3.46</td>
<td>8100</td>
<td>0.235</td>
<td>930</td>
<td>0.471</td>
<td>12.6</td>
<td>0.477</td>
<td>1.12e-04</td>
</tr>
<tr>
<td>8</td>
<td>169</td>
<td>3.04</td>
<td>10138</td>
<td>0.196</td>
<td>1392</td>
<td>0.326</td>
<td>11.5</td>
<td>0.461</td>
<td>3.34e-04</td>
</tr>
<tr>
<td>9</td>
<td>154</td>
<td>4.23</td>
<td>10308</td>
<td>0.146</td>
<td>1505</td>
<td>0.269</td>
<td>11.3</td>
<td>0.625</td>
<td>1.36e-04</td>
</tr>
<tr>
<td>10</td>
<td>132</td>
<td>3.76</td>
<td>8850</td>
<td>0.197</td>
<td>1112</td>
<td>326</td>
<td>10.8</td>
<td>0.530</td>
<td>3.12e-04</td>
</tr>
</tbody>
</table>

A literature search for simvastatin intra-individual variability did not find any advisement on the intra-individual variability of simvastatin PK/PD parameters, the closest indication was found reported in Kinlay (2012) [164] that an intra-individual variability of 15% had been recorded in the LDL-C level of patients prescribed another statin drug, rosuvastatin.
Three parameters, \( k_a \), \( k_e \) and \( k_{in} \), were selected to vary within their distributions with respect to time to study intra-individual variability. Due to the relationships between all the parameters, varying just these three variables caused the entire patient PK/PD to vary with time. In absence of intra-individual variability indication, the lognormal distributions of \( k_a \), \( k_e \) and \( k_{in} \) were described by \( \ln N(\ln(\text{para}), \text{para}) \) where \( \text{para} \) is the value of the respective parameters in Table 7-1.

In the MATLAB product stage\(^4\), the virtual patient parameters were used to inform the PK/PD model for simvastatin [40]. The ten virtual patients were simulated twenty times through both therapy arms; independently, so treatment in one arm does not affect the treatment in the other and vice versa. This led to four hundred computer analysis jobs being submitted to Condor.

In the standard care arm simulated patients were given an initial starting dose of 10-20mg of simvastatin and then the dose is increased by 10mg each time the LDL-C concentration is above the desired target. The second, stochastic control arm of simulation involves the same patient treated with dosage regimens estimated from the stochastic control algorithm. In both arms the maximum daily dosage of simvastatin allowed to be prescribed is 80mg as per medical guidelines.

In this example, the stochastic differential equations are assumed to be true indicators of the PK/PD responses. So as to ensure that the stochastic control algorithms are comparable to standard therapy, measurement and prediction

\(^4\) MATLAB product code provided in Appendix IV
errors were simulated into the system when needed. Firstly, the system will, as for an *in vitro* trial, receive the feedback in the form of noisy output measurements. These are generated by the stochastic differential equation output with a random amount of extra noise added. The boundaries of the noise are approximately 7% of the true value of LDL-C, in accordance with literature on LDL-C assay error [165, 166]. These noisy measurements will be used by both the standard arm and the stochastic control arm. Secondly, the predictions, used by the Kalman Filter and cost function, in the stochastic control arm of the simulation will be subject to a random amount of noise within the 10% boundary around the stochastic differential equation output.

The target of the control will be a reduction of LDL-C to 77.3mg/dl, which is recommended for individuals who are at a high risk of hypercholesterolemia. Therefore the cost function for stochastic control arm of the study is,

$$u_t^* = \arg\min_{u_t} \sum_{t=1}^{T} \sum_{k=1}^{5} (LDL_t - 773)^2$$ \(\text{7.5}\)

where \(T=672\) hours (28 days) and \(LDL_t\) is the noisy prediction of the LDL-C concentration in the body.

The specific endpoints of interest are the difference in time between the standard treatment and stochastic control arms to reach the target LDL-C level of 77.3mg/l, the average LDL-C levels, the final LDL-C levels and the variability of LDL-C levels.
over treatment period. These were retrieved from the Condor pool of computers using the MATLAB collection stage^5.

### 7.1.2.1 Methods Summary

To summarise this example, these steps are taken:

- **MATLAB Initialisation**: Random parameters are generated from the PK/PD parameter distributions along with a starting LDL-C level to form ten virtual patients.
- **MATLAB Product**: The set of virtual patients is subject to the standard dosing arm for up to ten clinic visits (four weeks apart) or upon reaching the target LDL-C level, whichever is soonest.
  - The patient is started on either 10mg or 40mg depending on initial LDL-C level, four weeks of treatment is simulated.
  - If target is not reached (according to the noisy measurement value), dose is increased by 10mg and another four weeks of treatment is simulated; this continues, if target is not met, until ten clinic visits.
- **The same virtual patient (reset to their starting level) is put through the stochastic dosing arm for ten clinic visits or upon reaching the target LDL-C.**
  - Patient dosing is determined by forecasting, from the initial LDL-C value, four weeks ahead to find optimal dose for the patient. Patient is then simulated on the optimal dose for four weeks.
  - If target is not reached (according to the noisy measurement value), the measurement value is reconciled with noisy prediction value from the stochastic differential equations to make an estimate of the LDL-C level. Then, from the estimate of LDL-C level, the optimal dose for the next four weeks of treatment is estimated. The patient is then simulated for four weeks on the optimal dose. This process is repeated until ten clinic visits unless the LDL-C target is met.
- **The two arms of simulation were repeated twenty times for each of the ten patients leading to four hundred simulations.**

^5 MATLAB collection code provided in Appendix IV
MATLAB collection: Results were collected from the Condor pool of computers.

### 7.1.3 Results

The results of the simulation indicate a small improvement in treatment when using stochastic control methods. A small improvement was to be expected with large time intervals between measurements. In eight out of the ten patients the stochastic control algorithm estimated doses that led the patient to an average LDL-C lower than with standard therapy, this is shown in Figure 7-2.

![Figure 7-2: The comparison of average LDL-C levels of patients on standard therapy and stochastically controlled therapy (bars indicate standard deviation).](image)

Figure 7-3 shows that only five of the ten patients benefitted from stochastic control estimated dosing to reduce their final LDL-C level.
Figure 7-3: The comparison of end LDL-C levels of patients on standard therapy and stochastically controlled therapy (bars indicate standard deviation).

The variability that is generated by introducing noise to the three parameters and incorporating a compliance factor in simulation is evident as some patients have end LDL-C levels larger than their respective averages. This suggests that patient’s final LDL-C levels are not the lowest measured in the trial.
Figure 7-4: The comparison of the variation in LDL-C levels of patients on standard therapy and stochastically controlled therapy.

Figure 7-4 displays the variability of LDL-C levels between measurements. The graph shows that the dosage regimens estimated from the stochastic control algorithm induce a ‘smoother’ change to LDL-C levels between clinic visits compared to the standard dosing arm, causing less severe rises and falls in the LDL-C levels.

7.1.4 Conclusions

Overall, the results were encouraging in this application of the stochastic control algorithm. Whilst not all endpoints proved significant, this was to be expected due to various factors relating to simvastatin therapy. Firstly, LDL-C levels are only measured every four weeks (at the most frequent), which means vital feedback is
not given to the stochastic control algorithm for lengthened periods. Secondly, simvastatin will only then be prescribed at the one daily dosage until the next LDL-C level measurement meaning targets are harder to hit precisely. With these difficulties it was encouraging to observe large differences in average LDL-C levels of patients receiving two different arms of therapy. As evidenced by the final LDL-C levels not being too dissimilar between the two arms, the dosage regimens from the two arms eventually caused LDL-C levels to converge.

The stochastic controlled dosing caused reduced variability of LDL-C levels, this was encouraging as a steady decline in cholesterol would be more reassuring to patients than drastic reductions or gains. Reassurance of the patient is one of the targets when utilizing drug dose algorithms and the results here suggest that, even in a reduced feedback application, that algorithms could prove beneficial.

Increasing the number of routine clinic visits would not be feasible for a drug such as simvastatin as the drug has an established therapy routine and side effects are manageable. However, if information was provided on the LDL-C level of the patient in between routine clinic visits this could be fed back into the control. This could be used if the patient is experiencing complications or is generally concerned with the dosage regimen they have been prescribed.

Previous studies into simvastatin dosing mainly consist of fixed dose comparisons with other statin drugs; in these studies the drugs are compared by their ability to reduce cholesterol across the population. Whilst the efficacy of the statin drugs is being compared in these previous studies, the individual PK/PD response is rarely investigated. This is shown in a study by Tuomilehto et al. (1994) [167] where
despite multiple different simvastatin dosages being investigated the clinical endpoints are not adjusted for individual PK/PD parameters leading to uninformative results.

Kim et al. (2011) [40] derived the PK/PD model that was used in this study to individualise dosage regimens. Similar studies are recommended to investigate individual PK/PD response to drugs; with these forms of studies the full potential of the drug can be analysed as dosages can be estimated to hit clinical targets precisely.

Using Condor to share computational burden enabled this study to be conducted. Whilst simulations have been used previously to determine the benefit of individualised therapies [168-170] the use of high throughput computing, such as Condor, has not been research. The use of high throughput computing is recommended when individualising therapy, especially when considering multiple dosage regimens, often computational burden is large when the control is performed on a single computer.

In conclusion, whilst the stochastic control methods in this example caused significant improvements in clinical endpoints, there are considerations based on the nature of the drug therapy. Firstly, drug therapies with more frequent measurements are more likely to show the full adaptability of the stochastic control approach. More measurements will reduce discrepancies between what is predicted and the actual PK/PD response of the patient, leading to estimated dosage regimens causing PK/PD responses within a desired range.
Secondly, drug therapies where dosage regimens are allowed to be changed more regularly depending on feedback also ensure the drug dose algorithm is fully adaptable to the patient. Over four months, a constant daily dose is the best option to ensure that compliance is not hindered with patients becoming unsure of their drug therapy. However, to induce clinical targets more frequent dosage regimen modification may be required.
8 CONCLUSIONS AND FURTHER WORK

This thesis details research into constructing a drug dose algorithm that uses stochastic control methodology to estimate an individualised dosage regimen for the patient.

The previous chapters have explained different aspects of this research. In this conclusion chapter, particular and novel sections are evaluated. Where applicable, recommendations for replication of research and potential future work are provided to allow the research of this thesis to be extended.

8.1 Overview

The transition from the ‘one size fits all’ paradigm of drug dosing to individualised drug dosing is appealing to both patient and clinician as it could lead to safer and more effective dosing with reduced costs potentially due to lower adverse drug reaction rates and reduced drug burden [14]. The transition is ideally timed with the advancement of areas such as pharmacogenetics [63] providing deeper insight into patient drug responses.

Various methodologies are available to enable individualised dosing; these methodologies investigate the variability between patients and potential clinical factors that cause the variability. This explained variability can then be used to estimate individualised dosage regimens for new drug therapy patients.
A large amount of research has been conducted in the area of *a priori* dose prediction algorithms that are derived using linear regression methods. The appeal of these algorithms potentially lies in the ease of analysis afforded to linear regression methods. If linear regression methods of individualising therapy for the patient were of an acceptable standard then invasive PK/PD data would not be required to be routinely collected. However, as shown in the example of section 3.1, sources of individual variability are not fully utilised in linear regression algorithms meaning the full possibility of patient outcomes are not considered in dose estimation.

Based on the review of linear regression methods, in Chapter 4 stochastic control methodology was laid out and then new research was conducted on certain components of the approach.

Intra-individual variability, the variability over time of an individual patient’s PK/PD parameters, appears to be rarely considered in control theory. In current methodology, patient parameters were derived by either calculating a point estimate with no variability attached (MAP Bayesian control) [145] or by reweighting a population distribution of PK/PD parameters and assuming inter-individual variability indicated intra-individual variability (MM stochastic control) [90]. This motivated research in this thesis into whether individualised dosing can become more accurate when the patient’s PK/PD is fully considered. In an imatinib dosing example, section 5.3, PK/PD parameters were represented as distributions that consider intra-individual variability.
In many drug therapy situations an absence of PK/PD response data for the patient complicates the estimation of individualised dosing. In these situations, patient PK/PD parameters can be calculated from covariate information. However, some covariates are difficult to measure or require a long period to identify.

In the example of section 5.2, an altered MM approach was utilised, in contrast to the standard MM approach that does not consider covariate information [136], a patient with an unknown covariate had multiple possible PK parameter sets that were weighted by the prevalence of the covariate in the population. This led to an estimated dosage regimen that considered possible outcomes for different covariate values. Using the altered MM approach means patients can be individually dosed according to various predicted PK/PD responses.

Cost functions are used to determine the optimal dosage regimen that causes a therapeutic effect in the patient. Both single PK and PD targets [88, 94] have been included in cost functions to perform estimations of individualised dosage regimens. However, work in this thesis extended cost functions to include more than just one PK or PD target.

As a novel step, the integration of a Markov model and the cost function was investigated in section 6.4 to provide dosage regimen estimation that considered probabilities of future patient response. The future patient response could be negative such as an adverse event or positive, a therapeutic effect of a drug on the body.
An example of imatinib dosing in section 6.5 showed an enhanced level of adaptability to the patient due to this research. The extra adaptability was confirmed as more informed estimates were made for an individual patient dosage regimen. This meant that if the condition of the patient being prescribed imatinib changed then their dosage regimen could be changed as well, subject to the probabilities derived from patient response data. The potential benefits of this adaptability include better treatment of the patient and the potential to reduce adverse event rates that are dose dependent.

Individualised dosage regimen estimation can incur a large amount of computing time; for the simvastatin dosing example, section 7.1, high throughput computing was utilised to reduce computational burden. The simvastatin example was fragmented into four hundred simulations that were performed at the same time on a cluster of parallel computers.

In summary, this thesis focused on identifying the appropriate methodology to perform individual dosage regimen estimation. Stochastic control was selected to be researched further due to the entire distribution of PK/PD response being considered and the adaptive properties included in the approach. Research was conducted to improve PK/PD parameter representation currently seen in stochastic control, by considering intra-individual variability appropriately. The MM stochastic control approach was altered to individualise dosage regimens for patient with missing covariates. The cost function in control theory was adapted to provide estimates of dosage regimen in drug therapies that are consequential on multiple
clinical targets. Finally, high throughput computing was investigated in simvastatin therapy to reduce computation time.

## 8.2 Limitations

In absence of *in vivo* PK/PD data, such as in the lidocaine, warfarin and simvastatin control examples presented in this thesis, alternative methods were used to inform the drug dose algorithm. These examples demonstrate the estimation of individualised dosage regimens however the adaptive elements of control theory are not utilised. This is seen as a limitation of such examples, as measurements of PK/PD response are not fed back to the drug dose algorithm meaning the error between prediction and actual measurement is not analysed.

The intra-individual distributions within this thesis were constructed around point estimates calculated in NONMEM®. Information on the distribution of intra-individual variability was not found in literature for the drug therapies studied in examples. Due to this estimated dosage regimens are estimated with the assumption that the hypothesised intra-individual distributions appropriately described PK/PD parameter behaviour.

In the example of individualised simvastatin therapy, the limited feedback from clinic visits every four weeks appeared to hinder the adaptability of control. The adaptability was hindered by reliance on the prediction of LDL-C in the patient for an extended period of time that can lead to large divergence from the actual LDL-C levels in the patient.
With new methodology being introduced in this thesis, validation on an external dataset/population is required to determine the ability of the algorithm to individualise patient drug dosing outside a derivation dataset. This validation process allows methodology to be generalised to patients not used in derivation dataset ensuring that widespread use is feasible and effective.

### 8.3 Integration with Current Research

Research in this thesis has studied the individualisation of dosage regimens. This section explains suggestions for investigating intra-individual variability in current control theory applications.

In MAP Bayesian control theory, point estimates of the individual PK/PD parameters are derived by the product of the prior distribution of the PK/PD parameters and the likelihood of PK/PD response measurements [145]. To appropriately predict future PK/PD response, a distribution of intra-individual variability can be constructed around MAP Bayesian point estimates.

In absence of intra-individual distribution research, as was encountered in this thesis, distributions can be provisionally set as \( \lnN(\ln(\text{para}), \text{para}) \) where \( \text{para} \) is the value of the MAP Bayesian point estimate.

The MM approach produces estimates of PK/PD response based on the posterior distribution of individual patient PK/PD parameters [90]. However, as indicated in this thesis, the posterior is derived by recalculating the probability of discrete parameter points contained in the population PK/PD [43]. In this approach intra-
individual variability is assumed to be described by inter-individual variability present in the population PK/PD distribution.

To obtain a posterior PK/PD parameter distribution the Kalman filter is used, reconciling the probabilities of each discrete population PK/PD parameter point with the likelihood of PK/PD response measurements [109]. After Kalman filtering, the likelihood does not remain in the posterior distribution [109]. The likelihood is the most accurate indication of a patient’s PK/PD parameters at the measurement time therefore to understand further about intra-individual response this information should remain in the posterior distribution. If the likelihoods of each measurement remain in the distribution then further measurement likelihoods can be compared to investigate intra-individual variability.

8.4 Recommendations for Researchers

The probabilities generated from a Markov model provide an alternative individualised drug therapy target when a PD model has not been established. The requirements for the Markov model are a hypothesised site of action and an associated level of this site. This alternative form of analysis is an extra option when analysing drug response and as shown in this thesis leads to more informed dosage regimen estimation.

An advisement for any researcher in the area would be careful consideration of the weighting of probabilities in the cost function. When several clinical outcomes are being considered in the cost function their respective importance must be correctly interpreted by weightings. However, in the process of weighting determination,
bias should be minimised. Potential actions to minimise bias would be to consider clinical expertise from multiple sources and ranking of outcomes, discussed in section 6.4.1.

The simvastatin study in this thesis alludes to a general consideration for application of stochastic control methods to estimate dosage regimens. Whilst the application in this study was entirely feasible, reduced feedback (as clinic visits where dosage regimens could be altered were a large amount of time apart) meant dosage regimens were based largely on predicted levels of LDL-C. These recommendations should be considered before future research into the dosage regimen estimation for simvastatin or a drug that has similarly reduced feedback and dosage regimen change points.

Notably, including noise within the model for patient response invokes a larger computational need. This causes dose estimation for a singular patient to become longer than would be required for bedside drug therapy decisions. Advancements in research to reduce the time required would be recommended before application in ‘real-time’ healthcare.

One potential solution may be through high throughput computing, which was utilised in the simvastatin study. High throughput computing works by splitting a large computer analysis into a series of smaller analyses performed on a group of networked computers. As ‘cloud’ computing, where information is transferred away from a user’s computer, laptop or tablet to be analysed elsewhere, becomes more widely used there is potential for high throughput computing to be utilised to great effect in individualised drug therapy. For example, a clinician could send a plasma
concentration sample through cloud computing to be analysed with indications of
dosing metrics required; in reply an individualised dosage regimen is sent back
alongside results of analysis.

### 8.5 Further Work

Stochastic control methods have already included the process of parameter
estimation in response to measurements taken from a patient [90, 145]. However,
parameters will be best estimated in recognition of the intra-individual variability in
PK/PD response to a drug. In section 8.3, suggestions were given as to how intra-
individual variability could be considered with current control theory approaches in
drug therapy. However, even with these suggestions, parameters are assumed to
change value only when measurements taken from the patient (time invariant
parameters).

To understand intra-individual variability further PK/PD parameters should be time
variant, represented by distributions that indicate the value the PK/PD parameters
could be at any given time. Potentially Markov chain Monte Carlo (MCMC) and
random walk methods could provide a means to calculate time variant parameters.
Lunn and Aarons (1997) [171] investigated using MCMC methods to estimate
interoccasion variability however the main focus was looking at variability across
the patient population.

As this thesis presents is the first application of Markov models to the cost function
in a stochastic control method, suggested future work would be application in a
different drug. Further application will test the approach and develop the
methodology for a wider audience. Two examples of data which would be interesting to apply, through a Markov model, to control theory would be toxicological and health economics data. Both of these forms of data would provide additional terms in the cost function to estimate a dose based on multiple outcomes. For example, whilst a dosage regimen may be estimated that hits a PK target exactly the patient may also be at a high risk of adverse drug effect or the cost of therapy could be greatly increased.

Within imatinib dosing there is further work required to identify the potential for dose reduction after cytogenetic and molecular effect has been achieved. Jabbour et al. (2008) [172] presented evidence that dose reduction after a target effect had been achieved did not affect event-free survival. This leads to a hypothesis that two distinct dosing stages could be needed in imatinib therapy, the first stage, which involves bringing the patient to cytogenetic and molecular effect, and the second, a dose adjustment phase where the patient dosage regimen is reduced carefully avoiding any relapse in patient response. If this is achieved the drug burden on the patient can be relieved leading to reduced costs of healthcare.

Different PK responses could be linked to the PD response to improve the predictive capabilities of the drug dose algorithm. The effects of imatinib therapy are often expected to occur up to a year or more after dose commencement [39]. Therefore, the PK profile of imatinib that involves daily cycles of probabilities may be too frequent to directly link to effects happening over a time course of several months. Counts of cells in the blood may be better indicator of drug response, the research by Peng et al. (2004) linking the plasma concentration of imatinib to the
white blood cell count of the patient [138] suggests one option, however, other blood cell counts may be more indicative of drug response.

Possible extensions on the simvastatin model presented in section 7.1.2 (see in Figure 7-1 and equations 7.1-7.4) would be to improve the predictive capabilities of the PD model compartment. The model could benefit from further data analysed to confirm whether it is appropriate enough for prediction purposes. For example, pharmacogenetic information suggests that genetic variation accounts contributes to the variable response to statin therapy [173]. This information could be incorporated to construct a superior model for predicting the LDL-C levels of a patient between clinic visits.

To encourage further use of high throughput computing in the area of drug therapy, individualisation guidelines on how to conduct the task could be established. Two aspects to consider in these guidelines would be computational needs and application requirements. Computational needs would include how best to run the simulation including, which programme to use to run the code and if the simulation is large enough to require multiple computers, just as the example in this thesis required. Application requirements would include steps to parallel the simulation with healthcare in general. Issues to consider, naming two, are patient compliance and number of patient replications required.
%% Drug Dose Algorithm for Imatinib Dosing in MATLAB(R)
%% This drug dose algorithm is based on Pharmacokinetic Targets

%% Read Data and Use Kalman Filter to Loop In Measurements
% Data Read

dosres=xlsread('Imat.xlsx');
patlist=unique(dosres(:,1));
doselist=[];
allP=[];

%% Start of Patient Loop

for q=1:1:length(patlist)
clearvars -except dosres patlist doselist q b con2list doselist allP

    target=patlist(q);
    vi=find(dosres(:,1)==target);
    patres=dosres(vi,:);
    patres(1,1);

dose=patres(1,6),patres(1,7)*1000,patres(1,8)*1000];
kag=p(1); cl=p(2); vol=p(3); keg=(p(2)/p(3));
peak=round(60*(1/(kag-keg))*log(kag/keg));

% Target Metrics
dorange=[patres(1,9) patres(1,10)]; dodays=7; tar=1000;

% Kalman filter
dosam=size(patres); pos=patres(1,4);
con1=[]; kaplot=[]; keplot=[];
xpred=[kag keg patres(1,3)*1000000 pos];

for l=2:1:dosam(1)
    pre=[];
    mp= [patres(l-1,2), patres(l-1,3), patres(l-1,4), patres(l-1,5)];
    m= [patres(l,2), patres(l,3), patres(l,4), patres(l,5)];
    qk=500+20*m(1);
    for kalp=1:1:5
        [t,xpred] = ode45(@imat,[mp(1):1/60:(m(1)-1/60)],[kag keg xpred(end,3) pos],[],p);
        pre=[pre xpred(:,4)];
    end
    pred=mean(pre(end,:));
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\[ pk_{1k_1} = \text{std}(\text{pre}(\text{end},:)) \]
\[ \text{covkk}_{1} = (pk_{1k_1}) + qk \]
\[ \text{diff} = m(3) - \text{pred}; \]
\[ \text{rk} = m(3) \times m(4); \]
\[ \text{sk} = \text{covkk}_1 + \text{rk}; \]
\[ \text{kalk} = \text{covkk}_1 / \text{sk}; \]
\[ \text{time} = m(1); \]
\[ \text{pos} = \text{pred} + (\text{kalk} \times \text{diff}); \]
\[ pk_{1k_1} = (1 - kalk) \times \text{covkk}_1; \]
\[ \text{con1} = \text{vertcat}(\text{con1}, \text{pre}); \]

% Kalman filter up to 24 Hours
\[ \text{xpred} = [\text{kag keg xpred} (\text{end},3) \text{ pos}]; \]
\[ \text{if } m(1) < 24 \]
\[ \text{pre} = []; \]
\[ \text{for k1e=1:1:5} \]
\[ [t, \text{xpred}] = \text{ode45}(@imat, [m(1):1/60:24], [\text{kag keg pos mean(\text{con1}(\text{end}))}], [], p); \]
\[ \text{pre} = [\text{pre xpred}(:,4)]; \]
\[ \text{end} \]
\[ \text{con1} = \text{vertcat}(\text{con1}, \text{pre}); \]
\[ \text{end} \]

\[ \text{con2} = \text{con1} ; \]
\[ \text{tim} = [0:1/60:24]'; \]
\[ \text{bestd} = []; \]
\[ s = \text{patres}(1,11) + 1; \]

% Dosage Regimen Estimation
% Dose For Loop
\[ \text{for } i=1:1: \text{dodays} \]
\[ \text{concrep} = []; \]
\[ \text{pen} = []; \]
\[ \text{if } i == 1 \]
\[ \text{xst} = [\text{kag keg xpred} (\text{end},3) \text{ mean(\text{con1}(\text{end}))}]; \]
\[ \text{xsst} = [\text{xpred} (\text{end},3) \text{ mean(\text{con1}(\text{end}))}]; \]
\[ \text{else} \]
\[ \text{xst} = [\text{kag keg xdo} (\text{end},3) \text{ mean(\text{con1}(\text{end}))}]; \]
\[ \text{xsst} = [\text{xdo} (\text{end},3) \text{ mean(\text{con1}(\text{end}))}]; \]
\[ \text{end} \]
\[ \text{ode select three top dosages} \]
\[ \text{for } d = 1:1:8 \]
\[ [t, \text{xode}] = \text{ode45}(@imatode, [0:1/60:(24 - (1/60))], [d \times 100000000 + \text{xsst}(\text{end},1) \times \text{xsst}(\text{end},2)], [], p); \]
\[ \text{endconc} (d) = \text{xode} (\text{end},2); \]
\[ \text{level} (d) = ((\text{xode} (\text{end},2) / \text{tar} - 1)^2); \]
\[ \text{add a row of indices} \]
\[ \text{bose} = [1:length(\text{level}); \text{level}]; \]
\[ \text{sort by value of vector (in row 2)} \]
\[ [Y, I] = \text{sort} (\text{bose}(2,:)); \]
\[ \text{end} \]
\[ \text{Narrowed to best three dosage regimens} \]
\[ \text{bounds} = I(1:3); \]
\[ \text{for } j = 1:1:length(\text{bounds}) \]
\[ \text{d} = (100000000 \times \text{bounds}(j)); \]
\[ \% SDE repeat 5 times \]
\[ \text{concrep} = []; \]
\[ \text{for rep=1:1:5} \]
\[ [t, \text{xdo}] = \text{ode45}(@imat, [0:1/60:(24 - (1/60))], [\text{kag keg} \text{ d xst}(\text{end},4)], [], p); \]
\[ \text{concrep} = [\text{concrep xdo}(:,4)]; \]
concsto=[concsto xdo(:,4)];
end
endstoconc(j)=mean(concsto(end,:));
endstderr(j)=std(concsto(end,:),0,2);
pen(j)=((endstoconc(j)/tar-1).^2);
end
[r,c]=find(pen==min(min(pen)));
bdi(j)=bounds(c);
con1=vertcat(con1,concrep(:,(((c-1)*5)+1):(c*5)));
error=std(con1,0,2);
end
bestd=bd*100000000;
II APPENDIX: NONMEM CODE FOR SECTION 6.5

$PROBLEM IMATINHIB AErun

$DATA imatAEdatafile.CSV IGNORE=

$INPUT ID TIME DV MDV PRES IKA ICL IV CMT AMT ADDL II SS EVID

$SUBROUTINE ADVAN6 TRANS1 TOL=5

$MODEL
COMP=(GUT)
COMP=(CEN)
COMP=(EFF)

$PK
KA=IKA
CL=ICL
V=IV
S2 = V/1000

$DES
RATEIN=KA*A(1)
DADT(1)=-RATEIN
DADT(2)=RATEIN-CL*A(2)

$ERROR
; ------------------------PD------------------------

; Baseline values
B1 =THETA(1)
B2 =B1+THETA(2)
BSVEM=ETA(1)
EMAX =THETA(3)*ETA(1)
IF(PRES.EQ.1) THEN
B1 =THETA(4)
B2 =B1+THETA(5)
EMAX = THETA(6)
ENDIF
IF(PRES.EQ.2) THEN
B1 = THETA(7)
B2 = B1 + THETA(8)
EMAX = THETA(9)
ENDIF
; Conc-Effect
EC50 = THETA(10)
CE = F + 0.001
EFF = EMAX * (CE / (CE + EC50))
; Logits
A1 = B1 + EFF
A2 = B2 + EFF
C1 = EXP(A1)
C2 = EXP(A2)
; Probabilities
P1 = C1 / (1 + C1)
P2 = C2 / (1 + C2)
PA = 1 - P1
PB = P1 - P2
PC = P2
IF(DV.EQ.0) Y = PA
IF(DV.EQ.1) Y = PB
IF(DV.EQ.2) Y = PC
$THETA
(-60, -1.60, 60); B1
(-60, -2.33, 60); B2
4.80 FIX; eMAX1
(-60, -0.001, 60); B3
(-60, -1.18, 60); B4
5.21 FIX ; eMAX2
(-60, -20, 60); B5
-2.00 FIX ; B6
3.00 FIX ; eMAX3
1000 FIX ; EC50
$OMEGA
0.05 ; EC50
$ESTIMATION NUMERICAL MAX=9999 PRINT=1 POSTHOC METHOD=COND LAPLACE LIKE
$COVARIANCE
%% Drug Dose Algorithm for Imatinib Dosing in MATLAB(R)
% This drug dose algorithm is based on Pharmacokinetic
% and Probabilistic Pharmacodynamic Targets derived
% from a Markov Model.

%% Read Data and Use Kalman Filter to Loop In Measurements
% Data Read
dosres=xlsread('Imat.xlsx');
patlist=unique(dosres(:,1));
doselist=[];
allP=[];

% Start of Patient Loop
for q=1:1:length(patlist)
    clearvars -except dosres patlist doselist q b con2list doselist allP
    target=patlist(q);
    vi=find(dosres(:,1)==target);
    patres=dosres(vi,:);
    patres(1,1); % Patient Parameters
    p= [patres(1,6),patres(1,7)*1000,patres(1,8)*1000];
    kag=p(1); cl=p(2); vol=p(3); keg=(p(2)/p(3));
    peak=round(60*(1/(kag-keg))*log(kag/keg));

% Target Metrics
dorange=[patres(1,9) patres(1,10)]; dodays=7; tar=1000;

% Kalman filter
dosam=size(patres); pos=patres(1,4);
con1=[];
kaplot=[];
keplot=[];
xpred=[kag keg patres(1,3)*1000000 pos];

for l=2:1:dosam(1)
    pre=[];
    mp= [patres(l-1,2), patres(l-1,3), patres(l-1,4), patres(l-1,5)];
    m= [patres(l,2), patres(l,3), patres(l,4), patres(l,5)];
    qk=500+20*m(1);
    for kalp=1:1:5
        [t,xpred] = ode45(@imat,[mp(1):1/60:(m(1)-1/60)],[kag keg xpred(end,3) pos],[],p);
        pre=[pre xpred(:,4)];
    end
pred = mean(pre(end,:));
pk_1k_1 = std(pre(end,:));
covkk_1 = (pk_1k_1) + qk;
diff = m(3) - (pred);
rk = m(3) * m(4);
sk = covkk_1 + rk;
kalk = covkk_1 / (sk);
time = m(1);
pos = pred + (kalk * diff);
pk_1k_1 = (1 - kalk) * covkk_1;
con1 = vertcat(con1, pre);
end
%

Kalman filter up to 24 Hours
xpred = [kag keg xpred(end,3) pos];
if m(1) < 24
    pre = [];
    for k1e = 1:1:5
        [t, xpred] = ode45(@(imat, [m(1):1/60:24], [kag keg pos mean(con1(end))]), [], p);
        pre = [pre xpred(:,4)];
    end
    con1 = vertcat(con1, pre);
end

con2 = con1;
tim = [0:1/60:24]';
bestd = [];
s = patres(l,11) + 1;
%

Dosage Regimen Estimation
% Dose For Loop
for i = 1:1:dodays
    concrep = [];
    pen = [];
    if i == 1
        xst = [kag keg xpred(end,3) mean(con1(end))];
        xsst = [xpred(end,3) mean(con1(end))];
    else
        xst = [kag keg xdo(end,3) mean(con1(end))];
        xsst = [xdo(end,3) mean(con1(end))];
    end
% ode select three top dosages
for d = 1:1:8
    [t, xode] = ode45(@(imatode, [0:1/60:(24 - (1/60))], [d*100000000+xsst(end,1) xsst(end,2)], [], p);
% state dependent probability
    fC1 = [];
    fC2 = [];
    for jp = 1:1000
        b = [-1.21 + 0.224 * randn(1) - 2.35 + 0.536 * randn(1) 4.8; 2.33 + 0.339 * randn(1) - 2.6 + 0.343 * randn(1) 5.21; 3 + 0.274 * randn(1) - 2.3];
        DEFF = ((xode(:,2)./(xode(:,2)+500))).*b(s,3);
        C1 = exp(b(s,1) + DEFF);
        C2 = exp(b(s,1) + b(s,2) + DEFF);
        fC1 = vertcat(fC1, mean(C1));
        fC2 = vertcat(fC2, mean(C2));
    end
    P1 = fC1. / (1 + fC1);
    P2 = fC2. / (1 + fC2);
    endconcd = xode(end,2);

level(d) = (0.3*((\text{ode}(\text{end},2)/\text{tar}-1)^2)+0*(1-\text{mean}(\text{P1}))-0*(\text{mean}(\text{P1})-\text{mean}(\text{P2}))-0*(\text{mean}(\text{P2}))+0*(d-(\text{patres}(1,3)/100))^2);\%
% add a row of indices
bose = [1:length(level); level];
% sort by value of vector (in row 2)
[Y,I] = sort(bose(2,:));

% Narrowed to best three dosage regimens
bounds=I(1:3);
for j=1:1:length(bounds)
    d = (100000000*bounds(j));
    % SDE repeat 5 times
    concsto=[];
    for rep=1:1:5
        [t,xdo] = ode45(@imat,[0:1/60:(24-(1/60))],kag,keg,d,xst(\text{end},4),[],[],p);
        concrep=[concrep xdo(:,4)];
        concsto=[concsto xdo(:,4)];
    end
    MMOL=concsto;
    fC1=[];
    fC2=[];
    for g=1:1000
        b=[-1.21+0.224*randn(1) -2.35+0.536*randn(1) 4.8; 2.33+0.339*randn(1) -2.6+0.343*randn(1) 5.21; 3+0.274*randn(1) -2 3];
        DEFF=((MMOL./(MMOL+500))).*b(s,3);
        C1=exp(b(s,1)+DEFF);
        C2=exp(b(s,1)+b(s,2)+DEFF);
        fC1=vertcat(fC1,mean(C1));
        fC2=vertcat(fC2,mean(C2));
    end
    P1=mean(fC1)./(1+mean(fC1));
    P2=mean(fC2)./(1+mean(fC2));
    endstococonc(j)=mean(concsto(end,:));
    endstostostd(j)=std(concsto(end,:),0,2);
    pen(j)=(0.3*(((endstococonc(j)/\text{tar}-1))^.2)*endstostostd(j)+0*(1-\text{mean}(\text{P1}))-0*(\text{mean}(\text{P1})-\text{mean}(\text{P2}))-0*(\text{mean}(\text{P2}))+0*(bounds(j)-(\text{patres}(1,3)/100))^2);
end
[r,c]=find(pen==min(min(pen)));
bd(i)=bounds(c);
con1=vertcat(con1,concrep(:,((c-1)*5)+1:(c*5)));
error=std(con1,0,2);
end
bestd=bd*100000000;
%% Drug Dose Algorithm for Simvastatin Dosing in MATLAB(R) parallel computed using Condor
% This drug dose algorithm is based on Pharmacodynamic Targets

%%%%Condor index file
job=1;
excel=[];
for is=0:9
    p= [randi([198,453])/100, randi([1500,2030]),
        randi([1300,1700]), randi([7445,10800]), randi([873,1520]),
        randi([325,464]), randi([868,1440])/100, 1, randi([429,637])/1000
        , randi([15,3960])/10000000];
    for k=0:1
        for jh=0:19
            job=job+1;
            filename=strcat('input',int2str(job));
            save(filename, 'is', 'jh', 'k', 'p')
        end
    end
end

%%%%Condor product file
function product
    load input.mat;
    pat=is; num=jh; arm=k;
    seed=40*pat+1+num+(20*arm)
    rng(seed)
    if arm==0
        base=p(3);
        kag=p(1); keg=p(2)/p(4); k1=p(2)/p(4); volP=p(4); volA=p(5);
        k2=p(6)/p(5); k3g=p(7); k4=p(7)/p(3); Emax=p(9); ec=p(10);
        %stanstartdosing
        high=1546;
        if (base+normrnd(0,0.5*(0.07*base)))>high
            stdoses=40;
        else
            stdoses=10;
        end
    end

    %%standardSIMULATION loop
    %firstdose
    dose=[]; time=[]; conmeas=[]; acidmeas=[];
    LDLmeas=[]; con=[]; acid=[]; LDLcon=[];
    [t,xpred] = ode23(@simv,[0:1:23],[p(1) p(2) p(7) stdoses 0 0 base],[],p);
    con=vertcat(con, xpred(:,5));
    acid=vertcat(acid, xpred(:,6));
    LDLcon=vertcat(LDLcon, xpred(:,7));
    %repeateddosing
for ih=1:1:27
    if rand(1)<0.1
        doses=0;
    else
        doses=stdoses;
    end
    [t,xpred] = ode23(@simv,[0:1:23],,[p(1) p(2) p(7) doses xpred(end,5) xpred(end,6) xpred(end,7)],[],p);
    con=vertcat(con, xpred(:,5));
    acid=vertcat(acid, xpred(:,6));
    LDLcon=vertcat(LDLcon, xpred(:,7));
end
    time=vertcat(time, 24);
    conmeas=vertcat(conmeas, xpred(end,5)+normrnd(0,0.5*(0.1*xpred(end,5))));
    acidmeas=vertcat(acidmeas, xpred(end,6)+normrnd(0,0.5*(0.1*xpred(end,6))));
    LDLmeas=vertcat(LDLmeas, xpred(end,7)+normrnd(0,0.5*(0.07*xpred(end,7))));
    dose=vertcat(dose, stdoses);
    doses=stdoses;
    LDLmeas(end);
end
%dosing until target
reps=1;
while (LDLmeas(end))>773 && reps<10/0.0259
    reps=reps+1;
    newdose=doses+10;
    if newdose>80
        newdose=80;
    end
    for ih=1:1:28
        if rand(1)<0.1
            doses=0;
        else
            doses=newdose;
        end
        [t,xpred] = ode23(@simv,[0:1:23],,[p(1) p(2) p(7) doses xpred(end,5) xpred(end,6) xpred(end,7)],[],p);
        con=vertcat(con, xpred(:,5));
        acid=vertcat(acid, xpred(:,6));
        LDLcon=vertcat(LDLcon, xpred(:,7));
    end
    dose=vertcat(dose, newdose);
    time=vertcat(time, time(end)+24);
    conmeas=vertcat(conmeas, xpred(end,5)+normrnd(0,0.5*(0.1*xpred(end,5))));
    acidmeas=vertcat(acidmeas, xpred(end,6)+normrnd(0,0.5*(0.1*xpred(end,6))));
    LDLmeas=vertcat(LDLmeas, xpred(end,7)+normrnd(0,0.4*(0.07*xpred(end,7))));
    doses=newdose;
    LDLmeas(end);
end
%randomtimes
simmeas=[pat*ones(length(time),1) num*ones(length(time),1) arm*ones(length(time),1) time dose conmeas acidmeas LDLmeas];
end
%%%%sto SIMULATION
if arm==1
    base=p(3);
\[ k_{ag} = p(1); \quad k_{eg} = p(2)/p(4); \quad k_{1} = p(2)/p(4); \quad \text{volP} = p(4); \quad \text{volA} = p(5); \]
\[ k_{2} = p(6)/p(5); \quad k_{3g} = p(7); \quad k_{4} = p(7)/p(3); \quad E_{max} = p(9); \quad e_{c} = p(10); \]

\% forcast forwards
\con = []; \quad \text{acid} = []; \quad \text{LDLcon} = [];
\% dose loop
measgiven = base + normrnd(0, 0.5*(0.07*base));
for \( kh = 1:1:8 \)
controlLDL = [];
\% multiple dose chains
for \( r = 1:1:5 \)
\[ [t, xmu] = \text{ode23}(@(\text{simv}, [0:1:23]), [p(1) \ p(2) \ p(7) \ kh*10 0 0 \text{measgiven}]); \]
controlLDL = vertcat(controlLDL, xmu(:,7));
for \( i = 1:1:27 \)
\[ [t, xmu] = \text{ode23}(@(\text{simv}, [0:1:23]), [p(1) \ p(2) \ p(7) \ kh*10 \text{xmu(end,5)} \text{xmu(end,6)} \text{xmu(end,7)}]); \]
controlLDL = vertcat(controlLDL, xmu(:,7));
end
end
\[ J(kh) = \sum((\text{controlLDL} - 773).^2); \]
end
min(J);
[r, c] = find(J == min(min(J)));
\% firstdose with control dose
dose = []; \quad \text{time} = []; \quad \text{conmeas} = []; \quad \text{acidmeas} = [];
\text{LDLmeas} = []; \quad \text{con} = []; \quad \text{acid} = []; \quad \text{LDLcon} = [];
\[ [t, \text{xpred}] = \text{ode23}(@(\text{simv}, [0:1:23]), [p(1) \ p(2) \ p(7) \ c*10 0 0 \text{base}]); \]
\text{con} = vertcat(con, \text{xpred(:,5)});
\text{acid} = vertcat(acid, \text{xpred(:,6)});
\text{LDLcon} = vertcat(LDLcon, \text{xpred(:,7)});
\% repeated dosing with control dose
for \( i = 1:1:27 \)
if \( \text{rand}(1) < 0.1 \)
doses = 0;
else
doses = c*10;
end
\[ [t, \text{xpred}] = \text{ode23}(@(\text{simv}, [0:1:23]), [p(1) \ p(2) \ p(7) \ doses \text{xpred(end,5)} \text{xpred(end,6)} \text{xpred(end,7)}]); \]
\text{con} = vertcat(con, \text{xpred(:,5)});
\text{acid} = vertcat(acid, \text{xpred(:,6)});
\text{LDLcon} = vertcat(LDLcon, \text{xpred(:,7)});
end
dose = vertcat(dose, c*10);
time = vertcat(time, 24);
\text{conmeas} = vertcat(\text{conmeas}, \text{xpred(end,5)} + \text{normrnd}(0, 0.5*(0.1*\text{xpred(end,5)})));
\text{acidmeas} = vertcat(\text{acidmeas}, \text{xpred(end,6)} + \text{normrnd}(0, 0.5*(0.1*\text{xpred(end,6)})));
\text{LDLmeas} = vertcat(\text{LDLmeas}, \text{xpred(end,7)} + \text{normrnd}(0, 0.5*(0.07*\text{xpred(end,7)})));
dose = vertcat(dose, c*10);
\% update measurement
\text{reps} = 1;
while (\text{LDLmeas(end)}>773 \&\& \text{reps}<10; \text{reps}=\text{reps}+1;
pred = \text{xpred(end,7)} + \text{normrnd}(0, 0.5*(0.1*\text{xpred(end,7)}));
pk_{1k} = 0.1*\text{xpred(end,7)};
covkk_1=pk_1k_1;
diff=LDLmeas(end)-pred;
rk=0.07*xpred(end,7);
sk=covkk_1+rk;
kalk=covkk_1/(sk);
pos=pred+(kalk*diff);

%forcastforwards
%dose range loop
for kh=1:1:8
    controlLDL=[];
    %multiple dose chains
    for r=1:1:5
        [t,xmu] = ode23(@simv,[0:1:23], [p(1) p(2) p(7) kh*10 conmeas(end) acidmeas(end) pos],[],p);
        controlLDL=vertcat(controlLDL, xpred(:,7));
    end
    J(kh)=sum((controlLDL-773).^2);
end

min(J);
[r,c]=find(J==min(min(J)));
%dosing with update dose
newdose=c*10;
for ih=1:1:28
    if rand(1)<0.1
        doses=0;
    else
        doses=newdose;
    end
    [t,xpred] = ode23(@simv,[0:1:23], [p(1) p(2) p(7) doses xpred(end,5) xpred(end,6) pos],[],p);
    con=vertcat(con, xpred(:,5));
    acid=vertcat(acid, xpred(:,6));
    LDLcon=vertcat(LDLcon, xpred(:,7));
end

dose=vertcat(dose, newdose);
time=vertcat(time, time(end)+24);
conmeas=vertcat(conmeas, xpred(end,5)+normrnd(0,0.5*(0.1*xpred(end,5))));
acidmeas=vertcat(acidmeas, xpred(end,6)+normrnd(0,0.5*(0.1*xpred(end,6))));
LDLmeas=vertcat(LDLmeas, xpred(end,7)+normrnd(0,0.5*(0.07*xpred(end,7))));

save('output.mat', 'simmeas','reps','p');
%% Condor collection file
function collsimv
allsimmeas=[];
allreps=[];
allp=[];
for index=[0:399]
    stanres = strcat( 'output', int2str( index ) );
    load( stanres );
    allsimmeas=vertcat(allsimmeas, simmeas);
    allreps=vertcat(allreps, reps);
    allp=vertcat(allp, p);
end
save('fulloutput.mat', 'allsimmeas','allreps','allp');
### Glossary of Terms and Abbreviations

<table>
<thead>
<tr>
<th>Term</th>
<th>Meaning</th>
<th>Abbreviation (if used)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Drug Reaction</td>
<td>A patient response caused by the administration of a drug that is deemed harmful or detrimental to the patient.</td>
<td>ADR</td>
</tr>
<tr>
<td>Area Under the Curve</td>
<td>The area under the line on a graph displaying the concentration of a drug in the body on the y-axis against time on the x-axis</td>
<td>AUC</td>
</tr>
<tr>
<td>Bayesian Methods</td>
<td>A statistical methodology that calculates the current probability based in the previously calculated probability and the current data.</td>
<td></td>
</tr>
<tr>
<td>Bottom-up</td>
<td>An approach to a problem that seeks to analyse the expected response from information about the parameters of the system.</td>
<td></td>
</tr>
<tr>
<td>Controller</td>
<td>The designer of a control system. In PK/PD application often the controller is likened to the clinician to aid comprehension.</td>
<td></td>
</tr>
<tr>
<td>Cost Function</td>
<td>A function that discerns the optimal estimated output of a system subject to different inputs.</td>
<td></td>
</tr>
<tr>
<td>Central Plasma Compartment</td>
<td>The compartment of a pharmacokinetic model that represents the concentration at the site of drug action.</td>
<td></td>
</tr>
<tr>
<td>Densely Sampled Data</td>
<td>Data that has been sampled from patients with high frequency, e.g., four or more samples per dose interval.</td>
<td></td>
</tr>
<tr>
<td>Discrete Outcome</td>
<td>A distinct event that is solely observable and is independent of a continuous scale.</td>
<td></td>
</tr>
<tr>
<td>Discrete Patient Response</td>
<td>A response from a patient that is considered distinct from another response and therefore solely observable.</td>
<td>DPR</td>
</tr>
<tr>
<td>Term</td>
<td>Meaning</td>
<td>Abbreviation (if used)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Dosage Regimen</td>
<td>A collection of doses subsequent to each other.</td>
<td></td>
</tr>
<tr>
<td>Drug Dose Algorithm</td>
<td>A process that is designed to estimate the optimal dosage regimen to give to patient given based on clinical targets.</td>
<td></td>
</tr>
<tr>
<td>Finite Horizon Problem</td>
<td>A stochastic control where the state is considered over a finite amount of time.</td>
<td></td>
</tr>
<tr>
<td>Infinite Horizon Problem</td>
<td>A stochastic control where the state is considered over an infinite amount of time.</td>
<td></td>
</tr>
<tr>
<td>International Normalised Ratio</td>
<td>A measure of coagulation in the blood derived using the prothrombin time.</td>
<td>INR</td>
</tr>
<tr>
<td>Laboratory of Applied Pharmacokinetics</td>
<td>Group based in Los Angeles, California dedicated to the research into individualisation of dosage regimens.</td>
<td>LAPK</td>
</tr>
<tr>
<td>Low-density Lipoprotein Cholesterol</td>
<td>A type of cholesterol used to determine the health risk associated with hypercholesterolemia</td>
<td>LDL-C</td>
</tr>
<tr>
<td>Multiple Model</td>
<td>The stochastic control of parameter distributions that have discrete points that are considered in parallel by a cost function to estimate an optimal dosage regimen.</td>
<td>MM</td>
</tr>
<tr>
<td>Peripheral Compartment</td>
<td>A compartment used in a pharmacokinetic model in tandem from the central plasma compartment to represent different phases of movement of a drug through the body.</td>
<td></td>
</tr>
<tr>
<td>Personalised Medicine</td>
<td>The ideology that healthcare is a process that is orientated by the individual needs of the patient.</td>
<td></td>
</tr>
<tr>
<td>Pharmacodynamics</td>
<td>The study of what the drug does to the body.</td>
<td>PD</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>The study of what the body does to the drug.</td>
<td>PK</td>
</tr>
<tr>
<td>Pharmacokinetics/Pharmacodynamics</td>
<td>The dual study of what the body does to the drug for the drug to then have effect on the body</td>
<td>PK/PD</td>
</tr>
<tr>
<td>Pharmacometrics</td>
<td>The use of models to represent processes in pharmacology.</td>
<td></td>
</tr>
<tr>
<td>Term</td>
<td>Meaning</td>
<td>Abbreviation (if used)</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Plasma Concentration</td>
<td>The amount of a drug in the plasma of the blood, often the primary output of pharmacokinetic models.</td>
<td></td>
</tr>
<tr>
<td>Randomised Control Trial</td>
<td>An experiment in biological creatures to compare the efficacy of two or more interventions.</td>
<td>RCT</td>
</tr>
<tr>
<td>Simulation</td>
<td>The process of emulating a system based on information that is suggestive of system behaviour.</td>
<td></td>
</tr>
<tr>
<td>Sparsely Sampled Data</td>
<td>Data that has been sampled from patients with low frequency, for example, one or two samples per dose interval.</td>
<td></td>
</tr>
<tr>
<td>State</td>
<td>A broad term for the output of a stochastic control system.</td>
<td></td>
</tr>
<tr>
<td>Stochastic Control</td>
<td>The mathematical management of a system that involves parameters that are inherently random.</td>
<td></td>
</tr>
<tr>
<td>Top-down</td>
<td>An approach to a problem that seeks to analyse the parameters of the system from measurement of the system output. Contrasts with the bottom-up approach.</td>
<td></td>
</tr>
</tbody>
</table>
### Glossary of Reoccurring Mathematical Notation

<table>
<thead>
<tr>
<th>Mathematical Notation</th>
<th>Representation</th>
<th>Alternative Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PK/PD based</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k$</td>
<td>The rate at which PK/PD quantities move between compartments in a PK/PD model.</td>
<td></td>
</tr>
<tr>
<td>$V_d$</td>
<td>The volume of distribution in a PK/PD model.</td>
<td></td>
</tr>
<tr>
<td>$Cl$</td>
<td>The clearance in a PK/PD model.</td>
<td>$Cl/\text{bio}$ (the apparent clearance)</td>
</tr>
</tbody>
</table>
| $C$                   | The concentration of PK/PD response in a compartment of a PK/PD model | $C$ (central plasma concentration)  
$CA$ (oral dose compartment concentration)  
$CP$ (peripheral compartment concentration)  
$C_{ss}$ (steady state compartment concentration)  
LDLC (LDL-C compartment concentration) |
<p>| EFF                   | The theoretical concentration of effect at the site of drug action in the body. |                   |
| $E_{\text{base}}$    | The baseline value of EFF in absence of a drug. |                   |
| $E_{\text{max}}$     | The highest value of EFF possible with drug intervention. |                   |
| $EC_{50}$             | The concentration of the drug at the site of action that causes 50% of the drug effects. |                   |
| $\theta$             | A set of one or more PK/PD parameter(s) |                   |</p>
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<tbody>
<tr>
<td>Stochastic Control based</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$u$</td>
<td>The action of control in stochastic control methodology. For PK/PD this is the dosage regimen. $U$ represents the set of all possible $u$</td>
<td>IV (intravenous dose) I (IV bolus dose) $u^*$ (maximal dosage regimen)</td>
</tr>
<tr>
<td>$x$</td>
<td>The state of the system in stochastic control methodology. For PK/PD application this is a PK/PD response. $X$ represent the set of all possible $x$</td>
<td>$x^*$ (the state induced by the maximal dosage regimen) $\hat{x}$ (the predicted state value) $\tilde{x}$ (the estimated state value after adjustment in the Kalman Filter) Alternative forms also include $C$.</td>
</tr>
<tr>
<td>$T$</td>
<td>The set of discrete time points in a stochastic control problem. For PK/PD application this is the time course of drug therapy.</td>
<td></td>
</tr>
<tr>
<td>$\omega$</td>
<td>The process noise in the system of the stochastic control problem.</td>
<td></td>
</tr>
<tr>
<td>$y$</td>
<td>Measurements to be feedback into stochastic control methodology. For PK/PD application an example is blood samples of drug concentration.</td>
<td></td>
</tr>
<tr>
<td>$\nu$</td>
<td>The variance of $y$. For PK/PD application an example is the assay error of a blood sample.</td>
<td></td>
</tr>
<tr>
<td>$J(U)$</td>
<td>The cost function used to determine $u^*$ from the set $U$</td>
<td></td>
</tr>
<tr>
<td>$\alpha, \beta$</td>
<td>Weight and target used within $J(U)$ to determine $u^*$</td>
<td></td>
</tr>
<tr>
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<td>Representation</td>
<td>Alternative Forms</td>
</tr>
<tr>
<td>-----------------------</td>
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</tr>
<tr>
<td>( P )</td>
<td>The variance of ( x ).</td>
<td>( \hat{P} ) (the predicted state variance in the Kalman Filter) ( \hat{P} ) (the estimated state variance after adjustment in the Kalman Filter)</td>
</tr>
<tr>
<td>( F )</td>
<td>The state transition model.</td>
<td></td>
</tr>
<tr>
<td>( Q )</td>
<td>The variance of ( \omega ).</td>
<td></td>
</tr>
<tr>
<td>( H )</td>
<td>The measurement relationship model of ( y ) to ( x ).</td>
<td></td>
</tr>
</tbody>
</table>


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