Population Pharmacokinetic-Pharmacodynamic Models: Application to the simulation data

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Abstract

The optimal prescription and utilisation of medicines to effectively manage and treat infectious and non-communicable diseases is a major goal of adequate healthcare systems. This goal is, however, hampered by variable responses to standard medicinal doses amongst a significant number of individuals. Individual drug responses can vary from none, to partial, to adverse and are attributable to environmental, pathophysiological and genetic influences, amongst others. This project has two main foci:

Assessing models of population pharmacokinetic-pharmacodynamic that use parametrized system of differential equations. The project will discuss Bayesian models of groups of individuals who may have taken several drugs doses at various times throughout the course of a clinical trial. The Bayesian approach will help the derivation of predictive distributions that contribute to the optimization of the treatments for different target populations. Through simulation of population pharmacokinetic and Pharmacodynamic models and real data of plasma concentration, we aim at assessing different approaches of modelling population pharmacokinetic-pharmacodynamic.

Declaration

I, the undersigned, hereby declare that the work contained in this research project is my original work, and that any work done by others or by myself previously has been acknowledged and referenced accordingly.

Nadia Solime Taou, 22 May 2014

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1. Introduction and Review of the Literature

1.1 Mechanistic Basis for Ethnic Differences in Response to Medications

Since the beginning of human medicine, population or ethnic variability in drug efficacy and safety has been known to exist. Human cells have about $30,000$ nuclear genes distributed on 46 chromosomes (i.e 22 pairs of autosomes and 1 pair sex chromosomes) and 37 mitochondrial genes encoded in the circular mitochondrial DNA that is passed maternally. Most of the information about the human body is contained in the chromosomes (structure of DNA, protein, and RNA found in cells) (Moroi et al., 2008).

Ethnic groups vary in many ways and this is due to many facts such as diet, genetic make-up and exposure to the environment factors. These variations play critical roles in health and in response to specific drugs. Ethnicity is one factor that may account for the observed difference in both pharmacokinetics (PK) and pharmacodynamics (PD) of drugs resulting in the variability for response to drug therapy. Moreover, factors that may contribute to such ethnic sensitivity of a drug include genetic differences in the expression of enzymes that metabolise or transport drugs or in the expression of targets of drug therapy, steep dose-response curves and high intersubject variations in bioavailability. The potential contribution of critical drug-metabolising enzymes, drug transporters, and drug targets to the ethnic variability in drug exposure or in drug response can be gleaned from a review of differences in variant alleles with respect to function and prevalence in different populations. However, there is little evidence in the literature that these factors have been evaluated with respect to drug response (Norrgard, 2008).

A large number of modern drugs approved by the Food and Drug Administration (FDA) and similar organisations, has been developed with relevance to the Caucasian ancestry descent populations while not addressing the fact that subtle differences in the genetic make-up of other populations, such as Asian, South American and in particular African populations. It is well-known that genetic variability of African populations is far greater than in other regions in the world. This is particularly important when considering that African populations are under-represented in most studies on the hereditary diseases and pharmacogenomics. It is therefore crucial to question how well current approaches for establishing the relationship between the genetic variation and drug/treatment responses can capture African genetic variation in identified genes underlying ethnic difference in drug/treatment and drug dosaging responses (Kalow, 2004).

1.2 Opportunities and Challenges of Personalized Medicine

Although, genetic forces including mutation, recombination, and natural selection that contribute to an increase or decrease in risk to disease and response to drugs/treatment arise all the time (McIntire et al., 2003), human migrations have played a critical role in shaping the genetic diversity of human populations, yielding difference in drugs/treatment response (Bhaskar et al., 2007). Over the last few years, many new genetic associations to diseases have been identified by Genome-Wide Association Studies (Kearns-Jonker et al., 2012), and there are potentially many uses of these identified genes includes a better understanding of disease aetiology, personalized medicine, new leads for studying underlying risk prediction and clinical prediction of the treatment (Feidt et al., 2010). However, such

equivalent studies from the samples of African ethnic groups are underway and are in its infancy. In addition, despite these considerable enthusiasm successes mostly in Caucasian populations (Feidt et al., 2010), the proportion of the heritability of most complex phenotypes that have been studied to date remains small (Kearns-Jonker et al., 2012), making it difficult to inform strategies for disease mapping, prediction of complex traits, understanding the individual's variability in response to drug therapy or drug dosaging and subsequently clinical prediction of the treatment. This is an important challenge known as "missing heritability" problem generally caused by epigenetic variations. Epigenetic is the study of heritable changes in gene expression or cellular phenotype that do not involve changes in the underlying DNA sequence. The genetic epistasis for instance is one of the common "missing heritability" problem which can be found in some families. Empirically, the models used to quantify heritability mostly accounted for additive genetic effects. Actually this is addressed by using more complex models which have a larger number of parameters compared to the simpler models. However it limits the statistical power of analyses based on limited data but Bayesian analysis for example the Bayesian LASSO (BL) and the Bayesian random effects models are useful in order to solve this statistical limitation (Makowsky et al., 2011).

Due to the multiple genetic, patho-physiological and the environmental factors that contribute to the development of complex phenotypes, variability drugs therapy and dosaging, current approaches to study the genetic association to traits and the relationship between the variation of patient's DNA and drug/treatment and drug dosaging disposition have exhibited different outcomes from different populations. Furthermore these approaches may be limited due to different environmental context into medical genetics in particular among African ethnic group known of low linkage disequilibrium, high diversity and complex admixture (Lachance et al., 2012). It is therefore crucial to question how well current approaches from local ancestry inferences, disease mapping to the methods establishing relationship of genetic variation and drug/treatment responses can capture African genetic variation in identified genes underlying ethnic difference in drug/treatment drug dosaging responses. While sequencing information of African populations is going to be increased through recently launched projects, such as H3Africa (Djouadi et al., 2011), it would likely hasten to investigate appropriate approaches for African-specific genomic discoveries to clinical practices that may have the potential to change health and wellness of African ethnic groups.

1.3 Motivation of the Essay

Genetics and genomics researchers have been interested in studying populations of Africa known as the origin of modern humans to understand the original source of all human genetic diversity (Pickrell et al., 2012). African populations face a heavy burden of diseases including Human Immunodeficiency Virus/AIDS, Tuberculosis, Influenza and a growing burden of non-communicable diseases (Webb et al., 2008). Different environmental context into medical genetics and genetic factors that contribute to diseases, drug dosaging and drug response in most African populations are challenges for the world-wide researchers (Webb et al., 2008). Today the technology exists to sequence the whole genome of an individual which becomes more and more cheap and has already facilitated the analysis of human genome-wide variation, genetic variant underlying ethnic difference in drug/treatment response in most population of Caucasian ancestry (Feidt et al., 2010). In addition, a number of genes which have a role in pharmacogenetics (i.e. pharmacogenes) are highly polymorphic, and studies have shown that certain functionally-relevant alleles are present at significant levels in certain populations (Suarez-Kurtz and J Pena, 2006). This can have a significant influence on how these drugs are metabolised in different population groups. Moreover, hundreds of thousands of people die each year as a result of adverse

drug reactions, which could be due to multiple factors, including disease determinants, environmental exposure, and genetic factors (Feidt et al., 2010).

The optimal prescription and utilisation of medicines to effectively manage and treat infectious and non-communicable diseases is a major goal of adequate healthcare systems. This goal is, however, hampered by variable responses to standard medicinal doses amongst a significant number of individuals. Individual drug responses and drug dosaging can vary from none, to partial, to adverse and are attributable to environmental, pathophysiological and genetic influences, amongst others. The central premise of this essay is concerned with the review of population pharmacokinetic-pharmacodynamic models and the discussion of Bayesian models of groups of individuals who may have taken several drugs doses at various times throughout the course of a clinical trial using simulation data. This essay aims to simulate real data in order to assess drug metabolism and drug effect in human body using PKfit and IVIVC software (Sangkuhl et al., 2008).

1.4 Human Genetics Variations

1.4.1 Genetic variations. The human genome is composed about 3×10^9 base pairs of DNA. The focus in medical population genetics is the understanding of the consequence of the past human migrations, the causes of human diversity and its implication in diseases/traits and drugs/treatments and drug dosaging variability in the world today. The patterns of geographical genetic diversity include mutation, natural selection, genetic drift and gene flow may change within and between populations. These factors can also vary between two individuals from the same population. A number of studies have examined how genetic variation is distributed geographically; and have established that human population differences are mainly due to the presence of low-frequency alleles that have not diffused far from their geographic place of origin (Norrgard, 2008). In addition, a recent study by Rosenberg and colleagues demonstrated that the worldwide human genetic variation within human populations is larger $(93 - 95\%)$ than that seen between populations $(5 - 7\%)$, suggesting that classification of the human species according to racial or continental lines appears to be inappropriate descriptors of the distribution of human genetic variation. The literature was surveyed to quantify the human genetic variation within and between human population using Wrights F_{ST} statistic. To describe the degree of population substructure(or the degree of population differentiation), scientists use the fixation index (F_{ST}) (NHGRI, 1999).

The fixation index F_{ST} is a measure of how populations differ genetically. The deviation of this fixation index is $F_{ST} = \frac{H_T - H_S}{H_T}$, where H_T and H_S represent the heterozygosity (cell) of the total population and of the sub-population (sampled population), respectively. F_{ST} measures the ampleness of the genetic differentiation; is the differences between populations allele frequencies at one or more loci, or in mean phenotypes in a common environment or in the sub-population. The range of F_{ST} is between 0.0 and 1.0. If F_{ST} is 0.0 that means no differentiation, there is zero variation within sub-populations, but when it is 1.0 that means there is a complete differentiation. Generally high (F_{ST}) values reflect a low level of shared alleles between individuals in the sampled population and the total population. Inversely, low F_{ST} values indicate that members of the sub-population share alleles with the total population (Norrgard, 2008).

1.4.2 Architecture of Complex Diseases. Complex diseases (also known as multifactorial or polygenic diseases) are genetic abnormalities diseases caused by the effects of genetic variation and mutation in multiple genes; and as well as the interaction of multiple genes with the environmental factors. Complex diseases such as asthma, cancers, diabetes, Alzheimer's, heart disease, high blood pressure, Parkinson's, autism, kidney diseases, obesity etc do not follow a pattern of inheritance as with Mendelian diseases

caused by a single gene. The implication of multiple gene-gene and gene-environment interactions in complex diseases, constitute a serious challenge for the researchers to identify genes that are associated with risk for developing complex diseases and associated with drugs response. Nevertheless, complex diseases are found in many cluster families called familial aggregation. In fact, this does not imply that the disease has necessarily a genetic contribution. Family members do not have only genes in common, they also share the same environment exposure, same diet, same behaviour and cultural attitude that contributes to the development of complex diseases (Nussbaum et al., 2007).

The identification of genes that are associated with risk for developing complex diseases is an important goal of modern medical genetics studies. The hope is that such knowledge can ultimately be used in understanding the biological mechanisms underlying these diseases and for generating individualized risk profiles that are useful in a public health context. Genetic linkage-based studies have discovered more than 1300 single disease genes which can cause complex diseases. Unfortunately, genetic linkage-based methodology fails to identify genetic variations and risk alleles that influence an individual's likelihood of developing a complex disease, the rate of disease progression, and the patient's response to treatment and drug dosaging (Moroi et al., 2008). Interaction between genetic and environmental factors in complex disease remains a critical challenge for researchers. Understanding these factors will help scientists to improve human health care and advance the Pharmacogenetics/Pharmacogenomics (Personalized Medicine) (Craig et al., 2008).

1.5 An Introduction to Pharmacogenetics and Pharmacogenomics

1.5.1 Introduction. The increasing number of the individuals affected by the complex diseases such as cancer, diabetes and obesity contribute to the rapid development of the new sciences like personalized medicine, pharmacogenomics and pharmacogenetics. Pharmacogenomics and pharmacogenetics use genomic information to improve human health care by making drug specific to each person. These sciences try also to reduce the drug negative effects and increase positive effects of medications on the human body.

1.5.2 Origins and definition. In the 18th century, the terms pharmacology and genetics appeared in scientific literature starting by Claude Bernard's and Oswald Schmiedeberg's research in pharmacology; but also Gregor Mendel's and Francis Galton's work in genetics. In 1931 Sir Archibald Garrod introduced the pharmacogenetics idea in his book entitled Inborn Factors in Diseases. This idea became more realistic when in 1957 Motulsky summarised all the research published in this area in a paper entitled *reactions, enzymes, and biochemicalgenetics* (Kalow, 2004). It was only in 1959, the term "pharmacogenetics" was used for the first time by the German geneticist Friedrich Otto Vogel (1925-2006). He used it to refer to the genetic differences in pharmacokinetic factors, particularly metabolic enzymes and DNA sequence variations.

Pharmacogenetics was introduced in the scientific literature in 1990 and in 1997, a new term "pharmacogenomics" emerged from pharmacogenetics. In 2000, the National Institute of Health **(NIH)** funded Genome-Wide Association Studies **(GWAS)** with a goal to examine many common genetic variants in different human ethnic groups and investigate for possible genes associated with complex diseases or traits. In the same year the first comprehensive pharmacogenetic Knowledge-Base the "PharmGKB" website was constructed by NIH. PharmGKB is a short name of Pharmacogenomics Knowledge-Base. It is an interactive web tool for researchers who are looking for how genetic variation can affect human drug response. The following, year 2001, the draft of a human sequence was published. Then in 2003 the "HapMap" project started to built a map of human genome sequence. In 2004 the single

nucleotide polymorphisms SNP_s Consortium published the characterization of more than 1.8 million SNP_s (Meyer, 2004).

The terms pharmacogenetics/pharmacogenomics appear identical but they are not the same. For instance pharmacogenetics is from the combination between pharmacology and genetics and therefore, it is the study of genetics factors that influence drug action in the human body. Furthermore, pharmacogenetics try to understand adverse drug reaction or drug beneficial effects reactions by looking at the human genetic. On the other hand, pharmacogenomics is the study of how genes affect a person's response to drugs. It is a new area of research which combines pharmacology and genomics (field in genetics that applies recombinant DNA, DNA sequencing methods). Pharmacogenomics look at the genetic difference within the population or across-ethnic groups that can justify the adverse reaction or beneficial effects reactions to a given drug. Pharmacogenetics wishes to develop efficacy and safety drugs with the correct doses that will be conformed to each patient's genetic marke-up. This involves gathering knowledge from drug metabolism, genetic variation and drug responses (Barlow-Stewart and Saleh, 2012).

1.5.3 Principles of Drugs Metabolism. Medication (or medicine) usually called a drug is a chemical substance compounded by more than one ingredient combined with other pharmacologically active substance use to cure or to treat diseases. Today, many drug efficacies in a given patient population is about 25% to 60% (Wilkinson, 2005), however hundreds of thousands of people die each year as a result of adverse drug reactions, which could be due to multiple factors, including disease determinants, environmental exposure, and genetic factors (Zackrisson et al., 2010).

According to the Food and Drug Administration (FDA), 49.5% of the reports of deaths and 61% of hospitalizations in United States are caused by adverse drug reactions in people younger than 60. The risk of an adverse drug reaction is about 33% higher in people aged 50 to 59 than it is in people aged 40 to 49. This example shows that the drug adverse response is a real public health problem. In their effort to solve this problem, scientists discovered that genetic factors can be used to explain individual variability in drug therapy. Genetic variations contribute to drug targeting, drug transport, metabolism, disease susceptibility and drug safety (Harrison et al., 2014). Individual drug response effects have genetic and non-genetic causes. Figure 1.1 explains the principles of drug metabolism. It also shows genetics variations in drug pharmacokinetics and pharmacodynamics. The non-genetic causes are for instance environment, dietary (example: smoking and alcohol), physiological factors and traits (age, sex, weight, etc). Absorption, distribution, metabolism and extraction can be affected by genetic polymorphism. That will have as a consequence adverse reactions or beneficial effects reactions.

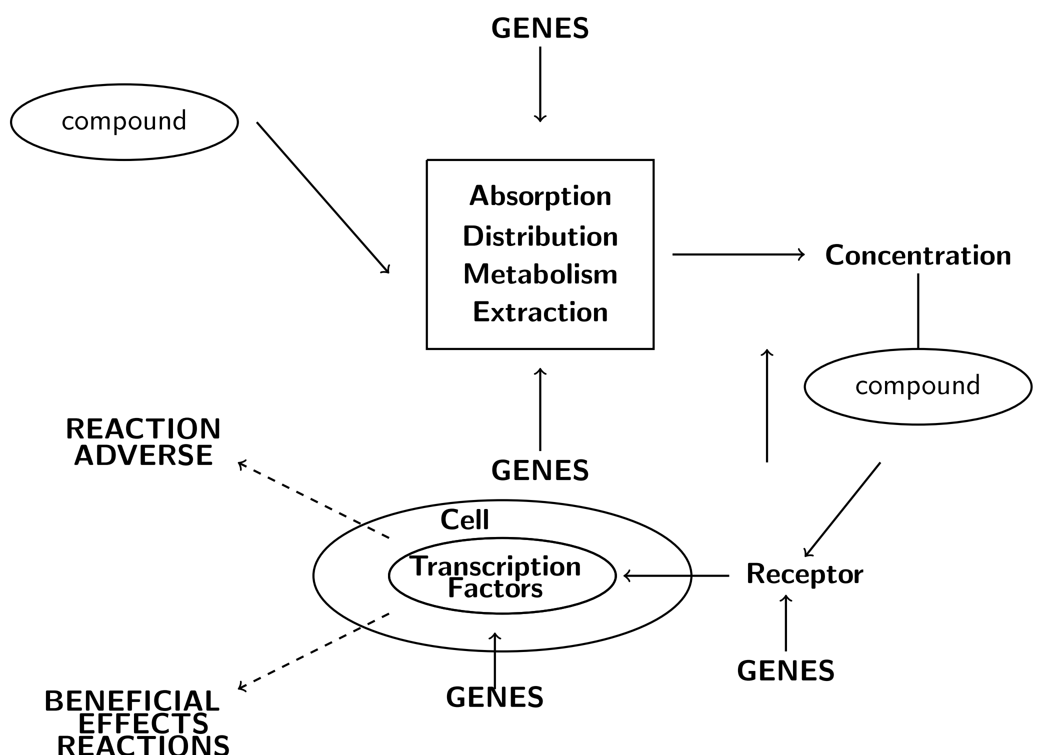


Figure 1.1: Drug metabolism circuit (Ma and Lu, 2011).

Figure 1.1 illustrates drug metabolism in different steps: drug interaction with genes and with organs (cells, tissues). It also shows the effects of that drug on the human body. There are two effects: adverse drug reaction (ADR) and benefit effects (positives reactions).

1.5.4 Genetic Variability: Drug response and inheritance. Drug response in human population differ from one patient to another. This inter-individual differences has many reasons as well as genetic polymorphisms, drug transporters (enzymes) and drug targets (receptors). The genetic inheritance can alter drug sensitivity of the patient to the treatment by changing the pharmacokinetics and pharmacodynamics of medicines. There are many factors that explain variability in drug effects including individual physiology (age, weight race, organ function, etc), environment and dietary (smoking, alcohol, etc) factors, chronic diseases, concomitant therapy, concomitant illnesses and drug interactions. Among those factors, which can influence the efficacy or toxicity of drug; the most important are the inherited differences in the metabolism and disposition of drugs, genetic polymorphisms in the targets of drug therapy like drugs receptors . Those variabilities in drug response and drug dosaging among patients have different factors as well as environmental, genetic variations, and disease causes that can alter transformation processes as well as absorption, distribution, metabolism, and excretion (ADME) of a given drug in the human body (Ma and Lu, 2011).

Cytochrome $P-450$ enzymes, which are a superfamily of microsomal drug-metabolising enzymes that are fundamental for the metabolism of many drug. These enzymes metabolize several chemicals present in food, drugs and environment (Wilkinson, 2005). Drug metabolism processes use competitive chemical processes which require oxidation, reduction and hydrolysis or glucuronidation, sulfation, acetylation, and methylation. Cytochrome $P-450$ enzymes are able to reduce and facilitate the elimination of the pharmacologic activity of many drugs. Knowing that, we can explain and predict individual differences

in drug response by genetic variability (polymorphism), and drug dosaging/drug interaction (Wilkinson, 2005). The toxicity of the drugs depends on the low therapeutic index (or therapeutic ratio: which is a comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes death in the case of animal studies or toxicity for human studies) which cannot be activated by a polymorphic enzyme such as azathioprine or fluorouracil. Inversely, a high therapeutic ratio alter the pharmacokinetics in CYP2D6-deficient individuals but do not significantly change the drugs effects. On the other hand the efficacy of drugs is determined by its activation through an enzyme exhibiting genetic polymorphism for instance codeine. Codeine is medication used to relieve mild to moderate pain. It is used, usually in combination with other drug, to reduce coughing. The recent advances in genome studies provide powerful tools to explain polygenic determinants of disease pathogenesis and drug response (Ma and Lu, 2011).

1.5.5 Overview on Pharmacokinetics-Pharmacoydnamics. Dealing with drugs in the human body is very complex because of several drug metabolism processes such as ADME (absorption, distribution, metabolism, and elimination) and the effect site. The effect site denote the place in the human body where all the pharmacokinetics/pharmacoydnamics reactions happen. To efficiently predict the drug's behaviour and their effects by pharmacokenetics and pharmacodynamics in the human body, we have to simplify human body as a compartment model. Using mathematics like statistics/probability, numerical analysis, etc to model the different processes the drugs will pass through. Pharmacokinetics (PK) is a branch of pharmacology which study the time course of drugs and their metabolites within the body whereas pharmacodynamics (PD) is looking for the effect of the drug on the human body.

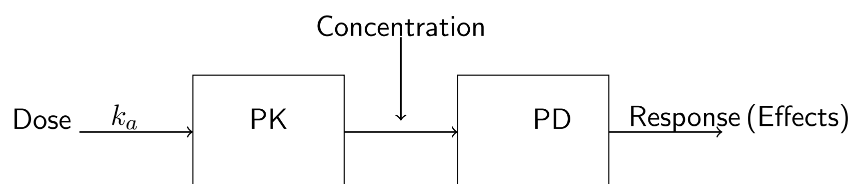


Figure 1.2: PK/PD Diagram (Derendorf and Meibohm, 1999).

Figure 1.2 represents how the relation between PK and PD is addressed. After the drug is administrated into the human body, it follows absorption and elimination in the PK site. The concentration from PK site is used in PD to generate the effects.

The pharmacodynamics model depends on the concentration provided by the PK models to observe the produced effect. The classical and common PD model is the sigmoid E_{max} model. E_{max} is the non-linear function used to describe the concentration-effect (the effect can be positive or negative). E_{max} can be expressed by the following equation called the Hill equation:

$$E = \frac{E_{max} C_e^n}{EC_{50}^n + C_e^n}, \tag{1.5.1}$$

where E is the effect and E_{max} is the maximum effect of medication. C_e is the concentration of the drug at the effect site, EC_{50} is the concentration of the drug that produces half of the maximum effect, n is shape factor (number of molecules interacting with one receptor). n is also called Hill constant and it is used in practice to improve data fits. (Derendorf and Meibohm, 1999).

There exists different attributes in modelling pharmacodynamics/pharmacokinetics (PK/PD) regarding the relation between the concentration and the drug response mechanism:

(a) Direct link versus indirect link models: In the direct link model, the concentration measurement of the human body is directly linked to the effect site concentration. The indirect link model involves a temporal dissociation between the time courses of the concentration of the effect (Derendorf and Meibohm, 1999).

$$\text{Direct link: one-compartment,} \quad E = \frac{E_{max} C_e}{EC_{50} + C_e}. \tag{1.5.2}$$

$$\text{Indirect link: two-compartments,} \quad E = \frac{E_{max} C_e}{EC_{50} + C_e}. \tag{1.5.3}$$

Indirect link: one compartment with hypothetical effect compartment (C_{he})

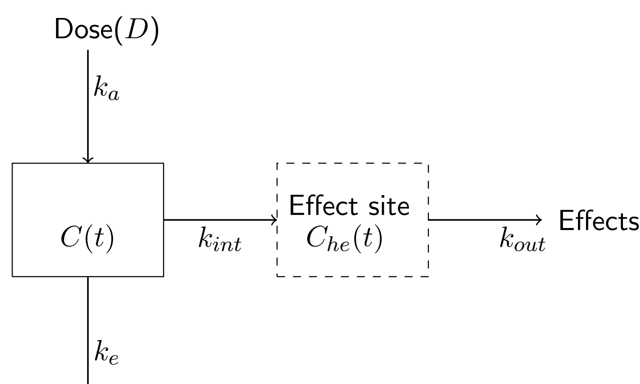


Figure 1.3: **PK/PD One-compartment with hypothetical effect site** (Derendorf and Meibohm, 1999).

Figure 1.3 represents the one compartment model with the hypothetical effect site for PD.

$$\begin{cases} C_{he} = \frac{D k_{out}}{V_d (k_{out} - k_{int})} (e^{-k_{int} t} - e^{k_{out} t}) \\ E = \frac{E_{max} C_{he}}{EC_{50} + C_{he}} \end{cases}$$

(b) Direct response versus indirect response models. In direct response model, the observed effect is given by the effect site concentration without the time lag. The Tlag is the latent time, there is the time during which drug actions are awaited. For indirect response, it exists temporal dissociation between the time courses of the concentration of the effect (Derendorf and Meibohm, 1999).

(c) Soft link versus hard link models. Soft link model use measured data sets of concentration and effect to define the link function between PK/PD to predict and extrapolate the time course of the effect, whereas the hard link model utilizes unidirectional flow of the information to predict the time course of the effect (Derendorf and Meibohm, 1999).

(d) Time-invariant versus time-variant models. In time-invariant model the effect intensity is always secondary to the concentration and request PK/PD model parameters over time. For time-variant model, the parameters are time depending, that change the effect intensities but the drug concentration at the site effect does not change (Derendorf and Meibohm, 1999).

As we expressed pharmacodynamic mathematically, we will write pharmacokinetic mathematically using pharmacology parameters such as clearance and bioavailability. We will also apply statistical approaches to the population PK/PD.

2. Population Pharmacokenetics-Pharmacodynamics:Non-Parametric Adaptive Grid and Bayesian

2.1 Introduction

Many biological, processes are commonly modelled by differential equations (ODE, PDE and DDE). But all those methods do not always consider the noise parameter (error) which is present most of the time in the system dynamics of many biological processes. Noise depends on the size of the system we have, for instance the ODE well describes the dynamic of the large molecular systems but fail to describe the dynamic for the small systems which contain a few dozen of molecules. Noise in differential equations describes the behaviour of the system that is why it cannot be neglected. To be able to consider the noise system, researchers introduced a new concept of stochastic differential equations (SDE) models and mixed-effects models as well. Biomedical research is based on the multiple experiments (sequences of measurement) taken from different individuals. In this type of study they assume that the response for all the individuals follows a similar functional form (same model) but the parameters vary randomly among the patient population. All these methods are useful in biomedical research for instance pharmacokinetic/pharmacodynamic (PK/PD) modeling (Donnet and Samson, 2013).

2.2 Physiologically-Based Pharmacokinetic (PBPK) Models

Sheiner, Rosenberg, and Melmon, (1972) were the first persons to introduce the population pharmacokinetic models and analysis in pharmacology. The physiologically-based pharmacokinetic (PBPK) model is based on the biological information regarding the route and the nature of the drug entry around the human body via the blood. PBPK models have several applications such as the pharmacokinetics drugs prediction in a human body, pharmaceutical research and drug development processes, in the other words, the health risk assessment. It is also used to evaluate the effects of intrinsic factors for example organ dysfunction, age, sex, weight and genetics and extrinsic factors such as drug-drug interactions, drug-genes interactions, or any others combinations of drug exposure. Recently in 2008, the Investigational New Drugs (IND) and New Drug Applications (NDA) started to use PBPK modeling and simulation to make the following types of decisions about some medications: require specific clinical pharmacology studies, requires a specific designs study and appropriates labelling language (Zhao et al., 2011). The PBPK models are used as the basis or extrapolation from animals to humans and from high to low doses. They are also useful in improving the characterization of the dose-adverse response relationships (Banks et al., 2009).

The central aims of the population PK modelling and analysis is to understand the mechanism of PK for the population using model parameters, especially how these mechanisms are represented explicitly and how the parameters change for each individual in a given population. Individuals from different populations such as human populations vary considerably in their underlying Absorption-Distribution-Metabolism-Elimination (ADME) mechanisms that imply to varying the values of the parameters in the model. The relevant parameters values and known characteristics of individuals usually used, are gender, ethnicity, health status, genotypic information, etc (Banks et al., 2009).

2.3 Stochastic Pharmacokinetics-Pharmacodynamics Models

2.3.1 From Deterministic to Stochastic Model in PK. The type of model used in pharmacokinetics is the compartmental model which is classified by the number of compartments used to explain the drug's behaviour in the body. The compartments do not represent a specific tissue or fluid but may represent a group of similar tissues or fluids. There exists three different types of compartmental models: one-compartment model, two-compartments model and multi-compartments model. Pharmacokinetic (PK) models use the equations to simulate the time courses of the drugs and their metabolites in different tissues through the body. These models are used to relate internal concentrations of active compounds to different organs (Wei et al., 2012).

For the first order one and two compartments models we will build, we shall take the following assumptions: The existence of the effect site (receptors) where the drug will have its effects, the magnitude of the response and toxicity depend on the drug concentration in the receptor. We cannot measure the concentration in the effect site immediately after absorption. The concentration at the effect site are determined by ADME.

Let D be the oral dose, $k_e > 0$ and $k_a > 0$ be respectively the elimination and the absorption rate. $A(t)$ is the amount of drug, $A_a(t)$ and $C_a(t)$ are respectively the amount and the concentration of drug at the absorption site. B is the biovailability of drug, $Cl = k_e V$ is the clearance and V the compartment volume.

(A) **First-order one compartment model**

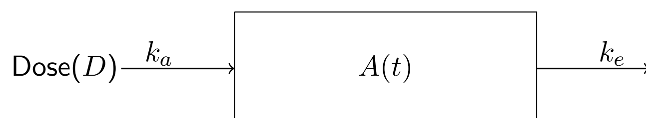


Figure 2.1: **One-compartment models** (Banks et al., 2009).

Figure 2.1, is the representation of the human body as a single organ. A dose (D) of drug is introduced and the ADME will be done in the organ.

From Figure 2.1, we can derive the equivalent deterministic differential equations of the model as follows,

$$\frac{dA_a(t)}{dt} = -k_a A_a(t), \tag{2.3.1}$$

$$\frac{dA(t)}{dt} = k_a A_a(t) - k_e A(t), \tag{2.3.2}$$

with initial condition $A(0) = 0$ and $A_a(0) = DB$.

Equation 2.3.1 describs the kinetic of the drug in the human body and has the following solution.

$$\begin{cases} A_a(t) = BDe^{-k_a t}, \\ C_a(t) = \frac{BD}{V} e^{-k_a t}. \end{cases} \tag{2.3.3}$$

Equation 2.3.2 is non-homogeneous therefore in order to solve it, we first solve the homogeneous equation 2.3.1. This gives us the the solution $A(t)$ for the non-homogeneous equation which is,

$$A(t) = \frac{BDk_a}{k_a - k_e}\{e^{-k_e t} - e^{-k_a t}\}. \tag{2.3.4}$$

Using the amount of the drug $A(t)$, we computed the concentration in the compartment (human body).

$C(t) = \frac{A(t)}{V}$ and $k_e = \frac{Cl}{V}$, hence

$$C(t) = \frac{BDk_a}{V(k_a - k_e)}\{e^{-k_e t} - e^{-k_a t}\}. \tag{2.3.5}$$

We now assume that k_e is randomly oscillated around a mean value equals to $k_a + \xi_t$, where ξ_t is a Gaussian white noise process (collection of uncorrelated random variables with constant mean and variance). Let $B(t)$ be the Brownian motion, γ the constant parameter (the diffusion coefficient) and $\xi dt = \gamma dB(t)$. Adding the noise in the one compartment model, equations 2.3.3 and 2.3.5 become respectively a stochastic process called geometric Brownian motion ($C_{GB}(t)$) and Ornstein-Uhlenbeck process ($C_{OU}(t)$). These two equations are stochastic differential equation (SDE) and can be written as follow:

$$\frac{dC_{GB}(t)}{dt} = -k_a C(t)dt + \gamma C(t)dB(t), \tag{2.3.6}$$

$$\frac{dC_{OU}(t)}{dt} = (\frac{k_a}{V} - k_e C(t))dt + \gamma dB(t). \tag{2.3.7}$$

Equations 2.3.6 and 2.3.7 have respectively the following solutions:

$$dC_{GB}(t) = -k_a C_{GB}(t)dt + \gamma C_{GB}(t)dB(t) \tag{2.3.8}$$

$$dC_{OU}(t) = (\frac{k_a}{V} - k_e C_{OU}(t))dt + \gamma dB(t) \tag{2.3.9}$$

(B) **First order two compartment model.**

We denote by $A_c(t)$ and $C_c(t)$ respectively the amount and concentration of the drug in the central compartment. $A_p(t)$ and $C_p(t)$ are respectively the amount and concentration of the drug in peripheral compartment, V_c and V_p are the volumes in the central compartment and the peripheral compartment. The elimination rate constant is k_e, the clearance of the elimination is Cl and the absorption rate constant is k_a. Let α be the first rate constant and β be the second

rate constant. We define k_{12} and k_{21} as the inter-compartment clearance.

$$\begin{aligned} \alpha + \beta &= k_e + k_{12} + k_{21}, \\ \alpha\beta &= k_e k_{21}, \end{aligned}$$

$$\alpha = \frac{2k_e k_{21}}{(k_e + k_{21} + k_{12}) \pm \sqrt{(k_e + k_{12} + k_{21}) - 4k_e k_{21}}} \tag{2.3.10}$$

$$\beta = \frac{(k_e + k_{12} + k_{21}) \pm \sqrt{(k_e + k_{12} + k_{21}) - 4k_e k_{21}}}{2} \tag{2.3.11}$$

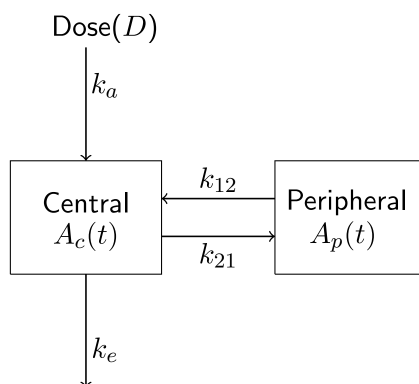


Figure 2.2: **Two-compartments models** (Lunn et al., 2002).

Figure 2.2 Illustrate the human body as a two organs or more.

From Figure 2.2, we can obtain the related differential equations for the model as follows,

Deterministic system of equations using the amount of drug

$$\begin{cases} \frac{dA_c(t)}{dt} = k_{12}A_p(t) - (k_{21} + k_e)A_c(t), \\ \frac{A_p(t)}{dt} = k_{21}A_c(t) - k_{12}A_p(t), \end{cases} \tag{2.3.12}$$

Deterministic system of equations using the concentration of drug

$$\begin{cases} \frac{dC_c(t)}{dt} = k_{12}C_p(t) - (k_{21} + k_e)C_c(t), \\ \frac{C_p(t)}{dt} = k_{21}C_c(t) - k_{12}C_p(t), \end{cases} \tag{2.3.13}$$

with the initial conditions: $D(t) = 0, \quad A_c(0) = 0, \quad A_p(0) = 0.$

Solving the system of equations 2.3.12 using Laplace transform we get the following solutions:

$$A = \frac{D(\alpha - k_{21})}{\alpha - \beta},$$

$$B = \frac{-D(k_{21} - \beta)}{\alpha - \beta}.$$

The amount of drug in the central compartment after elimination.

$$\begin{cases} A_c(t) & = Ae^{-\alpha t} + Be^{-\beta t}, \\ A_c(t) & = \frac{D}{\alpha - \beta}((\alpha - k_{21})e^{-\alpha t} - (k_{21} - \beta)e^{-\beta t}). \end{cases} \tag{2.3.14}$$

The concentration of drug in the central compartment after elimination.

$$\begin{cases} \frac{dC_c(t)}{dt} = (-k_{12}C_c(t) + k_{21}C_p(t) - k_eC_c(t))dt + \gamma_c dB_c(t), \\ \frac{dC_p(t)}{dt} = (k_{12}C_c(t) - k_{21}C_p(t))dt + \gamma_p dB_p(t). \end{cases}$$

Let $B_c(t)$ and $B_p(t)$ be the independent Brownian motions, by γ_c and γ_p be the diffusion coefficients for central and peripheral compartment. We assume that k_e,k_{12} and k_{21} are random variables. Then, we have the following system of SDE (Donnet and Samson, 2013).

$$\begin{cases} \frac{dC_c(t)}{dt} = (-k_{12}C_c(t) + k_{21}C_p(t) - k_eC_c(t))dt + \gamma_c dB_c(t), \\ \frac{dC_p(t)}{dt} = (k_{12}C_c(t) - k_{21}C_p(t))dt + \gamma_p dB_p(t). \end{cases} \tag{2.3.15}$$

2.3.2 Review of Stochastic Coupled Pharmacokinetics-Pharmacoydnamics Models. In this section, we assume that PK and PD model are stochastic. Ferrante et al in 2005 considered in their paper the stochastic PD model of the bacterial count $N(t)$ under antibiotic effect coupled to a two compartment deterministic PK model for the antibiotic concentration $C(t)$ (Ferrante et al., 2005). They obtained the following system:

$$\begin{cases} \frac{dN(t)}{dt} & = (r - bN(t)\text{log}N(t) - kC(t))N(t)dt + \gamma dB(t), \\ \frac{dC(t)}{dt} & = \frac{Dk_a}{V(k_a - k_e)}(e^{-k_e t} - e^{-k_a t}), \end{cases} \tag{2.3.16}$$

where r is the intrinsic growth rate, b is the bacterial deceleration growth rate and k is the effect of drug on the.

Previously in 2004, Christoffer and colleagues used the first-order one-compartment elimination deterministic PK model and an indirect response PD model (E_{max}) to find system of equations 2.3.17 :

$$\begin{cases} \frac{dC(t)}{dt} &= -k_e C(t) + \gamma dB_1(t), \\ \frac{dR(t)}{dt} &= (k_{int} - k_{out}(1 + \frac{C(t)}{EC_{50}+C(t)})R(t))dt + \gamma_R dB_R(t), \end{cases} \tag{2.3.17}$$

where $R(t)$ is the state variable for the PD response, EC_{50} is the drug concentration causing 50% of maximal effect, γ and γ_R are diffusion coefficients for one-compartment and response site. $B_1(t)$ is the independent Brownian motion for one-compartment and $B_R(t)$ is the independent Brownian motion for the effect site. k_{int} and k_{out} are the rates at which the drug coming in and going out of the response site respectively. However system of equations 2.3.17 does not have explicit solution (Tornøe et al., 2004).

2.4 Bayesian Framework: Non-Parametric Bayesian.

2.4.1 Introduction. Personalized medicine is a science which uses genetic and immune system information, family history, lifestyle, and environmental factors to customize medications and treatment. It is a very new field in medical sciences which has ability to determine an individual genetic variations and then use it to diagnose more finely an individual's disease, leading to choosing the right treatments. This will increase the chances of successful outcome and reduce or eliminate the adverse drug reactions (ARD). Personalized medicine based on pharmacogenomics (is defined as the study of the relationship between variations in drug effect(pharmacology) and genetic variation (genetic) in combination with clinical information) wish to be able to predict with a highly accuracy an individual's susceptibility to developing a specific diseases such as cancer, diabetes (Tatarinova et al., 2013). There are different methods to study personalized medicine, in the following paragraphs we will discuss some of them.

2.4.2 The Random Intercept Linear Model. This model is based on pharmacokinetic and pharmacodynamic models response for one patient. where, Y is the pharmacological (pharmacokinetic or pharmacodynamic) response, X is a vector of covariates demographic, clinical, genetic, environment, etc). $X = \{X_1, \ldots, X_M\}$ D is a dose of drug introduced in the body, β is a vector of unknown regression coefficients with is estimated by taking a several samples M from the patient. $\beta = \{\beta_1, \ldots, \beta_M\}$ and ϵ is the regression coefficient for the natural log of dosage. The natural log of dosage has to be estimated, α is a constant number that characterizes the patient. It is a random number called random intercept because it is different for each patient. ξ is intra-individual random error which we assumed to be statistically independent of α, μ_α is the population mean and σ_α^2 the population variance. ϵ, β, μ_α are considered to be population constants which means they do not change for any patient. For a complex random-effects model, β is assumed to be random. We assume that the response, the drug dosage and the clinical, environmental, biological or demographic covariates of this patient are related through Equation 2.4.1 (Diaz et al., 2012):

$$\log(Y) = \alpha + \beta^T X + \epsilon \log(D) + \xi. \tag{2.4.1}$$

If we take $\epsilon = 1$ in equation 2.4.1 we can explicit the drug concentration-to-dosage-ratio (which is usually defined as the a measure of the metabolic activity of a an individual) as

$$\log\left(\frac{Y}{D}\right) = \alpha + \beta^T X + \xi,$$

$$\frac{Y}{D} = \exp(\alpha + \beta^T X + \xi) \tag{2.4.2}$$

2.4.3 The Statistical Population PK/PD Model. We consider a population with N individuals subjects for a sequence of experiments. Each experiment consists of a dosage regimen and a set of measurements at several time points on one of the N individual subjects. We denote by the vector Y_i the observed measurements which are pharmacological responses for example PD effects; the vector θ_i corresponds to the unknown model. We defined the noise parameters(the noise vectors e_i) on the space Θ, where $h_i(\theta_i)$ represents the noise-free output depending on the dosage regimen and the measurement schedule. We assumed that the noise vectors e_i are independent, normal random variables with mean $\mu = 0$ and covariance $\Sigma_i = \Sigma_i(\theta_i)$ which may depend on θ_i or not. We consider that the θ_i are independent and identically distributed with the common but unknown probability distribution F. Now our goal is to estimate the population distribution F based on the data $Y^N = (Y_1, \ldots, Y_N)$ (Tatarinova et al., 2013). The measurement model for the ith subject is:

$$Y_i = h_i(\theta_i) + e_i, \quad i = 1, \ldots, N. \tag{2.4.3}$$

In the next chapter, we will simulation population pharmacokinetic/pharmacogynamic and pharmacogenomic using the information from this chapter.

3. Assessing Models of Pharmacokinetic-Pharamacodynamic

3.1 Introduction

Personalized medicine is an emerging field in medicine. This field tries to improve human health care by developing the new medication based on an individual genetic profile (genomes). Knowing a patient's genetic profile, physicians can prescribe the appropriate therapy with the correct dose. Personalized medicine wishes to avoid or to reduce the adverse drug reaction (ADR) as much as possible and to maximise the beneficial effects of medications. Personalized medicine uses pharmacogenomics and pharmacogenetics coupled with pharmacokinetic/pharmacodynamic to achieve its objectives. For example, in oncology especially in the case of breast cancer, researchers discovered specific tumour markers which guide this cancer therapy. Pharmacokinetic and pharmacodynamic show the drug behaviour in the human body and pharmacogenomics and pharmacogenetics will give information about the genetic impact on drug in human body.

Simulation is the imitation of real-world processes by using the models which represents the relationship between different variables over time. The model represents the system itself and the simulation represents the action over the time.

In this chapter, we wish to simulate different drug concentrations over several times in patient's and assess the model parameter from different dosage setting. We additionally aim to investigate the parameter models through a Bayesian regression implemented in PKfit and IVIVC.

3.2 Data Analysis and Methods

3.2.1 Data Description. Simulation Data: For the simulation we generate two data sets of a single patient's where the concentration decrease and increase respectively over the time. This data is composed by time, concentration and a second data which contains, time, concentration, the pH, the formulation, fraction of dose dissolved (FRD) used only by IVIVC. We assume that the drug is taken by intravenous (IV) extravascular single dose (SD) for that particular patient. The drug absorption (first-order absorption) follows the non route IV route without lag time. We choose three different single dosage $D = 80mg/l$, $200mg/l$, $300mg/l$ then we simulated each of them with time varying the concentrations. We took 15 different concentration for this patient.

Real Data Description:

The data we use in this study was obtained from College of Pharmacy, Kaohsiung Medical University (KMU), Kaohsiung, Taiwan (http://pkpd.kmu.edu/ivivc/) and from the article entitled "Simplified mathematical approach for back calculation in Wagner-Nelson method" (Gohel et al., 2005) (http://www.pharmainfo.net/). This data was collected after a pharmacokinetic study in one patient based on plasma concentration. A single dose of drug was administrated to the patient's by intravenous (IV) bolus.

3.2.2 Analytical methods with R packages PKfit and IVIVC. All the simulations are based on Section 2.3 and 2.4 in the Second Chapter. We also define the initial value for the volume of distribution

V_d, the elimination rate constant k_{el}, absorption rate k_a, inter-clearance and the dose of the drug k_{12} and k_{21}. These parameters will allow us to predict the estimate plasma concentration $C(t)$. We used the data from KMU and Pharmainfo.net to investigate the drug behaviour in the human body which is represented by one and two compartments models using R (PKfit and IVIVC) packages.

PKfit and in vitro in vivo correlation (IVIVC) are the packages in R that simulate the drug metabolism after IV bolus administration. The PKfit simulated KMU data is as follows: Normal Fitting and Simulation which is divided into two types: Simulation with error and Monte Carlo Simulation (Bonate, 2011). The PKfit is a statistical tool for pharmacokinetic/pharmacodynamic data analysis, used to fit non-linear models to kinetic and dynamic data as described in 2.4. The data manager is directly connected to the board, PKfit includes the non-compartmental analysis module, the compartmental analysis module, the non-linear kinetic process module, the drug absorption module, the pharmacodynamic data modelling module, the simultaneous fitting module, and the user-defined library module (Farenc et al., 2000).

The statistical software IVIVC works with a linear relationship between an in vitro (studies done in laboratory environment) characteristic drug for instance dissolution, and a biological in vivo (studies done in living organism like in human body) parameter like maximum plasma drug concentration (C_{max}), maximum time (T_{max}) and the Area Under the Curve (AUC). AUC is the area under the curve in the plot of drug plasma concentration versus time known mathematically as an integral and it can be calculate by using the trapezoidal rule. According to the FDA guidance document states the main aims of IVIVC is to allow the dissolution test to be used as in vivo bioavailability in the pharmacokinetic studies. The IVIVC simulated the data from KMU Pharmainfo.net (Lu et al., 2011). The correlation in the IVIVC is based in the relationship between an in vitro characteristic such as drug dissolution and a biological parameters for example C_{max} and T_{max}. This correlation is generated by using the fraction of dose dissolved (FRD) and the fraction of dose absorbed (FRA) from two or more formulations using the Wagner-Nelson method (estimate) (Gohel et al., 2005).

Let $A(t)$ be the amount of the drug absorbed at time t, A_∞ the amount of drug absorbed at time ∞, k_e is the elimination rate constant of the drug. V_d is volume of the dissolution (or the apparent volume of the distribution) and D is the dose of the drug administered. $\int_{t=0}^{t=t} C(t)dt$ is the area under the curve (AUC) of the plasma concentration versus time profile of the drug, for time period between $t = 0$ to $t = t$. Let $\int_{t=0}^{t=\infty} C(t)dt$ be the area under the curve (AUC) of the plasma concentration versus time the profile of drug, for time period between $t = 0$ to $t = \infty$ and $F(t) = \frac{A(t)}{A_\infty}$ be the fraction of the drug absorbed at time t.

$$\begin{cases} \frac{A(t)}{A_\infty} = \frac{C(t)+k_e\int_{t=0}^{t=t} C(t)dt}{k_e\int_{t=0}^{t=\infty} C(t)dt}, \\ F_t = \frac{C(t)+k_e\int_{t=0}^{t=t} C(t)dt}{k_e\int_{t=0}^{t=\infty} C(t)dt}, \\ k_e\int_{t=0}^{t=\infty} C(t)dt = \frac{F_\infty D}{V_d} = \frac{D}{V_d}, \quad \text{we suppose} F_\infty = 1, \end{cases} \tag{3.2.1}$$

3.3 Results and Interpretation

Results for Simulation

Simulation with IVIVC: One-compartment

For the three SD, we had the following parameters $k_a = 0.2$, $k_e = 0.1$ and $V_d = 10l$ V_d is the dissolution volume. Table 3.1 and Table 3.2 summarise the results of our simulation.

$D = 80mg/l$		
Parameters	Estimate	P-value
k_a	0.4736	0.9764
k_e	-0.1175	8.0600e−10
V_d	43.7416	0.0611
$D = 200mg/l$		
Parameters	Estimate	P-value
k_a	6.6712	0.9770
k_e	-0.1175	2.3200e−10
V_d	0.5447	0.01230
$D = 300mg/l$		
Parameters	Estimate	P-value
k_a	1.4693	0.2510
k_e	-0.1157	1.4700e−9
V_d	151.3429	2.8500e−6

Table 3.1: IVIVC results with increasing data.

$D = 80mg/l$		
Parameters	Estimate	P-value
k_a	14.2722	0.9832
k_e	0.1190	0.0416
V_d	0.0961	0.0831
$D = 200mg/l$		
Parameters	Estimate	P-value
k_a	4.55.3	0.9017
k_e	-0.1198	0.0456
V_d	19.4638	0.0011
$D = 300mg/l$		
Parameters	Estimate	P-value
k_a	0.1198	0.0458
k_e	4.5441	0.9012
V_d	0.7699	0.9042

Table 3.2: IVIVC results with decreasing data.

We observe that as the time, the concentration and the single dose increase, the P-values for all the parameters in Table 3.1 are significant, suggesting that the fit of the model parameters. Table 3.1 shows that the P-value for k_a is greater than 0.05 which means k_a cannot affect the linear regression model and can be neglected (i.e k_a is not correlated with either increasing or decreasing the concentration). The P-value for k_e is almost zero and less than 0.05, that implies that k_e is a significant parameter in the linear regression model expression (k_e is significantly associated in decreasing the concentration since the effect size is negative),

$$C(t) = f(k_e, k_a, V_d, D) \tag{3.3.1}$$

Let us define more specifically the linear regression model as follow:

$$C(t) = \frac{k_a D}{V_d(k_a - k_e)}(e^{-k_e t} - e^{-k_a t}). \tag{3.3.2}$$

Since $k_a \gg k_e, \quad \Rightarrow e^{-k_a t} \backsim 0$ and we know that k_a is not significant Equation 3.3.2 become 3.3.3,

$$C(t) = \frac{k_a D}{V_d(k_a - k_e)} e^{-k_e t}. \tag{3.3.3}$$

From Table 3.1, we observe that k_e has a negative impact by decreasing the $C(t)$ while V_d has a positive impact in increasing $C(t)$.

Table 3.2 shows that when the time and the concentration decrease, the P-value is not significant for all the parameters. This case is not an interesting with respect the relationship between dosage and concentration over time for any patients.

$D = 80mg/l$		
Parameters	Estimate	P-value
k_a	0.3072	0.5600
k_e	0.0000	1.000
V_d	13.5506	0.3330
$D = 200mg/l$		
Parameters	Estimate	P-value
k_a	0.2505	0.6080
k_e	0.000	1.000
V_d	31.9400	0.4450
$D = 300mg/l$		
Parameters	Estimate	P-value
k_a	0.2778	0.581
k_e	0.000	1.000
V_d	49.3505	0.386

Table 3.3: PKfit results with increasing data.

$D = 80mg/l$		
Parameters	Estimate	P-value
k_a	2.1780	0.9898
k_e	0.1190	0.1496
V_d	7.6690	0.0138
$D = 200mg/l$		
Parameters	Estimate	P-value
k_a	13.3831	0.0023
k_e	0.1191	0.0007
V_d	319.2361	1.33e−5
$D = 300mg/l$		
Parameters	Estimate	P-value
k_a	4.5703	0.9034
k_e	0.1198	0.0461
V_d	29.1949	0.0011

Table 3.4: PKfit results with decreasing data.

Simulation with PKfit: One-compartment.

For the three SD, we had the following parameters $k_a = 0.2$, $k_e = 0.1$ and $V_d = 50l$. Here V_d is the dissolution volume. Table 3.3 and Table 3.4 summarise the results of the simulation for one-compartment using PKfit.

Table 3.3 shows that the k_e estimation is zero which means the elimination is very slow. All the P-value values are greater than 0.05, the correlation between the parameters is not relevant. In Table 3.4 we can see that as time and concentration decrease the P-value also decrease and become more significant when the single dose concentration increase. It exist a strong relation between concentration and the following parameters V_d, k_a and k_e. The regression model can be write as follows,

$$C(t) = f(V_d, k_e, k_a). \tag{3.3.4}$$

Since we are dealing with one compartment we can still use the previous regression model in equation 3.3.2. But in this case all the parameters are relevant according to their P-value are less than 0.05, therefore we cannot neglected any of them. They have a positive impact in increasing $C(t)$ (see Tables 3.3 and 3.4).

Simulation with PKfit: Two-compartments.

For the three SD we had the following parameters $k_a = 0.2$, $k_e = 0.1$, $k_{12} = 0.5$, $k_{21} = 0.4$ and $V_d = 50l$ V_d is the dissolution volume. Table 3.5 and Table 3.6 summarise the results of our simulation. When we analysed Table 3.5, only V_d has a P-value less than 0.05. The other parameters have the P-values greater than 0.05 they are not correlated to the concentration $C(t)$ and they do not fit the linear regression model in equation . In Table 3.6 shows that all the P-value are greater than 0.05 except k_{12} P-value which is less than 0.05. k_{12} has a positive significant impact in the model, whereas others the parameters are not significant, they are not correlated to $C(t)$ so they do not fit the linear regression model in equation .

$$C(t) = f(k_e, k_a, k_{12}, k_{21}, V_d). \tag{3.3.5}$$

$D = 80mg/l$		
Parameters	Estimate	P-value
k_a	4.6890	0.8169
k_e	4.4120e-2	0.7362
k_{12}	7.0630e-6	0.9870
k_{21}	7.1540e1	0.5340
V_d	1.40701.33e1	0.0684
$D = 200mg/l$		
Parameters	Estimate	P-value
k_a	2.6050e4	1.0000
k_e	0.1191	0.4470
k_{12}	2.3400e-7	1.0000
k_{21}	4.5550e4	1.0000
V_d	1.9070e1	0.02420
$D = 300mg/l$		
Parameters	Estimate	P-value
k_a	6.3090	0.8920
k_e	0.1191	0.2390
k_{12}	1.0370e-8	1.0000
k_{21}	6.9550	1.000
V_d	2.912e1	0.2750

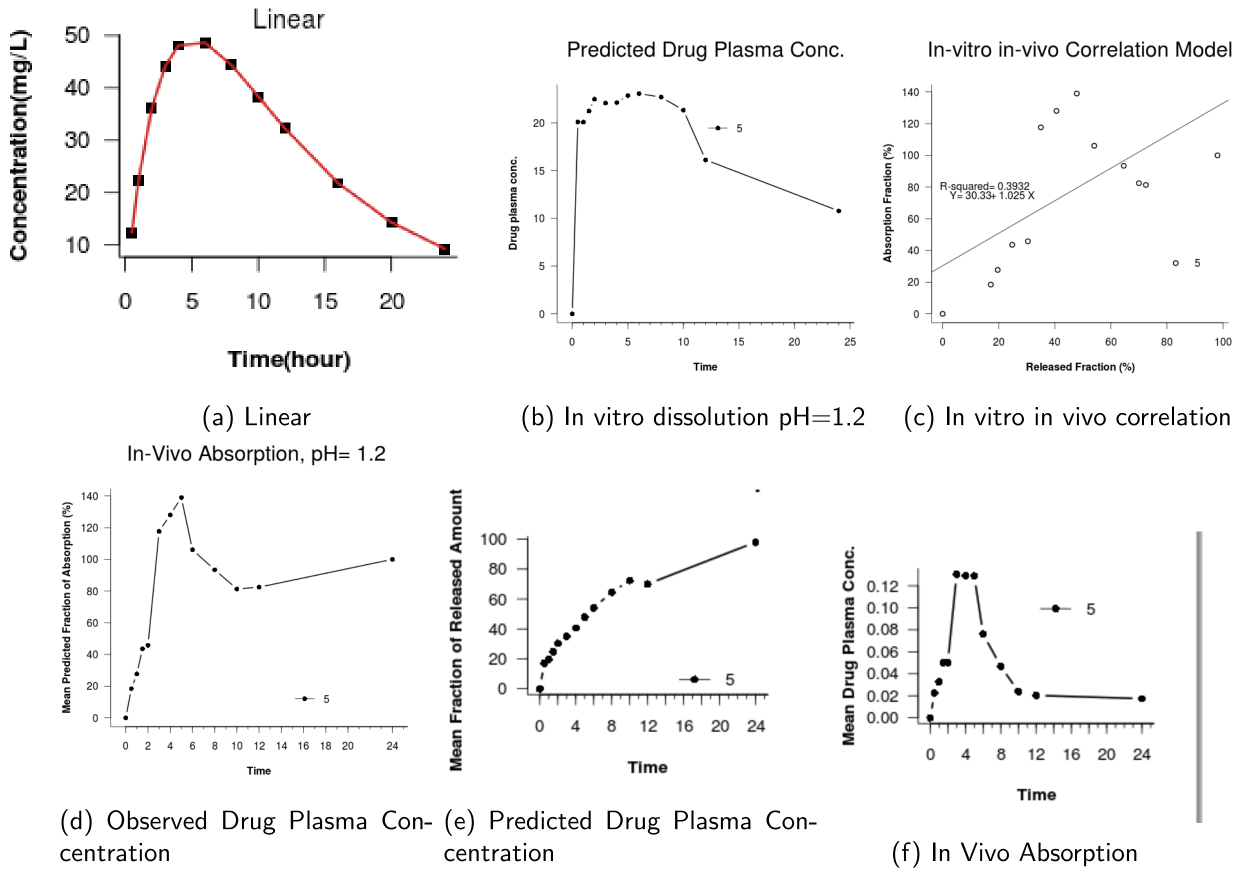
Table 3.5: PKfit results with decreasing data.

$D = 80mg/l$		
Parameters	Estimate	P-value
k_a	0.7055	0.5964
k_e	0.0000	1.0000
k_{12}	1.6020e-4	0.00428
k_{21}	2.8130e1	0.6267
V_d	1.72501.33e1	0.1469
$D = 200mg/l$		
Parameters	Estimate	P-value
k_a	0.5484	1.0000
k_e	0.0000	1.0000
k_{12}	2.3670	1.0000
k_{21}	4.7900	1.0000
V_d	2.8550	1.0000
$D = 300mg/l$		
Parameters	Estimate	P-value
k_a	3.7530e2	0.9720
k_e	0.0000	1.0000
k_{12}	1.2630	0.9150
k_{21}	1.6840	0.8940
V_d	3.2410e1	0.8040

Table 3.6: PKfit results with increasing data.

3.3.1 Results for Drug Plasma: Real Data. IVIVC packages

The IVIVC software is a predictive statistic model used to describe the relationship between in vivo property and a relevant in vivo response of a drug. Figure 3.1a reflects the drug plasma concentration evolution in an in vitro case as time increases. The absorption phase is between $(0$ to $5)h$ and the elimination phase is between $(5$ to $20)h$. Figure 3.1b shows the virtual dissolution drug profile which is in vivo dissolution estimation. The relationship between the absorption fraction in vivo and the dissolution fraction are represented by the Figure 3.1c. The solid line is the linear regression analysis of the data. The Figure 3.1d is the prediction of the absorption phase for the observed in the in vivo case. The maximum mean predicted fraction absorption is $C_{max} = 140\%$ at the maximum time $T_{max} = 5h$. Figure 3.1f is the same as Figure 3.3a but in the human body (in vivo). We observed the same behaviour for the drug plasma concentration in both of the them. The drug plasma concentration is predicted as seen in the Figure 3.1e. The prediction error (PE) is computed only for the maximum drug plasma concentration C_{max} and for the Area Under the curve AUC. PE is usually used to measure the accuracy



(a) Linear (b) In vitro dissolution pH=1.2 (c) In vitro in vivo correlation

(d) Observed Drug Plasma Concentration (e) Predicted Drug Plasma Concentration (f) In Vivo Absorption

Figure 3.1: IVIVC plots

for a given model and can be expressed as follows (Sakore and Chakraborty, 2011):

$$\%PE(C_{max}) = \frac{C_{max}(\text{Observed}) - C_{max}(\text{Predicted})}{C_{max}(\text{Observed})} \times 100, \tag{3.3.6}$$

$$\%PE(AUC) = \frac{AUC_{(\text{Observed})} - AUC_{(\text{Predicted})}}{AUC_{(\text{Observed})}} \times 100. \tag{3.3.7}$$

We assume the following parameters $D = 500mg/l$, $k_a = 0.32$, $k_e = 0.11$ and $V_d = 10$.

Parameters	Estimate	P-value
k_a	0.3200	1.8e−16
k_e	0.1100	1.8e−16
V_d	5.801	1.8e−16

Table 3.7: IVIVC results for one-compartment

Table 3.7 shows that all the parameters have the P-values are less than 0.05, so they are correlated to the plasma concentration $C(t)$. Those parameters have a positive impact on the linear regression model which is given in equation 2.3.5.

PKfit: Normal Fitting

We apply the drug plasma concentration data on the PKfit packages using:

(a) **First-order one compartment** For the simulation in first-order one-compartment, we assume that the drug was administrated through intravenous non route which requires the absorption step. Using the **method of residuals**, we plotted IV absorption data (amount of drug absorbed) versus time for the first-order one-compartment. We assume the following parameters $D = 500mg/l$, $k_a = 0.32$, $k_e = 0.11$ and $V_d = 5.8l$, where V_d is the dissolution volume.

Parameters	Estimate	P-value
k_a	0.3200	1.8e−16
k_e	0.1100	1.8e−16
V_d	5.800	1.8e−16

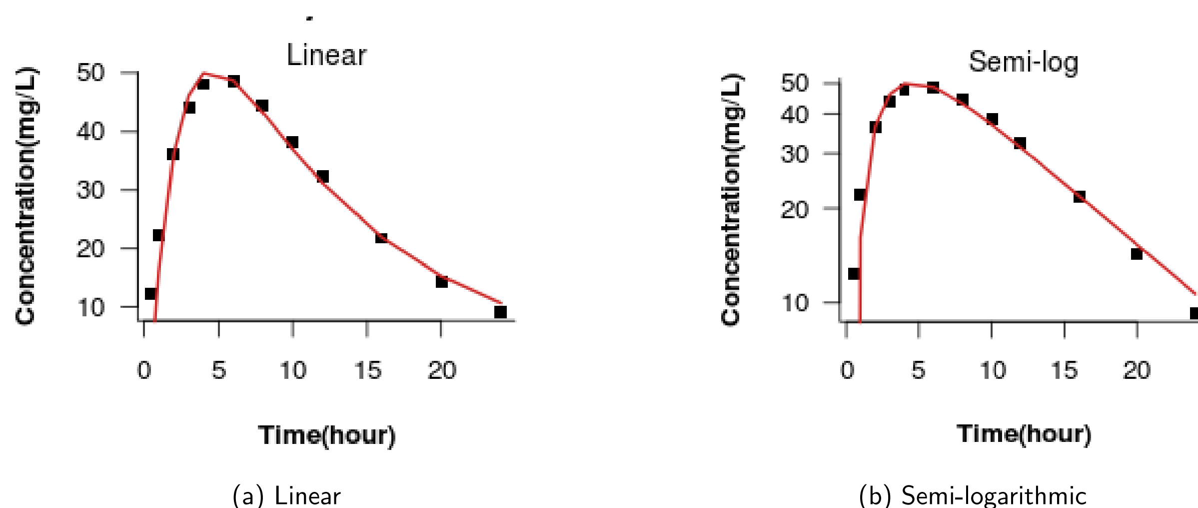
Table 3.8: PKfit results for one-compartment

Table 3.8 shows that the P-values for all the parameters are less than 0.05, that means the plasma concentration $C(t)$ is function (or associate with) of the absorption rate k_a and the elimination rate k_e (Figure 3.2a) and it is expressed in equation 2.3.5 which is the linear regression model.

In general for many drugs $k_a \gg k_e$ means that $e^{-k_a} \backsim 0$, then equation 2.3.5 becomes:

$$\begin{cases} C(t) = \frac{k_a BD}{V(k_a - k_e)} e^{-k_e t}, \\ \log C(t) = \log \frac{k_a BD}{V(k_a - k_e)} - \frac{k_e t}{2.303}, \end{cases} \tag{3.3.8}$$

where $-\frac{k_e}{2.303}$ represents the slope of the plot of $\log C(t)$ versus time (Gunaratna, 2000). Figure 3.2b gives the maximum peak of plasma concentration $C_{max} = 50mg/l$, at the maximum time $T_{max} = 5h$ (h is hour). That means at T_{max} the absorption rate is equal to the elimination rate $k_a A_a = k_e A$. On the Semi-log plot, we have between $(0 \text{ to } 50)mg/l$ the absorption phase $k_a A_a \gg k_e A$, between $(10 \text{ to } 20)mg/l$ the elimination phase $k_e A \gg k_a A_a$, between $(10 - 20)h$ elimination half time $t_{\frac{1}{2}}$ and the slope $\frac{-k_e}{2.303}$. The intercept of the plasma concentration versus time profile for a single dose is $\frac{k_a B A_a}{V(k_a - k_e)}$ (Jambhekar et al., 2009). The small black squares represent each sample in the data based we used.



(a) Linear

(b) Semi-logarithmic

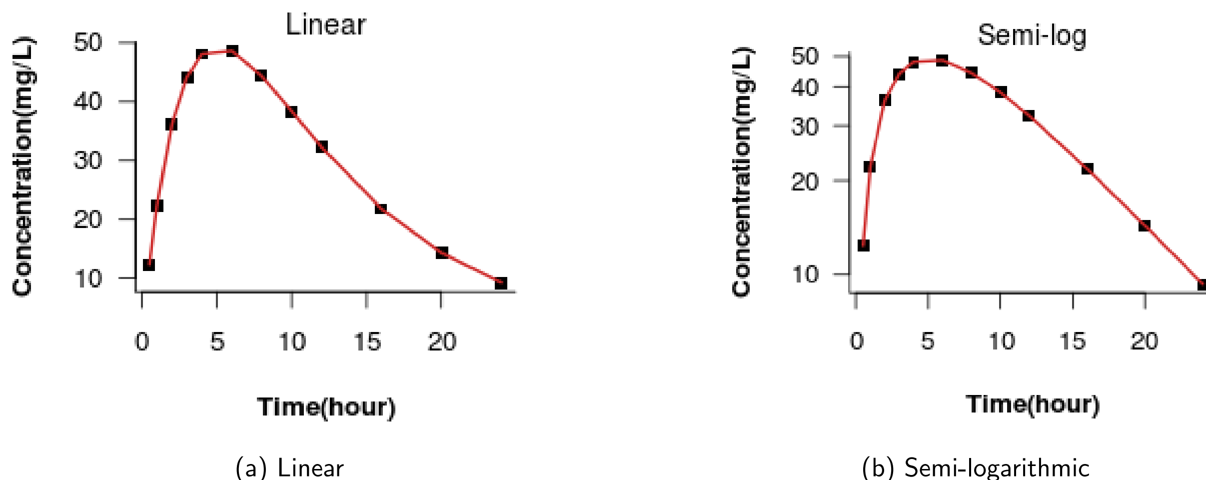
Figure 3.2: One-compartment plot of plasma concentration versus time (Linear) and semi-logarithmic (Semi-log) for extravascular absorption

(b) **First-order two compartment model** The drug is taken by intravenous injection which means it is quickly distributed into the peripheral tissues whereas the tissues concentration decreases faster than in the post-distributives phases. We assume the following parameters $k_a = 0.32$, $k_e = 0.11$ and $V_d = 5.8l$, $k_{12} = 0.24$, $k_{21} = 0.55$ and $D = 200mg/l$.

Parameters	Estimate	P-value
k_a	0.3200	1.8e−16
k_e	0.1100	1.8e−16
k_{12}	1.341e−2	1.8e−16
k_{21}	1.941e1	1.8e−16
V_d	2.318	1.8e−16

Table 3.9: PKfit results for two-compartment

Table 3.8 shows that all the parameters are significantly correlated with increasing the plasma concentration $C(t)$ because their P-values are less than 0.05. Those parameters have a positive impact on the linear regression model which is given in equation 2.3.15. Using equation 2.3.15, we can explicit the following pharmacokinetic parameters: the Area Under the Curve (AUC) $AUC = \frac{A}{\alpha} + \frac{B}{\beta}$, the clearance $Cl = \frac{D}{AUC}$ and the Area Under the first Moment Curve (AUMC) $AUMC = \frac{A}{\alpha^2} + \frac{B}{\beta^2}$. Figure 3.3a provides the maximum peak of plasma concentration $C_{max} = 50mg/l$ at the maximum time peak $T_{max} = 5h$ whereas Figure 3.3b shows the slope (ln)= α under the curve and slope (ln)= β above the curve when $\alpha > \beta$.



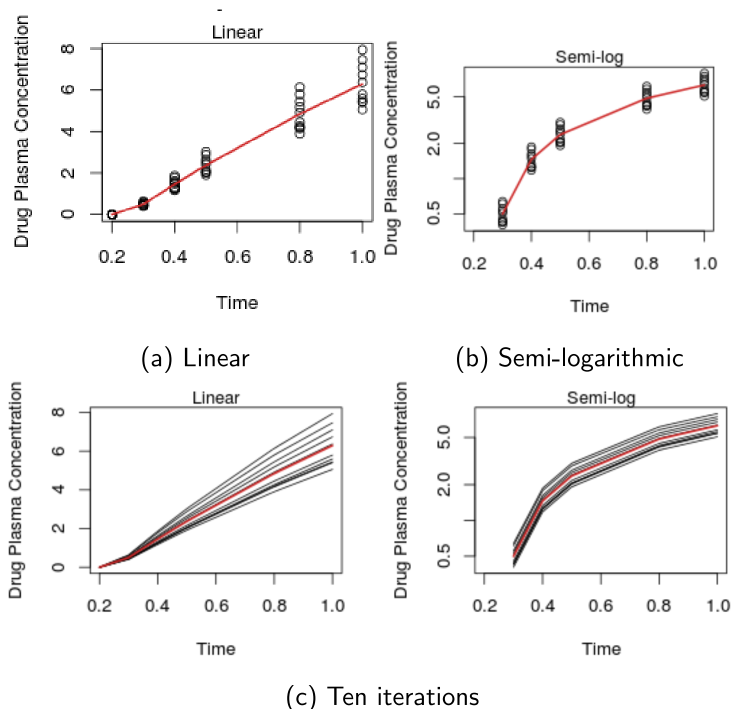
(a) Linear

(b) Semi-logarithmic

Figure 3.3: IV Extra-vascular absorption for two compartments

3.3.2 PKfit: Monte Carlo Simulation based on Drug Plasma Concentration data.

(a) **First-Order One-Compartment Model** The drug is administrated by IV bolus and it spreads in the human body by a non-IV route with Tlag. Figure 3.4a shows the predicted drug plasma concentrations versus time during the drug metabolism. The solid line represents the pharmacokinetics profile for IV. Figure 3.4c shows the simulation with ten iterations. The small black circle represent each sample in the data based we used.

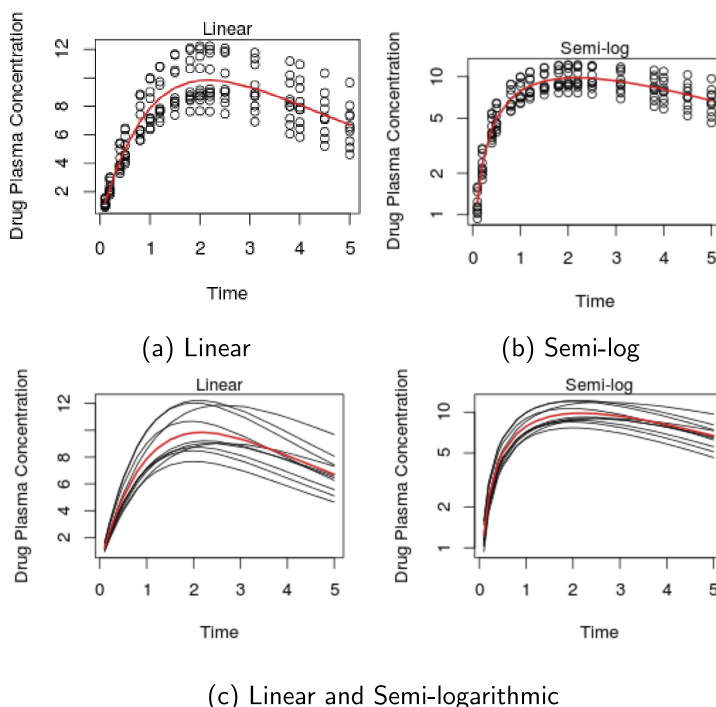


(a) Linear (b) Semi-logarithmic

(c) Ten iterations

Figure 3.4: IV Extra-vascular absorption one compartment

(b) **First-Order Two-Compartment Model** Figure 3.5a shows the predicted drug plasma concentration versus time after the drug was administrated by IV bolus. The drug spreads in the human body by non-IV route with Tlag and the solid line represents the pharmacokinetics profile for IV. Figure 3.5c represents simulation for 10 iterations.



(a) Linear

(b) Semi-log

(c) Linear and Semi-logarithmic

Figure 3.5: IV Extra-vascular absorption two compartment.

3.3.3 Discussion. The simulation results for both IVIVC and PKfit show that one-compartment model fits better the parameters when using different doses by increasing the concentration over the time. Moreover, the PKfit simulation with the two-compartments model also fits better the parameters using different doses when concentrations are increased over the time. However, for both one and two-compartments using IVIVC and PKfit, respectively we have observed that the models did not fits the parameters when adjusting the dose and decreasing the concentration over the time.

Our results from the real data of drug plasma concentration (real data) show significant P-values (close to zero ($\sim 1.8\text{e}-16$)) of the association between concentration and model parameters in both IVIVC and PKfit. That means there is a strong correlation between parameters and the plasma concentration.

4. Conclusion

The optimal prescription and utilisation of medicines to effectively manage and treat infectious and non-communicable diseases is a major goal of adequate healthcare systems. In this essay, we have broadly discussed various population pharmacokinetic-pharmacodynamic models and the Bayesian models of groups of individuals who may have taken several drugs doses at various times throughout the course of a clinical trial.

Our simulation results have demonstrated that one-compartment model fits better the parameters when using different doses by increasing the concentration over the time. Furthermore, two-compartments model also fits better the parameters using different doses when concentrations are increased over the time. Decreasing the concentration using different dose, has shown to not fit any of the model parameters for one and two-compartments design. Our simulation results are strongly supported by the the result from the real data of drug plasma concentration which show significant P-values (mostly close to zero ($\sim 1.8\text{e} - 16$) of the association between increasing the concentration and model parameters using IVIVC and PKfit packages.

Given our current results, more opportunities are given to further investigate on in depth the Bayesian-based approach for population pharmacokinetic-phamarcodynamic which may be helpful in the derivation of the predictive distributions that contribute to the optimization of treatments for different target populations. In addition, other possible direction is the development of interactive system linking to a designed relational database that integrates pharmacological network, predicted drug information and link genes to information that is accessible into biological public databases.

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