KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY

Linear Pharmacokinetic Model of First Order Metabolism in the Liver

By

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Declaration

I hereby declare that this submission is my own work towards the M.Phil and that, to the best of my knowledge, it contains no material previously published by another person nor material which has been accepted for the award of any other degree of the University, except where due acknowledgment has been made in the text.

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Abstract

In this study we demonstrate the added value of mathematical model of metabolism for drug modification into metabolites. We show that for specified parameter values, the model proposed by Polkings et al. (2005) can be substituted into a proposed metabolism model, which can describe the dynamics of drug change in the liver. When we ingest a drug into our body, the body absorbs the drug into the blood stream. Then the body breaks that drug into smaller pieces called metabolites. This conversion of drugs into metabolite is the third phase of the Pharmacokinetic phenomenon (ADME). Mathematical modeling of Pharmacokinetics (PK) is the rate of change in concentration of a medical drug as it goes through different compartments in the human body. In the third phase of drug processing in the body, it is expected that the absorbed drug has to undergo biotransformation in the liver before final excretion of the metabolites through the kidney or any other excretory system. This third phase of PK (drug metabolism) is an inevitable processing stage of a drug in order to prevent toxicity build-up due to re-absorption of un-metabolised active substrate (drug concentration). This work is an extension of the study done by Polking, Boggess and Arnold (2005). Their research findings shows that drug substrate in the human organ or tissue can be analytically determined using first-order differential equation. However their model encapsulates only the first two phases (AD) of the whole (ADME) process and moreover their model hardly tells us the fate of the active substrate after pharmacological action (healing effect) in the human organ (tissue). We develop a first-order differential equation model characterizing the metabolism

reaction in the liver after direct transportation of active substrate from the tissue compartment. Primarily, this goal is achieved by using principles in mixing problems, methods of integration factor and integration by parts. This study combines the first three phases (ADM) of (ADME) and our analysis reveals and also demonstrate the critical conditions under which liver metabolism transpires. The result of our analysis will help improve medical dosing treatment strategies for non-linear drugs.

Contents

List of Tables

List of Figures

List of Abbreviations

PK	Pharmacokinetics
PD	Pharmacodynamics
ADME	Absorption, Distribution, Metabolism, Excretion
ADM	Absorption, Distribution, Metabolism
AD	Absorption, Distribution
PBPK	Physiology Based Pharmacokinetics
F	Bioavailability
V	Volume of Distribution
I.V.	Intravenous
P.O.	Per Oral

Dedication

I dedicate this thesis to the Glory of God and to the Brantuoh family.

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My humble gratitude goes to God almighty for his guidance and confidence that has enabled me to complete this work successfully.

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On the other hand, I am completely answerable for any limitation that may be detected in this work.

Chapter 1

INTRODUCTION

Overview

The selection of a compartment model solely depends upon the distribution characteristics of a drug following its administration. The equation required to characterize the plasma concentration versus time data, however, depends upon the compartment model chosen and the route of drug administration. The selected model should be such that it will permit accurate predictions in clinical situations. As mentioned above, the distribution characteristics of a drug play a critical role in the model selection process. Generally, the slower the drug distribution in the body, regardless of the route of administration, the greater the number of compartments required to characterize the plasma concentration versus time data, the more complex is the nature of the equation employed. On the basis of this observation, it is, therefore, accurate to state that if the drug is rapidly distributed following its administration, regardless of the route of administration, a one-compartment model will do an adequate job of accurately and adequately characterizing the plasma concentration versus time data. After a drug is administered, it is subjected to a number of processes (ADME) whose rates control the concentration of drug in the elusive region known as "site of action". These processes affect the onset of action, as well as the duration and

intensity of pharmacological response. Some knowledge of these rate processes is, therefore, essential for a better understanding of the observed pharmacological activity of the administered drug. The terms rapid and slow distribution refer to the time required to attain distribution equilibrium for the drug in the body. The attainment of distribution equilibrium indicates that the rate of transfer of drug from blood to various organs and tissues and the rate of transfer of drug from various tissues and organs back into the blood have become equal. Therefore, rapid distribution simply suggests that the rate of transfer of drug from blood to all organ and tissues and back into blood have become equal instantaneously, following the administration of the dose of a drug. Therefore, all organs and tissues are behaving in similar fashion toward the administered drug.

1.1 Background of Study

Pharmacokinetics, sometimes abbreviated as PK, (from Ancient Greek *pharmakon* "drug" and *kinetikos* "to do with motion") is a branch of pharmacology dedicated to the determination of the fate of substances administered externally to a living organism (Alberts et al., 2013). The substance of interest here is pharmaceutical agents and it attempts to discover the fate of a drug from the moment that it is administered up to the point at which it is completely eliminated from the body. Pharmacokinetics describes how the body affects a specific drug after administration through the mechanisms of absorption and distribution, as well as the chemical changes of the substance in the body (e.g. by metabolic enzymes such as *cytochrome P450* or *glucuronosyltransferase enzymes*), and the effects and routes of excretion of the metabolites of the drug .

1.1.1 Drug Disposition

For a given drug product, it is of interest to study how the drug moves through the body and the process of movement such as absorption (A), Distribution (D),

Metabolism (M), and Excretion (E) after drug administration. The best way to technically define pharmacokinetic (PK) is to differentiate it from pharmacodynamics (PD). The key concept of pharmacokinetic (PK) phenomenon is to study what the body does to the drug while the key concept of pharmacodynamics (PD) study is to study what the drug does to the body (Jambhekar and Breen, 2009). The next phase of drug handling is distribution and this refers to the dispersion of drug backwards and forwards between blood and the various tissue fluids of the body. Metabolism is the irreversible transformation of parent compounds into daughter compounds (metabolites). This process is the chemical modification of a drug by the body. The metabolite will then be disposed of in the urine or bile. The last Phase of the elimination process is the excretion and this is the removal of metabolite from the renal or hepatic compartment.

1.1.2 Definitions

The following are the most commonly measured pharmacokinetic metrics:dose, dosing interval, C_{max}, t_{max}, C_{min}, volume of distribution, concentration, elimination half-life, elimination rate constant, infusion rate, clearance and bioavailability (Tomlin, 2010). Dose refers to amount of drug administered whiles dosing interval indicate the time between drug dose administrations. The peak plasma concentration of a drug after administration is C_{max} and t_{max} is the time to reach C_{max}. On the contrary, the lowest concentration that a drug reaches before the next dose is administered is C_{min}. Volume of distribution refers to the apparent volume in which a drug is distributed (i.e., the parameter relating drug concentration to drug amount in the body). Concentration is the amount of drug in a given volume of plasma and elimination half-life is the time required for the concentration of the drug to reach half of its original value. The rate at which a drug is removed from the body is termed as the elimination rate constant and the rate of infusion required to balance elimination is the infusion rate. Clearance is the volume of plasma cleared of the drug per unit time. The systemically available

fraction of a drug is called bioavailability.

1.1.3 Physiologically Based Pharmacokinetics

Physiologically based pharmacokinetic (PBPK) modeling is a mathematical modeling technique for predicting the absorption, distribution, metabolism and excretion (ADME) of synthetic or natural chemical substances in humans and other animal species. PBPK modeling is used in pharmaceutical research and drug development, and in health risk assessment for cosmetics or general chemicals. PBPK models strive to be mechanistic by mathematically transcribing anatomical, physiological, physical, and chemical descriptions of the phenomena involved in the complex ADME processes. A large degree of residual simplification and empiricism is still present in those models, but they have an extended domain of applicability compared to that of classical, empirical function based, pharmacokinetic models. PBPK models may have purely predictive uses, but other uses, such as statistical inference, have been made possible by the development of Bayesian statistical tools able to deal with complex models. A dose that will be therapeutic but not toxic in an individual patient, possessing a particular set of Physiological characteristics is of particular interest to clinical practitioners and therapeutic drug development (Anderson et al., 2005). PBPK models try to rely a priori on the anatomical and physiological structure of the body, and to a certain extent, on biochemistry. They are usually multi-compartment models, with compartments corresponding to predefined organs or tissues, with interconnections corresponding to blood or lymph flows (more rarely to diffusions). A system of differential equations for concentration or quantity of substance on each compartment can be written, and its parameters represent blood flows, pulmonary ventilation rate, organ volumes etc., for which information is available in scientific publications. Indeed the description they make of the body is simplified and a balance needs to be struck between complexity and simplicity. Besides the advantage of allowing the recruitment of a prior information about parameter values, these models also

facilitate inter-species transpositions or extrapolation from one mode of administration to another (Kallen, 2008). The first pharmacokinetic model described in a scientific literature was in fact a PBPK model. It led, however, to computations intractable at that time. The focus shifted then to simpler models, for which analytical solutions could be obtained (such solutions were sums of exponential terms, which led to further simplifications.) The availability of computers and numerical integration algorithms marked a renewed interest in physiological models in the early 1970's (Davidson et al., 2005).

1.1.4 Pharmaceutical Products

If a drug company is hoping to market a new molecular entity or a new dosage form of an existing product, they need to be confident that it will be possible to device a dosing regimen that will be convenient, effective and safe. The idea would be a product that can be administered once daily as oral tablets or capsules and that this will provide blood levels that remain comfortably within the ideal zone-high enough to be effective, but well short of producing side effects. It is always possible to achieve precisely this ideal, but any drug company would prefer to avoid a product that has to be administered several times a day or where blood levels are constantly teetering on the verge of ineffectiveness and/or toxicity. Experimental work to determine and identify pharmacokinetic (PK) problems will take place very early in the development cycle, so that candidate products with serious pharmacokinetic (PK) problems can be terminated before too great a wastage of resources (Whelpton and Curry, 2011).

1.1.5 Absorption Phase

In pharmacology (and more specifically pharmacokinetics), absorption is the movement of a drug into the bloodstream. Absorption involves several phases. First, the drug needs to be introduced via some route of administration (oral, topical-dermal, etc.) and in a specific dosage form such as a tablet, capsule, so-

lution and so on. In other situations, such as intravenous therapy, intramuscular injection, enteral nutrition and others, absorption is even more straightforward and there is less variability in absorption and bioavailability is often near 100%. It is considered that intravascular administration (e.g. IV) does not involve absorption, and there is no loss of drug (Michaela et al., 2005; Jambhekar and Breen, 2009). The fastest route of absorption is inhalation, and not as mistakenly considered the intravenous administration. Absorption is a primary focus in drug development and medicinal chemistry, since the drug must be absorbed before any medicinal effects can take place. Moreover, the drug's pharmacokinetic profile can be easily and significantly changed by adjusting factors that affect absorption. In the most common situation, a tablet is ingested and passes through the oesophagus to the stomach. The rate of dissolution is a key target for controlling the duration of a drug's effect, and as such, several dosage forms that contain the same active ingredient may be available, differing only in the rate of dissolution. If a drug is supplied in a form that is not readily dissolved, the drug may be released more gradually over time with a longer duration of action. Having a longer duration of action may improve compliance since the medication will not have to be taken as often. Additionally, slow-release dosage forms may maintain concentrations within an acceptable therapeutic range over a long period of time, as opposed is quick-release dosage forms which may result in sharper peaks and troughs in serum concentrations.

1.1.6 Distribution Phase

Distribution in pharmacology is a branch of pharmacokinetics which describes the reversible transfer of drug from one location to another within the body. Once a drug enters into systemic circulation by absorption or direct administration, it must be distributed into interstitial and intracellular fluids. Each organ or tissue can receive different doses of the drug and the drug can remain in the different organs or tissues for a varying amount of time. The distribution of a drug between

tissues is dependent on vascular permeability, regional blood flow, cardiac output and perfusion rate of the tissue and the ability of the drug to bind tissue and plasma proteins and its lipid solubility. pH partition plays a major role as well. The drug is easily distributed in highly perfused organs such as the liver, heart and kidney. It is distributed in small quantities through less perfused tissues like muscle, fat and peripheral organs. The drug can be moved from the plasma to the tissue until the equilibrium is established (for unbound drug present in plasma). The concept of compartmentalization of an organism must be considered when discussing a drug's distribution. This concept is used in pharmacokinetic modelling. There are many factors that affect a drug's distribution throughout an organism, but Pascuzzo considers that the most important ones are the following: an organism's physical volume, the removal rate and the degree to which a drug binds with plasma proteins and/or tissues. This concept is related to multi-compartmentalization. Any drugs within an organism will act as a solute and the organism's tissues will act as solvents. The differing specificities of different tissues will give rise to different concentrations of the drug within each group. Therefore, the chemical characteristics of a drug will determine its distribution within an organism. For example, a liposoluble drug will tend to accumulate in body fat and water-soluble drugs will tend to accumulate in extracellular fluids. The volume of distribution (V_D) of a drug is a property that quantifies the extent of its distribution. It can be defined as the theoretical volume that a drug would have to occupy (if it were uniformly distributed), to provide the same concentration as it currently is in blood plasma. A drug's removal rate will be determined by the proportion of the drug that is removed from circulation by each organ once the drug has been delivered to the organ by the circulating blood supply. Some drugs have the capacity to bind with certain types of proteins that are carried in blood plasma. This is important as only drugs that are present in the plasma in their free form can be transported to the tissues. Drugs that are bound to plasma proteins therefore act as a reservoir of the drug within the organism and

this binding reduces the drug's final concentration in the tissues. The binding between a drug and plasma protein is rarely specific and is usually labile and reversible (Rowe, 2012).

1.1.7 Metabolism Phase

When a drug is destroyed by chemical alteration, we call it metabolism. The metabolite will probably be disposed of in the urine or bile, but this overall process is referred to as 'metabolism' not 'excretion'(Noreddin, 2012). Drug metabolism and renal excretion represent the two main pathways for clearing drug from the body. Drug metabolism takes place for the most part in the liver, but other sites may be involved, including the GI wall, lung, brain, kidney and in plasma (e.g., hydrolysis of suxamethonium by cholinesterase). For most drugs, metabolism is a detoxification process, making lipid-soluble drugs more water soluble so that they are excreted in urine more readily. For a few, metabolism converts an inactive precursor prodrug into the active, and therefore, more useful species (enalapril to enalaprilat). The sulfate metabolite of minoxidil is the active potassium channel activator responsible for lowering blood pressure in severe hypertension; azathioprine is metabolized to mercaptopurine. For some drugs, the metabolite remains active for longer than the parent compound. For example, elimination of allopurinol is mainly by metabolic conversion to oxipurinol by xanthine oxidase and aldehyde oxidase, with less than 10% of the unchanged drug excreted in the urine. Allopurinol has a plasma half-life of about 1-2 h. Oxipurinol is a less potent inhibitor of xanthine oxidase than allopurinol, but its plasma half-life is far more prolonged (13-30 h); it is eliminated unchanged in the urine, but has a long elimination half-life because it undergoes tubular reabsorption. Therefore, effective inhibition of xanthine oxidase is maintained over a 24-h period with a single daily dose of allopurinol. Sometimes, the drug metabolites are more harmful than the parent compound, e.g., the oxidation product of paracetamol, *N*-acetyl-*p*-benzoquinoneimine is responsible for life-threatening

hepatotoxicity seen in overdose. At therapeutic doses, the production of acrolein from cyclophosphamide results in hemorrhagic cystitis unless the antidote mesna is coadministered. Metabolism can be divided into two phases. Phase one is catabolic in nature and involves oxidation, reduction, and hydrolysis. Phase two encompasses a number of synthetic (anabolic) reactions such as glucuronidation and sulfation where the metabolite is conjugated covalently with a more water-soluble compound. Many drugs undergo both processes; for example, a hydroxyl group introduced by hydrolysis in Phase 1 is a point of attack for a subsequent glucuronidation in Phase 2. To reach the microsomal enzymes in hepatocytes, drugs must be relatively lipid soluble to penetrate intracellularly. Water-soluble drugs are usually excreted without further modification because they are more readily excreted in urine anyway and cannot reach the microsomal enzymes in the first place. Many drugs undergo Phase 1 metabolism followed by Phase 2, but this is not always the case.

1.1.8 Excretion Phase

Drug excretion can take place via a number of routes. Anesthetic gases are eliminated by exhalation and some drugs and/or their metabolites undergo excretion into bile and elimination in the faeces. Small quantities of drugs may be excreted in sweat and saliva. The major route of elimination for most drugs is the kidney, either directly or as metabolites. In pharmacology the elimination or excretion of a drug is understood to be any one of a number of processes by which a drug is eliminated from an organism either in an unaltered form (unbound molecules) or modified as a metabolite (Rowe, 2012). The kidney is the main excretory organ although others exist such as the liver, the skin, the lungs or glandular structures, such as the salivary glands and the lacrimal glands.

1.1.9 Drug Dose

In general medicine, we give a drug to a patient at a recommended dose and anticipate a therapeutic response. Most Phase 3 clinical trials produce data that tell us what a ballpark dose should be for an average patient to achieve a usual effect, and if we are lucky, what to expect in terms of side effects at usual doses or if doses are exceeded. We are sometimes surprised when the usual dose either fails to elicit any kind of response or produces side effects that, according to our evidence, should be observed only at much higher doses. Most drug effects are achieved by the interaction of a drug with receptors on the target organ. The intensity and duration of that effect are usually determined by the number of drug molecules present, their receptor site binding affinity, and their residence time at the receptor site(s). This pharmacodynamic aspect of drug therapy is next to pharmacokinetic process. After administration, by whatever route, the drug concentration at the target site is governed by the often tortuous route its takes to get there. Like any journey, it can be planned in terms of route directions, load, and time, and calculations can be used to show what load can be delivered at a particular speed over what terrain, and what hazards must be overcome to reach the destination successfully. This road map is the essence of PK–the study of time-dependent drug movement into, around and out of the body.

In a healthy population, there is a natural variation in the pharmacokinetic processes of absorption, distribution, metabolism, and excretion; that is why, average doses will produce average responses, and for many drugs with wide safety margins, this is sufficient. However, some drugs do not have wide safety margins and knowledge of clinical pharmacokinetics in the individual is vital to ensure that therapy with these drugs is effective and as safe as possible. It is also important to recognize that organ disease, particularly that of the liver and kidney, can affect pharmacokinetics profoundly and patients with such co-morbidities should be monitored appropriately. Nowhere is this more important than in critical care where patient status may change rapidly with time, requiring a thorough

knowledge of pharmacokinetics. To use the above analogy, the road map may be poorly defined, particularly for new drugs, and subject to frequent and sometimes misleading updates along the way.

1.1.10 Therapeutic Action

A drug is a substance that is taken, or administered, to produce an effect, usually a desirable one. These effects are assessed as physiological, biochemical or behavioural changes. Primitive therapeutics relied heavily on a variety of mixtures prepared from botanical and inorganic materials. The botanical materials included some extremely potent plant extracts, with actions for example on the brain, heart and gastrointestinal tract, and also some innocuous potions, which probably had little effect. The inorganic materials were generally alkalis, which did little more than partially neutralize gastric acidity. Potassium carbonate (potash, from wood fires) was chewed with coca leaves to hasten the release of cocaine. Inevitably, the relative importance of these materials has declined, but it should be recognized that about a dozen important drugs are still obtained, as purified chemical constituents, from botanical sources and that alkalis still have a very definite value in certain conditions. Amongst the botanical drugs, are the alkaloids: morphine is still obtained from opium, cocaine is still obtained from coca leaves, and atropine is still obtained from the deadly nightshade (belladonna).

1.1.11 Blood Composition and Plasma Proteins

The body is made up of approximately 60% water, 18% protein, 15% fat and 7% minerals. Body water can be subdivided into that in the cells [intracellular water (ICF, 40% of total)] and the remaining extracellular water (ECF, 20%), which can be subdivided further into interstitial fluid (15%) and plasma (5%). The blood volume is (9%) of total body water (TBW); the (4%) of body water associated with the red cells is part of the intracellular volume. Clearly plasma protein binding has a major influence on the distribution of drugs. Extensive

binding to plasma proteins reduces the apparent volume of distribution because a larger proportion of the amount of drug in the body will be in the plasma. It is usual to measure the "total" concentration of drug (i.e. bound + unbound) in plasma. Binding to plasma proteins, provides an efficient way of transporting drugs in the circulation, sometimes at concentrations that exceed their solubility in plasma water. Binding has an important role in absorption, as it maintains a favourable concentration gradient for the unbound drug. It is generally assumed that plasma protein binding reduces the proportion of a dose of drug available to its receptors and so it can have a major influence on drug activity.

1.1.12 Exceptions to linearity

There are a few drugs that do reach concentrations that cause significant molecular saturation. The best known culprits are: Phenytoin, Salicylates and Ethanol. Phenytoin provides the one clinically significant case. It is a drug with a narrow therapeutic window and serious toxicity in overdose, so controlling its blood concentrations is a real concern.

Salicylates do cause saturation, but they are not drugs where clinical practitioners are involved in trying to control concentration within some narrow band. Their non-linear kinetics are largely academic.

Ethanol in doses high enough to cause noticeable effects, will fully saturate the liver..

There is evidence of a degree of saturation with theophylline, however the effect is quite small and for practical, clinical purposes its kinetics are treated as linear.

1.1.13 Effect of non-linearity on the relationship between dose and drug concentration.

When a drug is given long-term, we eventually achieve steady state, where the amount of drug administered every day is balanced by daily drug elimination.

1.1.14 Clinical Significance of non linear kinetics

Given the potential toxicity of phenytoin, dosage adjustment is a specialist job; the normal concepts and rules just don't apply. General pharmacokinetics assumes first order drug elimination where the metabolism rate constant is a valid concept. With non-linear kinetics, there is no longer a constant proportionality between rate of elimination and drug concentration and the idea of an metabolism rate constant linking the two no longer applies.

1.1.15 Non-linear kinetics and drug development

Clinical workers are subjected to considerable additional complexity when trying to use a non-linear drug like phenytoin and given a choice of drugs that are otherwise equally acceptable, they would undoubtedly choose one with simple linear kinetics over a non-linear one. There is therefore a strong commercial disinclination to proceed with the development of any further non-linear drugs;companies would want to establish at an early stage, that any candidate drug did not suffer from this problem.

1.2 Statement of the Problem

Unhealthy or sick persons ingest drug because they need some cure. Active drug molecules enters an organ/tissue at a certain volume rate. Thus the drug is absorbed into the blood stream and circulate through the body and distribute to the site of action or tissue. Then the drug effect occurs and thereafter the drug is transported and metabolised in the liver. This chemical alteration of the drug substances is critically inevitable after drug actions. However if active drug remains un-metabolised in the liver, recursive re-absorption will invoke a repeated drug effect and this will consequently risk into loss of human life as a result of long stay of foreign substances in the body. The human body through the process of evolution has developed mechanism of getting rid of foreign substances

like drugs. Clinical workers are subjected to considerable additional complexity when trying to use a non-linear drug like phenytoin and given a choice of drugs that are otherwise equally acceptable, they would undoubtedly choose one with simple linear kinetics over a non-linear one. There is therefore a strong commercial disinclination to proceed with the development of any further non-linear drugs;pharmaceutical companies would want to establish at an early stage, that any candidate drug did not suffer from this problem. The focus of thesis is to evaluate and single out the conditions necessary for first order metabolism of drugs in the liver.

1.3 Objectives of the Thesis

The objectives of the thesis are:

- To develop a first-order kinetic drug metabolism model.
- To investigate the necessary conditions underlying active drug metabolism.

1.4 Methodology

- Clinical workers are subjected to considerable additional complexity when trying to use a non-linear drug like phenytoin and given a choice of drugs that are otherwise equally acceptable, they would undoubtedly choose one with simple linear kinetics over a non-linear one. There is therefore a strong commercial disinclination to proceed with the development of any further non-linear drugs;companies would want to establish at an early stage, that any candidate drug did not suffer from this problem.
- We will begin by developing the metabolism model of pharmacokinetics associated with the transport of tissue/organ drug substrate into the liver compartment.

- The source of parameter values are obtained from Crooks et al. (2000).
- The methods used for obtaining the solution to the metabolism model are differentiation and integration.
- The numerical computation of the model will be graphed using the MATLAB software.
- The sources of reading materials are obtained from the Internet.

1.5 Justification of the Thesis

This thesis will be relevant to drug pharmaceutics and clinical workers as follows:

- Drug pharmaceutics at the early stage of drug development can ensure that new candidate drug molecule obeys simple linear kinetics in order to improve the current treatment strategies.
- Clinical workers would be relieved from the critical observation and attention given to such patients under non-linear drug.

1.6 Organization of the Thesis

This thesis is organized into five Chapters. Chapter one is the introduction comprising of background to the study, statement of the problem, objectives, methodology, justification and the organization of the thesis. Chapter two focuses on the previous research works related to the thesis. Chapter three examines the methodology involved and Chapter four discusses the analysis and result obtained from the research with the model equations. Finally Chapter five gives the conclusions and recommendations drawn from the studies.

Chapter 2

LITERATURE REVIEW

2.1 Introduction

In this chapter, we review the previous related works done by researchers. Advance knowledge into pharmacokinetics has over the years extended into developing new and better strategies to improving medical dosing treatment through various kinds of drug models.

2.2 Elderly Pharmacokinetics

Crooks et al. (2000) did a thorough review of pharmacokinetics in the elderly. There was at present insufficient data on which to make recommendations with respect to doses of drugs in the elderly. The elderly are generally considered to be different from young people in terms of drug response and this applies particularly to quantitative differences. While altered drug handling is a major potential source of difference in responsiveness to drug, the relative contribution of pharmacokinetics and pharmacodynamics to this difference is not clear. The present review examined the available data of pharmacokinetics in the elderly. In the past, data pertaining to animals have been extrapolated to man and in the absence of human experimentation these assumptions have tended to hold sway. The absorption of active transported substances may in fact be diminished in the

elderly. However, most drugs are absorbed by passive diffusion and the recently available evidence in man indicate that there is no age-dependent change. While definitive data on the effect of old age on drug metabolising ability in animals is available, no direct assessments have been made in man. Many of the studies carried out using drug plasma half-life and clearance assessments are complicated by changes in distribution. This is best illustrated by a definitive study with diazepam, in which marked prolongation of plasma half-life was accompanied by an increase in apparent volume of distribution in the elderly. This latter change influences plasma drug clearance and possibly drug concentration at its site of action. Thus, the implications of drug effect of such changes in volume of distribution remain to be clarified. In theory, the rate of elimination of antipyrine provide a good index of drug metabolising ability. Both plasma half-life and clearance values suggest a decrease in metabolism in the elderly. Thus, while it is likely that the metabolism of some drugs is impaired in old age, it is not possible at this time to generalise with regard to the effect of age on drug metabolising ability in man. It is also difficult to generalise about age-related changes in plasma protein binding of drugs. With some drugs, binding to plasma protein does not appear to be altered and for two drugs–warfarin and phynetoin, the findings of different investigators conflict. With digoxin and sulphamethizole, the evidence is that renal excretion is diminished in the elderly. They recommended that future studies must combine pharmacokinetic and pharmacodynamic aspect in the relevant clinical setting so that the practical significance, if any, of altered kinetic emerges.

2.3 Economic Influence

Cheymol and Georges (2000) demonstrated that obesity is a worldwide problem, with major health, social and economic implications. The adaptation of drug dosages to obese patients is a subject of concern, particularly for drugs with a

narrow therapeutic index. The main factors that affect the tissue distribution of drugs are body composition, regional blood flow and the affinity of the drug for plasma proteins and/or tissue components. Obese people have larger absolute lean body masses as well as fat masses than non-obese individuals of the same age, gender and height. However, the percentage of fat per kg of total bodyweight (TBW) is markedly increased, whereas that of lean tissue is reduced. Cardiac performance and adipose tissue blood flow may be altered in obesity. There is uncertainty about the binding of drugs to plasma proteins in obese patients. The dosage of these drugs should be based on the ideal bodyweight (IBW). However, some of these drugs (e.g. antibacterials and some anticancer drugs) are partly distributed in adipose tissues, and their dosage is based on IBW plus a percentage of the patient's excess bodyweight.There is no systematic relationship between the degree of lipophilicity of markedly lipophilic drugs.

Cheymol (2000) did a study about the effects of obesity on pharmacokinetics: implications for drug therapy Obesity is a worldwide problem, with major health, social and economic implications. The adaptation of drug dosages to obese patients is a subject of concern, particularly for drugs with a narrow therapeutic index. The main factors that affect the tissue distribution of drugs are body composition, regional blood flow and the affinity of the drug for plasma proteins and/or tissue components. Obese people have larger absolute lean body masses as well as fat masses than non-obese individuals of the same age, gender and height. However, the percentage of fat per kg of total bodyweight (TBW) is markedly increased, whereas that of lean tissue is reduced. Cardiac performance and adipose tissue blood flow may be altered in obesity. There is uncertainty about the binding of drugs to plasma proteins in obese patients. Some data suggest that the activities of hepatic cytochrome P450 isoforms are altered, but no clear overview of drug hepatic metabolism in obesity is currently available. There is no systematic relationship between the degree of lipophilicity of markedly lipophilic drugs and their distribution in obese individuals. The distribution of a drug between

fat and lean tissues may influence its pharmacokinetics in obese patients. Thus, the loading dose should be adjusted to the TBW or IBW, according to data from studies carried out in obese individuals. Adjustment of the maintenance dosage depends on the observed modifications in clearance. Our present knowledge of the influence of obesity on drug pharmacokinetics is limited. Drugs with a small therapeutic index should be used prudently and the dosage adjusted with the help of drug plasma concentrations.

Siebert (2005) thesis is concerned with differences in drug and solute pharmacokinetics and distribution in perfused organs under varying pathological conditions. It falls in two parts, and two organ systems are considered: The perfused (rat) liver and the perfused (rat and human) limb. Two important different aspects of drug and solute disposition have been determined: basic drug/solute binding, metabolism and clearance (in the healthy and the diseased liver) and drug effects and distribution in healthy and diseased tissue (oncological treatment of tumours of the limb). Two major implications arose from this work. Firstly, the typically 2-3-fold increase of cytotoxic drug concentration given in high dose chemotherapy compared with standard drug concentration may be considered insufficient to produce the expected increase in tumour response to treatment, and secondly, an increase of melphalan dose above a certain threshold does not greatly increase tumour response combination therapies could be more promising and beneficial for patients.

2.4 Models of Specific Drugs

Henningsson (2005) examined Mechanism-Based Pharmacokinetic and Pharmacodynamic Modelling of Paclitaxel. Paclitaxel (Taxol) is now widely used against breast, ovarian and non-small-cell lung cancer. Anticancer agents generally have narrow therapeutic indices, often with myelosuppression (mainly neutropenia) as dose-limiting side effect. A further complicating factor is that paclitaxel when

given as Taxol has a nonlinear pharmacokinetic (PK) behaviour in plasma. Identifying risk groups more sensitive to chemotherapy due to either a PK or pharmacodynamic (PD) interindividual variability is of importance. The aim of the thesis was to develop predictive mechanism-based PK and PD models applicable for paclitaxel. PK and PK/PD models were developed for patient data from studies with relatively frequent sampling or sparse sampling schedules. Population analyses were performed using the software NONMEM. The developed mechanism-based models promote a better understanding of paclitaxel PK and PD and may be used as tools in dosing individualisation and in development of dosing strategies for new administration forms and new drugs in the same area.

Hennig (2006) observed the Population pharmacokinetics of itraconazole. A 2-compartment model with first order absorption and elimination best described itraconazole kinetics, with first order formation for metabolism to the hydroxy-metabolite. There was no evidence of nonlinearity in the PK of itraconazole and no screened covariate significantly improved the fit to the data. There was high inter-patient variability confirmed previous results in CF. The optimal design performed well for estimation of model parameters from a complex parent-metabolite popPK model. Due to the sampling windows, most of the samples could be collected within the daily hospital routine, but at times that were "near-optimal" for estimating the popPK parameters. Simulations from the final model showed that the current dosing regimen of 200 mg twice daily would provide a trough target concentration at steady state in only 35% of patients when administered as the solution, and 31% when administered as the capsules. The optimal dosing schedule was 500 mg b.d. for both formulations. Since the therapeutic target for itraconazole, is still unresolved, the potential risks of these dosing schedules need to be assessed on an individual basis.

2.5 Quantitative Drug Effects Predictions

Csajka and Verotta (2006) discovered that a major goal in clinical pharmacology is the quantitative prediction of drug effects. The field of pharmacokinetic/pharmacodynamic (PK/PD) modelling has made many advances from the basic concept of the dose response relationship to extended mechanism-based models. The purpose of this article is to review, from a historical perspective, the progression of the modelling of the concentration response relationship from the first classic models developed in the mid-1960s to some of the more sophisticated current approaches. The emphasis is on general models describing key PD relationships, such as: simple models relating drug dose or concentration in plasma to effect, biophase distribution models and in particular effect compartment models, models for indirect mechanism of action that involve primarily the modulation of endogenous factors, models for cell trafficking and transduction systems. We also discuss some future possible directions for PK/PD modelling, report equations for general classes of novel semi-parametric models, as well as describing two new classes, additive or set-point, of regulatory, additive feedback models in their direct and indirect action variants.

Yates (2006) proposed when starting a project in drug kinetics it is necessary to test a priori whether there is sufficient information in the experimental input-output design to estimate unique values of internal rate constants. This is an important test if the pharmacokinetics of a drug are to be characterised in some way by the parameter values estimated from the observed plasma or blood concentration profile. Various modifications of the well-perfused Physiologically Based Pharmacokinetic model (PBPK) are considered here. More complex PBPK models can be considered to consist of subsystems, representing groups of tissues, which are connected in parallel to the central compartment. A novel method of structural identifiability analysis is presented here that considers these subsystems individually. This makes analysis of subsequently modified models much

simpler. It is found in a number of cases that these more complex systems remain globally identifiable and at worst reduce to locally identifiable for the additional parameters. A caveat is added about having more than one eliminating peripheral tissue.

Storehagen (2007) applied Ciclosporin A (CsA) for the development of a pharmacokinetic population model. A pharmacokinetic population model predicts individual pharmacokinetic parameters not only based on patient observations, but also upon population data. The large pharmacokinetic variability of CsA seen in the population as well as significant patient demographics are implemented in such a model. A pharmacokinetic population model of CsA can therefore be a valuable tool used to optimize CsA dosing. The purpose of this study was to develop a pharmacokinetic population model for CsA. Methods Twelve hour concentration-time profiles of CsA from 17 renal transplant recipients were used to develop a pharmacokinetic population model using the nonlinear mixed effect approach as implemented in NONMEM. Different compartment models and especially different absorption processes were examined in order to find the best pharmacokinetic population model for CsA. This population model provides a good basis for the development of a model that can serve as a Bayesian prior when designing dosing regimens in new kidney transplant patients.

Post et al. (2007) worked on extensions to the visual predictive check to facilitate model performance evaluation. The visual predictive check (VPC) is a valuable and supportive instrument for evaluating model performance. However in its most commonly applied form, the method largely depends on a subjective comparison of the distribution of the simulated data with the observed data, without explicitly quantifying and relating the information in both. In recent adaptations to the VPC this drawback is taken into consideration by presenting the observed and predicted data as percentiles. In addition, in some of these adaptations the uncertainty in the predictions is represented visually. However, it is not assessed whether the expected random distribution of the observations around the pre-

dicted median trend is realised in relation to the number of observations. The proposed extensions to the VPC are illustrated by pharmacokinetic simulation example and applied to a pharmacodynamic disease progression example.

2.6 Dosing Regimen for Chronic Kidney Patients

Myrna et al. (2007) proposed drug dosing adjustments in patient with chronic kidney disease which affects renal drug elimination and other pharmacokinetic processes involved in drug disposition (e.g., absorption, drug distribution, nonrenal clearance[metabolism]). Dosages of drugs cleared renally should be adjusted according to creatinine clearance or glomerular filtration rate and should be calculated using online or electronic calculators. Recommended methods for maintenance dosing adjustments are dose reductions, lengthening the dosing interval, or both. Analysis on the chronic kidney disease reveals that Physicians should be familiar with commonly used medications that require dosage adjustments.

Li and Nekka (2007) proposed that the adherence phenomenon is now well recognized to seriously compromise drug efficacy. In this paper, they analyze the role of compliance through drug intake history as an integral part of the pharmacokinetic process. Being concerned with what is accessible in medical practice, we develop a stochastic approach to model the drug intake behavior that we combine with a conventional pharmacokinetic model in order to investigate the effect of drug intake history on the pharmacokinetic time-course. For this purpose, they explicitly formalize the plasma concentration variations for the most common administration routes. This analytical approach allows to characterize drug concentration variations directly inherited from patient compliance.

Seng et al. (2007) said that statistical techniques have been traditionally used to deal with parametric variation in pharmacokinetic and pharmacodynamic models, but these require substantial data for estimates of probability distributions. In the presence of limited, inaccurate or imprecise information, simulation with

fuzzy numbers represents an alternative tool to handle parametric uncertainty. Existing methods for implementing fuzzy arithmetic may, however, have significant shortcomings in overestimating (e.g., conventional fuzzy arithmetic) and underestimating (e.g., vertex method) the output uncertainty. The purpose of the present study is to apply and compare the applicability of conventional fuzzy arithmetic, vertex method and two recently proposed numerical schemes, namely transformation and optimization methods, for uncertainty modeling in pharmacokinetic and pharmacodynamic fuzzy-parameterized systems. It turned out that the choice of a suitable method for fuzzy simulation of the non-monotonic function depended on the required accuracy of the results: the vertex method was capable of eliciting an initial approximate solution with few function evaluations; for more accurate results, the transformation method was the most superior approach in terms of accuracy per unit CPU time.

Munar et al. (2007) investigated drug dosing adjustments in patients with chronic kidney disease. Chronic kidney disease affects renal drug elimination and other pharmacokinetic processes involved in drug disposition (e.g., absorption, drug distribution, nonrenal clearance[metabolism]). Drug dosing errors are common in patients with renal impairment and can cause adverse effects and poor outcomes. Dosages of drugs cleared renally should be adjusted according to creatinine clearance or glomerular filtration rate and should be calculated using online or electronic calculators. Recommended methods for maintenance dosing adjustments are dose reduction, lengthening the dosing interval, or both. Physicians should be familiar with commonly used medications that require dosage adjustments. Resources are available to assist in dosing decisions for patients with chronic kidney diseases.

Czock and Keller (2007) proposed mathematical modeling of drug effects maximizes the information gained from an experiment, provides further insight into the mechanisms of drug effects, and allows for simulations in order to design studies or even to derive clinical treatment strategies. We reviewed modeling of antimi-

crobial drug effects and show that most of the published mathematical models can be derived from one common mechanism based PK/PD model premised on cell growth and cell killing processes. Furthermore, the common model allows the parameters of these models to be related to the MIC and to a common set of PK/PD indices. Theoretically, a high Hill coefficient and a low maximum kill rate indicate so-called time-dependent antimicrobial effects, whereas a low Hill coefficient and a high maximum kill rate indicate so-called concentration-dependent effects, as illustrated in the garenoxacin and meropenem examples. Finally, a new equation predicting the time to microorganism eradication after repeated drug doses was derived that is based on the area under the kill-rate curve.

2.7 Analytical Solution to Michaelis-Menten Kinetics

Tang and Xiao (2007) provided the analytical solutions of one-compartment models with Michaelis-Menten elimination kinetics for three different inputs (single intravenous dose, multiple-dose bolus injection and constant). All analytical solutions obtained in present paper can be described by the well defined Lambert W function which can be easily implemented in most mathematical softwares such as Matlab and Maple. These results will play an important role in fitting the Michaelis-Menten parameters and in designing a dosing regimen to maintain steady-state plasma concentrations. Therefore, the one-compartment model with therapeutic window is proposed, and further the existence of periodic solution, analytical expression and its period are analyzed. The analytical formula of period plays a key role in designing a dose regimen to maintain the plasma concentration within a specified range over long periods of therapy. Finally, the completely analytical solution for the constant input rate is derived and discussed which depends on the relations between constant input rate and maximum rate of change of concentration.

Kleist and Huisinga (2007) presented a sub-compartmentalized model of drug distribution in tissue that extends existing approaches based on the well-stirred tissue model. It is specified in terms of differential equations that explicitly account for the drug concentration in erythrocytes, plasma, interstitial and cellular space. Assuming, in addition, steady state drug distribution and by lumping the different sub-compartments, established models to predict tissue-plasma partition coefficients can be derived in an intriguingly simple way. This direct link is exploited to explicitly construct and parameterize the sub-compartmentalized model for moderate to strong bases, acids, neutrals and zwitterions. The derivation highlights the contributions of the different tissue constituents and provides a simple and transparent framework for the construction of novel tissue distribution models.

2.8 PK/PD Analysis using Data

Matthews (2008) realised that the goal of most population pharmacokinetic and pharmacodynamic analyses is to develop a model that adequately describes the available data and that can be used for predictive purposes. The assessment of covariates is of utmost importance to enhance predictive performance and ultimately to design rational dosing regimens. The increasing use of pharmacogenetics has opened up a whole new array of covariates that can potentially explain the observed between subject variability. In addition, the lack of information regarding drug therapy in special populations such as paediatrics needs to be addressed. The aims of this thesis were therefore to assess the impact of pharmacogenetics on the pharmacokinetics and/or pharmacodynamics of test compounds and to assess ways of including this covariate information into models. Furthermore, to develop models that can explain the differences between adults and paediatrics in order to develop rational dosing guidelines in the paediatric population.

Wolfsegger and Jaki (2008) proposed a non-compartmental estimation of phar-

macokinetic parameters in serial sampling designs. Pharmacokinetic studies are commonly analyzed using a two-stage approach where the first stage involves estimation of pharmacokinetic parameters for each subject separately and the second stage uses the individual parameter estimates for statistical inference. This two-stage approach is not applicable in sparse sampling situations where only one sample is available per subject. Nonlinear models are often applied to analyze pharmacokinetic data assessed in such serial sampling designs. Modelling approaches are suitable provided that the form of the true model is known, which is rarely the case in early stages of drug development. This paper presents an alternative approach to estimate pharmacokinetic parameters based on non-compartmental and asymptotic theories in the case of serial sampling when a drug is given as an intravenous bolus. The statistical properties of estimators of the pharmacokinetic parameters are investigated and evaluated using Monte Carlo simulations.

2.9 Population Pharmacokinetics

Wanga et al. (2009) incorporated Population pharmacokinetic/pharmaco dynamic mixture models via maximum a posteriori estimation. Pharmacokinetic/pharmacodynamic phenotypes are identified using nonlinear random effect models with finite mixture structures. Parameters for the conjugate prior densities can be based on prior studies or set to represent vague knowledge about the model parameters. A detailed simulation study illustrates the feasibility of the approach and evaluates its performance, including selecting the number of mixture components and proper subject classification. Kha (2009) analyzed local pharmacokinetics and pharmacodynamics of angiogenic growth factors in myocardial tissue. This thesis was designed to examine critically whether the lack of late efficacy of local delivery of angiogenic factors could be explained by a comprehensive understanding of local pharmacokinetics (PK) and pharmacodynamics

(PD) in the myocardial tissue. We characterized the baseline local myocardial PK through a series of ex-vivo isolated heart studies and mathematical analysis, examined the local coupling of PK and PD with an in-vivo ischemic heart model, created a computational model of myocardial PK and PD to predict distribution of growth factors and their biologic effects, discussed implications and future studies. Our findings suggest that microvascular washout impedes myocardial drug transport, early angiogenic response further exacerbates drug washout and is likely responsible for late vessel regression, modulating drug PK properties to mitigate drug clearance through washout can enhance late tissue response. These results imply that local PK-PD interdependence should be carefully examined to improve clinical efficacy of angiogenic therapy with local angiogenic growth factor delivery.

Dokoumetzidis and Macheras (2009) explored the use of fractional order differential equations for the analysis of datasets of various drug processes that present anomalous kinetics, i.e. kinetics that are non-exponential and are typically described by power-laws. A fractional differential equation corresponds to a differential equation with a derivative of fractional order. The fractional equivalents of the "zero-order" and "first-order" processes are derived. The fractional zero-order process is a power-law while the fractional first-order process is a Mittag—Leffler function. The proposed approach is compared conceptually with fractal kinetics, an alternative approach to describe datasets with non exponential kinetics. Fractional kinetics offers an elegant description of anomalous kinetics, with a valid scientific basis, since it has already been applied in problems of diffusion in other fields, and describes well the data.

2.10 Applications to Population Pharmacokinetics

Gibiansky et al. (2009) did a target-mediated drug disposition model: relationships with indirect response models and application to population PK—PD

analysis. The paper focuses on approximations of the target-mediated drug disposition (TMDD) model as applied to pharmacodynamic (target kinetics) modeling. The TMDD equation for the total target concentration is shown to coincide with the indirect response model with stimulation or inhibition of elimination. This correspondence allows estimation of pharmacodynamic TMDD parameters and unobservable free target concentrations using indirect-response models. The ability of the TMDD model and its approximations to estimate the unobservable free target concentration is investigated by simulation. Pharmacokinetic parameters used for simulations were parameters typical for monoclonal antibodies. TMDD binding and target turnover parameters were similar to those estimated for omalizumab. Free drug and total target concentrations were measured. The simulated population PK—PD study demonstrated that for drugs with TMDD, indirect–response models are in fact mechanistic models that can be used to estimate TMDD model parameters and unobservable free target concentrations that are important for pharmacodynamic modeling.

Li and Nekka (2009) did a probabilistic approach for the evaluation of pharmacological effect induced by patient irregular drug intake. Fine individual drug intake data, generally collected by electronic monitoring devices, reveal that individual marked random patterns are likely to persist through long therapeutic periods. This work aims to establish the relationship between irregularity in drug intake and its potential impact on therapeutic outcomes, which will also serve as a basis for more objective interventions. First we proposed a direct way to extract the necessary information representing the patient drug intake history. To provide a fair evaluation of the pharmacological performance, we revisited several classical pharmacological indices and proposed new ones in the stochastic context of patient's drug intake irregularity. As a direct fallout, we have discussed strategies to attenuate the impact of noncompliance through an optimal design of dosing regimen.

2.11 Paediatric Drug Development

Strougo et al. (2012) researched on first dose in children: physiological insights into pharmacokinetic scaling approaches and their implications in paediatric drug development. Dose selection for "first in children" trials often relies on scaling of the pharmacokinetics from adults to children. Commonly used approaches are physiologically-based pharmacokinetic modeling (PBPK) and allometric scaling (AS) in combination with maturation of clearance for early life. In this investigation, a comparison of the two approaches was performed to provide insight into the physiological meaning of AS maturation functions and their interchangeability. The results of this investigation showed that AS maturation functions do not solely represent ontogeny of enzyme activity, but aggregate multiple pharmacokinetic properties, as for example extraction ratio and lipophilicity (log P). Especially in children younger than 1 year, predictions using AS in combination with maturation functions and PBPK were not interchangeable. This highlights the necessity of investigating methodological uncertainty to allow a proper estimation of the "first dose in children" and assessment of its risk and benefits.

Krippendorff et al. (2012) predicted the F(ab)-mediated effect of monoclonal antibodies in vivo by combining cell-level kinetic and pharmacokinetic modelling. Cell-level kinetic models for therapeutically relevant processes increasingly benefit the early stages of drug development. Later stages of the drug development processes, however, rely on pharmacokinetic compartment models while cell-level dynamics are typically neglected. We here present a systematic approach to integrate cell-level kinetic models and pharmacokinetic compartment models. Incorporating target dynamics into pharmacokinetic models is especially useful for the development of therapeutic antibodies because their effect and pharmacokinetics are inherently interdependent. The approach is illustrated by analysing the F(ab)-mediated inhibitory effect of therapeutic antibodies targeting the epidermal

growth factor receptor. The multi-level model suggests that the F(ab)-mediated inhibitory effect saturates with increasing drug-receptor affinity, thereby limiting the impact of increasing antibody affinity on improving the effect. This indicates that observed differences in the therapeutic effects of high affinity antibodies in the market and in clinical development may result mainly from Fc-mediated indirect mechanisms such as antibody-dependent cell cytotoxicity.

Shen et al. (2012) worked on implementation of dose superimposition to introduce multiple doses for a mathematical absorption model (transit compartment model). A mathematical absorption model (e.g. transit compartment model) is useful to describe complex absorption process. However, in such a model, an assumption has to be made to introduce multiple doses that a prior dose has been absorbed nearly completely when the next dose is administered. This is because the drug input cannot be determined from drug depot compartment through integration of the differential equation system and has to be analytically calculated. We propose a method of dose superimposition to introduce multiple doses; thereby eliminating the assumption. The code for implementing the dose superimposition in WinNonlin and NONMEM was provided. For implementation in NONMEM, we discussed a special case (SC) and a general case (GC). In a SC, dose superimposition was implemented solely using NM-TRAN abbreviated code and the maximum number of the doses that can be administered for any subject must be pre-defined. In a GC, a user-supplied function (FUNCA) in FORTRAN code was defined to perform dose superimposition to remove the restriction that the maximum number of doses must be pre-defined.

Alskär et al. (2012) proposed a pharmacokinetic model for the glycation of albumin. Glycated haemoglobin (HbA1c) concentrations can be falsely lowered in circumstances when red blood cell (RBC) survival is reduced, e.g. in patients with chronic kidney disease (CKD). Glycated albumin (GA) has been suggested as an alternative marker of glycaemic control in these patients since it is independent of the RBC life span. The primary aim of this work was to develop a

pharmacokinetic model that describes the time course of GA. The secondary aim was to assess the performance of GA as marker for glycaemic control in comparison to HbA1c based on simulations. For the second aim, three different scenarios were considered in the simulations: 1) assessment of the effect of large intra-day fluctuations in mean blood glucose on GA concentrations, 2) initiation of antidiabetic treatment on the GA profile, and 3) a hypothetical phase II study for a new antidiabetic compound. The GA model, as well as a previously developed HbA1c model described literature data well. GA concentrations appear to be stable even in the presence of high intra-day fluctuations in mean blood glucose concentrations. Simulation of a decrease in mean blood glucose concentrations resulted in a faster change in GA compared to HbA1c. GA also provided a time to 90% power of the effect of a hypothetical antidiabetic drug that was 16 days shorter than when using HbA1c. These results indicate that GA could be used as alternative marker to assess blood glucose control in diabetic patients with CKD and also to follow an individual patient over time.

Tuija (2012) researched on Pharmacokinetic interactions and pharmacogenetics of aliskerin. Aliskiren is an antihypertensive drug approved for clinical use in 2007. It acts by inhibiting renin, the first enzyme in the renin-angiotensin-aldosterone system. Marked interindividual variability exists in the pharmacokinetics of aliskiren. Interestingly, the pharmacokinetic properties of aliskiren suggest an important role for drug transporters in its pharmacokinetics. Aliskiren is poorly absorbed, and therefore, its oral bioavailability is only 2-3%. The elimination of aliskiren occurs mainly as an unchanged drug by biliary and renal excretion, and only a small proportion is metabolized by cytochrome P450 (CYP) 3A4. In conclusion, aliskiren was found to be susceptible to transporter-mediated pharmacokinetic interactions of clinical significance. The interactions of rifampicin and itraconazole with aliskiren probably resulted from induction and inhibition of P-gp in the small intestine, respectively, with a minor contribution from a parallel effect on CYP3A4. Grapefruit, orange, and apple juices reduced the absorption

of aliskiren from the gastrointestinal tract, possibly by inhibiting intestinal OATP transporters.

Dette et al. (2012) worked on optimal designs for composed models in pharmacokinetic–pharmacodynamic experiments. We consider two frequently used PK/PD models and provide closed form descriptions of locally optimal designs for estimating individual parameters. In a novel way, we use these optimal designs and construct locally standardized maximin optimal designs for estimating any subset of the model parameters of interest. We do this by maximizing the minimal efficiency of the estimates across all relevant parameters so that these optimal designs are less dependent on the individual parameter or parameters of interest. Additionally, robust designs are proposed to further reduce the dependence on the nominal values of the parameters. We compare efficiencies of our proposed optimal designs with locally optimal designs and designs used in four real studies from the literature and show that our proposed designs provide advantages over those used in practice.

2.12 Transit Compartments and Lifespan Models

Koch and Schropp (2012) worked on a general relationship between transit compartments and lifespan models. Transit compartment models (TCM) are important tools in pharmacokinetic/pharmacodynamic (PKPD) modeling. In this work we investigate the relationship between TCMs with arbitrary initial values and lifespan models (LSM) with non-constant past and constant lifespan. We show that the total population in all transit compartments converges to a LSM, if the number of compartments n tends to infinity. The key to obtain this result is to establish a relationship between the initial values of the TCM and the non-constant past of the LSM. We apply the result to two already published PKPD models.

Gaz et al. (2012) did a geometrical approach to the PKPD modelling of in-

haled bronchodilators. The present work introduces a new method to model the pharmacokinetics (PK) and pharmacodynamics (PD) of an inhaled dose of bronchodilator, alternative to classic compartmental representations or computational fluid dynamics. A five compartment PK model comprising alimentary tract absorption (gut), bronchial tree mucosa, bronchial muscles, plasma, and elimination/excretion pathways has been developed. Many anatomical and physiological features of the bronchial tree depend on bronchial generation or on mean distance from the larynx. In the present work the construction of the model is detailed, with reference to literature data. Simulation of a hypothetical asthmatic subject is employed to illustrate the behaviour of the model in representing the evolution over time of the distribution and pharmacological effect of an inhaled dose of a bronchodilator. The relevance of particle size and drug formulation diffusivity on therapeutic efficacy is discussed.

Shaffer et al. (2012) used simcyp to project human oral pharmacokinetic variability in early drug research to mitigate mechanism-based adverse events. Positive allosteric modulators ('potentiators') of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) have been shown to display a mechanism-based exposure-response continuum in preclinical species with procognitive electrophysiological and behavioral effects ('efficacy') at low exposures and motor coordination disruptions at progressively higher exposures. This evaluation aided in the selection of compounds for preclinical progression, and represents a novel application of pharmacologically based pharmacokinetic (PBPK) software approaches to predict interpatient variability.

Lledõ–Garcĩa et al. (2012) proposed the modeling of red blood cell life-spans in hematologically normal populations. Despite the impact of red blood cell (RBC) Life-spans in some disease areas such as diabetes or anemia of chronic kidney disease, there is no consensus on how to quantitatively best describe the process. Several models have been proposed to explain the elimination process of RBCs: random destruction process, homogeneous life-span model, or a series of

4-transit compartment model. The aim of this work was to explore the different models that have been proposed in literature, and modifications to those. The impact of choosing the right model on future outcomes prediction–in the above mentioned areas- was also investigated. Both data from indirect (clinical data) and direct life–span measurement (biotin-labeled data) methods were analyzed using non-linear mixed effects models. Analysis showed that: (1) predictions from non-steady state data will depend on the RBC model chosen; (2) the transit compartment model, which considers variation in life-span in the RBC population, better describes RBC survival data than the random destruction or homogenous life-span models; and (3) the additional incorporation of random destruction patterns, although improving the description of the RBC survival data, does not appear to provide a marked improvement when describing clinical data.

Stevens et al. (2012) worked on mechanism-based PK–PD model for the prolactin biological system response following an acute dopamine inhibition challenge: quantitative extrapolation to humans. The aim of this investigation was to develop a mechanism-based pharmacokinetic–pharmacodynamic (PK–PD) model for the biological system prolactin response following a dopamine inhibition challenge using remoxipride as a paradigm compound. After assessment of baseline variation in prolactin concentrations, the prolactin response of remoxipride was measured following (1) single intravenous doses of 4, 8 and 16 mg/kg and (2) following double dosing of 3.8 mg/kg with different time intervals. The mechanistic PK–PD model consisted of: (i) a PK model for remoxipride concentrations in brain extracellular fluid; (ii) a pool model incorporating prolactin synthesis, storage in lactotrophs, release into- and elimination from plasma; (iii) a positive feedback component interconnecting prolactin plasma concentrations and prolactin synthesis; and (iv) a dopamine antagonism component interconnecting remoxipride brain extracellular fluid concentrations and stimulation of prolactin release. The most important findings were that the free brain concentration drives the prolactin release into plasma and that the positive feedback on pro-

lactin synthesis in the lactotrophs, in contrast to the negative feedback in the previous models on the PK–PD correlation of remoxipride. Following simulation of human remoxipride brain extracellular fluid concentrations, pharmacodynamic extrapolation from rat to humans was performed, using allometric scaling in combination with independent information on the values of biological system specific parameters as prior knowledge. The PK–PD model successfully predicted the system prolactin response in humans, indicating that positive feedback on prolactin synthesis and allometric scaling thereof could be a new feature in describing complex homeostatic mechanisms.

Cao and Jusko (2012) worked on applications of minimal physiologically-based pharmacokinetic models. Conventional mammillary models are frequently used for pharmacokinetic (PK) analysis when only blood or plasma data are available. Such models depend on the quality of the drug disposition data and have vague biological features. An alternative minimal-physiologically-based PK (minimal–PBPK) modeling approach is proposed which inherits and lumps major physiologic attributes from whole-body PBPK models. Adding a classical hepatic compartment with hepatic blood flow allowed joint fitting of oral and intravenous (IV) data for four hepatic elimination drugs (dihydrocodeine, verapamil, repaglinide, midazolam) providing separate estimates of hepatic intrinsic clearance, non-hepatic clearance, and pre-hepatic bioavailability. The basic model was integrated with allometric scaling principles to simultaneously describe moxifloxacin PK in five species with common K_p and f_d values. A basic model assigning clearance to the tissue compartment well characterized plasma concentrations of six monoclonal antibodies in human subjects, providing good concordance of predictions with expected tissue kinetics. The proposed minimal-PBPK modeling approach offers an alternative and more rational basis for assessing PK than compartmental models.

2.13 Drug elimination Effect

Weiss (2013) did Fractal structure of the liver: effect on drug elimination. Liver modeling in pharmacokinetics has been based on outflow curves of extracellular tracers obtained in single-pass perfused rat livers. These reference curves represent the hepatic transit time densities (TTD) of tracers. Since the fractal structure of the sinusoidal network implies a TTD with power-law tail, the question is whether the use of conventional empirical TTDs with exponential tail may lead to biased estimates of hepatic clearance. A simulation study using a novel TTD model that accounts for fractal heterogeneity of hepatic flow shows that the bias is less than about 5%. Using this approach to determine the influence of hepatic flow dispersion on drug extraction, only a minor effect was found. The results demonstrate that there is no need for specific fractal models of hepatic drug elimination.

Levy-Vehel (2013) did variability and singularity arising from poor compliance in a pharmacokinetic model I: the multi-IV case. We consider a simple multi-IV model for drug concentration in the case of poor patient compliance. The model is a stochastic one, and is thus able to take into account an irregular drug intake schedule. Under some assumptions, we study features of the drug concentration relevant for practical purposes such as its variability or the regularity of its cumulative probability distribution. We consider five variants: random instants for drug intake with either deterministic or random doses, both in continuous and discrete-time settings, plus a model with stochastically varying elimination rate. Our computations make it possible to assess in a precise way the effect of various significant parameters such as the mean rate of intake, the elimination rate, and the mean dose. They also quantify how much poor compliance will affect the regimen: in that view, we provide precise comparisons with the variability of concentration in the cases of (a) a fully compliant patient and (b) a population of fully compliant patients with lognormally distributed elimination rates.

The time discretized version of our models reveal unexpected links with measures known as infinite Bernoulli convolutions. Our findings help in understanding the consequences of poor compliance, and may have practical outcomes in terms of drug dosing and scheduling.

Barriere et al.(2013) did compliance spectrum as a drug fingerprint of drug intake and drug disposition. Since drug related variability arises from different origins, particularly driven by the behaviour or physiology of the patient, the problems of drug intake and drug disposition are separately presented in general. To overcome the potential drawbacks of this artificial split, we propose in this paper a combined illustrative approach, named compliance spectrum, such that these two subprocesses can be equitably studied and visualized. We construct the compliance spectrum based on the Bayesian decision method we previously developed for the inverse problem of patient compliance within the framework of Population-PK. This spectrum provides an intuitive and interactive way to evaluate the relationship between drug intake and drug disposition along with their consequences on PK profile. As well, it opens a new direction for model quality diagnostic.

Hudachek and Gustafson (2013) researched on physiologically based pharmacokinetic model of lapatinib developed in mice and scaled to humans. Lapatinib is an oral 4-anilinoquinazoline derivative that dually inhibits epidermal growth factor receptor and human epidermal growth factor receptor 2 (HER2). This drug is a mere decade old and has only been approved by the FDA for the treatment of breast cancer since 2007. Consequently, the intricacies of the pharmacokinetics are still being elucidated. In the work presented herein, we determined the biodistribution of orally administered lapatinib in mouse plasma, brain, heart, lung, kidney, intestine, liver, muscle and adipose tissue. This first-generation PBPK model of lapatinib can be further improved with a greater understanding of lapatinib absorption, distribution, metabolism and excretion garnered from subsequent in vitro and in vivo studies and expanded to include other phar-

macokinetic determinants, including efflux transporters, metabolite generation, combination dosing, etc., to better predict lapatinib disposition in both mouse and man.

Vogt and Denzer (2013) did estimation of parameters for the elimination of an orally administered test substance with unknown absorption. Assessment of the elimination of an oral test dose based on plasma concentration values requires correction for the effect of gastric release and absorption. Irregular uptake processes should be described 'model independently', which requires estimation of a large number of absorption parameters. To limit the associated computational effort a new approach is developed with a reduced number of unknown parameters. The absorption estimated for the IVIVC study demonstrated an in vivo–in vitro correlation comparable to published values. The newly developed MRA approach can be used to efficiently and accurately estimate elimination and absorption with a restricted number of adaptive parameters and with automatic adjustment of the complexity of the uptake.

Tatarinova et al. (2013) proposed a two general methods for population pharmacokinetic modeling: non-parametric adaptive grid and non-parametric Bayesian. Population pharmacokinetic (PK) modeling methods can be statistically classified as either parametric or nonparametric (NP). Each classification can be divided into maximum likelihood (ML) or Bayesian (B) approaches. In this paper we discuss the nonparametric case using both maximum likelihood and Bayesian approaches. We present two nonparametric methods for estimating the unknown joint population distribution of model parameter values in a pharmacokinetic/pharmacodynamic (PK/PD) dataset. The first method is the NP Adaptive Grid (NPAG). The second is the NP Bayesian (NPB) algorithm with a stick-breaking process to construct a Dirichlet prior. Our objective is to compare the performance of these two methods using a simulated PK/PD dataset. Our results showed excellent performance of NPAG and NPB in a realistically simulated PK study. This simulation allowed us to have benchmarks in the form

of the true population parameters to compare with the estimates produced by the two methods, while incorporating challenges like unbalanced sample times and sample numbers as well as the ability to include the covariate of patient weight. We conclude that both NPML and NPB can be used in realistic PK/PD population analysis problems.

Asmanova et al. (2013) did a coupled solutions of one- and two-compartment pharmacokinetic models with first-order absorption. This work emphasizes the importance of the fact, that plasma concentration profiles of one- and two-compartment linear pharmacokinetic (PK) models with first-order absorption introduce an uncertainty in data interpretation. PK-curve fitting results in a pair of valid solutions (coupled solutions), for which the derived PK parameters (such as AUC, MRT, Cmax, tmax, initial and terminal slope) are identical. Therefore, to make a proper choice of PK parameters of the drug in question, more information has to be considered, for example, which one of the solutions is more correlated with corresponding data, observed after iv administration. Comparison of different types of PK models and discussion on the transitions between the coupled solutions was carried out using a novel symbolic notation to provide more clarity and to simplify parameter indexing. Presented results were obtained by combined means of the method of statistic moments, Laplace transform and illustrated by the numerical experiment.

Shekar et al (2013) investigated that Extracorporeal membrane oxygenation (ECMO) is a supportive therapy and its success depends on optimal drug therapy along with other supportive care. Emerging evidence suggests significant interactions between the drug and the device resulting in altered pharmacokinetics (PK) of vital drugs which may be further complicated by the PK changes that occur in the context of critical illness. Such PK alterations are complex and challenging to investigate in critically ill patients on ECMO and necessitate mechanistic research. The aim of this project is to investigate each of circuit, drug and critical illness factors that affect drug PK during ECMO.

2.14 Pharmacokinetic Modelling of H.I.V.

Armaou (2013) released Pharmacokinetics Modelling for H.I.V. Treatment Strategies. The project focuses on modeling the dynamics associated with the uptake of medication during treatment of H.I.V. infection. The primary focus is on oral uptake (as compared to intravenous injection and inhalation). It focus on developing an accurate model of the pharmacodynamics employing Matlab. A working knowledge of programming is a partial objective of thesis. Upon the successful completion of the model, the simulation results is analyzed and compared to available experimental results in the literature. The ultimate focus of the project is the development of an accurate pharmacokinetics model that can be employed to improve the current treatment strategies.

2.15 PK/PD Models for Cancer Treatment

Armaou (2013) presented Pharmacodynamics and Pharmacokinetics Models for Cancer Treatment. The project focuses the development of spatially distributed models associated with the transport of from the blood vessels to brain tumors through the interstitial fluid. The project motivation stems from current complexities associated with how to attain high dosages to brain tumors through oral uptake. The project has two phases. The first is a critical review of current articles in the open literature. The second phase focus on developing an accurate model of the pharmacodynamics employing Matlab. A working knowledge of programming is a partial objective of the second phase. Upon the successful completion of the model, the simulation results will be analyzed and compared to available experimental results in the literature. The ultimate focus of the project is the development of an accurate pharmacokinetics model that can be employed to improve the current treatment strategies.

Chapter 3

METHODOLOGY

3.1 Introduction: Modeling and Applications

The discovery of the calculus occurred at the beginning of the scientific revolution in the seventeenth century. This discovery was not a side issue in the revolution. Rather, it was the linchpin on which much of what followed was based. For the first time, humankind had a systematic way to study how things changed. In many cases, the study of change has led to a differential equation, or to a system of differential equations through the process known as *modeling*.

Mathematical models are meant to explain what is happening in the real world. It is not enough to derive models from theoretical considerations. It is necessary to check the predictions of our models with what is happening in reality. This chapter presents first-order equations and theorems governing analytical approaches to solving first order ordinary differential equations.

3.2 Differential Equations

A *differential equation* is a relationship between an independent variable, x, a dependent variable y, and one or more derivatives of y with respect to x.

e.g.

$$x^2 \frac{dy}{dx} = y \sin x = 0$$

$$xy\frac{d^2y}{dx^2} + y\frac{dy}{dx} + e^{2x} = 0$$

Differential equations represent dynamic relationships, i.e. quantities that change, and are thus frequently occuring in scientific and engineering problems.

The *order* of a differential equation is given by the highest derivative involved in the equation.

$$x\frac{dy}{dx} - y^2 = 0 \qquad \text{is an equation of the 1st order}$$

$$xy\frac{d^2y}{dx^2} - y^2\sin x = 0 \qquad \text{is an equation of the 2nd order}$$

$$\frac{d^3y}{dx^3} - y\frac{dy}{dx} + e^{4x} = 0 \qquad \text{is an equation of the 3rd order}$$

3.2.1 Ordinary Differential Equations

An ordinary differential equation is an equation involving an unknown function of a single variable together with one or more of its derivatives. For example, the equation

$$\frac{dy}{dt} = y - t \tag{3.1}$$

ia an ordinary differential equation. Here y=y(t) is the unknown function and t is the independent variable.

The *order* of a differential equation is the order of the highest derivative that occurs in the equation. Thus the equation in (3.1) is a *first-order* equation since it involves only the first derivative of the unknown function.

3.3 Linear First Order Differential Equations

These equations take the general form

$$\frac{dy}{dx} = -p(x)y + g(x), \quad i.e., \frac{dy}{dx} + p(x)y = g(x),$$

where $p(x)$ and g(x) are continuous functions on some interval $a \leq x \leq b$. We refer to this first order differential equation as a *linear* differential equation because the unknown y appears linearly, i.e., to the first power with known coefficient, in the equation. The equation is *homogeneous* if g(x) $\equiv 0$, otherwise it is said to be inhomogeneous.

Homogeneous Case: Equation: $\dfrac{dy}{dx} + p(x)y = 0$. **Properties:**

- $y(x) \equiv 0$is a solution; the *trivial* solution.
- If y(x) is any solution of the homogeneous equation then, for any constant c, the multiple $cy(x)$ is also a solution of that equation.
- If a solution $y(x)$ is non-zero for some value, say x_1, of x, then it is non-zero for all values of x.

Method of Solution:

In the homogeneous case we have $\frac{dy}{dx} = -p(x)y$. Assuming that we are looking for a non-zero solution, we can write

$$\frac{1}{y(x)}\frac{dy}{dx} = -p(x).$$

Integrating both sides with respect to x, we have (natural logarithm)

$$\log|y(x)| = -\int^x p(s)\,ds + \hat{c} \equiv -P(x) + \hat{c},$$

where $P(x)$ is, as already indicated, an antiderivative of $p(x)$.

Example 1

Consider the differential equation $x\frac{dy}{dx} + y = 0$;in the standard form this is

$$\frac{dy}{dx} + \frac{1}{x}y = 0$$

, corresponding to $p(x) = \frac{1}{x}$; an antiderivative is $P(x) = \log|x|$. We therefor obtain solutions

$$y(x,c) = ce^{-\log x} = \frac{c}{e^{\log x}} = \frac{c}{x}.$$

For $y(x,c)$ thus specified we have $\frac{dy}{dx} = -\frac{c}{x^2}$ and we verify immediately that this is, indeed, a solution for every value of c. If we impose an initial condition, e.g., $y(2) = 1$, we require $\frac{c}{2} = 1$ which fixes the value of c at 2.

We can give a general formula for the solution of an initial value problem $y(x_0) = y_0$. Since the general solution is $ce^{-P(x)}$, satisfaction of this condition requires

$$ce^{-P(x_0)} = y_0 \Rightarrow c = e^{P(x_0)}y_0.$$

With this value of c the solution becomes

$$y(x) = \left(e^{P(x_0)}y_0\right)e^{(-P(x)-P(x_0))}y_0 = exp\left(-\int_{x_0}^{x} p(s)\,ds\right)y_0.$$

Thus if we want the solution of the above differential equation with $y(2) = 3$ the solution is

$$y(x) = exp\left(-\int_2^x \frac{ds}{s}\right)3 = 3exp(\log(2) - \log(x)) = 3exp\left(\log\left(\frac{2}{x}\right)\right) = 3\frac{2}{x} = \frac{6}{x}.$$

Inhomogeneous Case:

Consider the equation $\frac{dy}{dx} + p(x)y = g(x)$ with $g(x)$ not identically 0. First, some

Properties:

- If $y(x)$ is any solution of $\frac{dy}{dx}+p(x)y = g(x)$ and $z(x)$ is any solution of the homogeneous equation $\frac{dz}{dx}+p(x)z = 0$, then $w(x) = y(x)+z(x) is a solution of \frac{dw}{dx}+ p(x)w = g(x)$.

- The **general** solution of $\frac{dy}{dx} + p(x)y = g(x)$ has the form $y(x,c)+y_1(x)$,

where $y(x,c)$ is the general solution of the homogenous equation and $y_1(x)$ is any (particular) solution of the inhomogenous equation. Thus the general solution of the inhomogenous equation takes the form

$$y(x) = ce^{-P(x)} + y_1(x).$$

Verification of the first property follows, with $w(x) = y(x) + z(x)$, from

$$0 = \left(\frac{dy}{dx} + p(x)y - g(x)\right) + \left(\frac{dz}{dx} + p(x)z\right) = \frac{dw}{dx} + p(x)y - g(x).$$

The second follows from the equivalence of the equations

$$y(x_0,c) + y_1(x_0) = y_0 \quad \text{and} \quad y(x_0,c) = \hat{y_0} \equiv -y_1(x_0) + y_0.$$

Example 2

For the differential equation $x\frac{dy}{dx} + y = 0$ we have seen that the general solution takes the form $y(x,c) = \frac{c}{x}$. If we now consider a corresponding inhomogeneous equation

$$x\frac{dy}{dx} + y = x^3,$$

we can verify that one solution, i.e., a particular solution, is $y_1(x) = \frac{1}{4}x^3$. It follows that the general solution takes the form

$$y(x) = \frac{c}{x} + \frac{1}{4}x^3.$$

The initial value problem $y(2) = 1$ now requires $\frac{c}{2} + \frac{1}{4} \times 2^3 = 1$, i.e., $c = 2 = 2 \times \frac{8}{4} = -2$. So the solution of the initial value problem is $y(x) = \frac{-2}{x} + \frac{1}{4}x^3$.

General Method of Solution: Variation of parameters Formula

We now try to find a general method for solving the inhomogeneous equation

$$\frac{dy}{dx} + p(x)y = g(x).$$

The general solution of the homogeneous equation takes the form $\frac{dy}{dx} + p(x)y = g(x)$. The general solution of the homogeneous equation takes the form $y(x) = ce^{-P(x)}$, where $P(x)$ is an antiderivative of $p(x)$ and c is an arbitrary constant, or *parameter*. Various considerations lead us to try for solution of the inhomogeneous equation in which this parameter is replaces by a variable quantity:

$$y_1(x) = c(x)e^{-P(x)}.$$

Hence the name "method of variation of parameters". Substituting this assumed form of the solution into

$$\frac{dy}{dx} + p(x)y = g(x)$$

gives

$$\frac{dc}{dx}e^{-P(x)} - c(x)e^{-p(x)}p(x) + p(x)c(x)e^{-P(x)} = g(x)$$

so that

$$\frac{dc}{dx} = e^{P(x)}g(x).$$

We may then write

$$c(x)\int^x e^{P(s)}g(s)\,ds$$

and $y_1(x)$ assumes the form

$$y_1(x) = e^{-P(x)}\int^x e^P(s)g(s)\,ds.$$

A specific solution is obtained by fixing c and the lower bound for the integral, which have equivalent roles. If we want $y(x_0) = y_0$ it is often convenient to take the lower limit as x_0 so that

$$y(x, c) = ce^{-P(x)} + e^{-P(x)} \int_{x_0}^{x} e^{P(s)} g(s)\, ds.$$

When $x = x_0$ the integral vanishes and

$$y_0 = ce^{P(x_0)} \Rightarrow y(x) = e^{-(P(x)-P(x_0))} y_0 + e^{-P(x)} \int_{x_0}^{x} e^{P(s)} g(s)\, ds.$$

However, it is not generally essential to take the lower limit of the integral to be the initial value x_0, as we see from

Example 3

Let us consider the differential equation

$$x\frac{dy}{dx} + y = \sin x \qquad \text{or} \qquad \frac{dy}{dx} + \frac{1}{x} y = \sin x.$$

Here $p(x) = \frac{1}{x}$ with antiderivative $P(x) = \log x$. Then $e^{-P(x)} = \frac{1}{x}, e^{P(x)} = x$;
we can take

$$y(x, c) = \frac{c}{x} + \frac{1}{x} \int_{0}^{x} s \, \sin s \, ds.$$

Computing the integral, we have

$$y(x, c) = \frac{c}{x} + \frac{1}{x} (\sin x - x \cos x) = \frac{c}{x} + \frac{\sin x}{x} - \cos x.$$

Solutions satisfying particular initial conditions can now be obtained via appropriate choice of the parameter c. Thus if we want $y(\pi/2) = 0$
we need

$$\frac{2c}{\pi} + \frac{2}{\pi} - 0 = 0 \quad \rightarrow \quad c = -1$$

and the desired solution is

$$y(x) = -\frac{1}{x} + \frac{\sin x}{x} - \cos x.$$

Remark

Despite the singularity of $P(x) = \frac{1}{x}$ at $x = 0$ there is, in this case, a solution corresponding to the initial condition $y(0) = 0$. Since

$$\lim_{x \downarrow 0} \frac{\sin x}{x} = 1 = \cos 0$$

we obtain such a solution with the choice $c = 0$, i.e.,

$$y(x) = \frac{sinx}{x} - \cos x.$$

It should be noted, however, that we cannot give a general initial condition at $x = 0$; for example, if we wanted $y(0) = 1$ we would arrive at the equation $\frac{c}{0} = 1$, which makes no sense.

3.4 Applications: Mixture Problems

One type of problem that can be described in terms of a differential equation involves chemical mixtures, as illustrated in the next example. A chemical in a liquid solution (or dispersed in a gas) runs into a container holding the liquid (or the gas) with, possibly, a specified amount of the chemical dissolved as well. The mixture is kept uniform by stirring and flows out of the container at a known rate. In this process, it is often important to know the concentration of the chemical in the container at any given time. The differential equation describing the process

is based on the formula

$$\begin{pmatrix} \text{Rate of change} \\ \text{of amount in container} \end{pmatrix} = \begin{pmatrix} \text{rate at which} \\ \text{chemical arrives} \end{pmatrix} - \begin{pmatrix} \text{rate at which} \\ \text{chemical departs} \end{pmatrix}$$

If $y(t)$ is the amount of chemical in the container at time t and $V(t)$ is the total volume of liquid in the container at time t, then the departure rate of the chemical at time t is

Departure rate= $\frac{y(t)}{V(t)} \cdot$ (outflow rate). Accordingly,

$$\frac{dy}{dt} = (\text{chemical's arrive rate}) - \frac{y(t)}{V(t)} \cdot (\text{outflow}).$$

If, say, y is measured in pounds, V in gallons, and t in minutes, the units in the just above equation are

$$\frac{\text{pounds}}{\text{minutes}} = \frac{\text{pounds}}{\text{minutes}} - \frac{\text{pounds}}{\text{gallons}} \cdot \frac{\text{gallons}}{\text{minutes}}.$$

Example 4: A Mixture Problem

A tank contains 50 gallons of a solution composed of 90% water and 10% alcohol. A second solution containing 50% water and 50% alcohol is added to the tank at the rate of 4 gallons per minute. As the second solution is being added, the tank is being drained at the rate of 5 gallons per minute, as shown in Figure 15.7. Assuming the solution in the tank is stirred constantly, how much alcohol is in the tank after 10 minutes?

Solution

Let y be the number of gallons of alcohol in the tank at any time t. You know that $y = 5$ when $t = 0$. Because the number of gallons of solution in the tank at any time is $50 - t$, and the tank loses 5 gallons of solution per minute, it must

lose

$$\left(\frac{5}{50-t}\right)y$$

gallons of alcohol per minute. Furthermore, because the tank is gaining 2 gallons of alcohol per minute, the rate of change of alcohol in the tank is given by

$$\frac{dy}{dt} = 2 - \left(\frac{5}{50-t}\right)y \Rightarrow \frac{dy}{dt} + \left(\frac{5}{50-t}\right)y = 2.$$

To solve this linear equation, let $P(t) = 5/(50-t)$ and obtain

$$\int P(t)\,dt + \int \frac{5}{50-t}\,dt = -5\ln|50-t|.$$

Because $t < 50$, you can drop the absolute value signs and conclude that

$$e^{\int P(t)dt} = e^{-5\ln(50-t)} = \frac{1}{(50-t)^5}.$$

Thus, the general solution is

$$\frac{y}{(50-t)^5} = \int \frac{2}{(50-t)^5}\,dt = \frac{1}{2(50-t)^4} + C$$

$$y = \frac{50-t}{2} + C(50-t)^5.$$

Because $y = 5$ when $t = 0$, you have

$$5 = \frac{50}{2} + C(50)^5 \quad \Rightarrow \quad \frac{20}{50^5} = C$$

which means that the particular solution is

$$y = \frac{50-t}{2} - 20\left(\frac{50-t}{50}\right)^5.$$

Finally, when $t = 10$, the amount of alcohol in the tank is

$$y = \frac{50-10}{2} - 20\left(\frac{50-10}{50}\right)^5 = 13.45\text{gal}$$

which represents a solution containing 33.6% alcohol.

Example 5 A Falling Object with Air Resistance

An object of mass m is dropped from a hovering helicopter. Find its velocity as a function of time t, assuming that the air resistance is proportional to the velocity of the object.

Solution

The velocity v satisfies the equation

$$\frac{dv}{dt} + \frac{kv}{m} = g$$

where g is the gravitational constant and k is the constant of proportionality. Letting $b = k/m$, you can *separate variables* to obtain

$$dv = (g - bv)\,dt$$

$$\int \frac{dv}{g-bv} = \int dt$$

$$-\frac{1}{b}\ln|g-bv| = t + C_1$$

$$\ln|g-bv| = -bt - bC_1 g - bv = Ce^{-bt}$$

Because the object was dropped, $v = 0$ when t=0; thus g=C, and it follows that

$$-bv = -g + ge^{-bt} \quad \Rightarrow \quad v = \frac{g - ge^{-bt}}{b} = \frac{mg}{k}(1 - e^{-kt/m}).$$

Example 6 An Electric Circuit Problem

Find the current I as a function of time t (in seconds), given that I satisfies the differential equation $L(dI/dt) + RI = \sin 2t$, where R and L are nonzero constants.

Solution

In standard form, the given linear equation is

$$\frac{dI}{dt} + \frac{R}{L}I = \frac{1}{L}\sin 2t.$$

Let $P(t) = R/L$, so that $e^{\int P(t)dt} = e^{(R/L)t}$, and,

$$Ie^{(R/L)t} = \frac{1}{L}\int e^{(R/L)t}\sin 2t\,dt = \frac{1}{4L^2+R^2}e^{(R/L)t}(R\sin 2t - 2L\cos 2t) + C.$$

Thus, the general solution is

$$I = e^{-(R/L)t}\left[\frac{1}{4L^2+R^2}e^{(R/L)t}(R\sin 2t - 2L\cos 2t) + C\right]$$

$$I = \frac{1}{4L^2+R^2}(R\sin 2t - 2L\cos 2t) + Ce^{(R/L)t}.$$

3.5 Initial Value Problems

An ordinary differential equation has infinitely many solutions. In applications, it is necessary to use other information, in addition to the differential equation, to determine the value of the constant and to specify the solution completely. Such a solution is called a particular solution.

A first-order differential equation together with an initial condition,

$$y'(t) = f(t, y(t)), \quad y(t_0) = y_0, \tag{3.2}$$

is called an *initial value problem*. A solution of the initial value problem is a differentiable function y(t) such that

1. $y'(t) = f(t, y(t))$ for all t in an interval containing t_0 where y(t) is defined,

2. $y(t_0) = y_0$.

3.6 Uniqueness of Solutions

It is interesting to contemplate the existence theorem in conjunction with the physical systems that are modeled by the differential equations. The existence of a solution to an ordinary differential equation (ODE) simply reflects the fact that the physical systems change according to the relationships modeled by the equation. We would expect that solutions to equations that model physical behavior would exist. Next we turn to the questions of the number of solutions to an initial value problem. If there is only one solution, then the physical system acts the same way each time it is started from the same set of initial conditions. such a system is therefore deterministic. If an equation has more than one solution, then the physical response is predictable. Thus the uniqueness of solutions of initial value problems be unique.

3.6.1 Existence and Uniqueness

Here we concentrate on the solution of the first order IVP

$$y' = f(x, y), \quad y(x_0) = y_0 \tag{3.3}$$

We are interested in the following questions:

1. Under what conditions, there exists a solution to (3.3),

2. Under what conditions, there exists a unique solution to (3.3).

An ODE may have no solution, unique solution or infinitely many solutions. For example $y'^2+y^2+1=0; \quad y(0)=1$ has no solution. The ODE $y_0=2x; \quad y(0)=1$ has unique solution $y=1+x_2$, whereas the ODE $xy'=y-1; \quad y(0)=1$ has infinitely many solutions $y=1+\alpha x$, α is any real number.

3.6.2 Existence theorem

Suppose that $f(x,y)$ is continuous function in some region. $R=(x,y):|x-x_0|\leq a, |y-y_0|\leq b$ $(a,b>0)$. Since f is continuous in a closed and bounded domain, it is necessarily bounded in R, i.e., there exists $K>0$ such that —f(x,y)— $\leq K \ \forall (x,y)\in R$. Then the IVP (3.3) has at least one solution $y=y(x)$ defined in the interval $—x-x_0— \leq \alpha$

$$\alpha = \min\left\{a, \frac{b}{K}\right\} \tag{3.4}$$

3.6.3 Uniqueness Theorem

Suppose that f and $\frac{\partial f}{\partial y}$ are continuous function in R (defined in the existence theorem). Hence, both the f and $\frac{\partial f}{\partial y}$ are bounded in R, i.e.,

$$(a) \quad |f(x,y)|\leq K \qquad (b) \quad \left|\frac{\partial f}{\partial y}\right| \qquad \forall (x,y)\in R$$

Then the IVP (3.3) has at most one solution $y=y(x)$ $|x-x_0|\leq\alpha$. Condition (b) can be replaced by a weaker condition which is known as Lipschitz condition. Thus, instead of continuity of $\partial f/\partial y$, we require

$$|f(x,y_1)-f(x,y_2)|\leq L|y_1-y_2| \qquad \forall (x,y_i)\in R. \tag{3.5}$$

If $\partial f/\partial y$exists and is bounded, then it necessarily satisfies Lipschitz condition. On the other hand, a function f(x,y) may be Lipschitz continuous but $\partial f/partialy$ may not exists. For example $f(x,y)=x^2|y|$, $|x|\leq 1$, $|y|\leq 1$ is Lipschitz continuous in y but $\partial f/\partial y$ does not exist at $(x,0)$. The existence and uniqueness

theorem are also valid for certain system of first order equations. These theorems are also applicable to a certain higher order ODE since a higher order ODE can be reduced to a system of first order ODE.

Example 1

Consider the ODE

$$y' = 1 + y^2, \qquad y(0) = 0.$$

Consider the rectangle

$$S = (x, y) : |x| \leq 100, |y| \leq 1.$$

Clearly f and $\partial f/\partial y$ are continuous in S. Hence, there exists unique solution in the neighbourhood of $(0, 0)$. Now $f = 1 + y^2$ and $|f| \leq 2$ in S. Now $\alpha = \min\{100, 1/2\} = 1/2$.

Hence, the theorems guarantee existence of unique solution in $|x| \leq 1/2$, which is much smaller than the original interval $|x| \leq 100$.

Since, the above equation is separable, we can solve it exactly and find y(x) = tan(x). This solution is valid only in $(-\pi/2, \pi/2)$ which is also much smaller than $[-100, 100]$ but nevertheless bigger than that predicted by the existence and uniqueness theorems.

Example 2

Consider the ODE

$$y' = xy - \sin y, \qquad y(0) = 2.$$

Here f and $\partial f/\partial y$ are continuous in a closed rectangle about $x_0 = 0$ and $y_0 = 2$. Hence, there exists unique solution in the neighbourhood of $(0, 2)$.

Example 3

Consider the IVP

$$y' = x|y|, \qquad y(1) = 0.$$

Since f is continuous and satisfy Lipschitz condition in the neighbourhood of the $(1, 0)$, it has unique solution around $x = 1$.

Example 4 We now discuss the existence and unique solution for the IVP

$$y' = \frac{2y}{x}, \qquad y(x_0) = y_0$$

Here $f(x, y) = 2y/x$ and $\partial f/\partial y = 2/x$. Clearly both of these exist and bounded around (x_0, y_0) if $x_0 \neq 0$. Hence, unique solution exists in a interval about x_0 for $x_0 \neq 0$. For $x_0 = 0$, nothing can be said from the existence and uniqueness theorem. Fortunately, we can solve the actual problem and find $y = Ax^2$ to be the general solution. When $x_0 = 0$, there exists no solution when $y_0 \neq 0$. If $y_0 = 0$, then we have infinite number of solutions $y = \alpha x^2$ (α any real number) that satisfy the IVP $y_0 = 2y/x, \quad y(0) = 0$.

3.7

$$M(x, y)dx + N(x, y)dy = 0$$

3.7.1 Separation of variables

A first order DE

$$M(x, y)dx + N(x, y) = 0$$

is said to be *separable* if $M(x, y) = p(x)q(y)$ and $N(x, y) = r(x)s(y)$. Then it can be put into the form

$$f(x)dx = g(y)dy,$$

where $f(x) = p(x)/r(x)$ and $g(y) = -s(y)/q(y)$. A family of solutions can be obtained by integration to yield

$$\int f(x)\,dx = \int g(y)\,dy + C_1$$

where C_1 is an arbitrary constant. The integrals are evaluated, and a function for y in terms of x is found. This general technique is called the method of *separation of variables.*

Example 1.

Find the general solution of

$$(1-x)dy + ydx = 0.$$

Solution

First, we separate variables to yield:

$$\frac{dy}{y} = \frac{dx}{x-1},$$

where $x \neq 1$ and $y \neq 0$.

Second, we integrate both sides to yield:

$$\ln|y| + C_1 = \ln|1-x| + C_2.$$

Thirdly (this step is optional) we solve for y:

$$\ln|y| + C_1 = \ln|1-x| + C_2.$$

$$e^{\ln|y|+C_1} = e^{\ln|1-x|+C_2}$$

$$ye^{C_1} = (1-x)e^{C_2}$$

Thus

$$y = C(1-x)$$

is the *general solution.*

3.7.2 Exact equations

If there is a function in two variables $f(x, y)$ such that in the equation

$$M(x, y)dx + N(x, y)dy = 0$$

it is true that

$$M(x, y) = \frac{\partial f}{\partial x}$$

$$N(x, y) = \frac{\partial f}{\partial y}$$

then we call the differential equation of the form $M(x, y)dx + N(x, y)dy = 0$ is exact, it is enough to show that

$$\frac{\partial M}{\partial y} = \frac{\partial N}{\partial x}$$

This stems from the fact that for a continuous function f in two variables, $\frac{\partial^2 f}{\partial x \partial y} = \frac{\partial^2 f}{\partial y \partial x}$

To find the solution $f(x, y)$ for a given exact equation, we integrate

$$f(x, y) = \int M(x, y)\, dx + g(y)$$

where the function g serves serves as the "constant "of integration (constant with respect to x). The function $g(y)$ is determined using the function N(x, y):

$$N(x, y) = \frac{\partial f}{\partial y} = \frac{\partial}{\partial y}\left(\int M(x, y)\, dx + g(y)\right) = \frac{\partial}{\partial y}\left(\int M(x, y)\, dx\right) + g'(y).$$

Thus,

$$g'(y) = N(x,y) - \frac{\partial}{\partial y}\left(\int M(x,y)\,dx\right)$$

And so,

$$g(y) = \int N(x,y)\,dy - \int\left(\frac{\partial}{\partial y}\left(M(x,y)\,dx\right)\right)\,dy$$

Finally, we have solution

$$f(x,y) = \int M(x,y)\,dx + \int N(x,y)\,dy - \int\left(\frac{\partial}{\partial y}\left(\int M(x,y)\,dx\right)\right)dy = C_1$$

3.7.3 Bernoulli's Equation

Bernoulli's equation is a *nonlinear* first order differential equation of the form

$$y' + a_0(x)y = f(x)y^n, \qquad n \neq 0, 1.$$

Equations of this form can be reduced to linear equation through a suitable change of variable. We make the change of variable

$$z = y^{1-n}$$

Then,

$$z' = y^{1-n}y^{-n}y'$$

Substituting this into the Bernoulli equation $y' + a_0(x)y = f(x)y^n$ yields $\frac{y^n z'}{1-n} + a_0(x)y^n z = f(x)y^n$.

Upon simplifying, we get

$$z' + (1-n)a_0(x)z = (1-n)f(x).$$

Now, this linear equation can be solved using the methods.

3.7.4 Solution of the Airy Equation by Integral Representation

In this example, the Airy equation is solved using the Laplace representation. This equation is of exceptional importance both in its own right (for example, in optics) and as an approximation to the equation $w'' + f(x)w = 0$ near a point at which $f(x) = 0$. We obtain two linearly independent integral representation – as expected for a second-order differential equation. Since the integrand (the same in both cases) is entire and nowhere zero, the representations differ only in the directions in which the paths of integration go out to infinity. We will find solutions of the Airy equation:

$$w'' + zw = 0$$

in the form

$$w(z) = \int_\gamma f(t)e^{zt}dt \qquad (*)$$

where $f(t)$ is an as yet unknown function and γ is a path to be determined once $f(t)$ is known. We expect that there will be many choices of γ, two of which lead to linearly independent solutions of the differential equation. The function $f(t)$ will be uniquely determined up to (obviously) a multiplicative constant.

We start by substituting (*) into the differential equation, differentiating under the integral sign:

$$\int_\gamma (t^2 + z)f(t)e^{zt}dt = 0.$$

We cannot immediately say that the integral is identically zero so the integrand must vanish. However, we can determine circumstances in which the integrand will vanish, and if this gives two linearly independent functions, we are finished. The immediate problem is the presence of the z term in the integral. We can't alleviate the problem by a clever choice of $f(t)$ involving z, because we assumed when differentiating under the integral sign that f did not depend on z. Our

strategy, which will work for any polynomial in z, is to remove the z term by integrating by parts:

$$\begin{aligned}\int_\gamma zf(t)e^{zt}\,dt &= \int_\gamma f(t)\frac{\partial e^{zt}}{\partial t}\,dt \\ &= \int_\gamma \left(\frac{\partial(f(t)e^{zt})}{\partial t} - \frac{df}{dt}e^{zt}\right)\,dt \\ &= f(t)e^{zt}|_\gamma - \int_\gamma \frac{df}{dt}e^{zt}\,dt,\end{aligned}$$

where the first term of the last equation is to be evaluated at the endpoints of the path γ. Thus we require

$$f(t)e^{zt}|_\gamma + \int_\gamma (t^2 f(t) - f'(t))e^{f(t)}\,dt = 0.$$

This we can achieve if we choose $f(t)$ such that $t^2 f(t) - f'(t) = 0$ i.e. $f(t) = e^{\frac{1}{3}t^3}$, where the constant of integration in $f(t)$ has been omitted since it corresponds merely to an constant multiple in $w(z)$, and if we choose γ such that

$$e^{\frac{1}{3}t^3+zt}|_\gamma = 0. \qquad (**)$$

The obvious choice of γ which satisfies (**) is a closed curve. This works; but since the function $f(t)e^{zt}$, which appears in the integrand of $w(z)$, is entire the corresponding solution to the Airy equation is $w(z) = 0$. The only other possibility, in view of the fact that $f(t)e^{zt} \neq 0$ for any value of t, is a path that begins and ends in sectors of $t = \infty$ for which $f(t)e^{zt} \to 0$ as $t \to \infty$.

Chapter 4

ANALYSIS AND RESULTS

4.1 Introduction

In this chapter we will display the Polking, Boggess and Arnold distribution model depicting the exact drug mass active in the human organ or tissue. We will then proceed to construct a differential equation model characterizing the metabolism reaction of the transported drug mass into the liver compartment.

4.2 Model Description

Our model focuses on drug mass in a single tissue and divides the in vivo compartment into two classes: Extravascular space (Tissue) and Plasma (blood) Compartment. Apart from the rate of drugs absorption, we also need to consider the completeness of its absorption. Bioavailability (F)is used to report this and it is defined as the proportion of an administered dose that is absorbed chemically unchanged into the systemic blood circulation. We have chosen definitions that would be of interest to Mathematicians, Pharmaceutics, and Clinicians who are concerned with improving dosage regimen strategies. Extravascular drug concentration is the actual mass of drug distributed into the tissue compartment. Plasma drug concentration is the total mass of drug absorbed into the systemic circulation(plasma). The plasma drug mass is the whole administered mass since

Bioavailability is 100 Percent. The liver concentration is defined as the resultant drug concentration after transportation through the systemic circulation from the tissue after undergoing drug effect.

The following sections summarize the important aspects of pharmacokinetics in principles under the traditional headings of drug absorption, distribution, metabolism and excretion. In our PK model, the total population is divided into three separate compartments:Absorption (A), Distribution and Metabolism (M).The figure below indicates the whole general connective phases once a drug is liberated and ingested.

As seen in Figure below, the administered drug get absorbed into the blood stream (Plasma) and circulate through the body and distribute to the site of action. Then the Pharmacological effect occurs and the drug is metabolized. The dynamics of Pharmacokinetic (PK) Disposition (ADM) are modeled using the following system of coupled and uncoupled linear differential equations where $C_1(t), C_2(t)$ are the respective drug concentrations at time t.

The various parameters used in the modeling process for both compartment are described in the table shown above. We used seven different parameters in the model equation.

Table 4.1: Description of Model Parameters

Parameter	Description
α	Absorption rate from Plasma to Tissue
κ	Drug concentration absorbed from Plasma
β	Re-absorption rate from Tissue
V_0	Volume of Tissue compartment
r	Difference between Absorption and Re-absorption rate
$v(t)$	Total Volume of Tissue after absorption
V_1	Volume of liver compartment
h	Removal rate from liver Compartment

From the table above, the total volume $v(t)$ is the addition of the volume compartment to the product of time and rate difference.

The table below indicates the various parameter values that are used in the distribution and metabolism models. The parameter values were sourced the journal of pharmacokinetics. The four drugs that are indicated in the table below are mainly tablet and hence they are orally administered.

Table 4.2: Model Parameters for Various Drugs

Parameter	Paracetamol	Gentamicin	Flucloxacillin	Diclofenac	References
α	1.2	2.1	3.2	0.8	Crooks et al. (2000)
κ	4.5	12.4	18	3.1	Crooks et al. (2000)
β	0.15	1.5	20	0.15	Crooks et al. (2000)
v_0	10	8.9	20	12	Crooks et al. (2000)
r	0.85	0.6	1.2	0.62	Crooks et al. (2000)
v_1	8.1	9.1	9.1	8.0	Crooks et al. (2000)
h	0.9	1.1	4.2	2.0	Crooks et al. (2000)

From the table above we can easily deduce the rate difference parameter, r by simple subtraction if we are given the absorption and re-absorption rates.

4.3 Drug Distribution Model by Polkings, Arnold and Boggess

The drug concentration model flow chart is shown in the figure below. The broken lines indicates the drug distribution phase.

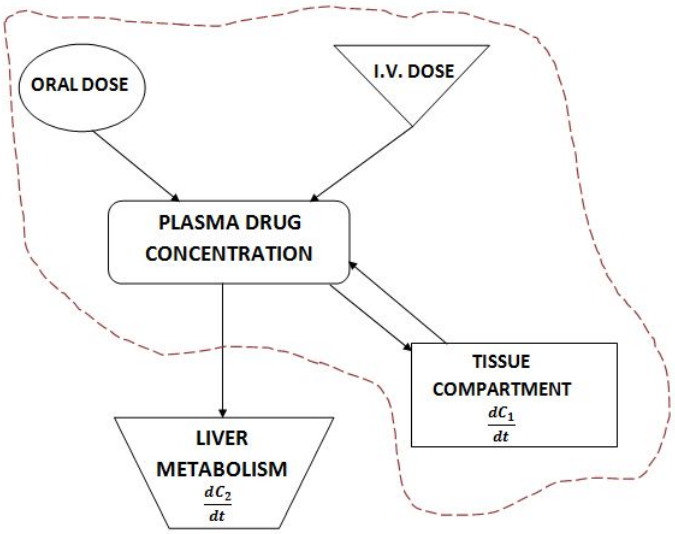


Figure 4.1: Flow Chart Showing Drug Distribution

We realize from the figure above that an administered drug is absorbed into the blood stream and then distributed to the target site for healing effect.

4.3.1 Model Formulation

Let C_1 = drug concentration in the tissue. let α represent absorption rate.

let κ represent drug concentration absorbed from Plasma.

let β represent re-absorption rate from tissue.

let v_0 represent volume of tissue.

let $v(t)$ represent total volume of tissue after absorption.

$$
\begin{aligned}
\frac{dc_1}{dt} &= \text{rate of change of drug concentration in the tissue.} \\
\frac{dc_1}{dt} &= \text{rate in - rate out} \\
\frac{dc_1}{dt} &= \text{ inlet rate} \times \text{Concentration} - \text{outlet rate} \times \text{Concentration} \\
\frac{dc_1}{dt} &= \alpha\kappa - \beta\frac{c_1}{v_0 + rt} \\
\frac{dc_1}{dt} &= \alpha\kappa - \beta\frac{c_1}{v_0 + rt}
\end{aligned}
\tag{4.1}
$$

α and κ in the above equation represent the input flow rate and it concentration. β and $\frac{c_1}{v_0+rt}$ represent the outlet flow rate and it concentration. The first term in equation (4.1) above describes the rate inlet whiles the second term describes the rate outlet.

4.3.2 Solution by Variation of Parameters

$$
\begin{aligned}
\text{Inhomogeneous Equation} \rightarrow c_1' &= \alpha\kappa - \beta\frac{c_1}{v_0 + rt} && (4.2) \\
\text{Homogeneous Equation} \rightarrow c_{1h}' &= -\beta\frac{c_{1h}}{v_0 + rt} && (4.3) \\
\text{Solution to Homogeneous Parts} \int \frac{dc_1}{c_1} &= -\int \frac{\beta}{v_0 + rt}\, dt \\
c_1(t) &= \frac{C}{(v_0 + rt)^{\frac{\beta}{r}}}
\end{aligned}
\tag{4.4}
$$

let v(t) be a yet to be determined function of t and by substitution
we obtain

$$
c_1(t) = \frac{v(t)}{(v_0 + rt)^{\frac{\beta}{r}}} \tag{4.5}
$$

substituting (7) into (13)

$$\begin{aligned} \Longrightarrow \qquad \left[\frac{v}{v_0+rt)^{\frac{\beta}{r}}}\right]' &= \alpha\kappa - \beta\frac{v}{(v_0+rt)^{\frac{\beta}{r}}(v_0+rt)} \\ v'(v_0+rt)^{\frac{-\beta}{r}} - \frac{v\beta}{(v_0+rt)^{\frac{\beta+r}{r}}} &= \alpha\kappa - \frac{\beta v}{(v_0+rt)^{\frac{\beta+r}{r}}} \end{aligned} \tag{4.6}$$

By comparison

$$v(t) = \frac{\alpha\kappa(v_0+rt)^{\frac{\beta+r}{r}}}{(\frac{\beta}{r}+1)r} + C \tag{4.7}$$

Substituting (4.7) into (4.5)

$$c_1(t) = \left(\frac{\alpha\kappa(v_0+rt)}{(\beta+r)} + \frac{C}{(v_0+rt)^{\frac{\beta}{r}}}\right) \tag{4.8}$$

$$\text{Since} c_1(0) = 0, \quad \text{initial Drug concentration in tissue}$$

Hence we obtain drug concentration in Tissue/Organ

Compartment as

$$C_1(t) = \frac{\alpha\kappa}{\beta+r}\left[1 - \left(\frac{v_0}{v_0+rt}\right)^{\frac{\beta+r}{r}}\right] \tag{4.9}$$

Graphical Solutions to the Distribution Model using Matlab

The figure below indicates the flow of paracetamol drug distributed in the tissue.

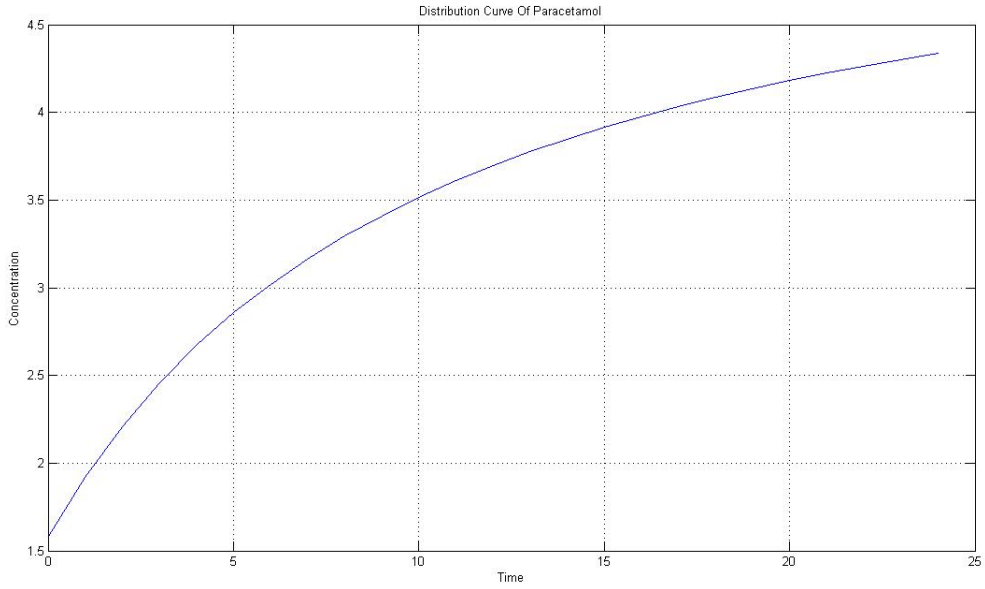


Figure 4.2: Distribution Curve of Paracetamol Drug

From the figure above, the concentration curve rises slowly dew to the minimum rate difference r. This is also dew to the small amount of drug mass absorbed into the tissue.

The flucloxacillin distribution curve is shown in the figure below.

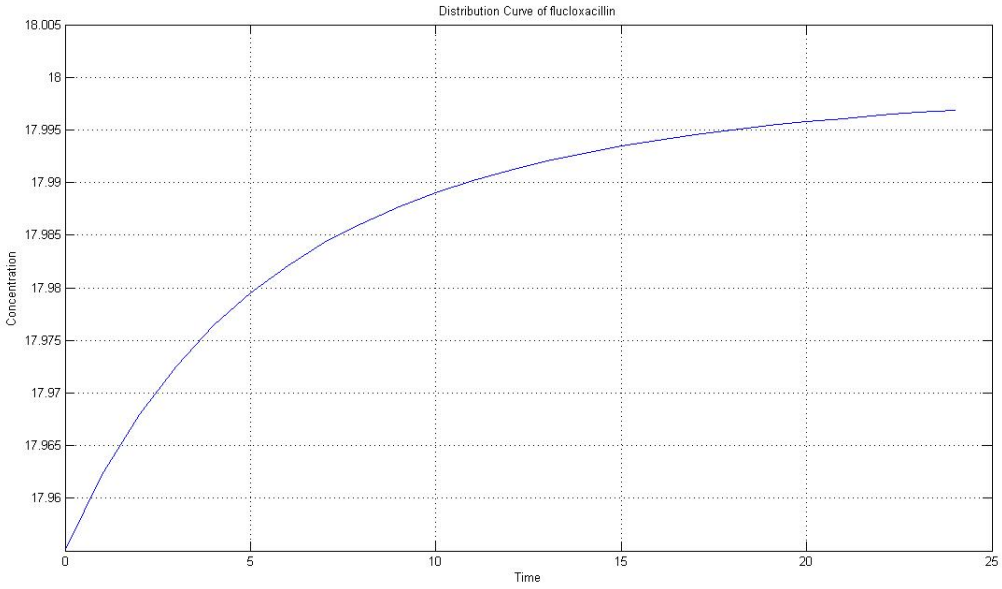


Figure 4.3: Distribution Curve of flucloxacillin Drug

From the figure above, the amount of drug mass absorbed into the tissue is about 18mg. We also observed that flucloxacillin has a high rate difference, r which account for the faster distribution.

The figure below is the gentamicin distribution curve.

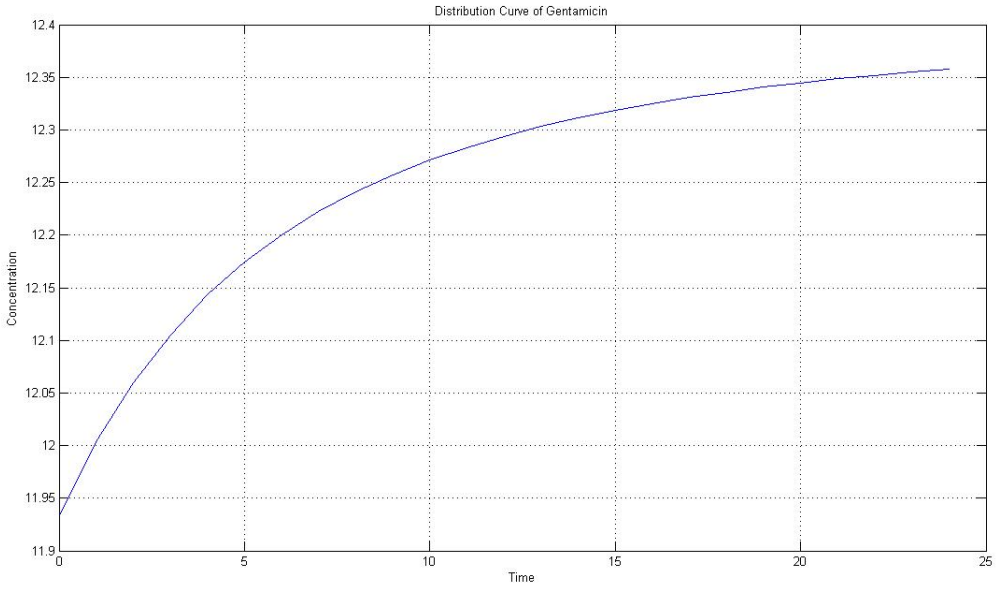


Figure 4.4: Distribution Curve of Gentamicin Drug

From the figure above, the amount of drug mass absorbed is about 12.4mg. The rate difference turns out to be very small whiles the absorption rate is high. Hence there is a faster distribution of gentamicin in the tissue.

The distribution curve of diclofenac drug is shown below.

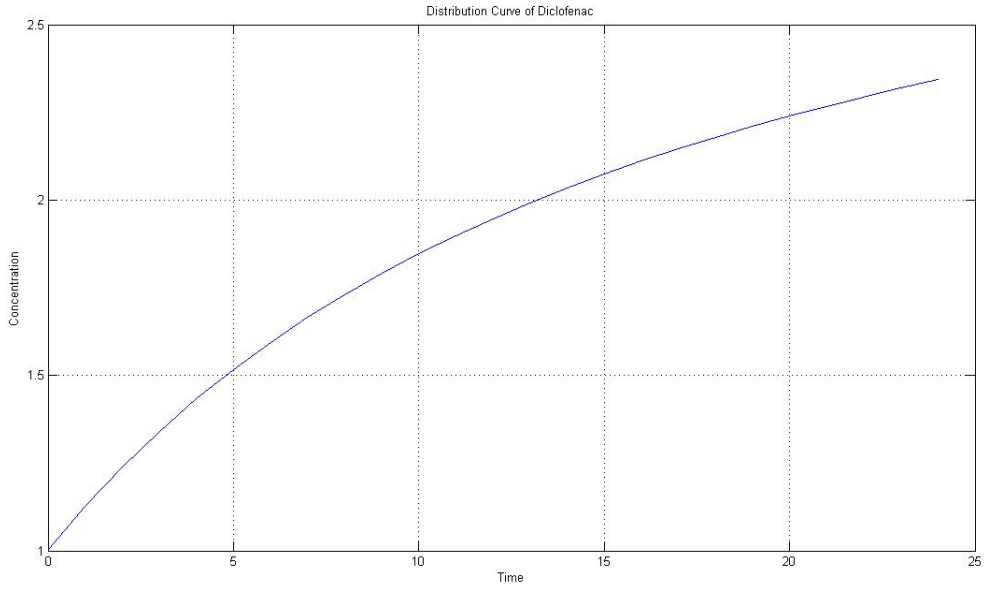
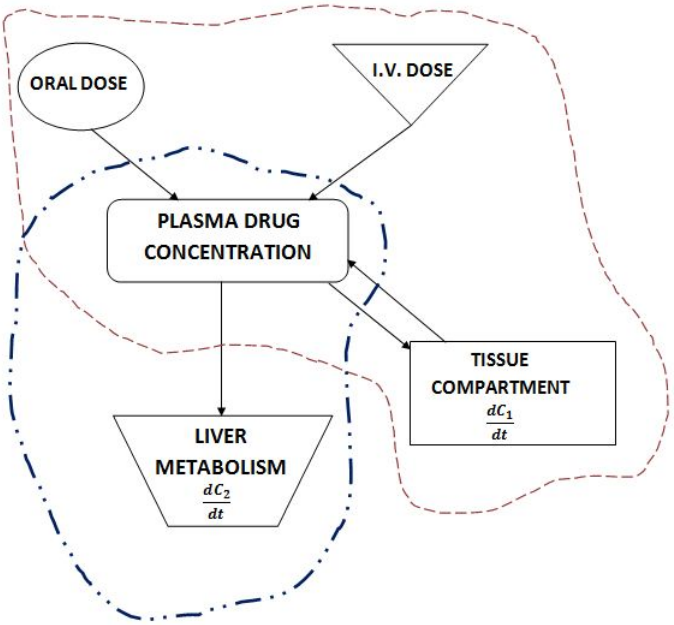


Figure 4.5: Distribution Curve of Diclofenac

From the figure above, we realize that the diclofenac drug has a very small absorbed drug mass dew to the small absorption rate, r.

4.4 Liver Compartment Model

The figure below shows the metabolism flow chart.



The figure above captures the distribution and metabolism phases. The two-dotted broken curve represent the metabolism process.

4.4.1 Model Formulation

Let C_2 represent the drug concentration in the liver.

let α represent absorption rate.

let κ represent drug concentration absorbed from Plasma.

let β represent re-absorption rate from tissue.

let v_0 represent volume of tissue.

let $v(t)$ represent total volume of tissue after absorption.

let v_1 represent volume of liver compartment.

let h represent removal rate from liver compartment.

$$
\begin{aligned}
\frac{dc_2}{dt} &= \text{rate of change of drug concentration in the liver.} \\
\frac{dc_2}{dt} &= \text{input rate - output rate} \\
\frac{dc_2}{dt} &= \text{inlet rate} \times \text{Drug molecule} - \text{outlet rate} \times \text{Drug molecule} \\
\frac{dc_2}{dt} &= \beta \cdot \frac{c_1}{v_0 + rt} - h \cdot \frac{c_2}{v_1}
\end{aligned}
\tag{4.10}
$$

In the equation above, β represent the re-absorption rate from the tissue whiles $v_0 + rt$ represent the total volume after absorption. C_1 is the drug concentration distributed in the tissue. h indicates the removal rate from the liver compartment and v_1 represent the volume of liver compartment. The term $\beta.\frac{c_1}{v_0+rt}$ represent the inlet flow whiles $h\frac{c_2}{v_1}$ represent the outlet flow.

4.4.2 Model Solution

The system of ordinary differential equation is described as uncoupled and coupled in equation (4.11) and (4.12) respectively. Let $C_1(t)$ and $C_2(t)$ respectively denotes the amount of drug concentration at time t in the tissue and liver compartment. results in the differential system below.

$$
c_1' = \alpha\kappa - \frac{c_1}{(v_0 + rt)} \cdot \beta \tag{4.11}
$$

$$
c_2' = \beta \cdot \frac{c_1}{v_0 + rt} - \frac{c_2}{v_1} \cdot h \tag{4.12}
$$

Substitute (4.9) into (4.12)

$$
\frac{dc_2}{dt} = \frac{\beta}{(v_0 + rt)} \frac{\alpha\kappa}{(\beta + r)} \left[1 - \left(\frac{v_0}{v_0 + rt} \right)^{\frac{\beta+r}{r}} \right] - \frac{hc_2}{v_1}
$$

let

$$k_1 = \frac{\alpha\kappa}{\beta + r}$$

and let

$$k_2 = \frac{\beta + r}{r}$$

By the method of integrating factor

$$c_2' + \frac{h}{v_1}c_2 = \frac{\beta k_1}{(v_0 + rt)}\left[1 - \left(\frac{v_0}{(v_0 + rt)}\right)^{k_2}\right]$$

$$e^{\frac{h}{v_1}t}c_2(t) = \beta k_1 \int \left\{ \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)}\, dt \right\} - \beta k_1 v_0^{k_2} \int \left\{ \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)^{(k_2+1)}}\, dt \right\} \tag{4.13}$$

let $k_3 = k_2 + 1$.

$$c_2(t)e^{\frac{h}{v_1}t} = \beta k_1 \int \left\{ \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)} \right\} dt - \beta k_1 v_0^{k_2} \int \left\{ \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)^{k_3}} \right\} dt \tag{4.14}$$

let

$$\int \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)}\, dt \qquad \cdots\cdots\cdots \quad I_1$$

and let

$$\int \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)^{k_3}}\, dt \qquad \cdots\cdots\cdots \quad I_2$$

so that our equation can be represented by

$$c_2(t)e^{\frac{h}{v_1}t} = \beta k_1 I_1 - \beta k_1 v_0^{k_2} I_2 \tag{4.15}$$

Applying integration by parts on I_1 yields

$$\frac{\ln(|v_0+rt|)}{r}e^{\left(\frac{h}{v_1}\right)t}-\frac{h}{v_1 r}\int\left(\ln|v_0+rt|\right)e^{\frac{h}{v_1}t}\,dt \tag{4.16}$$

Performing another Integration by Parts on (4.16) yields

$$\frac{v_1}{h}\left(\ln|v_0+rt|\right)e^{\frac{h}{v_1}t}-\frac{v_1 r}{h}\int\frac{e^{\frac{h}{v_1}t}}{(v_0+rt)}\,dt$$

Therefore

$$\beta k_1\int\frac{e^{\frac{h}{v_1}t}}{(v_0+rt)}\,dt=\frac{e^{\left(\frac{h}{v_1}\right)t}}{r}(\ln|v+rt|)-\frac{hv_1}{hv_1 r}(\ln|v_0+rt|)e^{\left(\frac{h}{v_1}\right)t}+\frac{hv_1 r}{hrv_1}\int\frac{e^{\frac{h}{v_1}t}}{(v_0+rt)}\,dt \tag{4.17}$$

From equation (4.15) above

$$C_2=\beta k_1 I_1-\beta k_1 v_0^{k_2} I_2 \tag{4.18}$$

But since

$$I_1=\int\frac{e^{\frac{h}{v_1}t}}{(v_0+rt)}\,dt$$

By simple algebra and substitution on (4.17)

$$\beta k_1 I_1-I_1=0$$

$$I_1(\beta k_1-1)=0$$

Thus

$$I_1=0$$

If and only if

$$(\beta k_1-1)=0$$

Solution to I_2

From (4.14), we let

$$\int \frac{e^{\frac{h}{v_1}t}}{(v_0+rt)^{k_3}}\,dt \quad \cdots\cdots\cdots \quad I_2$$

Integration by parts will yields

$$\begin{aligned}\beta k_1 v_0^{k_2}\int \frac{e^{\frac{h}{v_1}t}}{(v_0+rt)^{k_3}}\,dt &= e^{\frac{h}{v_1}t}\frac{(v_0+rt)^{(-k_3+1)}}{(-k_3+1)r} - \frac{hv_1(v_0+rt)^{(-k_3+1)}}{hv_1r(-k_3+1)}e^{\frac{h}{v_1}t} \\ &\quad + \frac{(-k_3+1)v_1rh}{v_1r(-k_3+1)h}\int \frac{e^{\frac{h}{v_1}t}}{(v_0+rt)^{k_3}}\,dt. \qquad (4.19)\end{aligned}$$

We remember from equation (4.15) above that

$$C_2 = \beta k_1 I_1 - \beta k_1 v_0^{k_2} I_2 \qquad (4.20)$$

Since

$$\int \left\{ \frac{e^{\frac{h}{v_1}t}}{(v_0+rt)^{k_3}} \right\} dt = I_2,$$

simple algebra and substitution on equation (4.19) result to

$$\begin{aligned}\beta k_1 v_0^{k_2} I_2 - I_2 &= 0, \\ I_2(\beta k_1 v_0^{k_2} - 1) &= 0.\end{aligned} \qquad (4.21)$$

Thus

$$I_2 = 0,$$

if and only if

$$(\beta k_1 v_0^{k_2} + 1) = 0.$$

4.4.3 Discussion

$\int \frac{e^{\frac{h}{v_1}t}}{(v_0+rt)}\,dt$ represented by I_1 resulted into $\int \ln|v_0+rt|e^{\frac{h}{v_1}t}\,dt$ and we had $\int \frac{e^{\frac{h}{v_1}t}}{(v_0+rt)}\,dt$ which was represented by our first integral I_1. On the other hand, $\frac{e^{\frac{h}{v_1}t}}{(v_0+rt)^{k_3}}$ represented by I_2 resulted to $\int (v_0+rt)^{(-k_3+1)}e^{\frac{h}{v_1}t}\,dt$.

When $u=(v_0+rt)^{-k3+1}$, $dv=e^{\frac{h}{v_1}t}$. Thus $\int \frac{e^h v_1 t}{(v_0+rt)^{k_3}}\,dt \rightarrow (\beta k_1 v_0^{k_2}+1)=0$. The results of the analysis shows that first order liver metabolism depends on the conditions: $(\beta k_1-1)=0$ and $(\beta k_1 v^{k_2}+1)=0$. $C_1 \longrightarrow 0$ as $t \longrightarrow 0$. As t increases, the concentration curve rises. However, as $C_1 \longrightarrow \infty$, the peak concentration of C_1 becomes $\dfrac{\alpha\kappa}{\beta+r}$. Hence the steady state solution of C_1 is dependent upon the absorption rate, drug mass, re-absorption and the rates differences. Thus C_1 depict the peak concentration level of drug with time. C_2 depends on two factors namely I_1 and I_2. The condition on I_1 is given as $\beta k_1-1=0$. The condition on I_2 is $\beta k_1 v_0 k_2+1=0$. Thus the determined parameters relevant for first order drug metabolism are $\beta, v_0, k_1=\dfrac{\alpha\kappa}{\beta+r}$ and $k_2=\dfrac{\beta+r}{r}$.

Metabolism Graphs plotted with MATLAB

The figure below is a subplot of the various drugs indicating their metabolism phases. The graphs were produced with the aid of MATLAB numerical solver known as ode45. This function produces numerical values and plot the numerical approximations.

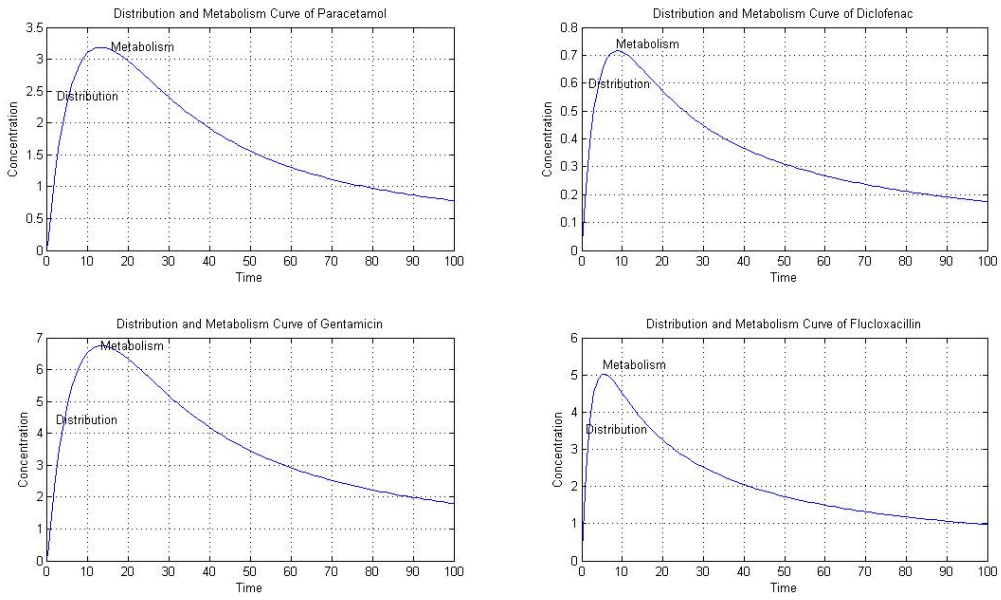


Figure 4.6: Sub-plot Showing Distribution and Metabolism Curves

From the figure above, Paracetamol has a small volume of distribution. This means that the drug molecules has a small affinity for tissue binding proteins. We notice that the distributed molecules quickly undergoes a chemical change known as metabolism. Secondly, diclofenac drug has a smaller affinity for tissue binding proteins. Hence a smaller amount of drug molecules are distributed in the tissue compartment. Gentamicin has a large volume of distribution resulting into large absorption of drug molecules into the target tissue. Flucloxacillin drug distribute moderately to the target site and metabolises faster than the above drugs. Hence we observe a significant occurrence of drug distribution prior to metabolism.

The figure below indicates a comparison between the four drugs.

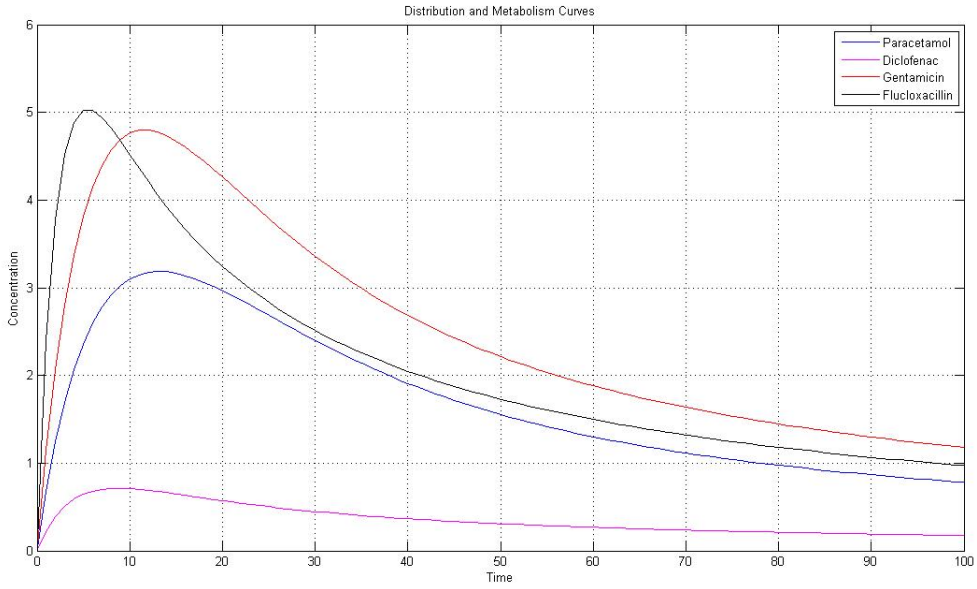


Figure 4.7: Distribution and Metabolism Curves on a Single Graph

We notice from the above figure that diclofenac drug distribute less and quickly metabolises. Paracetamol distributes much more than diclofenac and then undergoes a quick metabolism. Gentamicin distributes more molecules into the target site than diclofenac and then get metabolised. Flucloxacillin has the greatest distribution of molecules over the rest of the drugs and then get metabolised.

Chapter 5

CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

We introduced a simple mathematical model capturing the dynamics of liver metabolism. We formulated the metabolism equation based on the physiology of the human body. Our model is an extension of the drug distribution model. Our emphasis presented a mathematical proof of the complete existence of metabolite which invariantly means absence of drug mass after first-order drug metabolism. Our simple mathematical model eventually reveals certain conditions critical to linear kinetic metabolism. As a result of these satisfying conditions been met, the actual drug mass exiting the liver, C_2 becomes zero. Since the drug mass in the liver goes to zero after metabolism then we absolutely have no molecular drug traces in the metabolites. This is however accounted for by the first order metabolism action which totally biotransforms the drug substance into highly polarized and soluble substance called metabolite. Our first objective was to develop a first order kinetic metabolism model. This was achieved by the direct substitution of the distribution model given by: $C_1 = \frac{\alpha\kappa}{\beta+r}\left[1-\left(\frac{v_0}{v_0+rt}\right)^{\frac{\beta+r}{r}}\right]$ into C_2'. We performed integration and differentiation in order to arrive at our

goal. Our second objective was to use the developed model in order to investigate the necessary conditions underlying active drug metabolism in the liver. The metabolism equation was presented as $C_2 = \beta k_1 I_1 - \beta k_1 v_0^{k_2} I_2$. I_1 and I_2 were analytically solved using the above methods. The first condition on I_1 was computed from the equation:

$$\beta k_1 \int \frac{e^{\frac{h}{v_1}t}}{(v_0+rt)}\,dt = \frac{e^{\left(\frac{h}{v_1}\right)t}}{r}(\ln|v+rt|) - \frac{hv_1}{hv_1r}(\ln|v_0+rt|)e^{\left(\frac{h}{v_1}\right)t} + \frac{hv_1r}{hrv_1}\int \frac{e^{\frac{h}{v_1}t}}{(v_0+rt)}\,dt. \tag{5.1}$$

Direct substitution resulted into $\beta k_1 I_1 - I_1 = 0$ and change of subject gave us the condition given as $\beta k_1 - 1 = 0$. The condition on I_2 was computed from the equation:

$$\begin{aligned}\beta k_1 v_0^{k_2} \int \frac{e^{\frac{h}{v_1}t}}{(v_0+rt)^{k_3}}\,dt \quad &= \quad e^{\frac{h}{v_1}t}\frac{(v_0+rt)^{(-k_3+1)}}{(-k_3+1)r} \;-\; \frac{hv_1(v_0+rt)^{(-k_3+1)}}{hv_1r(-k_3+1)}e^{\frac{h}{v_1}t} \\ &\quad + \frac{(-k_3+1)v_1rh}{v_1r(-k_3+1)h}\int \frac{e^{\frac{h}{v_1}t}}{(v_0+rt)^{k_3}}\,dt. \end{aligned} \tag{5.2}$$

Direct substitution resulted into $\beta k_1 v_0^{k_2} I_2 - I_2 = 0$. and change of subject gave us the condition $\beta k_1 v_0^{k_2} - 1 = 0$.

Moreover, in the findings, it was realised that the volume of the liver compartment v_1 and the removal rate from the liver compartment h are independent of the linear metabolism conditions. Invariably this means that drug pharmaceutics can narrow their early pharmacokinetic experimental work to the parameters found in the linear conditions since there is elimination of the volume of the liver and the removal rate from the liver compartment.

5.2 Recommendations

The result of this work will benefit stakeholders namely:drug pharmaceutics and clinical workers. Pharmaceutical companies would not want to encounter non-linear behaviour during their experimental and developing stages of any candi-

date drug. The result of this thesis curbs and serves as a solution to pharmaceutical companies and clinical workers at large. These findings suggest that drug pharmaceutics can always achieve linear metabolism when $\beta k_1 - 1 = 0$ and $\beta k_1 v_0^{k_2} - 1 = 0$. The implementation of these conditions can be done by selecting right values which ensures that the product of the re-absorption rate and the ratio of the product of absorption rate and drug concentration to the addition of re-absorption rate and the rates difference is equal or approximate to one. Secondly, there must be a right selection of values which ensures that the product of re-absorption rate, k_1 and $v_0^{k_2}$ is equal or approximate to one: where k_1 is the ratio of the product of absorption rate and drug concentration to the addition of the re-absorption rate and rates difference: v_0 is the volume of the target tissue compartment: k_2 is the ratio of the addition of re-absorption rate and rates difference to the rates difference. Drug pharmaceutical companies can adjust drugs exhibiting non-linear kinetics to linear metabolism in the initial stages of drug development. During the early stages of drug development, drugs that are non-linearly inclined to liver metabolism can be adjusted in order to prevent unbalanced drug substrate levels by establishing the determined linear metabolism conditions: $\beta k_1 - 1 = 0$ and $\beta k_1 v_0^{k_2} - 1 = 0$ over such drugs. By so doing the addition of further substrate would not cause a swarm of molecules that are waiting for a chance to be metabolised. The implementation of these linear conditions by drug pharmaceutics would go a long way to benefit clinical workers since ingestion of linear drugs by medical patients would eliminate the need for regular and critical observation given to such patients under non-linear drugs.

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Appendices

Appendix A

Matlab Codes for the Distribution Graphs.

Parameter values were sourced from the internet.

```
subplot(2,2,1)
t=0:24;
a=1.2;b=0.15;v=10;r=0.85;k=4.5;
c=(a*k./(b+r))*(1-(v./(v+r*t).^(b+r./r)));
plot(t,c)
xlabel('Time')
ylabel('Concentration')
title('Distribution Curve Of Paracetamol')
grid on
%hold on

subplot(2,2,2)
t=0:24;
a=0.8;b=0.15;v=12;r=0.62;k=3.1;
c=(a*k./(b+r))*(1-(v./(v+r*t).^(b+r./r)));
plot(t,c)
xlabel('Time')
ylabel('Concentration')
title('Distribution Curve of Diclofenac')
grid on

subplot(2,2,3)
t=0:24;
a=2.1;b=1.5;v=8.9;r=0.6;k=12.4;
```

```
c=(a*k./(b+r))*(1-(v./(v+r*t).^(b+r./r)));
plot(t,c)
xlabel('Time')
ylabel('Concentration')
title('Distribution Curve of Gentamicin')
grid on

subplot(2,2,4)
t=0:24;
a=3.2;b=2.0;v=20;r=1.2;k=18;
c=(a*k./(b+r))*(1-(v./(v+r*t).^(b+r./r)));
plot(t,c)
xlabel('Time')
ylabel('Concentration')
title('Distribution Curve of flucloxacillin')
grid on
```

Appendix B

Matlab Codes for the Metabolism Graphs

Parameter values were sourced from the internet

```
function dc=para(t,c)
a=1.2;b=0.15;v0=10;r=0.85;k=4.5;v1=8.1;h=0.9;c1=50;c2=8;
dc=(b*c1/(v0+r*t))-(c/v1)*h;

function dc=diclo(t,c)
a=0.8;b=0.15;v0=12;r=0.62;k=3.1;c1=20.8;h=2;v1=8;
dc=(b*c1/(v0+r*t))-(c/v1)*h;
```

```
 function dc=genta(t,c)
 a=2.1;b=1.5;v0=8.9;r=0.6;k=12.4;v1=9.1;h=1.1;c1=9.2;c2=8;
 dc=(b*c1/(v0+r*t))-(c/v1)*h;

function dc=fluclo(t,c)
a=3.2;b=2.0;v0=20;r=1.2;k=18;v1=9.1;h=4.2;c1=30.85;c2=8;
dc=(b*c1/(v0+r*t))-(c/v1)*h;

[t dc]=ode45(@para,0:100,0)
plot(t,dc,'b')
xlabel('Time')
ylabel('Concentration')
grid on

%title('Distribution and Metabolism Curve of Paracetamol')
hold on
[t dc]=ode45(@diclo,0:100,0)
plot(t,dc,'m')
xlabel('Time')
ylabel('Concentration')
%grid on

%title('Distribution and Metabolism Curve of Diclofenac')
[t dc]=ode45(@genta,0:100,0)
plot(t,dc,'r')
xlabel('Time')
ylabel('Concentration')
%grid on
```

```
%title('Distribution and Metabolism curve of Gentamicin')
[t dc]=ode45(@fluclo,0:100,0)
plot(t,dc,'k')
xlabel('Time')
ylabel('Concentration')
%grid on

%title('Distribution and Metabolism Curve of Flucloxacillin')
title('Distribution and Metabolism Curves')
legend('Paracetamol','Diclofenac','Gentamicin','Flucloxacillin')

subplot(2,2,1)
[t dc]=ode45(@para,0:100,0)
plot(t,dc)
xlabel('Time')
ylabel('Concentration')
grid on
title('Distribution and Metabolism Curve of Paracetamol')

subplot(2,2,2)
[t dc]=ode45(@diclo,0:100,0)
plot(t,dc)
xlabel('Time')
ylabel('Concentration')
grid on
title('Distribution and Metabolism Curve of Diclofenac')

subplot(2,2,3)
```

```
[t dc]=ode45(@genta,0:100,0)
plot(t,dc)
xlabel('Time')
ylabel('Concentration')
grid on
title('Distribution and Metabolism Curve of Gentamicin')

subplot(2,2,4)
[t dc]=ode45(@fluclo,0:100,0)
plot(t,dc)
xlabel('Time')
ylabel('Concentration')
grid on
title('Distribution and Metabolism Curve of Flucloxacillin')
```

Appendix C

Detailed Solution to the Distribution and Metabolism Models

Model Formulation

Let C_1 = drug concentration in the tissue.

$$\begin{aligned}
\frac{dc_1}{dt} &= \text{rate of change of drug concentration in the tissue.} \\
\frac{dc_1}{dt} &= \text{rate in - rate out} \\
\frac{dc_1}{dt} &= \text{inlet rate} \times \text{Concentration} - \text{outlet rate} \times \text{Concentration} \\
\frac{dc_1}{dt} &= \alpha\kappa - \beta\frac{c_1}{v_0 + rt} \\
\frac{dc_1}{dt} &= \alpha\kappa - \beta\frac{c_1}{v_0 + rt}
\end{aligned} \tag{3}$$

α and κ in the above equation represent the input flow rate and it concentration. β and $\frac{c_1}{v_0+rt}$ represent the outlet flow rate and it concentration. The first term in equation (3) describes the rate inlet whiles the second term describes the rate outlet.

Solution by Variation of Parameters

$$\begin{aligned}
\text{Inhomogeneous Equation} \to c_1' &= \alpha\kappa - \beta\frac{c_1}{v_0+rt} && (4)\\
\text{Homogeneous Equation} \to c_{1h}' &= -\beta\frac{c_{1h}}{v_0+rt} && (5)\\
\text{Solution to Homogeneous Parts} \int \frac{dc_1}{c_1} &= -\int \frac{\beta}{v_0+rt}\,dt \\
\ln|c_1| &= -\frac{\beta}{r}\ln|v_0+rt| + C \\
|c_1| &= e^{\frac{-\beta}{r}\ln|v_0+rt|}\,e^C \\
c_1(t) &= C(v_0+rt)^{\frac{-\beta}{r}} \\
&= \frac{C}{(v_0+rt)^{\frac{\beta}{r}}} && (6)
\end{aligned}$$

let v(t) be a yet to be determined function of t and by substitution we obtain

$$c_1(t) = \frac{v(t)}{(v_0+rt)^{\frac{\beta}{r}}} \tag{7}$$

substituting (7) into (13)

$$\begin{aligned}
\implies \qquad \left[\frac{v}{v_0+rt)^{\frac{\beta}{r}}}\right]' &= \alpha\kappa - \beta\frac{v}{(v_0+rt)^{\frac{\beta}{r}}(v_0+rt)} \\
\frac{(v_0+rt)^{\frac{\beta}{r}}v' - \frac{v\beta}{r}(v_0+rt)^{\frac{\beta-r}{r}}r}{(v_0+rt)^{\frac{2\beta}{r}}} &= \alpha\kappa - \beta\frac{v}{(v_0+rt)^{\frac{b+r}{r}}} \\
v'(v_0+rt)^{\frac{-\beta}{r}} - \frac{v\beta}{(v_0+rt)^{\frac{\beta+r}{r}}} &= \alpha\kappa - \frac{\beta v}{(v_0+rt)^{\frac{\beta+r}{r}}} && (8)
\end{aligned}$$

By comparison

$$\begin{aligned}
(v_0 + rt)^{\frac{-b}{r}} v' &= \alpha\kappa \\
v' &= \alpha\kappa (v_0 + rt)^{\frac{\beta}{r}} \\
v(t) &= \alpha\kappa \int (v_0 + rt)^{\frac{\beta}{r}}\, dt \\
v(t) &= \frac{\alpha\kappa (v_0 + rt)^{\frac{\beta+r}{r}}}{(\frac{\beta}{r} + 1)r} + C
\end{aligned} \tag{9}$$

Substituting (9) into (7)

$$\begin{aligned}
c_1(t) &= \left(\frac{\alpha\kappa (v_0 + rt)^{\frac{\beta+r}{r}}}{\beta + r} + C \right) \times \frac{1}{(v_0 + rt)^{\frac{\beta}{r}}} \\
&= \left(\frac{\alpha\kappa (v_0 + rt)^{\frac{\beta+r}{r}}}{(\beta + r)(v_0 + rt)^{\frac{\beta}{r}}} + \frac{C}{(v_0 + rt)^{\frac{\beta}{r}}} \right) \\
c_1(t) &= \left(\frac{\alpha\kappa (v_0 + rt)}{(\beta + r)} + \frac{C}{(v_0 + rt)^{\frac{\beta}{r}}} \right)
\end{aligned} \tag{10}$$

$c_1(0) = 0$, initial Drug concentration in tissue

$$\Rightarrow \quad 0 = \frac{\alpha\kappa v_0}{(\beta + r)} + \frac{C}{(v_0)^{\frac{\beta}{r}}}$$

$$\Rightarrow \quad \frac{-\alpha\kappa v_0 v_0^{\beta/r}}{(\beta + r)} = C$$

$$\Longrightarrow \quad C = \frac{-\alpha\kappa (v_0)^{\frac{\beta+r}{r}}}{(\beta + r)}$$

Hence we obtain drug concentration in Tissue/Organ

Compartment as

$$\begin{aligned} C_1(t) &= \left[\frac{\alpha\kappa(v_0+rt)}{(\beta+r)} - \left(\frac{\alpha\kappa(v_0)^{\frac{\beta+r}{r}}}{(\beta+r)(v_0+rt)^{\beta/r}}\right)\right] \\ &= \frac{\alpha\kappa}{\beta+r}\left[(v_0+rt) - \left(\frac{(v_0)^{\frac{\beta+r}{r}}}{(v_0+rt)^{\beta}/r}\right)\right] \\ &= \frac{\alpha\kappa}{\beta+r}\left[1 - \left(\frac{(v_0)^{\frac{\beta+r}{r}}}{(v_0+rt)^{\frac{\beta+r}{r}}}\right)\right] \\ C_1(t) &= \frac{\alpha\kappa}{\beta+r}\left[1 - \left(\frac{v_0}{v_0+rt}\right)^{\frac{\beta+r}{r}}\right] \end{aligned} \tag{11}$$

Liver Compartment Model

$$\begin{aligned} \frac{dc_2}{dt} &= \text{rate of change} \\ \frac{dc_2}{dt} &= \text{input rate - output rate} \\ \frac{dc_2}{dt} &= \text{volume rate} \times \text{Drug molecule} - \text{volume rate} \times \text{Drug molecule} \\ \frac{dc_2}{dt} &= \beta \cdot \frac{c_1}{v_0+rt} - h \cdot \frac{c_2}{v_1} \end{aligned} \tag{12}$$

Model Solution

The system of ordinary differential equation is described as uncoupled in equation (13) and coupled for equation (14). We make substitution of (13) into (14). Let $C_1(t)$ and $C_2(t)$ respectively denotes the amount of drug at time t in the tissue and liver compartment.

$$c_1' = \alpha\kappa - \frac{c_1}{(v_0+rt)} \cdot \beta \tag{13}$$

$$c_2' = \beta \cdot \frac{c_1}{v_0+rt} - \frac{c_2}{v_1} \cdot h \tag{14}$$

Substitute (11) into (14)

$$\frac{dc_2}{dt} = \frac{\beta}{(v_0+rt)}\frac{\alpha\kappa}{(\beta+r)}\left[1-\left(\frac{v_0}{v_0+rt}\right)^{\frac{\beta+r}{r}}\right] - \frac{hc_2}{v_1}$$

Now let

$$k_1 = \frac{\alpha\kappa}{\beta+r}$$

and let

$$k_2 = \frac{\beta+r}{r}$$

Integrating factor yields

$$a(t) = -\frac{h}{v_1},$$

$$\mu(t) = e^{-\int a(t)\,dt},$$

$$\mu(t) = e^{\frac{h}{v_1}\int dt},$$

$$\mu(t) = e^{\frac{h}{v_1}t}.$$

Hence we obtain

$$c_2' + \frac{h}{v_1}c_2 = \frac{\beta k_1}{(v_0+rt)}\left[1-\left(\frac{v_0}{(v_0+rt)}\right)^{k_2}\right]$$

$$\begin{aligned}
e^{\frac{h}{v_1}t}\left[c_2' + c_2\frac{h}{v_1}\right] &= \frac{\beta k_1 e^{\frac{h}{v_1}t}}{v_0+rt} - \frac{\beta k_1}{v_0+rt}\left(\frac{v_0}{v_0+rt}\right)^{k_2} e^{\frac{h}{v_1}t} \\
\left[c_2(t)e^{\frac{h}{v_1}t}\right]' &= \frac{\beta k_1 e^{\frac{h}{v_1}t}}{(v_0+rt)} - \frac{\beta k_1}{(v_0+rt)}\left(\frac{v_0}{(v_0+rt)}\right)^{k_2}\left(e^{\frac{h}{v_1}t}\right) \\
e^{\frac{h}{v_1}t}c_2(t) &= \beta k_1\int\left\{\frac{e^{\frac{h}{v_1}t}}{(v_0+rt)}\,dt\right\} - \beta k_1 v_0^{k_2}\int\left\{\frac{e^{\frac{h}{v_1}t}}{(v_0+rt)^{(k_2+1)}}\,dt\right\}
\end{aligned} \tag{15}$$

let $k_3 = k_2 + 1$.

$$c_2(t)e^{\frac{h}{v_1}t} = \beta k_1 \int \left\{ \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)} \right\} dt - \beta k_1 v_0^{k_2} \int \left\{ \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)^{k_3}} \right\} dt \tag{16}$$

let

$$\int \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)}\, dt \qquad \cdots\cdots\cdots \quad I_1$$

and let

$$\int \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)^{k_3}}\, dt \qquad \cdots\cdots\cdots \quad I_2$$

so that our equation can be represented by

$$c_2(t)e^{\frac{h}{v_1}t} = \beta k_1 I_1 - \beta k_1 v_0^{k_2} I_2 \tag{17}$$

Integration by parts on I_1 yields

$$u = e^{\frac{h}{v_1}t},$$

$$du = \frac{h}{v_1} e^{\left(\frac{h}{v_1}\right)t}\, dt,$$

$$dv = \frac{1}{(v_0 + rt)},$$

$$v = \frac{\ln(|v_0 + rt|)}{r}.$$

$$\int v\, du = uv - \int v\, du$$

$$\frac{\ln(|v_0 + rt|)}{r} e^{\left(\frac{h}{v_1}\right)t} - \frac{h}{v_1 r} \int \left(\ln|v_0 + rt|\right) e^{\frac{h}{v_1}t}\, dt \tag{18}$$

Performing another Integration by Parts on (18) yields

$$u = \ln|v_0 + rt|,$$

$$du = \frac{r}{v_o + rt} dt,$$

$$dv = e^{\frac{h}{v_1}t},$$

$$v = \frac{v_1}{h} e^{\frac{h}{v_1}t}.$$

$$\int u\, dv = uv - \int v\, du$$

Hence we have the expression to be

$$\frac{v_1}{h} \left(\ln |v_0 + rt|\right) e^{\frac{h}{v_1}t} - \frac{v_1 r}{h} \int \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)}\, dt$$

Therefore

$$\beta k_1 \int \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)}\, dt = \frac{e^{\left(\frac{h}{v_1}\right)t}}{r} (\ln |v + rt|) - \frac{hv_1}{hv_1 r} (\ln |v_0 + rt|) e^{\left(\frac{h}{v_1}\right)t} + \frac{hv_1 r}{hrv_1} \int \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)}\, dt$$

But since

$$I_1 = \int \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)}\, dt$$

We make substitution to obtain

$$\beta k_1 I_1 - I_1 = 0$$

$$I_1(\beta k_1 - 1) = 0$$

Thus

$$I_1 = 0$$

If and only if

$$(\beta k_1 - 1) = 0$$

From (16), let

$$\int \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)^{k_3}}\, dt \quad \cdots\cdots\cdots \quad I_2$$

First Integration by parts yields

$$u = e^{\frac{h}{v_1}t},$$

$$du = \frac{h}{v_1} e^{\frac{h}{v_1}t}\, dt,$$

$$dv = (v_0 + rt)^{-k_3},$$

$$v = \frac{(v_0 + rt)^{-k_3+1}}{(-k_3+1)r}.$$

Then we have

$$e^{\frac{h}{v_1}t} \left\{ \frac{(v_0 + rt)^{(-k_3+1)}}{(-k_3+1)r} \right\} - \frac{h}{v_1 r(-k_3+1)} \int (v_0 + rt)^{(-k_3+1)} e^{\frac{h}{v_1}t}\, dt$$

Second Integration by Parts yields

$$u = (v_0 + rt)^{(-k_3+1)},$$

$$du = (v_0 + rt)^{-k_3}(-k_3+1)r\, dt,$$

$$dv = e^{\frac{h}{v_1}t},$$

$$v = \left(\frac{v_1}{h}\right) e^{\frac{h}{v_1}t}$$

Thus

$$\frac{v_1}{h}(v_0 + rt)^{(-k_3+1)} e^{\frac{h}{v_1}t} - \frac{(k_3+1)v_1 r}{h} \int \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)^{k_3}}\, dt$$

Hence

$$\begin{aligned} \beta k_1 v_0^{k_2} \int \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)^{k_3}}\, dt \quad &= \quad e^{\frac{h}{v_1}t} \frac{(v_0 + rt)^{(-k_3+1)}}{(-k_3+1)r} \; - \; \frac{h v_1 (v_0 + rt)^{(-k_3+1)}}{h v_1 r(-k_3+1)} e^{\frac{h}{v_1}t} \\ &\quad + \frac{(-k_3+1)v_1 r h}{v_1 r(-k_3+1)h} \int \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)^{k_3}}\, dt. \end{aligned} \tag{19}$$

Since

$$\int \left\{ \frac{e^{\frac{h}{v_1}t}}{(v_0 + rt)^{k_3}} \right\} dt = I_2,$$

our long equation above simplifies to

$$\begin{aligned} \beta k_1 v_0^{k_2} I_2 - I_2 &= 0, \\ I_2(\beta k_1 v_0^{k_2} - 1) &= 0. \end{aligned} \tag{20}$$

Therefore

$$I_2 = 0,$$

if and only if

$$(\beta k_1 v_0^{k_2} - 1) = 0.$$