Stochastic Effects and Fractal Kinetics in the Pharmacokinetics of Drug Transport

by

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I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Pharmacokinetics (PK) attempts to model the progression and time evolution of a drug in the human body from administration to the elimination stage. It is the primary quantitative approach used in drug discovery/development (in the pharma industry). The overwhelming majority of PK models are based on equilibrium kinetics with all the reaction kinetics occurring in a well mixed, homogeneous environment. Of course as is well known, the human body is comprised of heterogeneous media with non equilibrium chemical kinetics. As a result, the transport processes and reaction mechanisms are often atypical. In this thesis, we apply ideas from stochastic processes and fractal kinetics in order to better capture the time course of a drug through the body when there is spatial and temporal heterogeneity. We discuss the limitations of the Langevin equation and Bourret's approximation and apply Van Kampen's approach to the random differential equations arising from the stochastic formulation of standard one compartmental extra vascular model. Although one compartment models can produce good fits if a drug dispersed rapidly so that equilibrium is achieved (in all tissues) swiftly, in general they are oversimplification of a complex process . Thus we also extend the two compartmental model Kearns et al., to incorporate fractal Michaelis Menten kinetics and compare with experimental data from the literature for paclitaxel. Finally, we conclude with a discussion and appraisal of the contribution in the thesis to the field of pharmacokinetics.

Acknowledgements

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Dedication

I would like to dedicate this thesis to my loving family and friends, for their endless care and support.

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Chapter 1

Introduction

1.1 What is pharmacokinetics (PK)

The word Pharmacokinetics means the application of kinetics to a pharmakon (a Greek word, means drugs and poisons [83]). Knowledge about the change of one or more variables as a function of time is known as kinetics. The objective of Pharmacokinetics is to study the time course of drug and metabolite concentrations in biological fluids, tissues and excreta, and also of pharmacological response, and to construct suitable models to interpret such data. The data are analyzed using a mathematical representation of a part or the whole of an organism. Broadly speaking then, the purpose of pharmacokinetics is to reduce data to a number of meaningful parameter values, and to use the reduced data to predict either the results of future experiments or the results of a host of studies which would be too costly and time-consuming to complete.

A similar definition has been given by other authors (Gibaldi and Levy, 1976, page 129) as follows:

> 'Pharmaco-kinetics is concerned with the study and characterization of the time course of drug absorption, distribution, metabolism and excretion, and with the relationship of these processes to the intensity and time course of therapeutic and adverse effects of drugs. The ultimate role or purpose of PK methods is to predict tools that characterize the drug behavior over time with the ultimate objective of optimizing drugs efficacy (whilst simultaneously becoming toxic side effects to a minimum). It involves the application of mathematical and biochemical techniques in a physiologic and pharmacological context.'

The effects and the duration of action of the drug are also taken into account. By using experimental PK data from humans or animals which are typically a discrete time sequence of drug concentrations obtained from a fixed volume. The data obtained from such studies are useful for the design and execution of subsequent clinical trials, also for the important goals of drug development by the pharmaceutical industry. Clinical pharmacokinetics is the application of pharmacokinetic studies to clinical practice and to the safe and effective therapeutic management of the individual patient. There are diverse means of drug administration ranging from subcutaneous, intramuscular, oral, bolus, intravenous and infusion. In the last two cases, the drugs are introduced directly into the blood plasma and so no absorption phase has to be taken into consideration. Typically, as a drug dissipates through the body and is eliminated this gives rise to a prototypical concentration/time curve that rises to a maximum concentration as the absorption phase of the drug predominates and then decreases asymptotically to zero with time.

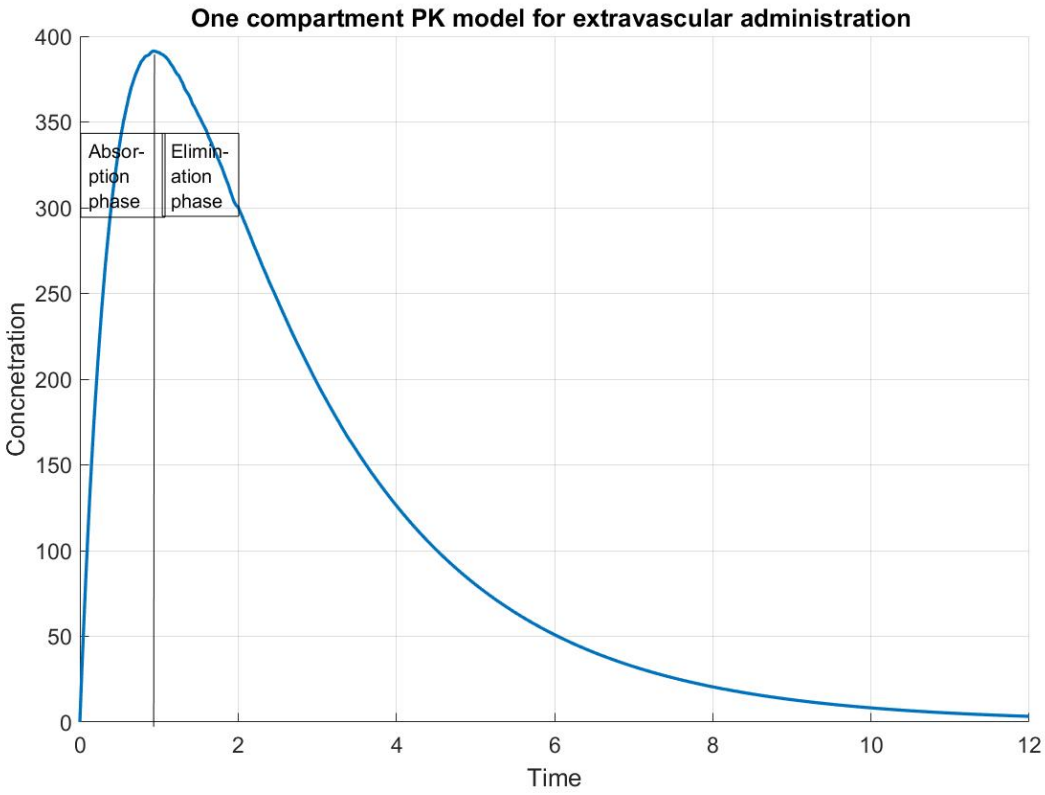

Figure 1.1: Typical time concentration profile for one compartmental absorption pk model

This descent may be very rapid or could stretch over several days depending on the elimination rate of the drug from the individual (see the figure 1.1).

1.2 Processes of PK

Absorption, Distribution, Metabolism and Excretion are four basic processes of pharmacokinetic studies and for this reason it is commonly known by the acronym ADME. We now briefly describe these four processes with the corresponding PK parameters. PK parameters are distinguished as primary, secondary and tertiary parameters. The parameters which are directly related to the physiology are known as primary parameters, such as

volume of distribution, clearance, absorption rate constant and dose. By using primary parameters we can calculate the secondary parameters, such as the elimination rate constant, area under the plasma concentration time data curve (AUC) and by using the secondary parameters we can calculate the tertiary parameters such as C_{max} (the maximum concentration), t_{max} (the time taken to reach at maximum concentration), $t_{1/2}$ (time taken for C max to drop its value to half). For details the reader is referred to reference [36].

Absorption is the process by which a drug moves from the administration site to the systemic circulation and this is fully dependent on the routes of drug administration, mainly oral, dermal, topical, subcutaneous, intravenous. Absorption is defined by a rate which is the amount of drug per unit time and an extent which is the total amount of drug. The parameter absorption rate constant usually is a first order rate constant for drug absorption from the site of administration to the systemic circulation and can be estimated using the curve stripping method (also known as the method of residuals) [36], [29], [86].The absorption rate is influenced by some factors such as, types of transport, the physicochemical properties of the drug, protein binding, dosage form, circulation at the site of absorption, concentration of the drug etc. Unless the administration is IV (intravenous), there is an absorption phase. Bioavailability is another important parameter related to the absorption process, which defines the fraction (F) of the administered drug that reaches the systemic circulation and it's value varies from 0 to 1. If F is less than 10 percent then the drug is classified as "low bioavailable" and if it is greater than 90 percent then it is said to be "high bioavailable". Absorption kinetics are the basis of classification of bioequivalence of generic drugs. If absorption profiles are identical for both the test formulation and reference formulation, then the two formulations are said to be bioequivalent.

Distribution is the process by which a drug moves from the systemic circulation to other tissues in the body. The process is largely determined by the physicochemical characteristic of the drug molecules. Distribution occurs throughout the drug time course in the body and it is very difficult to quantify the distribution with a PK parameter. There are two main factors that affect distribution, one is the rate of distribution (i.e., how fast the drug is distributed) and this is dependent on membrane permeability and blood perfusion [36], [29], [86]. and another is the extent of distribution (i.e., how far the drug is distributed) and this depends on the drug lipid (fat) solubility, pH-pKa, protein binding [36], [29], [86]. Distribution occurs in two different phases. In the first phase the heart, liver, kidney and brain receive most of the drug during the first few minutes of absorption. The second phase involves the muscles, most viscera, skin and adipose tissue.

To determine the appropriate drug dose regimen, the main PK parameter associated with the distribution process is, the volume of distribution or apparent volume of distribution. Volume of distribution does not have any true physiological significance but by this

parameter it is possible to identify the extent of drug distribution which help to determine dosage requirements. Typically, dosing and volume of distribution are proportional to each other. For instance, if the volume of distribution is large then the dosage should be proportionally large to obtain a desired target concentration [14]. The (apparent) volume of distribution can be calculated using the following equation:

$$\text{volume of distribution=[amount of drug administered (dose)]/[initial drug concentration]}$$
$$\implies V_d(l) = \frac{D(mg)}{C_0(mg/l)}$$

C_0 is the initial concentration, which is usually evaluated by direct measurement or can be estimated by back-extrapolation from concentrations time data which has been collected after the dose administered [14].

Metabolism or biotransformation refers to the chemical or enzymatic transformation of a parent drug to another chemical form (metabolite). Metabolites tend to be more polar which promotes excretion via the urine. The liver is primarily responsible for metabolism, but the kidneys, intestines and lungs also contribute to metabolism [36].

Metabolism is influenced by some factors such as:

Age: Older people have less efficient metabolism

Sex: Hormonal differences linked with the metabolic processes

Heredity: Genetic differences can influence the amounts and efficiency of metabolic enzymes

Disease state: The state of the liver, Kidney, cardiac disease also have impact on the metabolism

Enzyme induction and Enzyme inhibition have some effect on the metabolism.

Excretion is the process by which drugs (and metabolites) are removed from the body. Primarily excretion occurs through the kidney (urinary excretion), but it also occurs through the lungs (volatile compounds), saliva, breast milk, sweat and bile (fecal excretion).

Clearance is another important parameter in PK studies and quantifies the removal of a drug from a volume of plasma in a given unit of time (drug loss from the body). Clearance does not indicate the amount of drug being removed, it indicates the volume of plasma (or blood) from which the drug is completely removed [14]. A drug can be cleared

from the body by many different mechanisms, pathways, or organs, including hepatic biotransformation and renal and biliary excretion. Total body clearance of a drug is the sum of all the clearances by various mechanisms.

Another way of defining clearance is by using the relationship between drug dose and AUC. Since AUC is a secondary parameter, it can be exactly calculated from concentration-time data (or can be estimated). Some common AUC estimates are: exact AUC, AUC_{0-t} or AUC_{0-last}, AUC_{all}, $AUC_{0-\infty}$ [86].

Exact calculation of AUC for IV administration:

$$AUC = \int_0^\infty C(t)dt \tag{1.1}$$

and for IV we have

$$C(t) = \frac{D}{V_d} e^{-(CL/V_d)t} \tag{1.2}$$

Now by substituting this in the AUC definition we have

$$AUC = \int_0^\infty \frac{D}{V_d} e^{-(CL/V_d)t} dt \tag{1.3}$$

$$AUC = \frac{D}{CL} \tag{1.4}$$

that mean

$$CL = \frac{Dose}{AUC} \tag{1.5}$$

and if the administration is not IV, then this will be

$$CL = \frac{S \times F \times Dose}{AUC} \tag{1.6}$$

where S is the salt fraction which is used when the dose amount refers to the drug in salt form and F is the absolute bioavailability for the specific route. In cases where the bioavailability is unknown, the apparent clearance can be calculated as

$$\frac{CL}{F} = \frac{S \times Dose}{AUC} \tag{1.7}$$

Another PK parameter corresponding to elimination is rate of elimination and is given by: Rate of elimination (mg/hr)=Clearance CL (l/hr)$\times$ Concentration C(mg/l). Even though the clearance may be constant, the rate of drug elimination (mg/hr) can vary with

concentration. Again, for details the reader is referred to standard text books such as [36], [29], [86].

It takes on average 10 to 12 years for a drug to be approved and reach the clinical consumer market. Within this period of time it has to pass the four different phases. All these phases serve different purposes. Here is a brief description of these trial classifications (from the U. S. Food and Drug website) [21]:

> Phase I trial: In this trial the investigating drug is applied to a small group of healthy volunteers for the first time, to assess treatment safety, determine the safe dose regimen and related side effects [21].
>
> Phase II trial: After successful execution of a phase I trial, the drug is administered to a large group of people to determine the efficacy and safety on a larger scale [21].
>
> Phase III trial: In this, the trial drug is given to a large population over a six to twelve month period to assess efficacy more closely than Phase I and Phase II [21].
>
> Phase IV trial: This trial is based on the post marketing strategy and is done after the approval of FDA. Some additional information: drug's benefit, risk and best use are also determined through this trial [21].

All these trials are very costly and time consuming. To resolve these issues drug companies take initiatives to expedite these processes for the betterment of the patients without approving harmful drugs. Mathematical and statistical modeling plays a vital role in this context, by providing insights and quantitative predictions that provide rational guidence for clinical trials [60].

1.3 PK models

Pharmacokinetic models are generally classified as either individual-based or population-based. For individual-based models, PK parameters must be calculated based solely on each individual patient's characteristics (i.e., from data specific to a particular patient). For population-based models, however, parameters are determined from data gathered from many individuals. Hence the latter models, capture (in a sense) the average behavior of individuals in a particular population and take into account random and fixed effects, which give rise to variability between individuals in a population and within individuals. However, careful consideration must be taken (when using population-based PK models) of

the underlying assumptions made when combining different patient data from a particular study as well as patient data from different studies. In particular careful thought must be given to the choice of sampling distributions of population estimates. The most common and widespread approach in pharmacokinetics is the use of compartmental models. Here the body, is considered to be an interconnected system of compartments where, ideally each compartment can be given some physiological interpretation. Each compartment is assumed to be homogeneous and well mixed. The interchange and transfer of drug molecules between compartments is determined by the kinetic rate constants. The law of mass action is widely applied in classical pharmacokinetic compartmental models. Thus a chemical reaction rate is assumed to be directly proportional to the product of the concentrations of m reactants each raised to a power $n_i (i = 1, 2, ..., m)$. For a general PK model with $n-$ compartments, the governing system of DE's can be written as :

$$\frac{d\underline{C}(t)}{dt} = \underline{\underline{K}} C(t) \tag{1.8}$$

where $\underline{C^T}(t) = (C_1(t), C_2(t), ...C_n(t))$ and $\underline{\underline{K}}$ is the matrix of kinetic rate coefficients $\underline{\underline{K}} = k_{ij}$, where the k_{ij} are non-zero if compartments i and j are coupled in the model. The solution to the system (1.8) can be written down as:

$$C_i(t) = \sum_{j=1}^{m} a_{ij} \Big(\sum_{k=0}^{m_j - 1} b_{ijk} t^k \Big) exp(-\lambda_j t) \tag{1.9}$$

where a_{ij} and b_{ijk} are constants and the matrix $\underline{\underline{K}}$ has m distinct eigenvalues λ_j with multiplicity m_j [53]

Compartmental models are widely applicable and have the advantage of being able to be interpreted in terms of physiological processes or body organs/components. There are, of course, limitations to the classical compartmental models; the major objections relate to the assumption of homogeneity of each compartment and the assumption that each compartment is well mixed. However, a compartmental model might be assessed suitable if the relative mixing rates within the compartments is on a much faster time scale than the transfer rate between compartments.

1.3.1 Non-compartmental models

Non-compartmental models were developed to overcome some of the limitations of compartmental models. Approaches include linear Systems Analysis, Mean Residence Time

Theory and the Method of Moments amongst others. They have the distinct advantage that fewer assumptions are made, and many of these assumptions are based on experimental observations rather than on assumptions about the underlying mechanisms. The methodology is also applicable to a wide range of date.

There are clearly drawbacks and limitations to compartmental models, and to circumvent some of these problems, several non- compartmental models have been proposed in the literature. For example [85] uses the method of moments and quantifies such as mean residence time, and area under the moment curve to analyze and extract information from a data set. Another approach is taken by [61], where linear system analysis (convolution, deconvolution, disposition decomposition analysis) is applied to deduce information from a data set. The attraction of this approach is that fewer assumptions are usually made (compared to compartmental models), and even these are based generally on observed outcomes or behaviors rather than on the underlying mechanisms or state of the system. However [45] shows how a non-compartmental circulation model is equivalent to a multi compartmental model, where the compartments are connected in series. So it is apparent that in many cases "non-compartmental" models can be framed in terms of a corresponding compartmental model. In both contexts, the models can be formulated in terms of deterministic or random variables. Stochastic effects can be captured in the models by using either random inputs/random initial conditions, or by making the kinetic rate coefficients matrix $\underline{\underline{K}}$ a random matrix, or by using the random walk formalism.

1.3.2 Linearity and Non-linearity

If the output of a system is directly proportional to input then a system is generally classified as linear. Systems are governed by zeroth order or first order kinetics guarantee this property and are described, for one compartmental models, by the linear differential equation

$$\frac{dC}{dt} = kC \tag{1.10}$$

Solutions to linear differential equations satisfy the linear superposition principle. Thus if the drug concentration C is a linear function of the dosage d, then for any arbitrary constants a_1 and a_2, the concentration C for a dosage $d = a_1d_1 + a_2d_2$, is given by:
$C = a_1C_1 + a_2C_2$. Linear superposition indicates that the drug molecules interact in a stochastically independent fashion [82]. In contrast, for a molecular system the action of a drug molecule is altered and changed by the behavior of other drug molecules [13]. For example, assuming stochasticity of drug absorption and elimination, if random components

are added to the kinetic rate coefficient k then the system is still considered to be linear with a stochastic input, e. g., consider the one compartmental model

$$\frac{dC}{dt} = k^*C + i(t) \tag{1.11}$$

where $k^* = k + r$, and k represents the deterministic rate and r represents the stochastic contribution to the kinetic rate coefficient k^*, then equation (1.11) can be written as:

$$\frac{dC}{dt} = kC + [rC + i(t)] \tag{1.12}$$

where $[rC + i(t)]$ can be considered to be the stochastic input. However if the random effects are considered to be actually in the concentration C, then the effects are nonlinear.

The nonlinear dependence of the drug concentration on dosage and other factors, clearly adds a further complication for clinicians when trying to design effective dosage schedules, and in trying to predict a drug's efficacy and toxicity. Broadly speaking, nonlinearity in PK is split into dose-dependent and time-dependent. In phase I clinical trials, the concept of dose proportionality is commonly used when carrying out dose escalation experiments. Here, patient response to varying drug dosage is measured. If PK parameters remain constant with variation of dosage, the system PK is classified as dose independent (over the therapeutic range of interest). If increase in dosage of a drug produces a proportional increase in the PK parameters (AUC (area under the curve) or C_{max}), the system is classified as linear and dose dependent. If the variations in parameter values are not directly proportional to the variation in drug dosage, the system is classified as non-linear and dose dependent. PK parameters may also vary in time due to physiological change in the body or through drug induced changes in the body. Clearly, the PK parameters can be both dose-dependent and time-dependent. The proposed reasons and sources for this dependency appear to be similar in both cases. Lin [49], suggests that non-linear dose dependence is rooted in the absorption process, drug distribution variation in tissue and in the elimination process. [47] proposes that non-linear time-dependence arises from variations in absorption and elimination parameters, enzyme activity, plasma protein binding and the elimination processes.

1.3.3 Enzyme kinetics

Biological and biochemical processes are common characteristic features present in all animals and living organisms. There are complex biochemical reactions catalyzed by proteins

(known as enzymes) which react with certain compounds (substrates). In 1913, Michaeles and Menten proposed a characterization of one of the most basic of enzymatic reactions, which has been used as a standard formalism, since then for describing such reactions. This is represented schematically by;

$$S + E \underset{\mathrm{k}_{-1}}{\overset{\mathrm{k}_1}{\rightleftarrows}} (ES) \overset{\mathrm{k}_2}{\rightarrow} E + P ...(*)$$

where a substrate S reacts with an enzyme E to produce a complex (ES) which produces a product P and the enzyme E. k_1, k_{-1} and k_2 are reaction rate constants associated with particular reactions

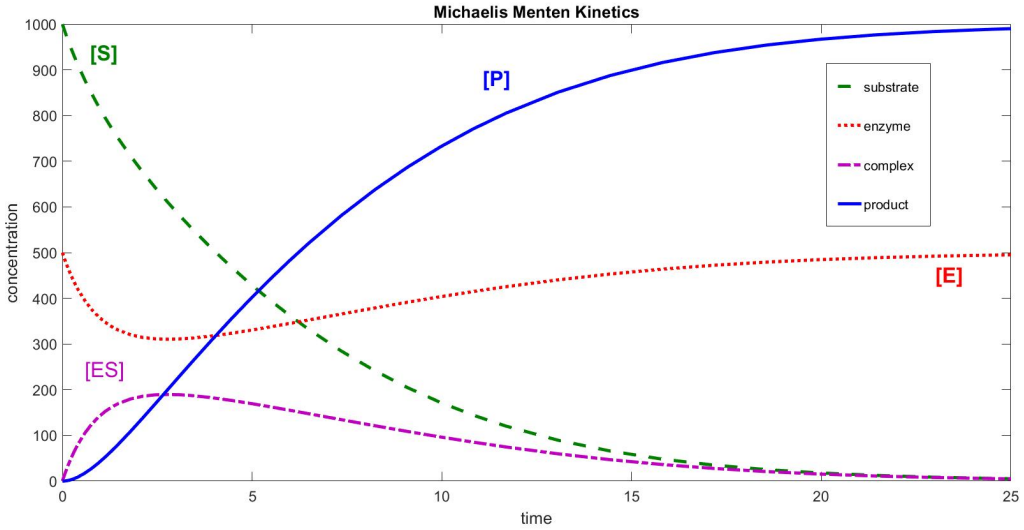

Figure 1.2: Michaelis Menten Kinetics: where we have taken reaction rates. $k_1 = 0.5e-3$, $k_2 = 0.5$ and $k_{-1} = 0.5e-4$ and initial substrate $S(0) = 1000$, initial enzyme $E(0) = 500$, initial product $P(0) = 0$.

Let [S], [E], [SE] and [P] denote the concentrations of reactants in the relation (*). Applying the law of mass action results in differential equation for each reactant, can be

described as following:

$$\begin{aligned} \frac{d[S]}{dt} &= -k_1[S][E] + k_{-1}[ES], \\ \frac{d[E]}{dt} &= -k_1[S][E] + (k_{-1} + k_2)[ES], \\ \frac{d[ES]}{dt} &= k_1[S][E] - (k_{-1} + k_2)[ES], \\ \frac{dP}{dt} &= v_p = k_2[ES]. \end{aligned} \tag{1.13}$$

The mathematical formulation is completed by a set of initial conditions, corresponding to the start of the whole process of conversion of S to P:

$$\text{S}(0)=[S]_0,\ \text{E}(0)=[E]_0,\ \text{ES}(0)=0,\ \text{P}(0)=0.$$

On adding the second and third DEs, we obtain

$$\frac{[dE]}{dt} + \frac{d[ES]}{dt} = 0, \tag{1.14}$$

i.e., E(t)+ES(t)=E_0 and by using this and substituting for [E] in the third DE (for the enzyme substrate complex), we obtain

$$\frac{d[ES]}{dt} = k_1(E_0 - [ES])[S] - (k_{-1} + k_2)[ES]. \tag{1.15}$$

Assuming that the initial formation of the complex [ES] is very rapid (after which it is, for all intents and purposes, at equilibrium), we have

$$k_1(E_0 - [ES])[S] - (k_{-1} + k_2)[ES] \approx 0, \tag{1.16}$$

from which we can evaluate:

$$[ES] = \frac{k_1[S]E_0}{k_{-1} + k_2 + k_1[S]},$$

or

$$[ES] = \frac{E_0[S]}{k_M + [S]},$$

where

$$k_M = \frac{k_{-1} + k_2}{k_1}$$

is the Michaeles Menten constant. Since the velocity of the reaction is given by: $v = k_2[ES]$, this implies

$$v = \frac{k_2 E_0[S]}{k_M + [S]} = \frac{v_{max}[S]}{k_M + [S]},$$

where $v_{max} = k_2 E_0$ is the maximum velocity of the reaction and k_M (the Michaelis-Menten constant) gives substrate concentration at $\frac{1}{2} v_{max}$

Chapter 2

The relevance of Stochasticity in PK models

2.1 Introduction

The traditional approach to the study of Pharmacokinetics (PK) is to imagine the human body as subdivided into various communicating compartments, in each of which a drug (administered in various forms) enters and exits at certain constant rates which must be determined from experimental data.

The translation of this hypothesis into a mathematical model leads to a set of coupled ordinary differential equations (ODEs), and the procedure and its uses are given in great detail in classic text books, such as Gibaldi and Perrier's "Pharmacokinetics" [29]

Although used successfully in many instances, this approach is not free of serious difficulties. For, on the one hand, to be physiologically accurate the number of compartments must be large in order to reflect the different ways in which organs process the drug; but, on the other hand, the larger the number of compartments the more unknown rates appear in the system of ODEs. As the aim of PK is to describe the total concentration of the drug in the body, the solution of the mathematical model would require many more concentration measurements than actually possible. Furthermore, the assumption that the rates are constant is also on shaky grounds, as the effects of (unknown) fluctuations from compartment to compartment suggest a time dependence of the rates.

In order to illustrate some of these difficulties, consider the problem of determining the rate of drug absorption and its related bioavailability. This has long been recognized as a

difficult problem. In fact, in the words of Gibaldi and Perrier(p.129) [29]

> "We must state at the outset that assessments of the rate of availability is one of the most difficult problems encountered in developing a pharmacokinetic profile of a drug since these assessments are always model-dependent and must frequently be attempted with the most shocking paucity of data".

Normally, one assumes that drug absorption after oral or intramuscular administration occurs by an apparent first order process, which leads to the introduction of an absorption constant k_a (or of an absorption half-life, that is, $\frac{ln\,2}{k_a}$), which in turn is commonly estimated using one of three methods from plasma concentration data and occasionally, from urinary excretion data:

- The method of residuals (sometimes called "curve stripping");
- The employment of plots of percent unabsorbed versus time;
- The method of nonlinear least squares regression analysis.

These methods have been in use for a long time, and have been critically discussed in the literature. The method of residuals is mathematically flawed, so that the estimated values of the rates of absorption must be considered (at best) as rough initial values. The second method has severe difficulties when a drug confers upon the body the characteristics of a multi compartment model; and regardless of what one sees often oral administration "virtually all drugs confer multi compartment characteristics on the body" (Gibaldi and Perrier, p.144) [29]. In that case, even the method of nonlinear least squares regression analysis, which is usually considered as the method of choice, has serious limitation. Firstly, one may not know whether the rate constants so determined represent k_a or the disposition rate constants α and β. Secondly, the method systematically overestimates the rate of absorption when there is a process that competes for the drug at the absorption site, such as first-order degradation.

In recognition of the above-mentioned difficulties, researchers have introduced a different approach over the last couple of decades. It basically consists of the assumption that any rate (of interest) in PK is a function of time that cannot be calculated deterministically; rather the rate fluctuates in time around a mean value, and the fluctuations are modeled as random functions whose statistical properties are assumed given.

This apparently simple assumption has a drastic effect on the mathematical status of the compartmental ODEs. As is well known, in the classical theory of ODEs (see,

e.g., Ince "Ordinary Differential Equations", [35]), once the coefficients and appropriate initial conditions are specified one can then prove fundamental theorems of existence and uniqueness, and then develop techniques for finding exact or approximate solutions. But if the coefficients are random variables, or random functions, no part of the classical theory applies and the resulting Stochastic Differential Equations (SDEs) require new concepts, starting with the meaning of "solutions" for them.

There is a vast literature on SDEs in mathematics and physics (going back to the beginning of the 20th century) which is impossible to review here. Suffice it to say that the interested reader can find excellent text books, such as "Stochastic Differential Equations: Theory and Applications" [3], whose focus is on rigorous mathematics. For those readers who are more interested in the applications of SDEs to physical and chemical phenomena the book by Van Kampen, "Stochastic Process in Physics and Chemistry" [79] is highly recommended. Also useful in this regard is the book by Gardiner, "Handbook of Stochastic Methods" [25], which contains many worked-out examples, including a thorough discussion of the most famous of all stochastic processes, namely Brownian motion, which we shall review momentarily.

The role played by stochastic processes in biological and pharmacological phenomena is not as well understood as in older areas of science. There have been early attempts at describing the drug's molecules as a discrete population of N particles whose steady state motion among m components is described probabilistically [58].

In the next section, we present some mathematical details relevant to the application of stochastic processes to PK.

2.2 Stochastic PK models and additive noise

Deterministic models are not capable of taking into account the uncertainties, which may rise either from the measurement errors or from the intrinsic fluctuations of the biological system itself. This has been recognized for a long time, and many stochastic models have been proposed where the fluctuations have been represented by random functions of time. Some of these studies we are going to discuss here. Limic [48] studied the stochastic nature of the compartment models due to randomness of the parameters. The focus of the study was to evaluate the statistical average of the model by considering transition rates as constant and fluctuations are described by Gaussian process. D'Argenio and Park [15], reviewed design, estimation, and control of uncertain PK/PD systems. The focus of this work was the study of biological systems for which measurement of some process

variables occurs infrequently and at irregular intervals that is, the analysis of sparse data system. The authors assumed that the model under consideration can be written as a linear continuous dynamical systems with uncertainty due to both system (biological) noise and to measurement error. Kalman filter formulation [38], used to compute the maximum likelihood function which determines the estimates of the unknown parameters. An important point in this paper is the assumption that the model parameters are constant, and therefore the noise is additive. Ramanathan [66], provided an introduction to Ito's calculus [25], for researchers in pharmaceutics. Ito's lemma is applied to the simplest case of PK (first order PK process with elimination rate constant k_e) and to the standard Michaelis-Menten effect E ($E = \frac{E_{\max}C}{E_{50}+C}$) of PD. As already mentioned, the noise is supposed to be white and additive. In the following study, Ramanathan[67], attempted to use ito's lemma to model and estimate the PK risks associated with drug interactions in populations. Unfortunately neither "drug interaction" nor the "risk" are clearly defined, thus making any objective assessment next to impossible. Ferrante et al., [20], demonstrated their study with a reminder of the deterministic description of a linear compartment model by the ODE

$$\frac{dx}{dt} = -k_e x(t) + f(t) \tag{2.1}$$

where $x(t)$ is the variable of interest (usually a concentration), $k_e > 0$ is the (constant) rate of elimination, and $f(t)$ is the input (infusion function) over an interval $[0, T]$. Study claimed that the input function may be subject to unpredictable fluctuation from many sources, which makes it reasonable to assume that $f(t)$ can be modeled as

$$f(t) = r + b\eta(t) \tag{2.2}$$

where r and b are constant and $\eta(t)$ is a Gaussian white noise. After a short review of SDE's defined by ito's calculus for Gaussian white noise, Ditlevsen et al., [16], studied random effects incorporating diffusion models for a simple PK case of the metabolism of a compound by first-order kinetics following a bolus injection, and were able to calculate the maximum likelihood estimators of the parameters, while simulation studies are done to check the estimators. Once again the stochastic aspects are treated by additive Gaussian white noise.

In the next section some basic definitions and assumptions will be discussed, by considering an example of a simple one compartmental model, which are necessary to solve a random process.

2.3 Some basic concepts before solving a random system

The basic assumptions of compartmental PK models have already been discussed in the previous chapter. We now focus on the basic (deterministic) one compartmental model, its extension to a random differential equation, and the concepts and methods used in the formulation and approximation of such random differential equations.

Suppose a drug is administered intravenously and the initial amount of the drug is A_0, we can now define the rate of drug loss from the body as:

$$\frac{dA}{dt} = -k_{el}A; \tag{2.3}$$

where the initial condition $A(0) = A_0$ is the dose administered initially. Here $A(t)$ is the amount of drug in the body after time t, k_{el} is the first order elimination rate constant. The solution to equation (2.3) is:

$$A(t) = A_0 e^{-k_{el}t}. \tag{2.4}$$

Now dividing by the volume of distribution V we can write equation (2.4) as:

$$C(t) = C_0 e^{-k_{el}t}, \tag{2.5}$$

where $C = \frac{A}{V}$ is the drug concentration in plasma. The unknown constants C_0 and k_{el} can be determined by fitting:

$$\ln C(t) = \ln C_0 - k_{el}t, \tag{2.6}$$

to the measured drug concentration in the plasma, commonly carried out by using the "least squares" method. It should be mentioned that our bodies can eliminate drugs via several pathways, and the elimination rate constant k_{el} is an effective rate constant that combines several rate constants of several individual processes,

$$k_{el} = k_e \text{ (renal elimination/excretion) } + k_m \text{ (metabolism elimination)} + \ldots.$$

as the elimination of a drug from the body can occur through several pathways. In standard textbooks on PK (e.g., Gibaldi and Perrier, chapter 1 [29]; Welling, Chapter 10 [86]), attempts to derive values for k_e, $k_{absorption}$ and k_m from same data, are described. These methods are related to the "method of residuals".

Let us examine this simple model from a different perspective. As we have mentioned in chapter 1 that, the one compartment open model treats the body as a homogeneous system but in reality, concentration of drugs are different in different organs and other tissues as well as in the plasma. So we can say that the elimination rate constants are not the same for different organs and also that the measurement of plasma concentration is relatively simpler than for other organ and tissues. By considering this situation we can modify our model. Let us assume that the main elimination pathway has the rate constant k_0 and thus appropriately we can write our deterministic differential equation as:

$$\frac{dA}{dt} = -k_0 A \tag{2.7}$$

with $A(0) = A_0 =$ dose (as mentioned earlier), $A(t)$ is the amount of drug in the plasma at time t and A_0 is the initial dose injected instantaneously at time $t = 0$. It seems clear that this measured amount will **fluctuate** in time since not all the drug is eliminated through the same pathways. In order to take these fluctuations into account we assume that the contributions from all other pathways are represented by a random function of time $k_1 L(t)$, here k_1 is a constant (which has the same dimensions as a rate) and $L(t)$ is the fluctuating extra amount of drug. Then we can rewrite the model as:

$$\frac{dA}{dt} = -k_0 A - k_1 L(t)$$

with $A(0) = A_0$ which we notice is a Langevin like random differential equation [25]. By the same procedure as before, we can divide the whole equation by the volume of distribution and can get RDE for the concentration $C(t)$ in the plasma as:

$$\frac{dC}{dt} = -k_0 C - k_1 l(t) \tag{2.8}$$

with $C(0) = C_0$ is the initial concentration and $l(t) = \frac{L(t)}{V}$.

Remark: The random function $l(t)$ in equation (2.8) is not known, and so we have one RDE for two unknown functions, $C(t)$ and $l(t)$. Furthermore, $l(t)$ fluctuates rapidly in time, which makes $C(t)$ a random function as well. If equation (2.8) were an ODE then we could complete the model by deriving another ODE for the extra unknown $l(t)$. But (2.8) is not a deterministic equation, that it is not a differential equation since $\frac{dC}{dt}$ doesn't exist [19]. Therefore we first of all decide what "solving a RDE" means.

Some preliminary notions are necessary. When we consider a random variable, we consider everyone of its possible outcomes associated with an associated probability for

that event to occur. And if the random variable X is continuous as our C is, then there are two probability distributions associated with it:

- a probability density function (pdf) of a continuous random variable X can be defined as prob $(x \leq X \leq x + dx) = p(x)dx$, which satisfies two conditions:
  1. $p(x) \geq 0$,
  2. $\int_{-\infty}^{\infty} p(x)dx = 1$,
- a cumulative distribution function (cdf) $P(x)$ is such that prob $P(X \leq x) = \int_{-\infty}^{x} p(x)dx$, so that $p(x) = \frac{dP}{dx}$.

We can define the average concentration of C of a random variable X as its expectation over the pdf, i.e.,

$$\langle C(X) \rangle = E\{C(X)\} = \int_0^X C(X')p(X')dX'. \tag{2.9}$$

Physically, the concentration

$$C = \lim_{\Delta V \to 0} \frac{A}{\Delta V}$$

In practice it is the number of drug molecules per unit volume when the volume is infinitesimally small. But our instruments can not count molecules; hence, what we actually measure is an average concentration at that instant. So we give up the idea of measuring the instantaneous concentration, and focus our attention on trying to calculate $\langle C(t) \rangle$ from the RDE (2.8).

A major concern is how the pdf $p(x)$ will be presented. From our knowledge about ODEs we know that to obtain a unique solution we require an initial condition, however the uniqueness theorem doesn't apply for RDEs. To handle this situation we look for possible initial conditions, and not taking just one condition but the probability distribution of all the possible initial conditions $p(x)$, which we can define as the initial ensemble.

Solving the RDE (2.8): By considering the above remarks, we start out considering the possibility of transforming equation (2.8) into an ODE for $\langle C(t) \rangle$. Therefore we take the expectation of each term of equation (2.8) and get:

$$\langle \frac{dC}{dt} \rangle = -\langle k_0 C(t) \rangle - \langle k_1 l(t) \rangle$$

where k_0 and k_1 are constants. Now as we saw above the average $\langle ... \rangle$ is an integral over the initial ensemble, and so $\langle ... \rangle$ and $\frac{d}{dt}\langle ... \rangle$ commute. Therefore we may rewrite the above equation as:

$$\frac{d}{dt}\langle C \rangle = -k_0 \langle C(t) \rangle - k_1 \langle l(t) \rangle.$$

From here we assign a statistical property to the random function $l(t)$ so that it has zero mean i.e., $\langle l(t) \rangle = 0$, which will give us a closed equation for $\langle C \rangle$. Now using this assumption, equation (2.8) becomes:

$$\frac{d}{dt}\langle C \rangle = -k_0 \langle C \rangle \tag{2.10}$$

with the initial condition $\langle C(0) \rangle = C_0$.

Comparing this result with equation (2.7) divided by V i.e, $\frac{dC}{dt} = k_0 C$, we see that the two are formally the same but are in reality different. The phenomenological equation (2.7) involves the instantaneous concentration $C(t)$, while(2.10) involves the average concentration $\langle C(t) \rangle$. This make sense, because the concept of instantaneous concentration is unrealistic due to the fact that it takes some time to measure C, so our instantaneous concentration really measures an average value.

Problem: our equation (2.10) contains no reference to the fluctuations in $C(t)$. Now to handle the situation we make the following observation. Instead of calculating $\langle C(t) \rangle$ by equation (2.10), we can find it directly from the RDE (2.8). In fact, by formally solving (2.8) we get:

$$C(t) = C_0 e^{-k_0 t} - k_1 e^{-k_0 t} \int_0^t e^{k_0 t'} l(t') dt' \tag{2.11}$$

and taking averages over the initial ensemble this leads to

$$\langle C(t) \rangle = C_0 e^{-k_0 t} - k_1 e^{-k_0 t} \int_0^t e^{k_0 t'} \langle l(t') \rangle dt'. \tag{2.12}$$

Hence, if we require as before that $\langle l(t) \rangle = 0$, then we get $\langle C(t) \rangle = C_0 e^{-k_0 t}$, which is just the solution of the ODE (2.10).

Remark: Here we notice that equation (2.11) makes more sense than the original RDE (2.8), because while derivatives of random functions are ill-defined their integrals are

perfectly respectable at least in the mean square sense.

Remark: Another important concept in the analysis of random processes deals with the moments. If we have a random function X taking (continuous) values x over the interval $(-\infty, \infty)$, its moments are given by the integral:

$$m_n = \int_{-\infty}^{-\infty} x^n f(x) dx. \tag{2.13}$$

The first moment m_1 which is usually denoted by μ is the average (usually called the mean).

$$\langle x \rangle = \mu = \int_{-\infty}^{-\infty} x f(x) dx, \tag{2.14}$$

the second moment m_2 is given by

$$\langle x^2 \rangle = m_2 = \int_{-\infty}^{-\infty} x^2 f(x) dx \tag{2.15}$$

and so on. Another important measure is the variance which can be defined as;
$\sigma^2 = \langle x^2 \rangle - \langle x \rangle^2$ and the positive square root of the variance is known as the standard deviation, σ, which describes the effect of the fluctuations.

Now we have already calculated the average concentration $\langle C(t) \rangle = C_0 e^{-k_0 t}$. So we can calculate the second moment by squaring the equation (2.11) and then taking the average we get the equation:

$$\begin{aligned} & \langle C^2(t) \rangle \\ = \; & (C_0 e^{-k_0 t})^2 - 2 C_0 k_1 e^{-2k_0 t} \int_0^t e^{k_0 t'} \langle l(t') \rangle dt' \\ + \; & k_1^2 e^{-2k_0 t} \int_0^t \int_0^t e^{k_0 (t + t'')} \langle l(t') l(t'') \rangle dt' dt'' \end{aligned} \tag{2.16}$$

and since we have already assumed in equation (2.12) that $\langle l(t) \rangle = 0$, it follows that the second term on the right hand side vanishes. However we don't know the value of the last term.

In order to find a specific value for the second moment of the concentration we must specify more statistical properties of the random function $l(t)$, since specifying the mean is not enough. In other words, we must specify the auto-correlation function of $l(t)$ which is:

$\langle l(t)l(t'')\rangle$. Now we can take $l(t)$ to be delta-correlated, as is done in the Langevin theory of Brownian motion, i.e; $\langle l(t)l(t'')\rangle = \delta(t-t'')$, which is the simplest assumption and using this relation we can write equation (2.16) as

$$\begin{aligned}\langle C^2(t)\rangle &= (C_0 e^{-k_0 t})^2 + k_1^2 e^{-2k_0 t}\int_0^t e^{2k_0 t'}dt' \\ &= \langle C(t)\rangle^2 + \frac{k_1^2}{2k_0}(1-e^{-2k_0 t})\end{aligned} \tag{2.17}$$

and therefore variance is given by;

$$\langle C^2(t)\rangle - \langle C(t)\rangle^2 = \frac{k_1^2}{2k_0}(1-e^{-2k_0 t}), \tag{2.18}$$

which reflects the effect of fluctuations around the average.

The Auto-Correlation function: as shown by equation (2.18) above, the effect of the uncertainty produced by the noise term in $C(t)$ i.e. the effect of the fluctuations can be estimated from the variance. However, a more interesting way of calculating the fluctuations is found by studying the auto-correlation function of the random variable.

First we will go back to the RDE (2.8) and multiply each term by $C(t')$, where $t' > t$:

$$C(t')\frac{d}{dt}C(t) = k_0 C(t')C(t) - k_1 C(t')l(t).$$

Since $C(t')$ does not depend on t i.e., $C(t')\frac{d}{dt}C(t) = \frac{d}{dt}C(t')C(t)$, and now by taking the average we get:

$$\frac{d}{dt}\langle C(t')C(t)\rangle = k_0\langle C(t')C(t)\rangle - k_1\langle C(t')l(t)\rangle \tag{2.19}$$

The last term is known as the cross-correlation of C and l (which is related to the covariance) and by the assumptions we have made, it vanishes. Thus equation (2.19) becomes:

$$\frac{d}{dt}\langle C(t')C(t)\rangle = k_0\langle C(t')C(t)\rangle \tag{2.20}$$

which shows that the auto-correlation function obeys the same (deterministic) ODE as the average $C(t)$ (comparing with the equation (2.10))

Remark: But this is true in general for additive noise only [25].

The calculation of the fluctuations from the auto-correlation function is similar to our previous calculation of the variance. Starting from the formal expression (2.11) and remembering that, $\langle C(t)\rangle = C_0 e^{-k_0 t}$, we set

$$\Gamma(t,t') = \langle \Delta C(t) \Delta C(t')\rangle,$$

where $\Delta C(t) = C(t) - C_0 e^{-k_0 t}$ and similarly for $\Delta C(t')$. Then equation (2.11) gives:

$$\begin{aligned}
\Gamma(t,t') &= \left\langle \Big(-k_1 e^{-k_0 t}\int_0^t e^{k_0 \bar{t}} l(\bar{t}) d\bar{t}\Big)\Big(-k_1 e^{-K_0 t'}\int_0^{t'} e^{k_0 \hat{t}} l(\hat{t}) d\hat{t}\Big)\right\rangle \\
&= k_1^2 e^{-k_0(t+t')}\int_0^t\int_0^{t'} e^{k_0(\bar{t}+\hat{t})}\langle l(\bar{t}) l(\hat{t})\rangle d\bar{t} d\hat{t} \\
&= k_1^2 e^{-k_0(t+t')}\int_0^t\int_0^{t'} e^{k_0(\bar{t}+\hat{t})}\delta(\hat{t}-\bar{t}) d\bar{t} d\hat{t} \\
&= k_1^2 e^{-k_0(t+t')}\int_0^t e^{2k_0\hat{t}} d\hat{t} \\
&= \frac{k_1^2}{2k_0} e^{-k_0(t+t')}(e^{2k_0 t}-1) \qquad (2.21)
\end{aligned}$$

From this we can immediately get the variance by setting $t = t'$:
Var $C(t) = \Gamma(t,t) = \frac{k_1^2}{2k_0}(1 - e^{-2k_0 t})$, which is just equation (2.18). Furthermore, the auto-correlation function becomes simpler if we normalize to 1, i.e.

$$\begin{aligned}
\frac{\Gamma(t,t')}{\Gamma(t,t)} &= e^{k_0(t-t')} = k(t-t') \\
&= \frac{e^{-k_0(t+t')}(e^{2k_0 t}-1)}{e^{-2k_0 t}(e^{2k_0 t}-1)} \\
&= e^{-k_0(t+t'-2t)} \\
&= e^{-k_0(t'-t)} \\
&= K(t'-t) \qquad (2.22)
\end{aligned}$$

which shows that the Stochastic process described by the Langevin-like equation (2.8) is stationary i.e., it is only dependent on the time difference $t - t'$

Now since t and t' are arbitrary, it is convenient to set $t' = t + \tau$, after which the auto-correlation function (2.22) becomes:

$$K(\tau) = e^{k_0 \tau}, \qquad (0 \leq < \infty) \qquad (2.23)$$

Remark: The simple exponential form of the auto-correlation function implies that the Stochastic process under study is stationary and Markovian, as proved by Doob [19]. In fact Doob proved that K obeys the functional equation $K(t_3 - t_1) = K(t_3 - t_2).K(_2{-}t_1)$, $(t_3 > t_2 > t_1)$ whose only non-singular solution is (2.23).

So far we are discussing the situation when a random function is added to the system, i.e., **additive noise** or in other words Gaussian white noise. When a random function is added to an ODE its statistical properties must be given. That is why when equation (2.8) was written down it was specified that the statistical properties of $l(t)$ are those of Gaussian white noise. These properties are easily expressed *in terms of moments* of $l(t)$; specifically they are the following:

- **(a)** $\langle l(t) \rangle = 0$ i.e., $l(t)$ has zero mean.
- **(b)** $\langle l(t_1)l(t_2) \rangle = \delta(t_1 - t_2)$, i.e., the process is stationary and its correlation function is a "delta function".
- **(c)** Higher moments are zero when they are odd e.g., $\langle l(t_1)l(t_2)l(t_3) \rangle = 0$; even moments are the sum of terms obtained by breaking them up is all possible ways into product of pairs and applying (b) to each pair e.g.,

$$\langle l(t_1)l(t_2)l(t_3)l(t_4) \rangle = \delta(t_1 - t_2)\delta(t_3 - t_4) + \delta(t_1 - t_3)\delta(t_2 - t_4) + \delta(t_1 - t_4)\delta(t_2 - t_3)$$

It is very important to understand the physical implications of these properties, for no properly defined stochastic process with these properties exists. "Gaussian white noise is a singular object, just as the delta function is a singular function" [80].

2.4 Limitations of the Langevin process

The example discussed in the preceding section illustrates the general philosophy behind the use of the Langevin equation. For simplicity, we consider again a one-compartmental model, but the method can be generalized to the multi-compartment one. In the linear case one knows the macroscopic (deterministic) ODE for a quantity of interest $x(t)$ of the form

$$\frac{dx}{dt} = -kx \tag{2.24}$$

where k is some rate constant. Then one notices that, for whatever reason, this equation is not correct because $x(t)$ **fluctuates** in time around the values given by it. These fluctuations are produced by the system itself, are not related to the measurement noise, are usually small, and vary very rapidly in time.

In order to take these fluctuations into account, one then supplement equation (2.24) with a random function of time **added** to the right hand side (as done in the original Langevin equation [79]) and having the statistical properties of Gaussian white noise,

$$\frac{dx}{dt} = -kx + bl(t), \tag{2.25}$$

which in turn is rewritten as an Ito equation, and solved by means of Ito's calculus [25]. Physically one can think of $l(t)$ as an infinite series of "pulses" which add or subtract from $x(t)$ completely at random, thus making it plausible to assume that $l(t)$ has zero mean. Hence, on taking the expectation of each term in Eq. (2.25)

$$\frac{d}{dt}\langle x\rangle = -k\langle x\rangle, \tag{2.26}$$

one sees that the mean of $x(t)$ obeys the same equation as the macroscopic ODE (2.24). This procedure no longer applies when the compartmental parameters that is, the coefficients of the macroscopic ODEs are fluctuating. For example, if one assumes that the rate constant k in Eq. (2.24) is a random function of time fluctuating about a mean $\bar{k}$, such as

$$k(t) = \bar{k} + \alpha\xi(t) \tag{2.27}$$

where α is a measure of the size of the fluctuations and $\xi(t)$ represents the noise, then Eq. (2.24) reads as

$$\frac{dx}{dt} = -(\bar{k} + \alpha\xi(t))x. \tag{2.28}$$

On taking the average of this equation one gets

$$\frac{d}{dt}\langle x\rangle = -\bar{k}\langle x\rangle - \alpha\langle \xi x\rangle, \tag{2.29}$$

which is not the same as the macroscopic equation (2.26) unless $\xi x = 0$; that is, unless $\xi(t)$ and $x(t)$ are uncorrelated. Now that is true only for white noise [80], in which case $\xi(t)$ is the Wiener process and equation (2.28) may be written as the Ito equation

$$dx = -\bar{k}xdt - \alpha x dW. \tag{2.30}$$

These facts explain why most of the literature in this area consists of stochastic PK/PD models assuming that the noise is white, and the reader can find many examples in the recent review by Donnet and Samson [18].

Another way of characterizing white noise is by means of the parameter t_c, the correlation time of the noise. As white noise is delta-function correlated we have $t_c = 0$; in contrast, non-white noise (also known as "colored noise") has a finite $t_c \neq 0$. Therefore, the question arises: Can Eq. (2.28) be "solved" in some sense when $\xi(t)$ is colored noise and $\langle \xi(t)\xi(t') \rangle \neq \delta(t-t')$? No exact method of solution is known in this case, but approximation methods have been developed and applied successfully in the physical sciences, at least in the case of *realistic noise whose correlation time is short, but not infinitely short*. Therefore the purpose of this thesis is to investigate whether these approximation techniques can also be successful in the study of stochastic PK/PD models. For the convenience of the reader these new methods will be reviewed in the next two sections. Furthermore, in order to avoid confusion with the terminology used in the literature when the noise is assumed to be white, it will be useful to refer to differential equations whose coefficients are random functions as *Random Differential Equations (RDE')* to remind ourselves that we are dealing with non-white noise.

2.5 The Bourret integral equation for the mean

In a series of papers starting in 1961, Bourret was the first to propose a systematic approximation method to deal with RDE's [6], [7], [8]. He borrowed mathematical techniques developed by physicists in Quantum field theory, and so his papers are very difficult to understand. Fortunately, however, Van Kampen [79] showed a decade later how to obtain Bourret's approximation by a much simpler heuristic method. Therefore, we shall follow Van Kampen's approach systematically.

We have already seen in Eq. (2.28) the structure of the RDE's one has to deal with in the study of stochastic PK models. That example pertained to a one-dimensional (one compartment) model, but it can be easily generalized to a multi-compartment model with random coefficients. Thus we shall consider the RDE

$$\frac{d\mathbf{u}}{dt} = (A_0 + \alpha A_1(t))\mathbf{u} \tag{2.31}$$

with the initial condition $u(0) = u_0$, where $\mathbf{u}$ is an n-component vector, A_0 is constant $n \times n$ matrix, α is a parameter determining the size of the fluctuations and is usually small, and A_1 is an $n \times n$ random matrix with zero mean, i.e., $\langle A_1 \rangle = 0$.

The goal here is to find deterministic equation for the moments of $\mathbf{u}$ by choosing a proper mathematical model, for small α. Now by simply averaging equation (2.31) we get:

$$\frac{d\langle \mathbf{u} \rangle}{dt} = A_0 \langle \mathbf{u} \rangle + \alpha \langle A_1(t)\mathbf{u} \rangle. \tag{2.32}$$

To approximate cross correlation $\langle A_1(t)\mathbf{u} \rangle$ following assumptions are commonly used in the literature:

1. $\langle A_1(t) \rangle = 0$

2. $A_1(t)$ has a finite (nonzero) correlation time say τ_c
   $\Longrightarrow$ for any two times t_1 and t_2, $|t_1 - t_2| >> \tau_c$,
   $A_1(t_1)$ and $A_1(t_2)$ are statistically independent.

Following Van Kampen [81], we first perform a change of variables in (2.31) by setting an interaction expression:

$$u(t) = e^{A_0 t} v(t) \tag{2.33}$$

obtaining in a straight forward way the new RDE

$$\begin{aligned} \frac{dv}{dt} &= \alpha V(t) v(t) \\ v(0) &= u(0) = u_0 \end{aligned} \tag{2.34}$$

where $V(t)$ is a new random matrix given by

$$V(t) = e^{-A_0 t} A_1(t) e^{A_0 t} \tag{2.35}$$

Since α is small the obvious method seems to be perturbation series in α:

$$v(t) = v_0(t) + \alpha v_1(t) + \alpha^2 v_2(t) + ... \tag{2.36}$$

where

$$\begin{aligned} u_0 &= v_0(0) + \alpha v_1(0) + \alpha^2 v_2(0) + ... \\ \Longrightarrow v_0(0) &= u_0; \quad v_i(0) = 0 \quad \forall i \geq 0 \end{aligned}$$

Substituting these into equation (2.34) we get:

$$\frac{dv_0}{dt} + \alpha \frac{dv_1}{dt} + \alpha^2 \frac{dv_2}{dt} + ... = \alpha V v_0 + \alpha^2 V v_1 + \alpha^3 V v_2 + ... \tag{2.37}$$

Equating α on both sides

$$\frac{dv_0}{dt} = 0$$
$$\frac{dv_1}{dt} = Vv_0$$
$$\frac{dv_2}{dt} = Vv_1$$

and so on. Now by solving the above relations we can get:

$$v_0 = \text{ constant} = u_0$$
$$v_1 = u_0 \int_0^t V(t')dt'$$
$$v_2 = u_0 \int_0^t \int_0^{t'} V(t')V(t'')dt'dt''$$

Now using all these values equation (2.36) becomes:

$$\begin{aligned} v(t) &= u_0 + \alpha\Big(\int_0^t V(t')dt'\Big)u_0 \\ &+ \alpha^2\Big(\int_0^t \int_0^{t'} V(t')V(t'')dt'dt''\Big)u_0 + ... \end{aligned} \tag{2.38}$$

Upon taking average with fixed u_0, one can get:

$$\begin{aligned} \langle v(t)\rangle &= u_0 + \alpha\Big(\int_0^t \langle V(t')\rangle dt'\Big)u_0 \\ &+ \alpha^2\Big(\int_0^t \int_0^{t'} \langle V(t')V(t'')\rangle dt'dt''\Big)u_0 + ... \end{aligned} \tag{2.39}$$

$$\implies \langle v(t)\rangle = u_0 + \alpha^2\Big(\int_0^t \int_0^{t'} \langle V(t')V(t'')\rangle dt'dt''\Big)u_0 + ... \tag{2.40}$$

since $V(t) = e^{-tA_0}A_1(t)e^{tA_0}$ and we assumed $\langle A_1(t)\rangle = 0 \implies \langle V(t)\rangle = 0$

From the perturbation, one can claim the previous expression of $\langle v\rangle$ is an approximation up to 2nd order in α but this is not a suitable perturbation as it is increasing not only in α but also in αt and is therefore valid only $\alpha t << 1$

To overcome the situation Bourret demonstrated a heuristic approach for which equation (2.34) is strictly equivalent to the integral equation

$$v(t) = a + \alpha \int_0^t V(t')v(t')dt'. \tag{2.41}$$

Equation (2.41), after one iteration can be written as:

$$\begin{aligned} v(t) &= u_0 + \alpha \int_0^t V(t')\Big(u_0 + \alpha \int_0^{t'} V(t'')v(t'')dt''\Big)dt' \\ &= u_0 + u_0\alpha \int_0^t V(t')dt' + \alpha^2 \int_0^t \int_0^{t'} V(t')V(t'')v(t'')dt''dt' \end{aligned}$$

and by taking average we can get (recall that $\langle V(t')\rangle = 0$):

$$\langle v(t)\rangle = u_0 + \alpha^2 \int_0^t \int_0^{t'} \langle V(t')V(t'')v(t'')\rangle dt''dt'. \tag{2.42}$$

This equation is exact but no help in finding $\langle v(t)\rangle$, as it contains higher order correlation $\langle V(t')V(t'')v(t'')\rangle$ [81].

In order to make progress Bourret assumed that the integrand in (2.42) can be approximated as

$$\langle V(t')V(t'')v(t'')\rangle \approx \langle V(t')V(t'')\rangle\langle v(t'')\rangle, \tag{2.43}$$

after which (2.42) becomes a closed integral equation for $\langle v(t)\rangle$ as

$$\langle v(t)\rangle = u_0 + \alpha^2 \int_0^t \int_0^{t'} \langle V(t')V(t'')\rangle\langle v(t'')\rangle dt''dt', \tag{2.44}$$

or equivalently

$$\frac{d}{dt}\langle v(t)\rangle = \alpha^2 \int_0^t \langle V(t)V(t'')\rangle\langle v(t'')\rangle dt'', \tag{2.45}$$

which in terms of the original variables read as

$$\frac{d}{dt}\langle u(t)\rangle = A_0\langle u(t)\rangle + \alpha^2 \int_0^t \langle A_1(t)e^{(t-t')A_0}A_1(t')\rangle\langle u(t')\rangle dt'. \tag{2.46}$$

Equation (2.46) is known as Bourret's integral equation and is a very impressive form to evaluate the mean of $u(t)$ as it is a closed equation. It is possible to find $\langle u(t)\rangle$ without knowing the higher moments and also without solving RDE: $\frac{du}{dt} = A(t;\omega)u$

Of course it remains to find out the region of validity of the approximation [81], and this in turn will depend on the region of validity of the basic approximation (2.43). This will be discussed in the next section.

2.6 Van Kampen differential equation for the mean

Van Kampen [81],[79], starts out by observing that Bourret's fundamental assumption (2.43) is unsatisfactory, because it is in general *not true* that the average of a product equals the product of the averages. He notices, however, that this assumption has been used successfully in the physics literature for a very long period of time, and therefore he sets out to determine under what condition the assumption represents a good approximation. The equation (2.34) determines two important time scales. The first one is the scale on which $v(t)$ varies, and is measured by α^{-1}; the second scale is represented by the correlation time t_c of $V(t)$, which is the time scale on which the random nature of $V(t)$ becomes appreciable. If we call $\triangle t$ a time interval large enough that its relation to the two time scales is given by

$$t_c << \triangle t << \alpha^{-1}$$

or equivalently (since $\alpha > 0$)

$$\alpha t_c << \alpha \triangle t << 1 \tag{2.47}$$

then at a time $t > t_c$ the autocorrelation of the noise has vanished, which means that by the time $\triangle t$ is reached the random function $V(t)$ has *"forgotten its past"*, and the stochastic process is *approximately Markovian* [81]. The same argument can be used in the next interval from $\triangle t$ to $2\triangle t$, and so on. Thus Van Kampen's argument shows that the Bourret integral equation (2.46) is simply the first step in a perturbation theory solution of Eq. (2.31) in powers of αt_c in which powers of the order $(\alpha t_c)^3$ have been neglected [79].

Next Van Kampen notices that Eq. (2.46) still contains the initial time, and therefore are restricted to solutions that are uncorrelated with $A_1(t)$ at that time. however this problem can simply be solved by the change of variables $t'' = t - t'$ in Eq. (2.45) to given

$$\frac{d}{dt}\langle v(t)\rangle = \alpha^2 \int_0^t \langle V(t)V(t-t')\rangle\langle v(t-t')\rangle dt', \tag{2.48}$$

and then by observing that as soon as $t > t_c$ the autocorrelation of $V(t)$ vanishes, so that no appreciable error is made by extending the integral to ∞. Hence, on the macroscopic time scale, Eq. (2.48) may be rewritten as

$$\frac{d\langle v(t)\rangle}{dt} = \alpha^2 \int_0^\infty \langle V(t)V(t-t')\rangle\langle v(t-t')\rangle dt', \tag{2.49}$$

where the initial time has disappeared so that this equation applies to all solutions of Eq. (2.31), regardless of the time instant at which the initial value is imposed. The final step

in van Kampen's argument is to show that (2.49) is equivalent to the ODE obtained by replacing $v(t-t')$ in the integral with $\langle v(t)\rangle$ namely

$$\frac{d}{dt}\langle v(t)\rangle = \alpha^2\Big[\int_0^\infty \langle V(t)V(t-t')\rangle dt'\Big]\langle v(t)\rangle. \tag{2.50}$$

In fact, since the integral is only different from zero over a time t_c, the relative error made by this replacement is of order

$$\frac{\langle \triangle v\rangle}{\langle v\rangle} \sim \frac{t_c \frac{\langle \triangle v\rangle}{\triangle t}}{\langle v\rangle}.$$

Moreover, according to the equation itself, we have

$$\frac{\langle \triangle v\rangle}{\triangle t} \sim \alpha^2 t_c \langle v\rangle$$

and so the relative error is of the order

$$\frac{\langle \triangle v\rangle}{\langle v\rangle} \sim \alpha^2 t_c^2. \tag{2.51}$$

But in the derivation of the perturbation solution terms of relative order (αt_c) were already neglected; therefore, the error (2.51) is of no consequence [79].

The conclusion is that the ODE for the average derived by Van Kampen (2.50) can be rewritten in the original variables as

$$\frac{d}{dt}\langle u(t)\rangle = \Big[A_0 + \alpha^2\int_0^\infty \langle A_1(t)e^{A_0 t'}A_1(t-t')\rangle e^{-A_0 t'}dt'\Big]\langle u(t)\rangle \tag{2.52}$$

and in the next section it will be applied to study the example of random harmonic oscillator. This ODE is also the basic equation of the study of stochastic models of PK in the following chapters.

2.7 The Random Harmonic Oscillator

2.7.1 Van Kampen approach

Here we are going to consider the harmonic oscillator and will solve them by using both the Van Kampen random differential equation and Bourret integral equation. We know the simple harmonic oscillator is described by the following equation:

$$\ddot{x} + \omega^2 x = 0 \tag{2.53}$$

with $x(0) = a$, $\dot{x}(0) = 0$. If ω is a constant, then the solution is trivially given by $x(t) = a \sin \omega t$. But if $\omega = \omega(t)$, then no analytical solution can be found. Suppose $\omega(t)$ is a random function of time, such as

$$\omega^2(t) = \omega_0^2(1 + \alpha\xi(t)),$$

where ω_0=constant. Then the differential equation can be written as

$$\ddot{x} + \omega_0^2(1 + \alpha\xi(t))x = 0, \tag{2.54}$$

which is a Random Differential Equation (RDE), physically the frequency of the oscillator varies in time in a random way i.e., unpredictable way, and we can interpret this as the result of an external perturbation of size α (the size of the fluctuation is ω), which usually is a small parameter. On the other hand, the random function $\xi(t)$ is not known except for some statistical properties such as, for example,

$$\langle \xi(t) \rangle = 0 \tag{2.55}$$

where $\langle . \rangle$ denotes the expectation (average) value. Rewrite the equation (2.54) in matrix form:

$$\begin{aligned} \frac{dx}{dt} &= \dot{x}, \\ \frac{d\dot{x}}{dt} &= -\omega_0^2(1 + \alpha\xi(t))x, \end{aligned}$$

where $x(0) = a$, $\dot{x} = 0$, and so

$$\frac{d}{dt} \begin{pmatrix} x \\ \dot{x} \end{pmatrix} \begin{pmatrix} 0 & 1 \\ -\omega_0^2(1 + \alpha\xi(t)) & 0 \end{pmatrix} \begin{pmatrix} x \\ \dot{x} \end{pmatrix}. \tag{2.56}$$

Furthermore, since the product $\alpha\xi$ is dimensionless, we can eliminate the constant ω_0^2 by making the whole problem dimensionless. Accordingly, we let $y = \frac{x}{a}$; $\tau = \omega_0 t$. Now we have the equation (2.54) in dimensionless form as

$$\ddot{y}(\tau) = -(1 + \alpha\xi(\tau))y(\tau), \tag{2.57}$$

where $y(0) = 1$, $\dot{y}(0) = 0$ and in matrix form which can be written as:

$$\frac{d}{d\tau} \begin{pmatrix} y \\ \dot{y} \end{pmatrix} = \left[\begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix} + \alpha\xi(\tau) \begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix} \right] \begin{pmatrix} y \\ \dot{y} \end{pmatrix}. \tag{2.58}$$

Hence using the notation introduced by Van Kampen [81] we have:

$$A_0 = \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix}, \tag{2.59}$$

$$A_1 = \xi(t)B = \xi(t) \begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix}, \tag{2.60}$$

and introducing the vector

$$\mathbf{u} = \begin{pmatrix} y \\ \dot{y} \end{pmatrix},$$

the RDE (2.58) becomes:

$$\frac{d\mathbf{u}}{dt} = (A_0 + \alpha\xi(t)B)\mathbf{u}, \tag{2.61}$$

to which we can apply Van Kampen's argument that, as long as α is small and the correlation time τ_c is short, we may neglect terms of order $(\alpha\tau_c)^3$ in the perturbation expansion to conclude that under these conditions the first moment $\langle u(t)\rangle$ i.e., the mean obeys a closed ODE, given by equation (10.4) of Van Kampen [81], viz:

$$\frac{d}{dt}\langle \mathbf{u}(t)\rangle = [A_0 + \alpha^2 \int_0^\infty \langle A_1(t)e^{A_0\tau}A_1(t-\tau)\rangle e^{-A_0\tau}d\tau]\langle \mathbf{u}(t)\rangle \tag{2.62}$$

using the definition (2.59) and (2.60) as well as dimensionless time τ

$$\frac{d}{d\tau}\langle \mathbf{u}(\tau)\rangle = [A_0 + \alpha^2 \int_0^\infty \langle \xi(\tau)\xi(\tau-\tau')\rangle Be^{A_0\tau'}Be^{-A_0\tau'}d\tau']\langle \mathbf{u}\rangle. \tag{2.63}$$

First we compute

$$\begin{aligned} e^{A_0\tau'} &= 1 + A_0\tau' + \frac{1}{2}(A_0\tau')^2 + ... \\ &= \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} + \begin{pmatrix} 0 & \tau' \\ -\tau' & 0 \end{pmatrix} + \frac{1}{2}\tau'^2 \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix}\begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix} + ... \\ &= \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} + \frac{1}{2}\tau'^2 \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix} + \tau' \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix} + ... \\ &= \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}\{1 - \frac{1}{2}\tau'^2 + \frac{1}{4!}\tau'^4 - ....\} + \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix}\{\tau' - \frac{1}{3!}\tau'^3 + ...\} \\ &= I\cos\tau' + A_0\sin\tau'. \end{aligned} \tag{2.64}$$

Next we compute the complete non-random term in the integrand in (2.63), namely the matrix products $Be^{A_0\tau'}Be^{-A_0\tau'}$ where A_0 and B are defined in (2.59) and (2.60). We have;

$$\begin{aligned} Be^{A_0\tau'} &= \begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix}\left[\begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}\cos\tau' + \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix}\sin\tau'\right] \\ &= \begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix}\cos\tau' + \begin{pmatrix} 0 & 0 \\ 0 & -1 \end{pmatrix}\sin\tau' \end{aligned}$$

$$\begin{aligned} Be^{-A_0\tau'} &= \begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix}\left[\begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}\cos\tau' - \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix}\sin\tau'\right] \\ &= \begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix}\cos\tau' - \begin{pmatrix} 0 & 0 \\ 0 & -1 \end{pmatrix}\sin\tau' \end{aligned}$$

$$\begin{aligned} Be^{A_0\tau'}Be^{-A_0\tau'} &= \left[\begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix}\cos\tau' + \begin{pmatrix} 0 & 0 \\ 0 & -1 \end{pmatrix}\sin\tau'\right]\left[\begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix}\cos\tau' - \begin{pmatrix} 0 & 0 \\ 0 & -1 \end{pmatrix}\sin\tau'\right] \\ &= \begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix}\begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix}\cos^2\tau' - \begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix}\begin{pmatrix} 0 & 0 \\ 0 & -1 \end{pmatrix}\sin\tau'\cos\tau' + \\ &\quad \begin{pmatrix} 0 & 0 \\ 0 & -1 \end{pmatrix}\begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix}\sin\tau'\cos\tau' - \begin{pmatrix} 0 & 0 \\ 0 & -1 \end{pmatrix}\begin{pmatrix} 0 & 0 \\ 0 & -1 \end{pmatrix}\sin^2\tau' \\ &= \begin{pmatrix} 0 & 0 \\ 0 & 0 \end{pmatrix}\cos^2\tau' - \begin{pmatrix} 0 & 0 \\ 0 & 0 \end{pmatrix}\cos\tau'\sin\tau' + \begin{pmatrix} 0 & 0 \\ 1 & 0 \end{pmatrix}\sin\tau'\cos\tau' - \begin{pmatrix} 0 & 0 \\ 0 & 1 \end{pmatrix}\sin^2\tau' \\ &= \begin{pmatrix} 0 & 0 \\ \sin\tau'\cos\tau' & 0 \end{pmatrix} + \begin{pmatrix} 0 & 0 \\ 0 & -\sin^2\tau' \end{pmatrix} = \begin{pmatrix} 0 & 0 \\ \sin\tau'\cos\tau' & -\sin^2\tau' \end{pmatrix}, \end{aligned} \tag{2.65}$$

which agrees with Van kampen's equation (14.3) [81]. Substituting (2.65) into (2.63) and switching back to the explicit matrix format gives us:

$$\begin{aligned} \frac{d}{d\tau}\begin{pmatrix} \langle y\rangle \\ \langle \dot{y}\rangle \end{pmatrix} &= \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix}\begin{pmatrix} \langle y\rangle \\ \langle \dot{y}\rangle \end{pmatrix} \\ &\quad + \alpha^2\int_0^\infty \langle \xi(\tau)\xi(\tau-\tau')\rangle \begin{pmatrix} 0 & 0 \\ \sin\tau'\cos\tau' & -\sin^2\tau' \end{pmatrix} d\tau' \begin{pmatrix} \langle y\rangle \\ \langle \dot{y}\rangle \end{pmatrix}. \end{aligned} \tag{2.66}$$

Next we are going to use the half-angle formula

$$\sin\tau'\cos\tau' = \frac{1}{2}\sin 2\tau',$$

$$-\sin^2\tau' = -\Big(\frac{1-\cos 2\tau'}{2}\Big),$$

and define the two coefficients

$$c_1 = \int_0^\infty \langle \xi(\tau)\xi(\tau-\tau')\rangle \sin 2\tau' \quad d\tau', \tag{2.67}$$

$$c_2 = \int_0^\infty \langle \xi(\tau)\xi(\tau-\tau')\rangle (\cos 2\tau' - 1) \quad d\tau', \tag{2.68}$$

in order to rewrite equation (2.66) in the simple form

$$\frac{d}{dt}\begin{pmatrix} \langle y\rangle \\ \langle \dot{y}\rangle \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix}\begin{pmatrix} \langle y\rangle \\ \langle \dot{y}\rangle \end{pmatrix} + \frac{\alpha^2}{2}\begin{pmatrix} 0 & 0 \\ c_1 & c_2 \end{pmatrix}\begin{pmatrix} \langle y\rangle \\ \langle \dot{y}\rangle \end{pmatrix} \tag{2.69}$$

or as a single ODE;

$$\frac{d^2}{d\tau^2}\langle y\rangle = \frac{\alpha^2}{2}c_2\langle \dot{y}\rangle - \Big(1 - \frac{\alpha^2}{2}c_1\Big), \tag{2.70}$$

and in dimensional form will be:

$$\frac{d^2}{dt^2}\langle x\rangle = \frac{1}{2}\alpha^2\omega_0 c_2\frac{d}{dt}\langle x\rangle - \omega_0^2\big(1 - \frac{1}{2}\alpha^2 c_1\big)\langle x\rangle \tag{2.71}$$

This coincides with Van kampen's equation (14.7) [81] for the special case $\omega_0 = 1$.

Remarks:

(a) On comparing our equation (2.71) with the non-random oscillator equation (2.53) that is:

$$\frac{d^2}{dt^2}x = -\omega^2 x$$

we see that RDE (2.54) introduces two important physical effects in the ODE for the first moment (the mean) of the oscillator's displacement:

- It's frequency is shifted by the quantity $\frac{1}{2}\alpha^2 c_1$ and
- Damping of the average $\langle x\rangle$ in the form $\frac{1}{2}\alpha^2\omega_0 c_2$ is produced by the small fluctuations of the oscillator's frequency.

(b) Van Kampen (1976, p. 201) [81] noticed that if there is resonance between the fluctuations and the double frequency of the oscillator, then the coefficient c_2 in (2.68) can become positive, in which case the mean $\langle x \rangle$ would grow exponentially.

To proceed further we need to specify the auto correlation function, in order to compute the coefficients c_1 and c_2. This means that we describe the statistical properties of $\xi(t)$ by prescribing

$$\begin{aligned} \langle \xi(t) \rangle &= 0, \\ \langle \xi(t)\xi(t-\tau) \rangle &= a(\tau), \end{aligned}$$

where $a(\tau)$ is a given function of τ. Note that specifying the auto-correlation function for a stationary stochastic process means that the variance is also specified. In fact, since

$$\Gamma(t,t') = \langle \xi(t)\xi(t+t') \rangle - \langle \xi(t) \rangle \langle \xi(t+t') \rangle,$$

and since $\Gamma(t,t') = \Gamma(t-t')$, due to stationary, we have

$$\Gamma(t') = \langle \xi(0)\xi(t') \rangle - \langle \xi(0) \rangle \langle \xi(t') \rangle,$$

and, for $t' = 0$,

$$\Gamma(0) = \langle \xi^2(0) \rangle - \langle \xi(0) \rangle^2,$$

which is just the variance.

The simplest assumption is to assume that the (normalized) auto-correlation function decays exponentially according to (recall that $\langle \xi \rangle = 0$)

$$B(\tau) = \langle \xi(0)\xi(\tau) \rangle = e^{-\gamma\tau}, \qquad \gamma > 0 \tag{2.72}$$

so that $\gamma^{-1} = \tau_c$ is the correlation time, which was assumed to be short both in Bourret and Van kampen approximations. In other words, we assume that the auto-correlation function is exponentially small after a duration of a few correlation times.

Now we can compute c_1 and c_2 from (2.67) and (2.68):

$$\begin{aligned} c_1 &= \int_0^\infty e^{-\gamma\tau} \sin 2\tau d\tau \\ &= \frac{2\tau_c^2}{1+4\tau_c^2}, \end{aligned} \tag{2.73}$$

$$
\begin{aligned}
c_2 &= \int_0^\infty e^{-\gamma\tau}\big(\cos 2\tau - 1\big)d\tau \\
&= -\frac{4\tau_c^3}{1+4\tau_c^2}.
\end{aligned} \tag{2.74}
$$

Substituting these expressions into (2.71) gives:

$$
\frac{d^2}{dt^2}\langle x\rangle = 2\alpha_0^2\omega_0\frac{\tau_c^3}{1+4\tau_c^2}\frac{d}{dt}\langle x\rangle - \omega_0^2\big(1-\frac{\alpha^2\tau_c^2}{1+4\tau_c^2}\big)\langle x\rangle \tag{2.75}
$$

and we see that the damping (1st term on the right hand side) has the proper negative sign that guarantees the stability of the motion. In other words, for a correlation function decaying exponentially (as in (2.72) above) the resonance mentioned by Van Kampen (Remark (b)) does not occur.

Now we are going to solve for this average using maple (code is in appendix C) and also by the observations we have made when we are taking the values of the parameter. The assumption is that the correlation time $\tau_c << 1$ that mean $\gamma >> 1$ we get the following solution:

$$
\begin{aligned}
\langle x(\tau)\rangle &= e^{(-9.62\times 10^{-6}\,\tau)}\cos(1.00\,\tau) \\
&+ (9.62\times 10^{-6}e^{(-9.62\times 10^{-6}\,\tau)}\sin(1.00\,\tau).
\end{aligned} \tag{2.76}
$$

From figure 2.1, it is clear that the effects of the correlation time vanish for long times although for short times the solution is seem to be highly oscillatory.

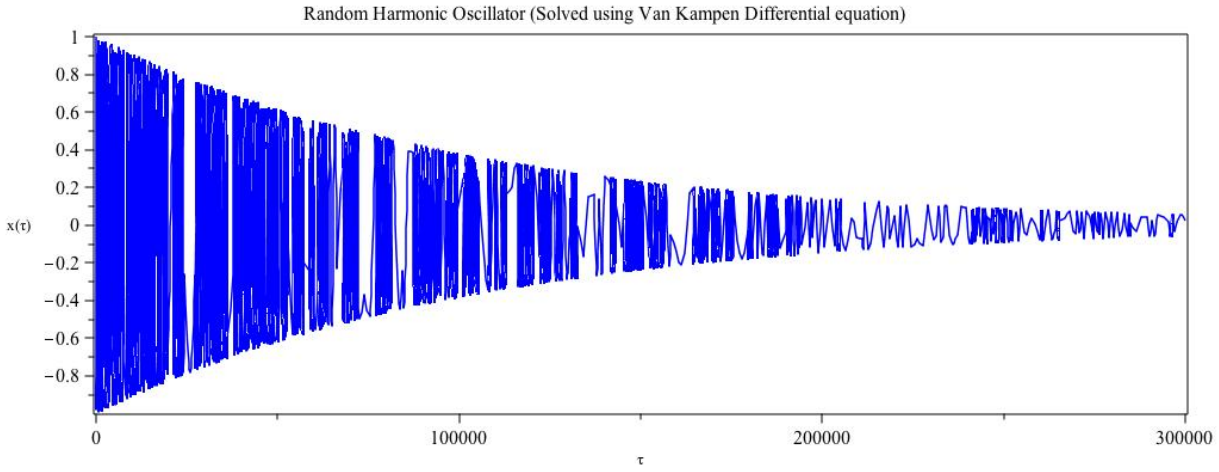

Figure 2.1: An illustration of the solution of random harmonic oscillator using Van Kampen differential equation of mean for $\alpha = .1$ and $\tau_c = .1$

.

2.7.2 Bourret's approach

Now we are going to solve equation (2.54) using Bourret's integral equation:

$$\frac{d}{d\tau}\langle \mathbf{u}(\tau)\rangle = A_0\langle \mathbf{u}(\tau)\rangle + \alpha^2 \int_0^\tau \langle A_1(\tau) e^{A_0(\tau-\tau')} A_1(\tau')\rangle \langle \mathbf{u}(\tau')\rangle d\tau', \tag{2.77}$$

where A_0 and A_1 are as in (2.59) and (2.60). Using the previous results, we can write

$$\begin{aligned} e^{A_0(\tau-\tau')}A_1(\tau') &= \Big(I\cos(\tau-\tau') + A_0\sin(\tau-\tau')\Big)B\xi(\tau') \\ &= B\xi(\tau')\cos(\tau-\tau') + A_0 B\xi(\tau')\sin(\tau-\tau') \\ &= \begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix}\xi(\tau')\cos(\tau-\tau') + \begin{pmatrix} -1 & 0 \\ 0 & 0 \end{pmatrix}\xi(\tau')\sin(\tau-\tau'), \end{aligned} \tag{2.78}$$

and so the kernel of the integral (2.77) is given by

$$\begin{aligned}\langle A_1(\tau)e^{A_0(\tau-\tau')}A_1(\tau')\rangle &= \left\langle \begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix} \xi(\tau) \left[\begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix} \xi(\tau')\cos(\tau-\tau') \right.\right. \\ &+ \left.\left. \begin{pmatrix} -1 & 0 \\ 0 & 0 \end{pmatrix} \xi(\tau')\sin(\tau-\tau') \right] \right\rangle \\ &= \left\langle \begin{pmatrix} 0 & 0 \\ 1 & 0 \end{pmatrix} \xi(\tau)\xi(\tau')\sin(\tau-\tau') \right\rangle \\ &= \begin{pmatrix} 0 & 0 \\ 1 & 0 \end{pmatrix} \sin(\tau-\tau')\langle \xi(\tau)\xi(\tau')\rangle, \end{aligned} \tag{2.79}$$

which reduces to (2.77) to

$$\frac{d}{d\tau}\langle \mathbf{u}(\tau)\rangle = A_0\langle \mathbf{u}(\tau)\rangle + \alpha^2 \begin{pmatrix} 0 & 0 \\ 1 & 0 \end{pmatrix} \int_0^\tau < \xi(\tau)\xi(\tau') > \sin(\tau-\tau')\langle \mathbf{u}(\tau')\rangle d\tau'. \tag{2.80}$$

Recalling that

$$\mathbf{u} = \begin{pmatrix} y \\ \dot{y} \end{pmatrix}.$$

The equation in vector form gives:

$$\begin{aligned}\frac{d}{d\tau}\begin{pmatrix} \langle y\rangle \\ \langle \dot{y}\rangle \end{pmatrix} &= \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix} \begin{pmatrix} \langle y\rangle \\ \langle \dot{y}\rangle \end{pmatrix} \\ &+ \alpha^2 \begin{pmatrix} 0 & 0 \\ 1 & 0 \end{pmatrix} \int_0^\tau f(\tau-\tau') \begin{pmatrix} \langle y\rangle \\ \langle \dot{y}\rangle \end{pmatrix} d\tau', \end{aligned} \tag{2.81}$$

where $f(\tau-\tau') = \langle \xi(\tau)\xi(\tau')\rangle \sin(\tau-\tau')$ and in component form

$$\frac{d}{d\tau}\langle y(\tau)\rangle = \langle \dot{y}\rangle, \tag{2.82}$$

$$\frac{d}{d\tau}\langle \dot{y}(\tau)\rangle = -\langle y(\tau)\rangle + \alpha^2 \int_0^\tau f(\tau-\tau')\langle y(\tau')\rangle d\tau', \tag{2.83}$$

with initial conditions $\langle y(0)\rangle = 1$ and $\langle \dot{y}(0)\rangle = 0$. Now by taking Laplace transform we get:

$$s\langle Y(s)\rangle - 1 = \langle \dot{Y}(s)\rangle, \tag{2.84}$$

$$s\langle \dot{Y}(s)\rangle = -\langle Y(s)\rangle + \alpha^2 F(s)\langle Y(s)\rangle. \tag{2.85}$$

By eliminating $\langle \dot{Y}(s) \rangle$ we get

$$\langle Y(s) \rangle = \frac{s}{s^2 - \alpha^2 F(s) + 1}. \tag{2.86}$$

To calculate $F(s)$ we assume the same correlation function as for the Van kampen case, i.e., $\langle \xi(\tau)\xi(\tau') \rangle = e^{-\gamma(\tau - \tau')}$ is a stationary Markov process. This gives:

$$\begin{aligned} F(s) &= L\{\langle \xi(\tau)\xi(\tau') \rangle \sin(\tau - \tau')\} \\ &= L\{e^{-\gamma(\tau-\tau')} \sin(\tau - \tau')\} \\ &= \frac{1}{(s+\gamma)^2 + 1}. \end{aligned} \tag{2.87}$$

Therefore

$$\begin{aligned} \langle Y(s) \rangle &= \frac{s}{s^2 - \frac{\alpha^2}{(s+\gamma)^2} + 1} \\ &= \frac{[(s+\gamma)^2 + 1]s}{s^2[(s+\gamma)^2 + 1] + [(s+\gamma)^2 + 1] - \alpha^2} \\ &= \frac{s[s^2 + 2\gamma s + (\gamma^2 + 1)]}{(s - z_1)(s - z_2)(s - z_3)(s - z_3)}, \end{aligned} \tag{2.88}$$

where z_1 z_2, z_3 and z_4 are the roots of the denominator. Calculating the inverse laplace transform directly involves finding the roots of a quartic which is extremely unwieldy, so we are going to solve it by using Maple (code is in appendix C) and also observe that correlation time $\tau_c << 1$ implies $\gamma >> 1$, and this obtain the following solution:

$$\begin{aligned} \langle y(\tau) \rangle &= -(1.02 \times 10^{-5}) e^{-5.00\,\tau} \cos(.50\,\tau) \\ &- (3.5 \times 10^{-5})\, e^{-5.00\,\tau} \sin(.50\,\tau) \\ &+ (\cos(1.00\,\tau) - (1.54 \times 10^{-5}) \sin(1.00\,\tau))\, e^{-1.82 \times 10^{-5}\,\tau}, \end{aligned} \tag{2.89}$$

which is almost the same answer as that obtained by using Van kampen's random differential equation approach and the figures 2.2 and 2.2 are almost indistinguishable.

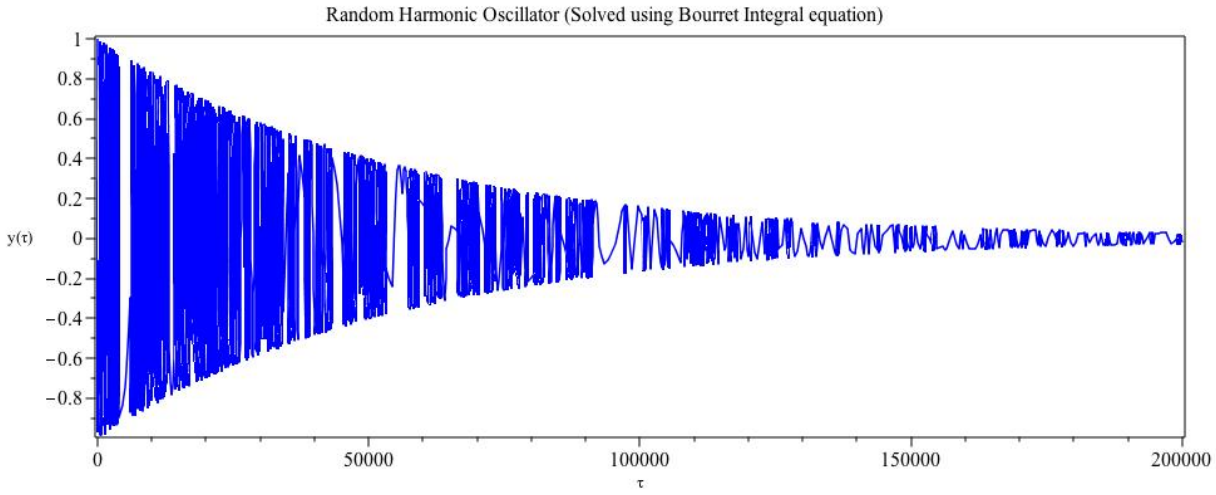

Figure 2.2: An illustration of the solution of random harmonic oscillator using Bourret integral equation of mean for $\alpha = .1$ and $\tau_c = .1$ where $\gamma = 1/\tau_c$

.

2.8 Some similar examples

We now examine the ideas of Van Kampen's approach in more detail through two specific examples.

2.8.1 Example:1

If we consider a decaying auto-correlation function fluctuating according to $B(\tau) = e^{-\gamma\tau}\cos\beta\tau$, then we can evaluate c_1 and c_2 using (2.67) and (2.68) as following:

$$\begin{aligned} c_1 &= \int_0^\infty e^{-\gamma\tau}\cos\beta\tau\sin 2\tau d\tau \\ &= \frac{1}{2}\Big[\frac{\beta+2}{(\beta+2)^2+\gamma^2} - \frac{\beta-2}{(\beta-2)^2+\gamma^2}\Big], \end{aligned} \tag{2.90}$$

$$
\begin{aligned}
c_2 &= \int_0^\infty e^{-\gamma\tau}\cos\beta\tau\big(\cos 2\tau - 1\big)d\tau \\
&= \frac{\gamma}{2}\Big[\frac{1}{(\beta-2)^2+\gamma^2} + \frac{1}{(\beta+2)^2+\gamma^2} - \frac{1}{\beta^2+\gamma^2}\Big].
\end{aligned} \tag{2.91}
$$

Substituting c_1 and c_2 in (2.70), we get

$$
\begin{aligned}
\frac{d^2}{d\tau^2}\langle x\rangle &= \frac{\gamma}{4}\alpha^2\omega_0\Big[\frac{1}{(\beta-2)^2+\gamma^2} + \frac{1}{(\beta+2)^2+\gamma^2} - \frac{1}{\beta^2+\gamma^2}\Big]\frac{d}{d\tau}\langle x\rangle \\
&- \omega_0^2\Big[1 - \frac{\alpha^2}{4}\Big(\frac{\beta+2}{(\beta+2)^2+\gamma^2} - \frac{\beta-2}{(\beta-2)^2+\gamma^2}\Big)\Big]\langle x\rangle.
\end{aligned} \tag{2.92}
$$

2.8.2 Example: 2

We now consider the following problem

$$
\ddot{x} = -\delta\dot{x} - \omega^2 x \tag{2.93}
$$

with $x(0) = a$, $\dot{x}(0) = 0$. Suppose $\omega(t)$ is a random function of time, such that

$$
\omega^2(t) = \omega_0^2(1 + \alpha\xi(t)) \tag{2.94}
$$

where ω_0=constant. Then the differential equation can be written as

$$
\ddot{x} = -\delta\dot{x} - \omega_0^2(1 + \alpha\xi(t))x \tag{2.95}
$$

where $\xi(t)$ is an external perturbation of size α and the size of the fluctuation is ω. The random function $\xi(t)$ is unknown except for some statistical properties such as, for example,

$$
\langle\xi(t)\rangle = 0. \tag{2.96}
$$

Rewriting the equation (2.95):

$$
\begin{aligned}
\frac{dx}{dt} &= \dot{x} \\
\frac{d\dot{x}}{dt} &= -\delta\frac{dx}{dt} - \omega_0^2(1 + \alpha\xi(t))x
\end{aligned}
$$

where $x(0) = a$, $\dot{x} = 0$, and so in matrix form, we have

$$\frac{d}{dt}\begin{pmatrix} x \\ \dot{x} \end{pmatrix}\begin{pmatrix} 0 & 1 \\ -\omega_0^2(1+\alpha\xi(t)) & -\delta \end{pmatrix}\begin{pmatrix} x \\ \dot{x} \end{pmatrix}. \tag{2.97}$$

Since the product $\alpha\xi$ is dimensionless, we can eliminate the constant ω_0^2 by making the whole problem dimensionless. Accordingly, we let $y = \frac{x}{a}$; $\tau = t\sqrt{\omega_0}$. Now equation (2.95) in dimensionless form becomes

$$\ddot{y}(\tau) = -k\dot{y} - (1+\alpha\xi(\tau))y(\tau), \tag{2.98}$$

where $y(0) = 1$, $k = -\frac{\delta}{\sqrt{\omega_0}}$ and in matrix form this equation can be written as:

$$\frac{d}{d\tau}\begin{pmatrix} y \\ \dot{y} \end{pmatrix} = \left[\begin{pmatrix} 0 & 1 \\ -1 & k \end{pmatrix} + \alpha\xi(\tau)\begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix}\right]\begin{pmatrix} y \\ \dot{y} \end{pmatrix}. \tag{2.99}$$

Using the notation introduced by Van Kampen (1976) [81] we have:

$$A_0 = \begin{pmatrix} 0 & 1 \\ -1 & k \end{pmatrix}, \tag{2.100}$$

$$A_1 = \xi(t)B = \xi(t)\begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix}, \tag{2.101}$$

and introducing the vector

$$\mathbf{u} = \begin{pmatrix} y \\ \dot{y} \end{pmatrix},$$

RDE (2.95) becomes:

$$\frac{d\mathbf{u}}{dt} = (A_0 + \alpha\xi(t)B)\mathbf{u}, \tag{2.102}$$

to which we can apply Van Kampen's argument that, as long as α is small and the correlation time τ_c is short, we may neglect terms of order $(\alpha\tau_c)^3$ in the perturbation expansion to conclude that under these conditions the first moment $\langle\mathbf{u}(\mathbf{t})\rangle$ i.e., the mean obeys a closed ODE, given by equation (10.4) of Van Kampen [81], viz:

$$\frac{d}{dt}\langle\mathbf{u}(t)\rangle = [A_0 + \alpha^2\int_0^\infty \langle A_1(t)e^{A_0\tau}A_1(t-\tau)\rangle e^{-A_0\tau}d\tau]\langle\mathbf{u}(t)\rangle, \tag{2.103}$$

using the definition (2.59) and (2.60) as well as dimensionless time τ, equation (2.103) becomes

$$\frac{d}{d\tau}\langle \mathbf{u}(\tau)\rangle = [A_0 + \alpha^2 \int_0^\infty \langle \xi(\tau)\xi(\tau-\tau')\rangle B e^{A_0\tau'} B e^{-A_0\tau'} d\tau']\langle \mathbf{u}\rangle. \tag{2.104}$$

We now evaluate the matrix exponential $e^{A_0\tau}$ by using the Cayley-Hamilton theorem, which is $e^{A_0\tau} = a_0 I + a_1 A_0$, where the coefficients a_0 and a_1 must be found.

$$\text{Eigenvalues of } A_0 \text{ are } \lambda = \tfrac{k \pm \sqrt{k^2-4}}{2}.$$
$$\text{let } \lambda_1 = \tfrac{k+\sqrt{k^2-4}}{2} \text{ and } \lambda_2 = \tfrac{k-\sqrt{k^2-4}}{2}.$$

By using the relation $e^{A_0\tau} = a_0 I + a_1 A_0$ we get the following:

$$e^{\lambda_1\tau} = a_0 + a_1\lambda_1 \text{ and } e^{\lambda_2\tau} = a_0 + a_1\lambda_2,$$

from which we get the values of a_0 and a_1 as following:

$$a_0 = \tfrac{\lambda_2 e^{\lambda_1\tau} - \lambda_1 e^{\lambda_2\tau}}{\lambda_2 - \lambda_1} \text{ and } a_1 = \tfrac{e^{\lambda_1\tau} - e^{\lambda_2\tau}}{\lambda_1 - \lambda_2}$$

Now

$$\begin{aligned} B e^{A_0\tau'} &= a_0 \begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix} \left[\begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} + a_1 \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix} \right] \\ &= a_0 \begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix} + a_1 \begin{pmatrix} 0 & 0 \\ 0 & -1 \end{pmatrix} \end{aligned}$$

and

$$\begin{aligned} B e^{A_0\tau'} B e^{-A_0\tau'} &= \left[a_0 \begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix} + a_1 \begin{pmatrix} 0 & 0 \\ 0 & -1 \end{pmatrix} \right] \left[a_0 \begin{pmatrix} 0 & 0 \\ -1 & 0 \end{pmatrix} - a_1 \begin{pmatrix} 0 & 0 \\ 0 & -1 \end{pmatrix} \right] \\ &= \begin{pmatrix} 0 & 0 \\ a_0 a_1 & a_1^2 \end{pmatrix}. \end{aligned} \tag{2.105}$$

Substituting the above expression into the equation (2.104) and switching back to the explicit matrix format we get:

$$\begin{aligned}\frac{d}{d\tau}\begin{pmatrix}\langle y\rangle\\ \langle \dot{y}\rangle\end{pmatrix} &= \begin{pmatrix}0 & 1\\ -1 & k\end{pmatrix}\begin{pmatrix}\langle y\rangle\\ \langle \dot{y}\rangle\end{pmatrix}\\ &+ \alpha^2\int_0^\infty \langle \xi(\tau)\xi(\tau-\tau')\rangle \begin{pmatrix}0 & 0\\ a_0a_1 & -a_1^2\end{pmatrix} d\tau' \begin{pmatrix}\langle y\rangle\\ \langle \dot{y}\rangle\end{pmatrix}. \end{aligned} \tag{2.106}$$

If we define the two coefficients

$$c_1 = \int_0^\infty \langle \xi(\tau)\xi(\tau-\tau')\rangle a_0a_1 \quad d\tau', \tag{2.107}$$

$$c_2 = -\int_0^\infty \langle \xi(\tau)\xi(\tau-\tau')\rangle a_1^2 \quad d\tau', \tag{2.108}$$

we can rewrite equation (2.106) in the simple form

$$\frac{d}{d\tau}\begin{pmatrix}\langle y\rangle\\ \langle \dot{y}\rangle\end{pmatrix} = \begin{pmatrix}0 & 1\\ -1 & k\end{pmatrix}\begin{pmatrix}\langle y\rangle\\ \langle \dot{y}\rangle\end{pmatrix} + \frac{\alpha^2}{2}\begin{pmatrix}0 & 0\\ c_1 & c_2\end{pmatrix}\begin{pmatrix}\langle y\rangle\\ \langle \dot{y}\rangle\end{pmatrix}, \tag{2.109}$$

or as a single ODE

$$\frac{d^2}{d\tau^2}\langle y\rangle = (1+k+\alpha^2c_2)\langle \dot{y}\rangle - (1-\alpha^2c_1)\langle y\rangle, \tag{2.110}$$

and in dimensional form as:

$$\frac{d^2}{dt^2}\langle x\rangle = \sqrt{\omega_0}\big(1-\frac{\delta}{\sqrt{\omega_0}}+\alpha^2c_2\big)\frac{d}{dt}\langle x\rangle - \omega_0\big(1-\alpha^2c_1\big)\langle x\rangle. \tag{2.111}$$

Chapter 3

Application of Van Kampen's theory to Pharmacokinetics

3.1 Deterministic formulation of the model

To model this situation deterministically, we proceed as follows. Let $X(t)$ be the amount of drug at the absorption site at time t, and let k_a be the apparent first-order absorption rate constant; then

$$\frac{dX}{dt} = -k_a X \tag{3.1}$$

is the rate of drug loss from the absorption site. Next let $A(t)$ be the amount of drug in the body at time t; then

$$\frac{dA}{dt} = k_a X - k_e A \tag{3.2}$$

is the rate of change of the amount of drug in the body, with the elimination rate constant k_e and the initial conditions

$$X(0) = X_0, \qquad A(0) = 0 \tag{3.3}$$

where X_0 is the dose administered at time $t = 0$ orally or intramuscularly, the solution of the system (3.1) to (3.3) is given by

$$\begin{aligned} X &= X_0 e^{-k_a t}, \\ A &= \frac{k_a X_0}{ka - ke}(e^{-k_e t} - e^{-k_a t}). \end{aligned} \tag{3.4}$$

The volume of distribution is often referred to as the apparent volume of distribution and can aid in the determination of dosage requirements. Generally, dosing is assumed to be proportional to the volume of distribution [14]. For example, the larger the volume of distribution, the larger the dose must be to achieve a desire target concentration. Now dividing by the volume of distribution V we can write A in concentration form as (where $C(t) = \frac{A(t)}{V}$ and V is the apparent volume of distribution [14]):

$$C(t) = \frac{k_a X_0}{V(k_a - k_e)}(e^{-k_e t} - e^{-k_a t}). \tag{3.5}$$

Now from the plasma concentration curve, we can extract the parameters k_a and k_e and the methods of extracting the parameter values from the concentration versus time curve have been discussed in chapter 2, along with their characteristics.

In the next section the stochastic version of this PK model will be introduced.

3.2 Stochastic formulation of the model

Drug absorption kinetics for oral or intramuscular administration is a complex phenomenon. The loss of a drug from the absorption site is due, in large part, to intrinsic absorption, that is to the passage of the drug directly into the circulation. However, a (usually) small fraction of the loss may be due to other phenomena, such as degradation of the drug at intramuscular sites or due to drug precipitation. The result is that there is uncertainty as to the meaning of the absorption rate constant k_a, used in the traditional deterministic model (3.1)-(3.3).

On the other hand, one can take the uncertainty into account in a statistical sense, by assuming that the absorption rate is not constant, but fluctuates in time around some average value $\overline{k_a}$. Therefore, one can write that the full absorption rate $k_a(t)$ is given by

$$k_a(t) = \overline{k_a}(1 + \alpha\xi(t)); \qquad k_e = \overline{k_e}, \tag{3.6}$$

where $\xi(t)$ is a random function and α is a (small) constant coupling the average absorption rate to the random fluctuations.

The random function ξ is not known, of course, but reasonable statistical assumptions about it can be made. Thus, since by definition $\langle k_a(t)\rangle = \overline{k_a}$ it follows from equation (3.6) that the expectation of $\xi(t)$ must vanish; i.e.,

$$\langle \xi(t)\rangle = 0, \tag{3.7}$$

A further statistical property of $\xi(t)$ can be prescribed by specifying its auto-correlation function, viz.

$$\Gamma(t, t') = \langle \xi(t)\xi(t') \rangle \tag{3.8}$$

which will be discussed in detail in a later section.

The result of these stipulations is that the system of deterministic ODE's (3.1)-(3.3) become a stochastic system of RDE's, namely

$$\frac{dX}{dt} = -\overline{k_a}(1 + \alpha\xi(t))X \tag{3.9}$$

$$\frac{dA}{dt} = \overline{k_a}(1 + \alpha\xi(t))X - \overline{k_e}A \tag{3.10}$$

3.3 The Van Kampen approximation of the model

In this section we are going to apply the Van Kampen approximation to solve our RDEs (3.9) and (3.10). For convenience we simplify these equations by making them dimensionless, for which proper scales need to be used. For both the amount of drug at the absorption site X and the amount of drug in the circulation A there is an obvious scale namely the initial dose X_0 so that their dimensionless version are simply

$$x = \frac{X}{X_0} \qquad y = \frac{A}{X_0} \tag{3.11}$$

However, there is no obvious time scale t . Hence, as done in these cases in ordinary perturbation theory, one can introduce a dimensionless time

$$\tau = \frac{t}{T_0} \tag{3.12}$$

and determine T_0 by choosing the value that makes the RDE's take the simplest possible form. Using the definitions (3.11)-(3.12) reduces the system of RDE's (3.9)-(3.10) to the following form:

$$\frac{dx(\tau)}{d\tau} = -\overline{k_a}T_0(1 + \alpha\xi)x(\tau) \tag{3.13}$$

$$\frac{dy(\tau)}{d\tau} = \overline{k_a}T_0(1 + \alpha\xi)x(\tau) - \overline{k_e}T_0 y(\tau) \tag{3.14}$$

and it is now obvious that the simplest form of these equations is obtained with the choice

$$T_0 = (\overline{k_a})^{-1}; \qquad \rho = \overline{k_e}(\overline{k_a})^{-1} \tag{3.15}$$

after which the final form of the model can be written in the form useful for the application of van kampen's theory, namely

$$\frac{du}{d\tau} = (A_0 + \alpha A_1(\tau))u(\tau), \tag{3.16}$$

$$u(0) = \begin{pmatrix} 1 \\ 0 \end{pmatrix}, \tag{3.17}$$

where

$$u = \begin{pmatrix} x \\ y \end{pmatrix}; \qquad A_0 = \begin{pmatrix} -1 & 0 \\ 1 & -\rho \end{pmatrix}; \qquad A_1(\tau) = \xi(\tau)B = \xi(\tau)\begin{pmatrix} -1 & 0 \\ 1 & 0 \end{pmatrix}. \tag{3.18}$$

When these quantities are substituted into van Kampen's general differential equation for the mean (reviewed in section 2.5), the result is:

$$\frac{d}{d\tau}\langle u(\tau)\rangle = \left[A_0 + \alpha^2 \int_0^\infty \langle \xi(\tau)\xi(\tau - \tau')\rangle B e^{A_0\tau'} B e^{-A_0\tau'} d\tau'\right]\langle u(\tau)\rangle, \tag{3.19}$$

which shows explicitly the importance of the noise auto-correlation function.

Now we are going to solve (3.19) for A_0 and A_1. First we are evaluating $e^{A_0\tau}$:

$$A_0 = \begin{pmatrix} -1 & 0 \\ 1 & -\rho \end{pmatrix}$$

Eigen values are: $\lambda = -1, -\rho$ and the corresponding Eigen vectors are : $\begin{pmatrix} 1 \\ \frac{1}{\rho - 1} \end{pmatrix}$ and $\begin{pmatrix} 0 \\ 1 \end{pmatrix}$. So the fundamental matrix for $\phi(\tau)$ for A_0 is:

$$\begin{aligned} \phi(\tau) &= \begin{bmatrix} e^{-\tau}\begin{pmatrix} \rho - 1 \\ 1 \end{pmatrix} & e^{-\rho\tau}\begin{pmatrix} 0 \\ 1 \end{pmatrix} \end{bmatrix} \\ &= \begin{bmatrix} e^{-\tau}(\rho - 1) & 0 \\ e^{-\tau} & e^{-\rho\tau} \end{bmatrix}, \end{aligned}$$

$$\phi^-(\tau) = \frac{1}{e^{-\tau}e^{-\rho\tau}(\rho-1)} \begin{bmatrix} e^{-\rho\tau} & 0 \\ -e^{-\tau} & e^{-\tau}(\rho-1) \end{bmatrix},$$

$$\phi^-(0) = \frac{1}{(\rho-1)} \begin{bmatrix} 1 & 0 \\ -1 & \rho-1 \end{bmatrix},$$

$$e^{A_0\tau} = \phi(\tau)\phi^-(0) = \begin{bmatrix} e^{-\tau} & 0 \\ \frac{e^{-\tau}-e^{-\rho\tau}}{\rho-1} & e^{-\rho\tau} \end{bmatrix},$$

$$e^{-A_0\tau} = \begin{bmatrix} e^{\tau} & 0 \\ \frac{e^{\tau}-e^{\rho\tau}}{\rho-1} & e^{\rho\tau} \end{bmatrix},$$

$$\begin{aligned} Be^{A_0\tau} &= \begin{pmatrix} -1 & 0 \\ 1 & 0 \end{pmatrix} \begin{pmatrix} e^{-\tau} & 0 \\ \frac{e^{-\tau}-e^{-\rho\tau}}{\rho-1} & e^{-\rho\tau} \end{pmatrix} \\ &= \begin{bmatrix} -e^{-\tau} & 0 \\ e^{-\tau} & 0 \end{bmatrix}, \end{aligned}$$

$$Be^{-A_0\tau} = \begin{bmatrix} -e^{\tau} & 0 \\ e^{\tau} & 0 \end{bmatrix}.$$

Now

$$Be^{A_0\tau}Be^{-A_0\tau} = \begin{bmatrix} 1 & 0 \\ -1 & 0 \end{bmatrix} \tag{3.20}$$

Substitute the equation (3.20) into equation (3.19), we get

$$\frac{d}{d\tau}\langle u(\tau)\rangle = \left[A_0 + \alpha^2 \int_0^\infty \langle \xi(\tau)\xi(\tau-\tau')\rangle \begin{bmatrix} 1 & 0 \\ -1 & 0 \end{bmatrix} d\tau'\right]\langle u(\tau)\rangle,$$

in matrix form:

$$\begin{aligned} \frac{d}{d\tau}\begin{pmatrix} \langle x\rangle \\ \langle y\rangle \end{pmatrix} &= \begin{pmatrix} -1 & 0 \\ 1 & -\rho \end{pmatrix}\begin{pmatrix} \langle x\rangle \\ \langle y\rangle \end{pmatrix} \\ &+ \alpha^2 \int_0^\infty \langle \xi(\tau)\xi(\tau-\tau')\rangle \begin{pmatrix} 1 & 0 \\ -1 & 0 \end{pmatrix} d\tau' \begin{pmatrix} \langle x\rangle \\ \langle y\rangle \end{pmatrix}. \end{aligned}$$

In practice, often, Orstein-Uhlenbeck process with mean zero and $\langle \xi(\tau)\xi(\tau-\tau')\rangle = e^{-|\tau'|/\tau_c}$ with a correlation time τ_c, used to describe colored noise. In our model we also considered $\xi(t)$ as an Orstein-Uhlenbeck process, with mean zero and auto-correlation function $e^{-|\tau'|/\tau_c}$ (i.e., $\int_0^\infty \langle \xi(\tau)\xi(\tau-\tau')\rangle d\tau' = \int_0^\infty e^{-|\tau'|/\tau_c} d\tau' = \tau_c$) and using this we will be able to get:

$$\frac{d}{d\tau}\begin{pmatrix}\langle x\rangle\\ \langle y\rangle\end{pmatrix} = \begin{pmatrix}-1 & 0\\ 1 & -\rho\end{pmatrix}\begin{pmatrix}\langle x\rangle\\ \langle y\rangle\end{pmatrix} + \alpha^2\begin{pmatrix}\tau_c\\ -\tau_c\end{pmatrix}\begin{pmatrix}\langle x\rangle\\ \langle y\rangle\end{pmatrix}. \tag{3.21}$$

Now it is possible to write our stochastic DE as following form:

$$\frac{d}{d\tau}\langle x\rangle = -(1-\alpha^2\tau_c)\langle x\rangle, \tag{3.22}$$

$$\frac{d}{d\tau}\langle y\rangle = (1-\alpha^2\tau_c)\langle x\rangle - \rho\langle y\rangle, \tag{3.23}$$

and the dimensional form will be (for simplicity we use k_a and k_e instead of $\bar{k_a}$ and $\bar{k_e}$):

$$\frac{d}{dt}\langle X\rangle = -k_a(1-\alpha^2\tau_c)\langle X\rangle, \tag{3.24}$$

$$\frac{d}{dt}\langle A\rangle = k_a(1-\alpha^2\tau_c)\langle X\rangle - k_e\langle A\rangle. \tag{3.25}$$

Equations (3.22) and (3.23) are the representation of the RDE's using Van Kampen approximation.

3.3.1 Calculation of the second moment using Van Kampen's method

We have calculated the mean equation using Van Kampen's method for both X and A. Our next step is to calculate the second moments which we will be able to use to capture the variability of the random effects, induced by the random variations in the absorption rate. We compare Van Kampen's approximation to the model with the full numerical solution by evaluating the variance. In this section we describe how we calculate the second moments of X and A using Van Kampen method.

The non dimensional form of the Van Kampen approximation to our model, i.e., (3.16) can be written as:

$$\frac{dX}{d\tau} = -(1+\alpha\xi(\tau))X, \tag{3.26}$$

$$\frac{dA}{d\tau} = (1 + \alpha\xi(\tau))X - \rho A. \tag{3.27}$$

Using the Einstein summation convention, it is convenient to write the linear system in indicial notation:

$$\frac{du_i}{dt} = A_{ij}u_j \tag{3.28}$$

$$\frac{d}{dt}u_i u_k = \dot{u}_i u_k + u_i \dot{u}_k = u_k A_{ij} u_j + u_i A_{kj} u_j \tag{3.29}$$

Now using (3.29) for our model we can write the system as:

$$\begin{aligned}
\frac{d}{d\tau}(AX) &= (-(1 + \alpha\xi(\tau)) - \rho)AX + (1 + \alpha\xi(\tau))X^2, \\
\frac{d}{d\tau}(A^2) &= 2A((1 + \alpha\xi(\tau))X - \rho A), \\
\frac{d}{d\tau}(X^2) &= 2X(-(1 + \alpha\xi(\tau))X).
\end{aligned} \tag{3.30}$$

In matrix form (3.30) can be written as:

$$\begin{aligned}
\frac{d}{d\tau}\begin{bmatrix} AX \\ A^2 \\ X^2 \end{bmatrix} &= \begin{bmatrix} -1-\rho & 0 & 1 \\ 2 & -2\rho & 0 \\ 0 & 0 & -2 \end{bmatrix}\begin{bmatrix} AX \\ A^2 \\ X^2 \end{bmatrix} \\
&+ \alpha\xi(\tau)\begin{bmatrix} -1 & 0 & 1 \\ 2 & 0 & 0 \\ 0 & 0 & -2 \end{bmatrix}\begin{bmatrix} AX \\ A^2 \\ X^2 \end{bmatrix}. \\
\implies \frac{dU}{d\tau} &= (A_0 + \alpha\xi(\tau)B)U
\end{aligned}$$

where

$$U = \begin{bmatrix} AX \\ A^2 \\ X^2 \end{bmatrix},$$

$$A_0 = \begin{bmatrix} -1-\rho & 0 & 1 \\ 2 & -2\rho & 0 \\ 0 & 0 & -2 \end{bmatrix},$$

$$B = \begin{bmatrix} -1 & 0 & 1 \\ 2 & 0 & 0 \\ 0 & 0 & -2 \end{bmatrix}.$$

Following the method we have used to evaluate the mean by using Van Kampen's approximation equation (3.19), also can be calculate the evolution equations for $\langle AX \rangle$, $\langle A^2 \rangle$ and $\langle X^2 \rangle$ as:

$$\begin{aligned} \frac{d}{d\tau} \begin{bmatrix} \langle AX \rangle \\ \langle A^2 \rangle \\ \langle X^2 \rangle \end{bmatrix} &= \begin{bmatrix} -1-\rho & 0 & 1 \\ 2 & -2\rho & 0 \\ 0 & 0 & -2 \end{bmatrix} \begin{bmatrix} \langle AX \rangle \\ \langle A^2 \rangle \\ \langle X^2 \rangle \end{bmatrix} \\ &+ \alpha^2 \tau_c \begin{bmatrix} 1 & 0 & -\frac{(2\rho-3)+\frac{\rho}{1+\tau_c(\rho-1)}}{\rho-1} \\ -2 & 0 & -\frac{2-\frac{2\rho}{1+\tau_c(\rho-1)}}{\rho-1} \\ 0 & 0 & 4 \end{bmatrix}, \begin{bmatrix} \langle AX \rangle \\ \langle A^2 \rangle \\ \langle X^2 \rangle \end{bmatrix} \end{aligned} \tag{3.31}$$

where we have considered as before $< \xi(\tau)\xi(\tau - \tau') >= e^{-|\tau'|/\tau_c}$, with a correlation time τ_c

3.4 Numerical solution of the model

3.4.1 To solve RDE's (3.9) and (3.10)

In this section we describe the method used to solve the model numerically. We have used the modified Euler's method to solve the system of DE, where the noise term is treated with the algorithm described by Gillespie [30] in his 1996 paper. The noise we consider is assumed to be an Ornstein-Uhlenbeck process [78], which is often used to model colored noise. Gillespie [30] developed an algorithm for any exact time step $\Delta t > 0$ for the Ornstein-Uhlenbeck process and its time integral. Detailed evaluation of the Ornstein Uhlenbeck process from Newton's second law is in the appendix B.

A Langevin equation governed by a Ornstein Uhlenbeck process can be written as:

$$\frac{dy}{dt} = G(y,t) + c(y,t)F(t), \tag{3.32}$$

where $F(t)$ is an Ornstein Uhlenbeck process and can be defined as:

$$\frac{dF(t)}{dt} = -\frac{1}{\tau_c}F(t) + \frac{1}{\tau_c}\eta(t) \tag{3.33}$$

where $\eta(t)$ represents the Gaussian white noise with mean zero and variance 1 and τ_c is the correlation time of the colored noise $F(t)$ [71].

Remark: The steady-state auto-correlation function of $F(t)$ can be written as :

$$\langle F(t)F(t-\tau)\rangle = \frac{1}{2\tau_c}e^{-|\tau|/\tau_c} \xrightarrow{\tau_c\to 0} \delta(\tau), \tag{3.34}$$

which shows that, if auto-correlation time approaches to 0, then the colored noise will be white noise, i.e, the noise will be δ correlated.

The simulation algorithm of a system of random differential equations of the form (3.32)-(3.33) consists of following steps [71]:

- Step 1: Initialize: $t = t_0$, $y = y_0$ and $F = F_0$;
- Step 2: We have to choose a suitable small $\Delta t > 0$ (according to the assumption (2.47));
- Step 3: Next we are going to draw a sample value n of the unit normal random variable $N(0, 1)$;
- Step 4: In this step the process will advance as following:
  $\bullet y(t+\Delta t) = y(t) + nc(y,t)[\Delta t]^{1/2} + G(y,t)\Delta t,$
  $\bullet\ F(t+\Delta t) = F(t)e^{-\Delta t/\tau_c} + n\left[(\frac{1}{2\tau_c})(1-e^{-2\Delta t/\tau_c})\right]^{1/2},$
  $\bullet\ t = t + \Delta t,$
  where n is the unit normal random variable chosen in step 3;
- Step 5: In this step we are going to record $y(t) = y$ and can use it for sample plotting and to continue the process further we have to return to step 3, otherwise stop.

The RDE system of our model has been solved following steps 1-5 above:

$$\begin{aligned}
\frac{dX}{dt} &= -k_a(1+\alpha\xi(t))X,\\
\frac{dA}{dt} &= k_a(1+\alpha\xi(t))X - k_eA,\\
\frac{d\xi(t)}{dt} &= -\frac{1}{\tau_c}\xi(t) + \frac{1}{\tau_c}\eta(t),
\end{aligned} \tag{3.35}$$

where $\eta(t)$ again represents Gaussian white noise with mean zero and variance 1 and τ_c is the correlation time [71].

Matlab 9.1 R2016b has been used to solve the RDE's (3.35). Following the steps described above for the random process (3.32), where in this particular case:

$$y(t) = \begin{pmatrix} y_1(t) \\ y_2(t) \end{pmatrix} = \begin{pmatrix} X(t) \\ A(t) \end{pmatrix}.$$

Now, comparing with equation (3.32), our system can be written as:

$$G(y,t) = \begin{pmatrix} -k_a X(t) \\ k_a X(t) - k_e A(t) \end{pmatrix},$$

$$c(y,t) = \begin{pmatrix} -k_a \alpha X(t) \\ k_a \alpha X(t) \end{pmatrix},$$

$$\text{and } F(t) = \xi(t).$$

At the initial time $t = 0$, we have considered the initial conditions $X(0) = X_0 =$ Dose and $A(0) = 0$ (as there is no drug in the system at initial time) and iterate until the final time t=tfinal. We run a large number of simulations to obtain individual trajectories (say 10000 or so) to get the ensemble mean and use the Matlab built in command "std" to get the standard deviation of the trajectories around the mean. (Detailed codes have been included in appendix B).

3.4.2 To solve Van Kampen's form of the model

We have used the Runge Kutta method to solve the Van Kampen form of the model (code is in the appendix B) for both the moments. Here we have a system of two decoupled equations: two equations for the mean and three for the second moments (i.e., the variance). The following relation has been used to evaluate the variances for both X and A:

- variance of X=$(\langle XX\rangle - \langle X\rangle^2)$;
- variance of A= $(\langle AA\rangle - \langle (A)\rangle^2)$.

Now before solving the system of DE (for mean and variance), we need to consider the conditions which will assure us to get the stable solutions, i.e, criterion for linear, homogeneous differential equations which will converge to zero. We are going to use the Routh-Hurwitz criterion for this purpose, which states that: the necessary and sufficient conditions for the roots of characteristic polynomial (with real coefficients) is to lie in the left half of the complex plane [23]. According to this criterion, a polynomial is stable if all the roots of the polynomial have strictly negative real parts, if and only if all the leading principal minors of a square matrix are positive. Using Matlab for equation(3.31) to evaluate the characteristic polynomial by neglecting τ_c^2 and τ_c^3 terms (as we are considering very small correlation time), we calculated the following cubic equation for eigenvalues λ:

$$\lambda^3+(-5\tau_c\alpha^2+3\rho+3)\lambda^2+(-\alpha^2\tau_c(14\rho+6)+(2\rho^2+8\rho+2))\lambda+(-\alpha^2\rho\tau_c(8\rho+12)+4\rho(\rho+1))=0 \tag{3.36}$$

Now using the Routh-Hurwitz criterion [23], for this cubic polynomial we can compare the coefficients of (3.36) to evaluate the conditions to get the stable solutions.

$$\alpha^2\tau_c < \frac{3(\rho+1)}{5} \tag{3.37}$$

and

$$\alpha^2\tau_c < \frac{3\rho^3+13\rho^2+13\rho+3}{22\rho^2+44\rho+14}. \tag{3.38}$$

From, conditions (3.37) and (3.38) we should choose the right hand side that is smaller (in order to satisfy both the conditions). Now, say (3.37)<(3.38) we obtain the following:

$$51\rho^3+133\rho^2+109\rho+27<0 \tag{3.39}$$

which is a contradiction as $\rho > 0$, so we can conclude the condition should be (3.38).

By applying the same criterion in the relation (3.21), we can calculate the stability for the mean is:

$$\alpha\tau_c < 1 \tag{3.40}$$

which is satisfied under the assumption only α is small enough.

3.4.3 Parameters choice and initial conditions

Example 1.

For the numerical simulation we use data and information from some practical applications (i.e., some regularly used drugs with their common dosage). Acetaminophen is a very

popular and common drug which has been used for a long time as a pain reliever and also to reduce fever. There are various other conditions which have also been treated with acetaminophen and these include head aches, muscle aches, arthritis, back aches, tooth aches, colds, and fevers. Acetaminophen is a major ingredient in most cold and flu medications which can be bought over the counter and is also present in some prescription medications.

A pharmaceutical window (or popularly known as therapeutic window) of a drug is a region of the drug dosage, where a disease can be effectively treated without showing noticeable evidence of toxic side effects. Drugs, which have a narrow or very small therapeutic window must be administered with extreme care and control, by measuring concentrations of the drug in the body, in order to minimize any harmful side effects. Acetaminophen has a narrow therapeutic window and due to its availability and wide range of use, there are clear possibilities for accidental or deliberate overdose. Overdose may create hepatoxicity, which can lead major problems, such as abnormalities in liver function, acute liver failure and even death [37].

According to the FDA, the standard dose of acetaminophen for adults (for 12 years and older) is 4000 mg per day [77].

The values of the parameters, we consider are taken from the study [60]. The half life of acetaminophen is 2.5 hours, so k_e can be calculated using the relation:

$$k_e = \frac{\ln(2)}{\text{half life}} = \frac{\ln(2)}{2.5} = .28/\text{hour} \tag{3.41}$$

Volume of distribution is .60 L/kg, which will be .60L/kg $\times$ 70kg = 42L for an average 70 kg adult. The absorption rate constant $k_a = 1.80$/hour and the bioavailability F=.89 (fraction of amount absorbed by the stomach) [60]. In this case we see that there is no possibility to get the "flip-flop" kinetics (i.e., k_e will not be greater than k_a).

For the choice of α and τ_c, we considered the conditions of mean and mean-squared stability to get the stable solutions, which is described in (3.38), where $\rho = \frac{k_e}{k_a}$.

To consider the initial conditions for mean X (amount of drug in the absorption site) and A (amount of drug in the systemic circulation), we chose $X(0) = X_0 = Dose = 1000\,\text{mg}$ and $A_0 = 0$ as there is no drug initially in the blood plasma. As we are considering multiple dosages, so we add a dose every six hours by dividing our total time (24 hours) into four sub intervals and adding a dose instantaneously at the beginning of each interval. For this reason, X has a jump discontinuity when ever the dose is added to the system, figure 3.1.

Now for the initial conditions to evaluate $\langle X^2 \rangle$, $\langle AX \rangle$ and $\langle A^2 \rangle$ we assume the following:

- X = the amount of drug before adding a dose at time t_1 and Y= amount of drug instantaneously after adding a dose at time t_1;
- then we can say $Y = X + \text{Dose}$ and can write $\langle Y \rangle = \langle X \rangle + \text{Dose}$;
- $\langle YY \rangle = \langle (X + Dose)^2 \rangle = \langle X^2 + 2X\text{Dose} + \text{Dose}^2 \rangle = \langle XX \rangle + 2\langle X \rangle \text{Dose} + \text{Dose}^2$;
- $\langle AY \rangle = \langle A(X + \text{Dose}) \rangle = \langle AX + A\text{Dose} \rangle = \langle AX \rangle + \langle A \rangle \text{Dose}$.

For the time step to solve the system we chose Δt by taking into consideration the constraint $\alpha t_c << \alpha \Delta t << 1$, from the assumption of theorem (2.47).

Example 2.

For this example we consider the drug Theophylline, which is a methylxanthine drug used in therapy for respiratory diseases, for example: chronic asthma, Chronic Obstructive Pulmonary Disease (COPD) or chronic bronchitis. The oral dose of the drug is well absorbed as tablet or as liquid solution [64]. Data is taken from Lixoft - Modeling and simulation software for drug development [50]. In this study, 12 subjects were chosen to administer the drug orally and the concentration of blood serum were collected at 11 times over the next 25 hours.

We use the method of residuals (describe below) to evaluate k_a and k_e for the drug Theophyline from the data provided by the study [50]. This data set is for 12 patients, we consider patient#1, a male of weight 79.6 kg, the amount of drug given is 4.02/kg. As we know from the equation (3.5) concentration can be represented as:

$$C(t) = \frac{k_a F X_0}{V(k_a - k_e)}(e^{-k_e t} - e^{-k_a t}). \tag{3.42}$$

Now if we assume $k_a > k_e$, then the term $e^{-k_a t}$ will approach zero faster than $e^{-k_e t}$, and so equation (3.42) can be approximated by:

$$C(t) = \frac{k_a F X_0}{V(k_a - k_e)} e^{-k_e t}. \tag{3.43}$$

By taking logarithm of both sides of the above equation we get:

$$\log(C(t)) = \log \frac{k_a F X_0}{V(k_a - k_e)} - \frac{k_e t}{2.303}. \tag{3.44}$$

Equation (3.44) can be used to evaluate k_e and also by extrapolating this line for $t = 0$ we can get the intercept=$\frac{k_a F X_0}{V(k_a - k_e)}$. Subtracting (3.42) from (3.43) obtain the residual plasma concentration equation:

$$C_r(t) = \frac{k_a F X_0}{V(k_a - k_e)} e^{-k_a t} \tag{3.45}$$

In terms of logarithm which will be:

$$\log(C_r(t)) = \log \frac{k_a F X_0}{V(k_a - k_e)} - \frac{k_a t}{2.303} \tag{3.46}$$

Hence we can calculate k_a from the equation (3.46). For our example we are considering

Table 3.1: **Concentration of Theophyline in serum for subject** #1 [50]

Time	**Cnc**	**log(Cnc)**	**ECnc**	**log(ECnc)**	**RCnc**	**log(RCnc)**
0	0		11.51	1.06	10.77	1.03
0.25	2.84	0.45	11.30	1.05	8.46	0.93
0.57	6.57	0.82	10.94	1.04	4.37	0.64
1.12	10.5	1.02	10.38	1.02	-0.12	NAN
2.02	9.66	0.98	9.35	0.97	-0.31	NAN
3.82	8.58	0.93	8.67	0.94	0.09	-1.023
5.1	8.36	0.92	7.75	0.89	-0.61	NAN
7.03	7.47	0.87	6.89	0.84	-0.58	NAN
9.05	6.89	0.84	5.76	0.76	-1.13	NAN
12.12	5.94	0.77	2.82	0.45	-3.12	NAN
24.37	3.28	0.52	11.68	1.07	8.40	0.92

subject # 1, who is a male of weight 79.06 kg. The amount of drug for this person was 4.02 mg/kg. Here are the PK parameters for subject # 1:

$$\text{slope of } k_e = \frac{.87-.92}{7.03-5.1} = -0.03 \text{ (highlighted in red)}$$

$$k_e = 0.03 \times 2.30 = 0.06$$

$$\text{Intercept=log(Cnc)} - \text{slope} * t = .84 - (-.03) \times 9.05 = 1.07 \text{ (highlighted in blue)}$$

$$\text{ECnc==} 10^{(\text{slope}*t+\text{Intercept})} \text{ (extrapolated concentration, column 4 of 3.4.3)}$$

RCnc=ECnc-Cnc (residual concentration, column 6 of 3.4.3)

$$\text{AI}= 10^{(\text{Intercept})}$$

$$\text{Amount}= 4.02 \text{ (given)}; \text{ Weight}= 79.6,$$

$$\text{Dose}=(\text{Amount})\times \text{ (Weight)}$$

$$\text{Slope residual } = \frac{.64-.93}{.57-.25} = -0.89 \text{ (highlighted in green)}$$

$$k_a\text{=-slope Residual } \times 2.303 = 2.062927706$$

$$V = (ka * \text{Dose} * F)/(\text{AI} * (ka - ke)) = 28.19$$

Where we have considered the bio-avalability of theophyline to be on average 96% ≈ 1 [64]

All these parameter values are used to solve the deterministic form, numerical form and Van Kampen form of the model and also to compare with the experimental data (Code is in the appendix C)

3.5 Results

3.5.1 Test case 1.

Fig. 3.1 is the comparison of the mean for all three forms of the model while drug is in the absorption site, i.e., for $X(t)$. Stochastic form of the model is the 10,000 iteration of the simulation to get the ensemble mean which is plotted along with the deterministic (evaluated using deterministic form of the model) and Van Kampen's form of the model to investigate whether all three coincide or not. From the figure 3.1, we can say that all these mean almost perfectly coincide with each other and we see a jump in every six hours as we administer a dose every six hours. Parameters for figure 3.1 are chosen: $\alpha = .2$, $\Delta = .25$ hour, $\tau_c = .001$ hour, $\rho = k_e/k_a = .17$ which satisfies our constraints $\alpha\tau_c = 4 \times 10^{-5} << \alpha\Delta t = .01 << 1$ (2.47).

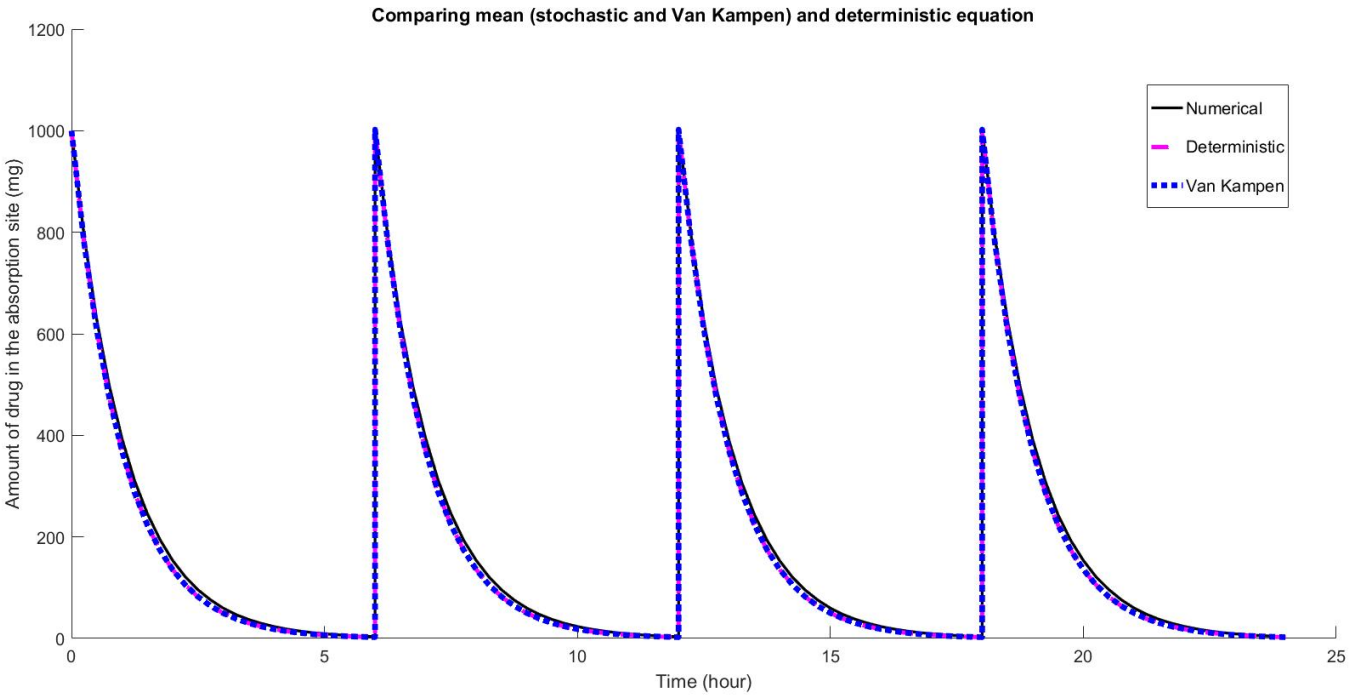

Figure 3.1: Comparing the deterministic solution with the mean of Stochastic and Van Kampen's form of the model, for $\alpha = .2$, $\Delta t = .25$ hour and $\tau_c = .001$ hour while drug in the absorption site

.

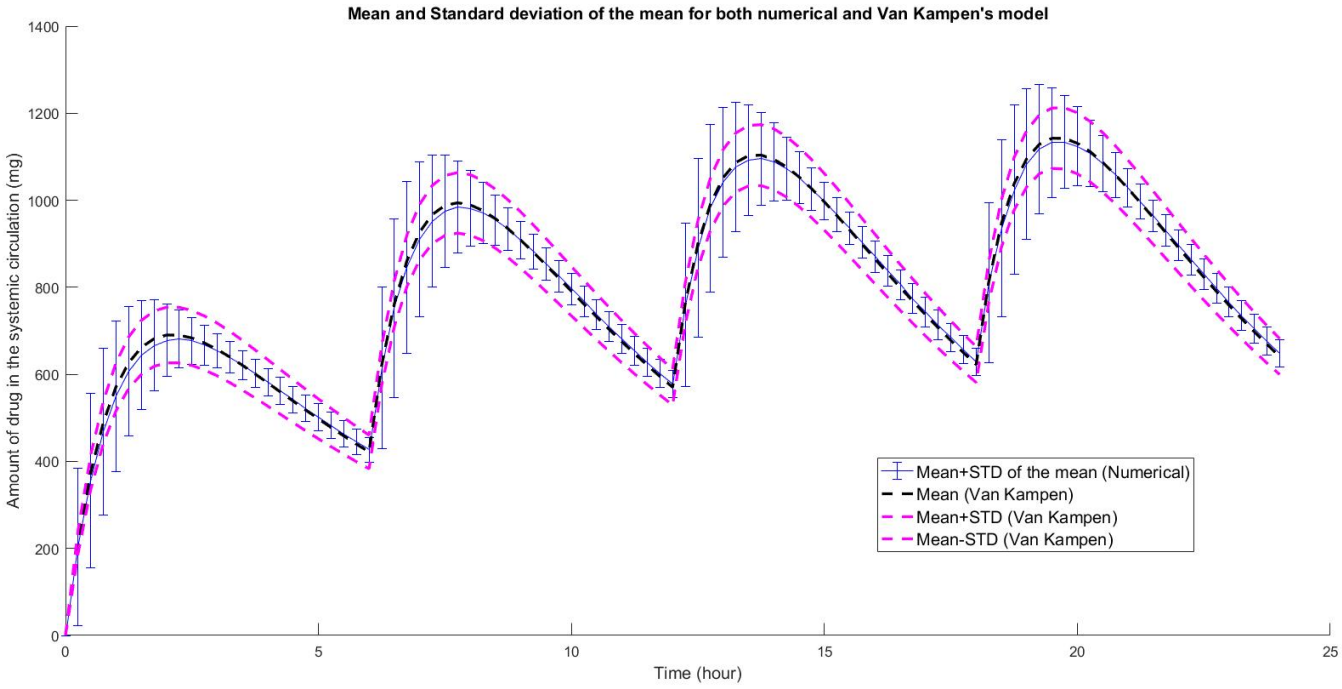

Figure 3.2: Comparison of stochastic standard deviation of the mean and approximate variance using Van Kampen method for $\alpha = .3$, $\Delta t = .3$ hour and $\tau_c = .01$ hour while drug in the blood plasma.

Figure 3.2 is a comparison of the standard deviation of the mean for both stochastic and Van Kampen's form of the model. To evaluate the standard deviation of the stochastic form of the model we have run the simulations 10,000 times and bounded the variability using error bars about the mean. For the case of Van Kampen's approximation the standard deviation is calculated by solving the system of ODE's for the second moments (which gives the variance). Parameters for figure 3.2 are: $\alpha = .3$, $\Delta t = .3$ hour and $\tau_c = .01$ hour. Although Van Kampen's form of the model is a first order approximation, it seems from figure 3.2 that, it is able to capture the stochastic standard deviation fairly well.

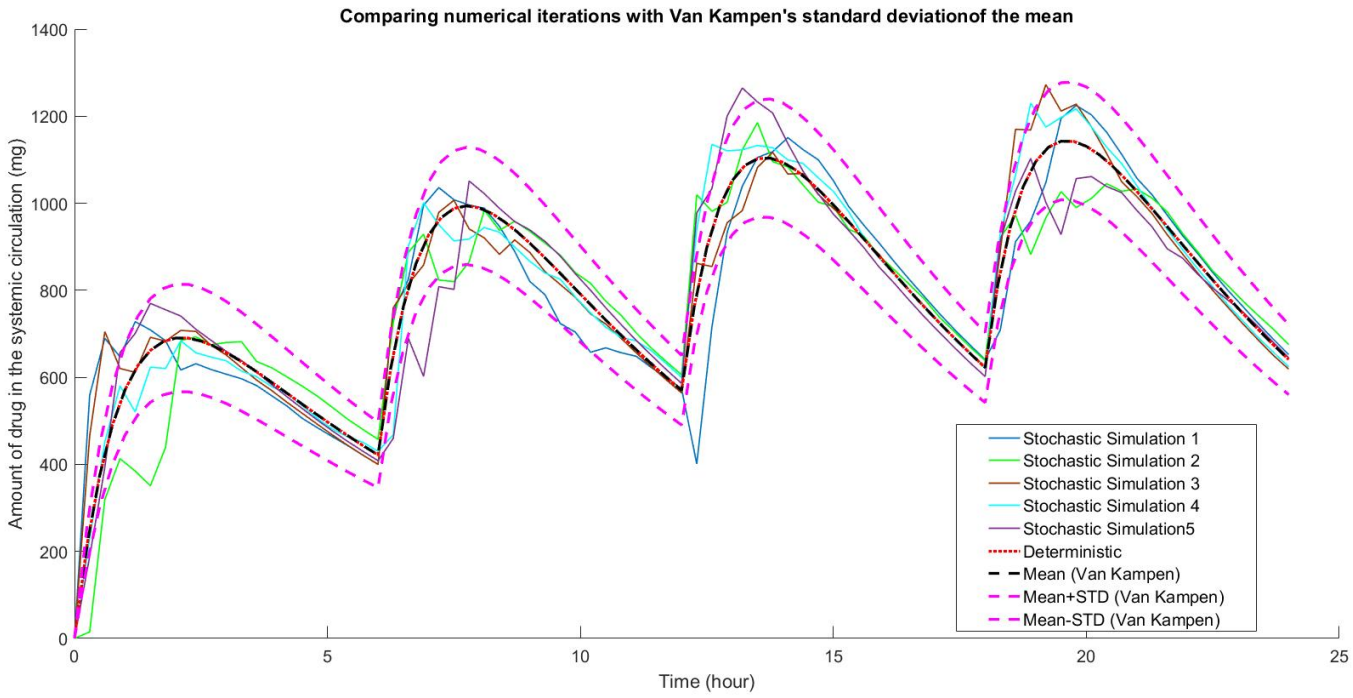

Figure 3.3: Comparison of a few stochastic simulations with the mean and variance of the Van Kampen approximation, for $\alpha = .1$, $\Delta t = .25$ hour and $\tau_c = .01$ hour.

Figure 3.3 is a numerical investigation of the standard deviation using Van kampen's approximation, to see how well this captures the stochastic variations for just 5 iteration. Parameters used to generate figure 3.3 are: $\alpha = .1$, $\Delta t = .25$ hour and $\tau_c = .01$ hour. Figure 3.3 suggests that the Van Kampen approximation $\pm$ standard deviation gives reasonable bounds on the stochastic variations that arise in a full numerical solution.

3.5.2 Test case 2.

Test case 2 is a comparison of experimental data, deterministic results and the stochastic mean with Van Kampen's approximation. Figure 3.4 illustrates that our approximation method for mean appears to merge well with the stochastic, deterministic and experimental data. The parameter values used for figure 3.4 are: $\alpha = .2$, $\Delta t = .25$ hour and $\tau_c = .01$ hour.

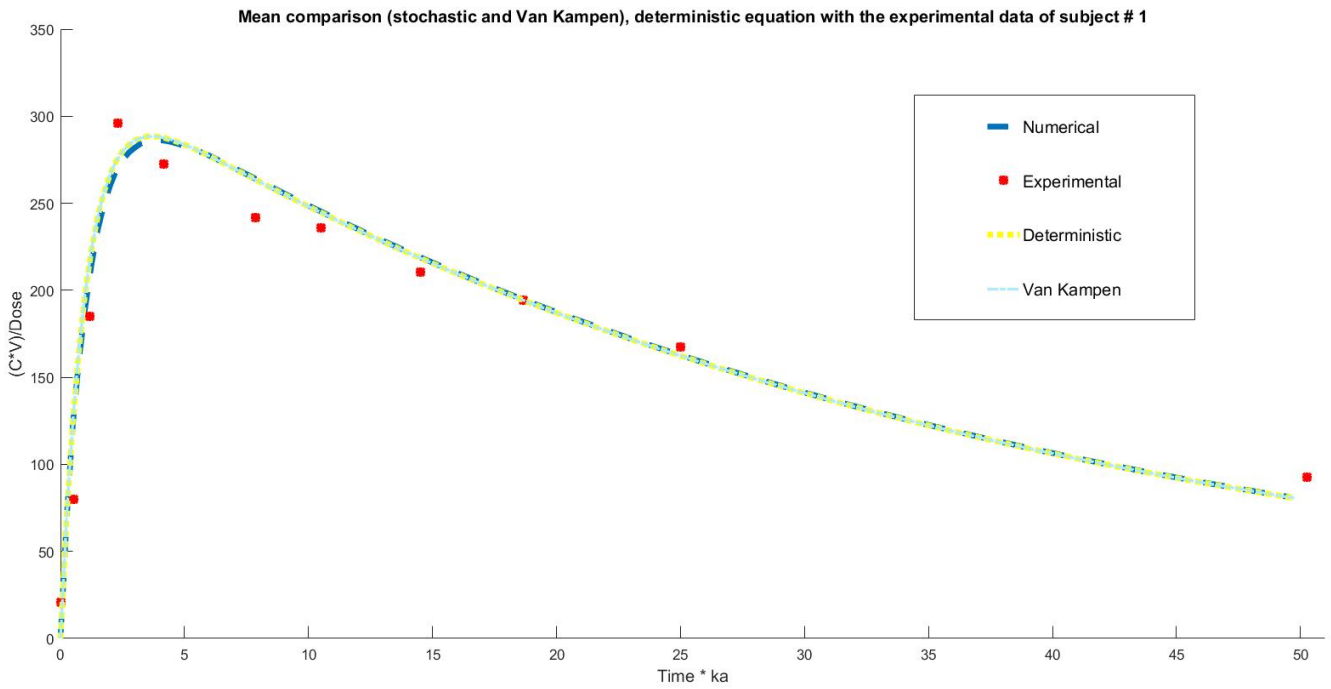

Figure 3.4: Comparison of the stochastic and Van Kampen means for $\alpha = .2$, $\Delta t = .25$ hour and $\tau_c = .01$ hour along with deterministic solution using the experimental data for subject # 1.

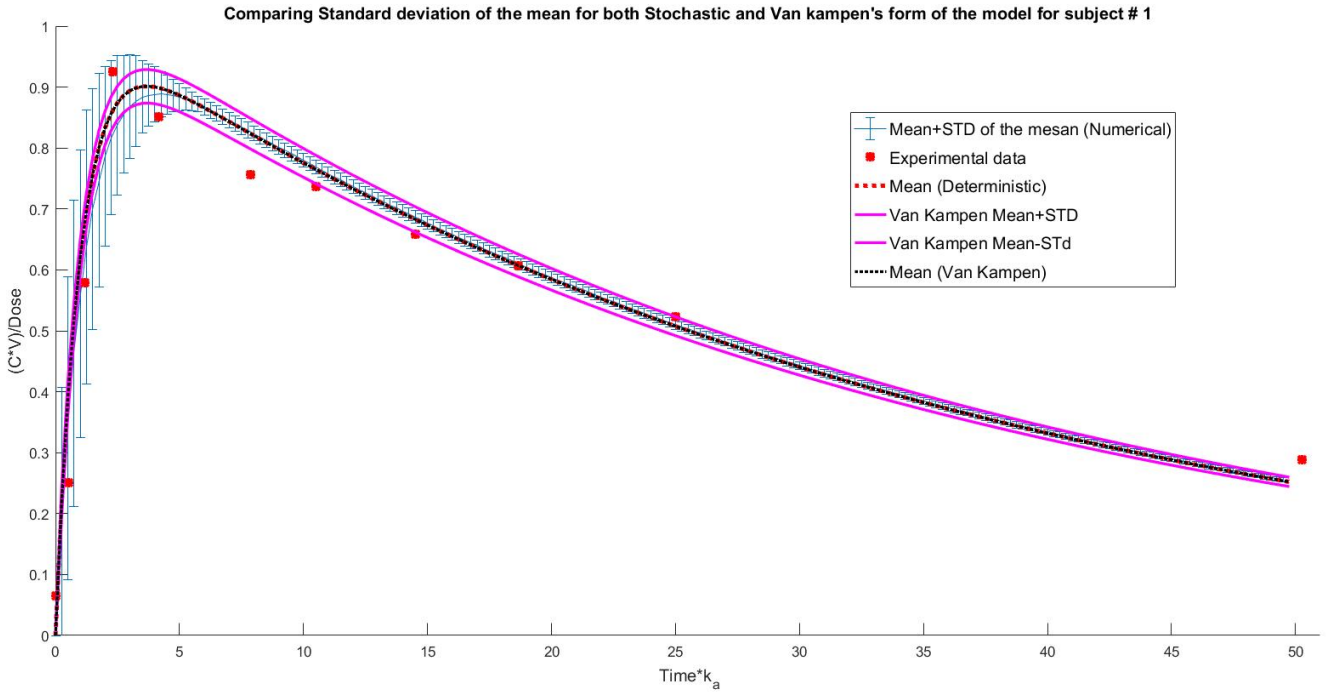

Figure 3.5: An illustration of the possible stochastic variability using Van Kampen's approximation mean $\pm$ standard deviation of the mean for $\alpha = .2$, $\Delta t = .25$ hour and $\tau_c = .01$ hour among the experimental data for subject # 1.

Figure 3.5, is a comparison between our approximation method along with the stochastic and deterministic method and shows the possible variability of the absorption from a single data set, although our approximation method under estimates the variability at the absorption phase when compared with the stochastic simulations. Parameters for the figure 3.5 are $\alpha = .2$, $\Delta t = .25$ hour and $\tau_c = .01$ hour. In this data set there are 12 individuals, and each of them has different absorption and elimination rates (not shown here), which explains the large variability, specially during the absorption phase.

3.6 Conclusion

Absorption is a physiological process that results in the uptake of a drug into the systemic circulation from the site of administration. It is clear that drug efficacy depends crucially on maintaining critical drug concentration levels during the therapeutic window. At the same time, this has to be balanced judiciously against the toxic side effects of a therapeutic drug. We have presented in this chapter an approximate model (based on Van Kampen's method) together with error bounds that delimit the stochastic variability of drug concentration levels in the body. Simulations of drug concentration that bound stochastic variability give us some confidence that an individual's plasma drug concentration levels are being maintained at appropriate levels for drug efficacy. In addition, the error bounds provide salutary warning of the possibility of exceeding toxic concentration levels which may have adverse effects on a patient and hence on therapeutic efficacy.

Biological systems are inherently stochastic, and hence it is not possible to develop a deterministic model with perfect predictive power. As in all of Applied Mathematics, perfection is unattainable, but through judicious application of Okham's razor and incorporating refinements guided by experiments, we may hope to arrive at a model that provides insight and rational guidance for clinicians and experimentalists.

Chapter 4

Saturable and fractal kinetics

4.1 Introduction

Identifying appropriate drugs and determining the right dosages are two prerequisites for successful treatment of cancer using chemotherapy. Searching for effective new drugs and evaluating their performance on various tumors is the main focus of pre-clinical and clinical studies [33]. Furthermore, the correct or optimum dose with minimum toxicity is also a crucial requirement for any effective therapy [33]. This in turn requires extensive experimental and empirical studies (both in vitro and in vivo). In this chapter we develop a mathematical model to study a well known chemotherapeutic cancer drug paclitaxel, in order to facilitate the design of dose administration strategies along with combination schedules. Paclitaxel was the first taxane to gain widespread clinical acceptance and is used now as a chemotherapeutic agent to treat a wide spectrum of tumors. Although paclitaxel was initially thought to display linear pharmacokientics, but Sonnichsen et al,[75], highlighted the fact that the pharmacokineticss is nonlinear by showing that a two compartmental model that incorporated saturable transport and saturable elimination best captured pediatric PK data. A three compartmental model that incorporated saturable transport from the central compartment to peripheral compartments, as well as saturable elimination was used by [27] to capture the concentration/time behavior of paclitaxel, in the case of adults. The data from Giani et al., [27], and Sonnichsen et al., [75] clearly demonstrated that drug distribution saturated and it was also clear from the data that saturation of transport processes occurred at lower plasma concentrations than for elimination. It is often the case that several PK models of varying complexity may be able to capture the behavior of any given data set. The choice of an appropriate model is often

guided by physiological considerations and the use of Ockham's Razor (or the law of parsimony). For drugs that are governed by underlying linear processes, compartmental PK models have provided excellent characterizations for a variety of pharmaceuticals. Similarly the incorporation of saturable elimination (based on the Michaelis Menten theory of bi-molecular chemical interaction between substrates and enzyme) has led to an even better characterization of the PK of these pharmaceuticals. Although saturable binding and transport are based on sound physiological principles, the processes by which paclitaxel is distributed through tissue suggest that saturable binding is the dominant process, not saturable transport. Thus a possible fruitful future direction of research might be the investigation of PK models that incorporate saturable binding compared with those that incorporate saturable transport (these latter have tended to predominate PK studies of paclitaxel.) From experimental studies it is well established that the time concentration profile of paclitaxel shows nonlinear dose dependence [40, 27, 56].

Various models have been developed based on linear and non-linear time-concentration profile of paclitaxel, using saturable distribution and elimination for two, three or more compartments [40, 27, 56, 57, 34, 59]. For example, Giani et al.,[27] developed a multi-compartmental model which includes a metabolite component. Sonnichsen et al., [75] developed a two compartmental model for children with solid tumors. Both models have assumed two saturable processes, one during the distribution phase and the other during the elimination phase. These saturable processes have been incorporated in the models by assuming Michaelis Menten kinetics [40].

The derivation of Michaelis Menten kinetics is based on traditional mass action kinetics. If the reaction occurs in dimensionally restricted environments (which occurs specially in vivo), then traditional mass action kinetics fail to capture well the underlying mechanism [69] and resulting behavior of drug concentration levels. Thus to better capture the chemical kinetics, the Michaelis Menten formalism has to be extended to (what is known in the literature) as fractal Michaelis Menten kinetics [69].

We extend the existing mathematical model in the literature of Kearns et., al [40], by incorporating fractal kinetics to better capture the saturable distribution process and elimination for the time concentration profile of the drug paclitaxel.

In section 4.2, we describe the mathematical formulation of the model along with a description of how the numerical simulations are carried out. In section 4.4, we briefly discuss the three experimental studies from which we have drawn data in order to validate our model. In section 4.5, we present the choice of parameter values for our study and compare these with those by Kearns et al., [40] in their model. In section 4.6, we discuss and appraise our findings.

4.2 Description of the Mathematical and Computational models

Classical compartmental Pk models treat the body as a combination of a number of compartments. This is a popular approach to describe biological systems transport of materials through the body. The usual practice is to consider the kinetic rates as constants. However the measurement of biological systems present unique challenges where drug molecules interact with membrane interfaces, metabolic enzymes and have to navigate through restricted and crowded micro-environments, where the system is clearly unstirred, heterogeneous and geometrically fractal [63]. Kopelman [41] first pointed out that, classical kinetics are unsatisfactory, especially if the microscopic environment of the reactants are spatially constrained. Fractal order of elementary reactions, rate coefficients with temporal memories, self ordering and self non-mixing criteria have a great impact on the heterogeneous reaction kinetics [41]. A number of publications on diffusion in fractal spaces using fractal calculus, have appeared in the literature. These studies show that all classical pharmacokinetics modeling are essentially a subset of fractal pharmacokinetics. Fuite et al., [22] discussed the fractal nature of the liver for the drug miberfradil, which is used to reduce ventricular fibrillation [73].

In this chapter, we focus on the anti cancer drug Paclitaxel. It is derived from the Pacific or European Yew tree [68]. In 1962 US National Cancer Institute studied the toxic effects of paclitaxel for the first time. Phase I trials were carried out in 1983, subsequently Phase II trials began 1988 [11]. Paclitaxel blocks the G2/M phase of the cell cycle and as a result, such cells can't go through normal mitosis [11]. Microtubules are responsible for cell shape, motility of cells, intracellular transport and mitosis and Paclitaxel is now well known as a mitotic inhibitor as it binds to microtubules [57]. It is now accepted as a most effective anticancer drug and has been used for solid tumors; such as breast, ovarian, lung, head and neck etc. Usually this drug is administered via intravenous infusion at a high dose [40]. It has a long residence time in the body and is capable of staying in cancer cells for over a week [59].

The characterization of drug transport and absorption has attracted much interest over the last several decades, and remains arguably the central focus of much PK research. Drugs interact with target organs by crossing epithelial membranes either by passive diffusion, pinocytosis or via carrier-mediated transport. Carrier mediated transport of drugs is the primary means of delivering drugs to a variety of tissues ranging from organs such as the kidney, gut and the choroid plexus in the central nervous system. The mathematical modeling and analysis of this process has been based on classical reaction kinetics

(with time independent rate constants). This has, however, been known to be far from satisfactory for media composed of heterogeneous micro environments, and especially for reactions that are spatially constrained. Fractal reaction kinetics have been proposed as a better approach to modeling the pharmacokinetics of drug transport in the human body. Work of Mandelbrot [52] and West et al., [87] have shown that organs such as the lungs, kidneys and anatomical structures such as the circulatory system have a fractal geometry. Other time dependent processes (leading to limit cycle oscillations) have been implicated as leading to nonlinear pharmacokinetics. This suggests that the extension of the Michaelis Menten formalism, incorporating fractal kinetics may be a better approach to study the time course of a drug in the body.

4.3 fractal Michaelis Menten kinetics

4.3.1 Batch/Transient case

The underlying assumptions of homogenity and well-stirred environments lead to time-independent constant reaction rates in classical chemical kinetics. However in the real case scenarios, reactions often occur in restricted geometries where the kinetics can be affected by fluctuations in concentration levels [31]. This situation can be captured mathematically by taking the rates time dependent [39]. If we want to consider the simplest applicable bimolecular elementary reaction:

$$A + B \rightarrow \text{ Products.} \tag{4.1}$$

By the law of mass action this has the macroscopic description [41]

$$\frac{dC}{dt} = -kC_A C_B, \tag{4.2}$$

where $C(t)$ is the reactant concentration and k is the "rate constant" which does not depend on time or concentration.

Another underlying mechanism influencing this reaction is diffusion, which arises from differences in drug concentration in different parts of the body. In this case the system can be described by two fundamental time scales: one is the diffusion time, time the particles require before meeting each other to react and the time particles will take to react with each other [4]. The process is known as reaction limited, when the reaction time is larger than the diffusion time and laws of mass actions are used to define the kinetic rates. On

the other hand law of mass action is not applicable when the diffusion time is larger than the reaction time and the process is known as diffusion limited. As a result reaction rates are not time independent any more [17]. Now to understand this time dependence for a long time, i.e, the asymptotic reaction situation ($t \to \infty$), studies are done to derive a relation between the microscopic diffusion constant D and the macroscopic rate constant k by stochastic approach [41, 74, 12], which is:

$$k \sim D \qquad t \to \infty. \tag{4.3}$$

At first the reactant molecules A considered by Smoluchowski and other researchers, as a random walker (drug molecules) and the reactant molecules of B as a sitter (traps), which idea was later expanded by considering both A and B as random walkers along with the "relative diffusion" ($D_A + D_B$) approach, precisely for different molecules. There are two different methods regarding this idea; one is stochastic, which says that the mean square displacement for the homogeneous system is linear in time where D is a proportionality constant [41]. The other method, is based on the first passage time (the time which is taken by a state variable to reach at specified target) and on the mean number of distinct sites $S(t)$ visited on the fractal at some resolution [41]. Havlin and Ben-Avraham introduced a scaling hypothesis between the quantity $S(t)$ and the spectral dimension d_s as [22]:

$$S(t) \propto t^{d_s/2}, \tag{4.4}$$

which means that the random walk steps are proportional to the time [22]. For transient reactions, in both homogeneous and heterogeneous media, the time derivative of quantity $S(t)$ is proportional to the macroscopic constant k, i.e, [41]:

$$k(t) \propto \frac{dS(t)}{dt} \propto t^{-(1-d_s/2)}, \tag{4.5}$$

or

$$k \propto t^{-h} \tag{4.6}$$

where

$$h = 1 - \frac{d_s}{2}, \qquad 0 \leq h \leq 1. \tag{4.7}$$

Now we can write the time dependent rate constant $k(t)$ as:

$$k = k' t^{-h} \tag{4.8}$$

where k' is the time independent constant and within the reaction medium and the spectral dimension of the path of the random walker is represented d_s [41]. If $d_s = 2$ then, by using

the above relation the value of h is 0, which means that $k = k'$ and we will be getting time independent rate constants.

In PK, both compartmental and non-compartmental studies include equation (4.8). For example, [51] has incorporated the equation (4.8) for the homogeneous heterogeneous model where they have calculated the overall quality of blood flow. Fuite et al., [22] has studied the fractal compartmental model for liver using the relation (4.8). In their study they have used the following relation for the rate of elimination via the liver:

$$\nu = k' t^{-h} C. \tag{4.9}$$

and reported that h has a significant impact on the shape of the concentration time profile.

One of the several attempts to incorporate equation 4.8 was carried out by Berry [5], using Monte Carlo simulations in low dimensional media to model enzyme kinetics and have used the equation the Michaelis Menten formalism to obtain the formula

$$\nu = \frac{v_{max} C}{k_{M_0} t^h + C} \tag{4.10}$$

4.3.2 Steady State/Steady Source

As a special case of (4.1), the reaction of A and A can be written as:

$$A + A = 2A \rightarrow \text{ Products}, \tag{4.11}$$

with the reaction rate equation

$$\frac{dC_A}{dt} = -kC_A^2. \tag{4.12}$$

In the steady state case (4.12) can be substituted for the steady state rate R as following:

$$R = kC_A^2 \tag{4.13}$$

where k is the time independent constant [41]. Anacker and Kopelman [2] have shown that, (4.13) should be replaced by

$$R = k_0 C_A^X, \tag{4.14}$$

where

$$X \equiv 1 + \frac{2}{d_s} = \frac{2-h}{2+h} \tag{4.15}$$

which is the new interpretation of the reaction order X i. e.:

$$X = \begin{cases} 1 + \frac{2}{d_s} & \text{for} \quad A + A \quad \text{reaction} \\ 1 + \frac{4}{d_s} & \text{for} \quad A + B \quad \text{reaction} \end{cases}$$

Quintela et al., [65] proposed a new approach to Michaelis Menten kinetics replacing the kinetic rates constants by the effective kinetic rate constants incorporating the observation scaling factor:

$$k_i^{eff} = A_i[S]^{1-D}, \tag{4.16}$$

where D is the fractal dimension of the space. By using these in the reaction equations:

$$S + E \underset{\mathrm{k}_{-1}^{\mathrm{eff}}}{\overset{\mathrm{k}_1^{\mathrm{eff}}}{\rightleftarrows}} (ES)^{eff} \overset{\mathrm{k}_2{}^{\mathrm{eff}}}{\rightarrow} E + P, \tag{4.17}$$

and relationship between the macroscopic constant k^{eff} and the quantity $S(t)$ proposed by Quintela et al., [65]:

$$k^{eff} \simeq \frac{dS(t)}{dt}. \tag{4.18}$$

One can obtain the following relation:

$$\nu = \frac{V_{max}^{eff}[S]^{2-D}}{k_M^{eff} + [S]}, \tag{4.19}$$

where the new constants V_{max}^{eff} and k_M^{eff} are defined in terms of k_1^{eff}, k_2^{eff} and k_{-1}^{eff}. From (4.19), we can see that if $D = 1$ then it will be the form of classical Michaelis Menten kinetics (the fractal dimension D is less than 1 and greater than 0; i.e; $0 \leq D \leq 1$). The resulting kinetics will be more and more complex as D deviates from unity [65].

Another approach proposed by Savageau [69] using power law and fractal concentration dependent kinetics for a multi-compartment reaction is given by:

$$\frac{dC_i}{dt} = \sum_{k=1}^{r} \alpha_{ik} \prod_{j=1}^{n} C_j^{g_{ijk}} - \sum_{k=1}^{r} \beta_{ik} \prod_{j=1}^{n} C_j^{h_{ijk}}, \tag{4.20}$$

where C_j is the concentraton of the specis j, α and β are the kinetic rate coefficients and g and h are the orders of kinetic rates related with each reactant [54]. Rate laws are linearised in terms of concentration or reaction affinities by using the power-law [70]. Although it is possible to model a number of essential properties using these concepts,

it is not applicable for other important biochemical effects like saturation [70]. Savageau [69] argues that although the power law formalism may have complex mathematical form, it nevertheless has significant benefits, as it is capable of capturing fractal phenomena mathematically. Marsh et al., [54] state that the equation proposed by Savageau [69] can be derived by summing over several Michaelis Menten reactions.

4.3.3 Dose dependent fractal Michaelis Menten kinetics

Kopleman [41] mentions that, for the transient state, reactants follow random distributions and reactants/walkers (drug molecules), gradually loose their efficiency while they are traversing the fractal space (which has dimension d_s). As a result of this, anomalous kinetics is observed in this state [54]. Where as in steady state, there is an inflow of the molecules, which can be treated as well stirred in Euclidean geometry, [41]. However, in the fractal case, as self stirring is unlikely, then it can be a result of extensive fluctuations in the regional concentration along with the growing isolation of molecules, which is known as reaction-diffusion phenomena and as a result of these, at the steady state, distribution molecules can be taken as partially ordered with a reduced reaction rate [54].

Marsh et al., [54] proposed an alternative formulation of fractal kinetics which depends on the dose concentration under steady state conditions. If we consider a single compartment model in the steady state, this implies that the drug concentration is constant as a function of time. Even though physiologically, there may be considerable variations in drug concentrations from one location to another, it may still be possible to achieve a steady state scenario if the drug concentration is far higher than enzyme concentration levels. Although drug molecules are lost through the elimination, the heterogeneity of the environment, can give rise to re-circulation of released drug molecules trapped long time at various locations. Thus modifying the DEs (1.15) appropriately, we can rewrite it for a heterogeneous environment as follows [54]:

$$\begin{aligned} \frac{d[ES]}{dt} &= k_1(E_0 - [ES])[S]^X - (k_{-1} + k_2)[ES] \\ \frac{dP}{dt} &= k_2[ES] \end{aligned} \tag{4.21}$$

where X is the fractal reaction order and using this relation in (1.17), we obtain the following form for the fractal Michaelis-Menten function:

$$v_0 = \frac{v_{max} S_0^X}{k_m + S_0^X}, \tag{4.22}$$

where v_{max} is the maximum velocity of the reaction, k_m is the Micaelis Menten constant and S_0 is the initial concentration of S.

Using this functional formula in a one-compartmental model with an intravenous infusion Marsh et al., [54] proposed the following model for the drug Miberfradil:

$$\frac{dS_0}{dt} = \frac{v_{max} S_0^X}{k_m + S_0^X} + \frac{i(t)}{v_d}, \tag{4.23}$$

where $i(t)$ is the infusion rate which has the unit mass/time and v_d is the volume of distribution which has the unit of volume.

In terms of the drug concentration C which can be written as:

$$\frac{dC}{dt} = \frac{v_{max} C^X}{k_m + C^X} + \frac{i(t)}{v_d}. \tag{4.24}$$

Following Marsh et al., [55], we want to use this dose dependent steady state fractal Michaelis Menten kinetics to model the infusion of the drug Paclitaxel for the two compartmental case.

In the following compartmental model, the blood plasma is taken to be the central compartment where the drug enters through infusion. Elimination is assumed to be a saturable process, the central compartment is connected to a second compartment which could be a tumor, an organ, or a mathematical construct encompassing a number of anatomical structures and physiological processes of interaction, with saturable distribution. The third (peripheral) compartment encompasses other regions and structures (not of direct interest), but where nevertheless linear binding (with the drug in the central compartment) may occur. Kearns et al., [40] used a three compartment model with Michaelis Menten kinetics (with saturable distribution and elimination) to capture the long tail behavior of paclitaxel's time concentration profile. In this chapter, we extend the Michaelis Menten kinetics to fractal Michaelis Menten kinetics for both distribution and elimination for two compartments (we do not consider the peripheral compartment) instead of three (as is done by Kearns et al., [40]) and compare the performance of our model with the model presented by Kearns et al., [40].

Figure 4.1 is a schematic presentation of the three compartmental model with fractal saturable kinetics for Paclitaxel. The model is described by the following system of equations:

$$\dot{C}_1 = -\frac{v_{max}^d C_1^p}{k_M^d + C_1^p} + k_{21} C_2 - k_{13} C_1 + k_{31} C_3 - \frac{v_{max}^e C_1^q}{k_M^e + C_1^q} + \frac{i(t)}{V_d}, \tag{4.25}$$

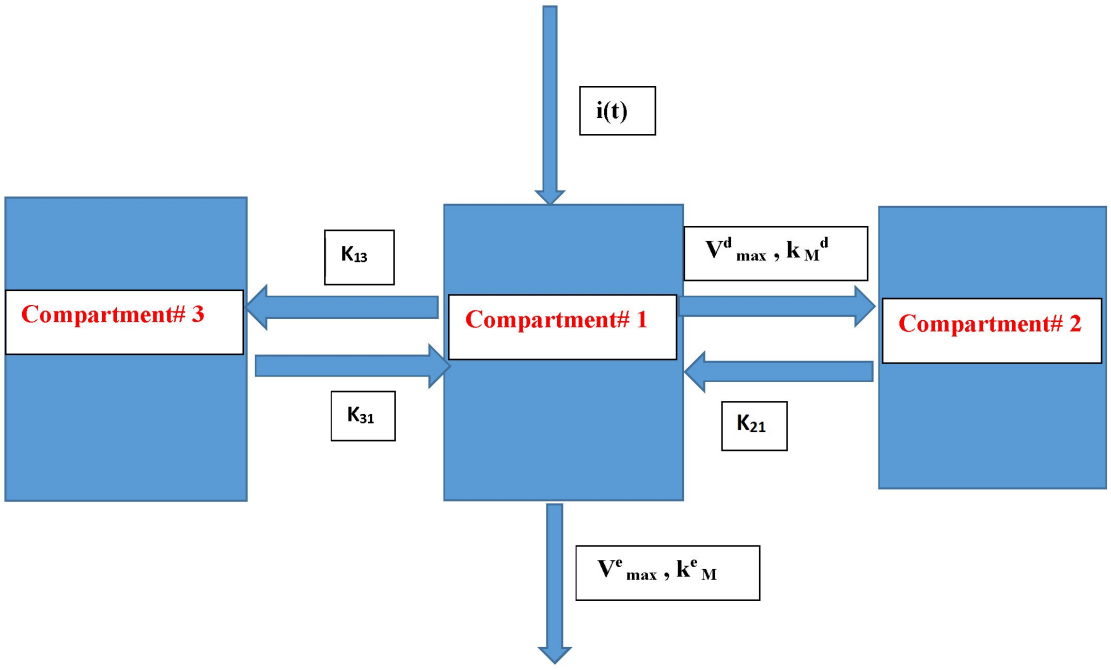

Figure 4.1: Schematic diagram of three compartmental model with both saturable distribution and elimination from the central plasma compartment

$$\dot{C}_2 = \frac{v_{max}^d C_1^p}{k_M^d + C_1^p} - k_{21} C_2, \tag{4.26}$$

$$\dot{C}_3 = k_{13} C_1 - k_{31} C_3. \tag{4.27}$$

Here superscripts d and e denote distribution and elimination respectively, $i(t)$ is the infusion rate and V_d is the volume of distribution. In this model, we consider two different fractal powers p and q, one is for the distribution (p) and the other is for elimination (q), since these two processes occur in two different organs. In the model described by Kearns et al., [40] $p = q = 1$ (fractal powers are not considered). In contrast, we consider two compartment model (i.e., $k_{13} = k_{31} = 0$) with fractal kinetics.

To solve the problem numerically and illustrate the results graphically, we have used Matlab 2017b. Subroutine ode45 has been used to solve the system of equations for both the fractal and non fractal models by setting initial concentrations zero at time $t = 0$ in all three compartments. We consider appropriate time points from the relevant data, for both models. To determine the optimal parameter values, we have used the Matlab built in optimization algorithm, which uses a genetic algorithm. It is an adaptive heuristic random search, algorithm which is based on the evolutionary ideas of natural selection and genetics and is capable of solving both constrained and unconstrained optimization problems (a brief overview of this algorithm is given in appendix B). The ideas underlying this optimization algorithm are derived from evolutionary concepts (from Charles Darwin's principle of "survival of the fittest"). A population of individual solutions is repeatedly modified by the algorithm. From a current population, GA randomly chooses a set of individuals at each time step and uses those individuals as parents to produce the offspring for the next generation and by repeating the procedure successively, the algorithm is able to find the population for the optimal solution. The simulation gives the opportunity to search for the parameters over a larger space and so avoid being trapped at local extrema. From Kearns et al., [40], we know that all these parameter values should be positive and we have used this as a constraint when running simulations, i.e., we have constrained the search domain from 0 to ∞. In order to run the simulations the genetic algorithm requires an objective function which can be used to optimize the target parameter values. The goal of the optimization is to minimize the distance between the observed concentration values and the predicted concentration values. We have the plasma concentration values at different time points from the data set, these represent the true values. From our model, we can predict concentrations at the same time points and these represent our predicted values. We use the Weighted Residual Sum Square (WRSS) as the objective function,

which will minimize the differences between the true and predicted values:

$$\text{WRSS} = \sum_{i=1}^{n} \left[\frac{(ConData_i - \widehat{ConPred}_i)^2}{\widehat{ConPred}_i^2} \right] \tag{4.28}$$

where $ConData_i$ are the concentration values from the data set and $\widehat{ConPred}_i$ are the predicted concentration values using the model and i represents the discrete time points at which the concentration values have been collected in the experiments.

The Matlab optimization tool box includes a function, Fmincon, which is used to minimize a scalar function of several variables, with linear constrains and specific bounds. Fmincon uses a gradient-based framework with five algorithm options: 'interior-point'(default), 'trust-region-reflective', 'sqp', 'sqp-legacy' and 'active-set', to find local optimum values. After obtaining the optimum parameter values from the GA simulation, we have some idea about the values as well as the range of the parameters. We now run the Fmincon function with the default algorithm (interior-point) and set the initial conditions very close to the parameter values (obtained from GA). This gives us greater confidence that our parameter values are indeed the locally optimum values.

To compare the goodness-of-fit of our model with that of Kearns et al., [40] we use the Akaike Information Criterion (AIC) (a brief discussion of AIC is presented in appendixB), which can be expressed as follows:

$$\text{AIC} = N_{obs} ln(WRSS) + 2N_{par}, \tag{4.29}$$

where N_{obs} represents the number of data points, N_{par} represents the number of parameters of the model. We know from the definition of AIC that the lower the value of the AIC, the better the fit (according to this criterion).

4.4 Experimental data

Paclitaxel is used to treat a variety of cancers ranging from ovarian, lung, breast, bladder, melanoma, esophageal, prostate, and many other solid tumor cancers. It has also been used for a different type of cancer known as Kaposi's sarcoma. It is poorly water soluble, but can be dissolved in organic solvents. To administer the drug to patients, the usual formulation of this drug is: 1:1 blend of Cremophor EL (polyethoxylated castor oil commonly known as CrEL) and ethanol which is diluted with 520-fold in normal saline or dextrose solution (5%) [72]. The PK nature of CrEL does not depend on dose, but the infusion time has a

great impact on the clearance of the drug [26]. In order to handle some of these side effects clinically, pre-medications are frequently administered.

Marsh et al., [56] carried out an analysis to demonstrate the power law behavior of paclitaxel. They utilized 41 sets of data from 20 published papers, and digitized the data in order to study the long time residence (in the body) of paclitaxel. They reported that there was power law behavior in the tail region using time-concentration profile data for paclitaxel.

Following Marsh et al., [56], we digitized data from three different studies and compared the predictions of our model with that of Kearns et al., [40]. A brief description of the studies (from which our data was drawn) is given below.

Brown et al.

Brown et al., [9] designed their phase I study for 31 patients of melanoma, lung, colon, head and neck, prostate, kidney and unknown cancers. Mean age of the patients was 58 years. Taxol was administered for 6 hour IV infusion and repeated every 21 days. Blood serum samples were collected before infusion at 5, 15, 30, 60, 90 minutes, and 2, 3, 4, 6, 8, 12, 24 and 48 hours after infusion. Their study focused on the previously reported toxic effects, which depended on the drug vehicle CrEL and duration of infusion time. As such they were trying to observe the situation by infusing at a rate of 43 cc/h, for the first 30 minutes, and if there were no major side effects by infusing at a higher rate of 180 cc/h for the next 5.5 hour. The doses used in their study were 175 mg/l, 250 mg/l and 275 mg/l. Their conclusions were that pre-medication does not necessarily reduce the toxic side effects. For the PK parameters, nonlinear regression analysis (NONLIN) was used with a weighting of $1/y^2$ (where y is the true value from the data). From their investigation, a dose of 225 mg/l was suggested for Phase II study.

We extracted plasma concentration data from this study at 11, 13 and 14 time points for a dose 175 mg/l, 250 mg/l and 275 mg/l, respectively.

Kearns et al. and Giani et al.

Giani et al., [27] studied PK characteristics and toxicity of Paclitaxel and 6α hydroxylpaclitaxel in humans, using a four compartmental model. This was carried out for 30 patients. Half of these patients had advanced ovarian cancer, and the other half had advanced breast cancer. The median age of the patients was 54 years. The administered dose for ovarian cancer was $135\,mg/m^2$, $175\,mg/m^2$ and for the breast cancer dose was $225\,mg/m^2$ by either

3 or 24 hours infusion. Blood plasma were collected at 1, 2 and 3 hours before infusion and at 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 6 hours, 12 hours during infusion and 21 hours post infusion. PK software package ADAPT II was used to fit the time concentration data for the compartmental analysis and regression models were used to evaluate the pharmacodynamic correlation. Study claimed, the nonlinear disposition of the drug in human specially in the short infusion period and a mathematical model can be a powerful tool in predicting paclitaxel disposition, regardless of the dose and schedule.

Using the data from Giani et al., [27], Kearns et al., [40] investigated pharmacokinetics and pharmacodynamics behavior of paclitaxel using three compartmental model. They concluded that hypersensitivity occurred due to the mixing vehicle CrEL and suggested pre-medication to alleviate this situation. The correlation between the neurotoxicity and the pharmacokinetics of the pacliteaxel was presented through the study and the recommendation was to use three hour infusion periods, with pre-medications to reduce neurotoxicity.

We extracted the concentration data at 11, 11 and 12 time points for doses of $135\,mg/m^2$, $175\,mg/m^2$ and $225\,mg/m^2$ respectively.

Zuylen et al.

Zuylen et al., [89] studied the effects of CrEL micelles on the disposition of paclitaxel. Seven solid tumor patients were treated for 3 hours infusion on a 3 week consecutive cycle of administration with doses of $135\,mg/m^2$, $175\,mg/m^2$ and $225\,mg/m^2$. Patients were 18 years or older with 3 months life expectancy without any previous taxane treatment. Blood plasma samples were collected at the following times before and after the infusion: 1, 2, 3, 3.08, 3.25, 3.5, 3.75, 4, 5, 7, 9, 11, 15 and 24 hours. The Siphar package (version 4; SIMED, Creteil, France) was used to evaluate the PK parameters, using a non compartmental model. The study claimed that the encapsulation of CrEl is one of the reasons that paclitaxel shows non-linear behavior as it is capable of altering blood distribution.

Based on this, they proposed a new pharmacokinetic model for whole blood and also for blood plasma analysis. The model was able to transform nonlinear time concentration profiles to linear ones by changing the formulation with the CrEl from the whole blood sample, but not from the blood plasma samples.

We extracted the concentration data at 11, 11 and 9 time points for doses of $135\,mg/m^2$, $175\,mg/m^2$ and $225\,mg/m^2$ respectively from the study, which was reported for the blood plasma samples.

Whatever the underlying mechanism for the non-linearity of the paclitaxel time - concentration profiles, our interest is in developing a model capable of capturing this non-linearity as a function of dose and infusion time, whether it is possible to minimize the toxic side-effects of paclitaxel (either via varying the CrEL vehicle mixing proportionality, or via change in the schedule of infusion time) is beyond the scope of our present study. We hope to demonstrate that the model recapitulates the behavior of the experimental data to within acceptable margins of error, and that the model can be utilized as a tool in further experimental investigations.

4.5 Parameter values and model simulation

In this section, we present simulations of both our fractal model and the Kearns model and compare both with the experimental data. We also compare the parameter values of both models (in tabular form) using a weighted Residual Sum Square (WRSS) statistical measure, as well as the Akaike Information Criterion (AIC), in order to assess the goodness of fit of both models.

For figure 4.2, data is taken from Kearns et al., [40]. Parameter values for the Kearns model are taken from Kearns et al., [40] and the parameter values for our fractal model are calculated using the Matlab Genetic Algorithm. Table 4.1 represents the parameter values for both models.

For the figure 4.3, data is taken from Van Zuylen et al [89]. There are no reported parameter values for this data set. The Matlab built in Genetic Algorithm has been used to evaluate the parameter values for both the models. Table 4.2 describes the values for both models.

As mentioned earlier, we wanted to apply our model for a different infusion time other than 3 hours and for that we chose another data set. Brown et al, [9], applied six hour infusion times for the doses of 175 mg/l, 250 mg/l and 275 mg/l in their phase I study. Figure 4.4, data is taken from Brown et al., [9]. Again there are no reported parameter values for this data set and so again the Matlab built in genetic algorithm was used to evaluate the parameter values for both models. Table 4.3 provides the values for both the models along with the WRSS and the AIC.

Table 4.1: Optimum parameter values reported by Kearns et al. [40] and the optimum values for the fractal model evaluated by a genetic algorithm (Matlab).

Parameters	Kearns Model	Fractal Model
K_{21} (/h)	.68	1.97
V_d^{max} (M/h)	10.20	12.32
V_e^{max} (M/h)	18.80	13.41
K_d^M (M)	.32	1.67
K_e^M (M)	5.50	6.39
V_d (L)	4	4.92
K_{13} (/h)	2.20	0.0
K_{31} (/h)	.65	0.0
p	1	1.20
q	1	1.70
WRSS	1.50	.83
AIC	20.35	12.89

Table 4.2: Optimum parameter values evaluated by using Genetic Algorithm (Matlab) for both Kearns et al. [40] model and the proposed fractal model (data digitized from Zuylen et al., [89]).

Parameters	Kearns Model	Fractal Model
K_{21} (/h)	0.47	0.20
V_d^{max} (M/h)	8.30	9.36
V_e^{max} (M/h)	22.50	17.33
K_d^M (M)	6.16	3.78
K_e^M (M)	14.59	11.84
V_d (L)	9.53	9.48
K_{13} (/h)	1.44	0.0
K_{31} (/h)	16.63	0.0
p	1	0.90
q	1	0.65
WRSS	1.45	0.52
AIC	19.41	9.10

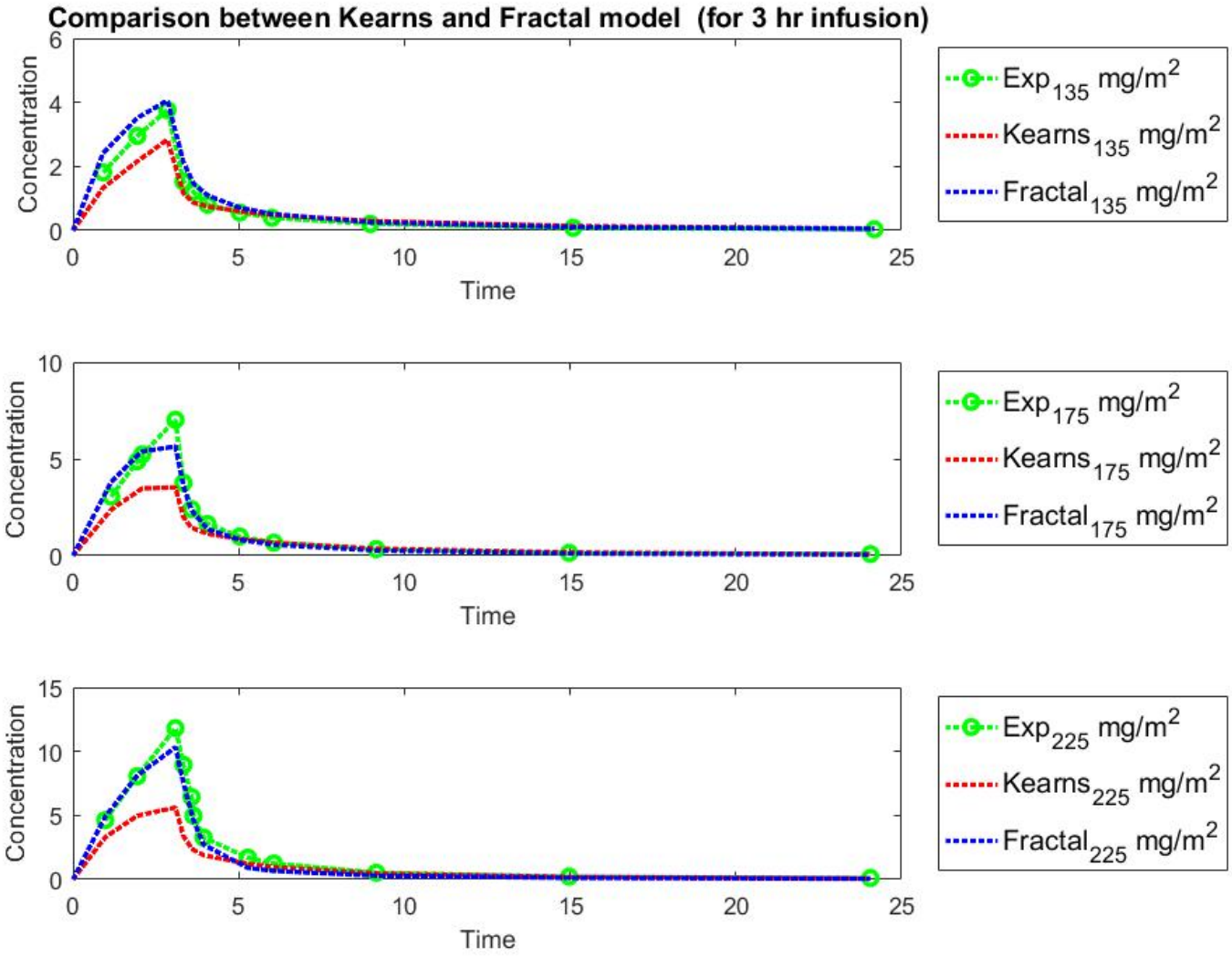

Figure 4.2: Comparing Kearns et al., three compartmental model with the proposed fractal two compartmental model (data from kearns et al., [40]).

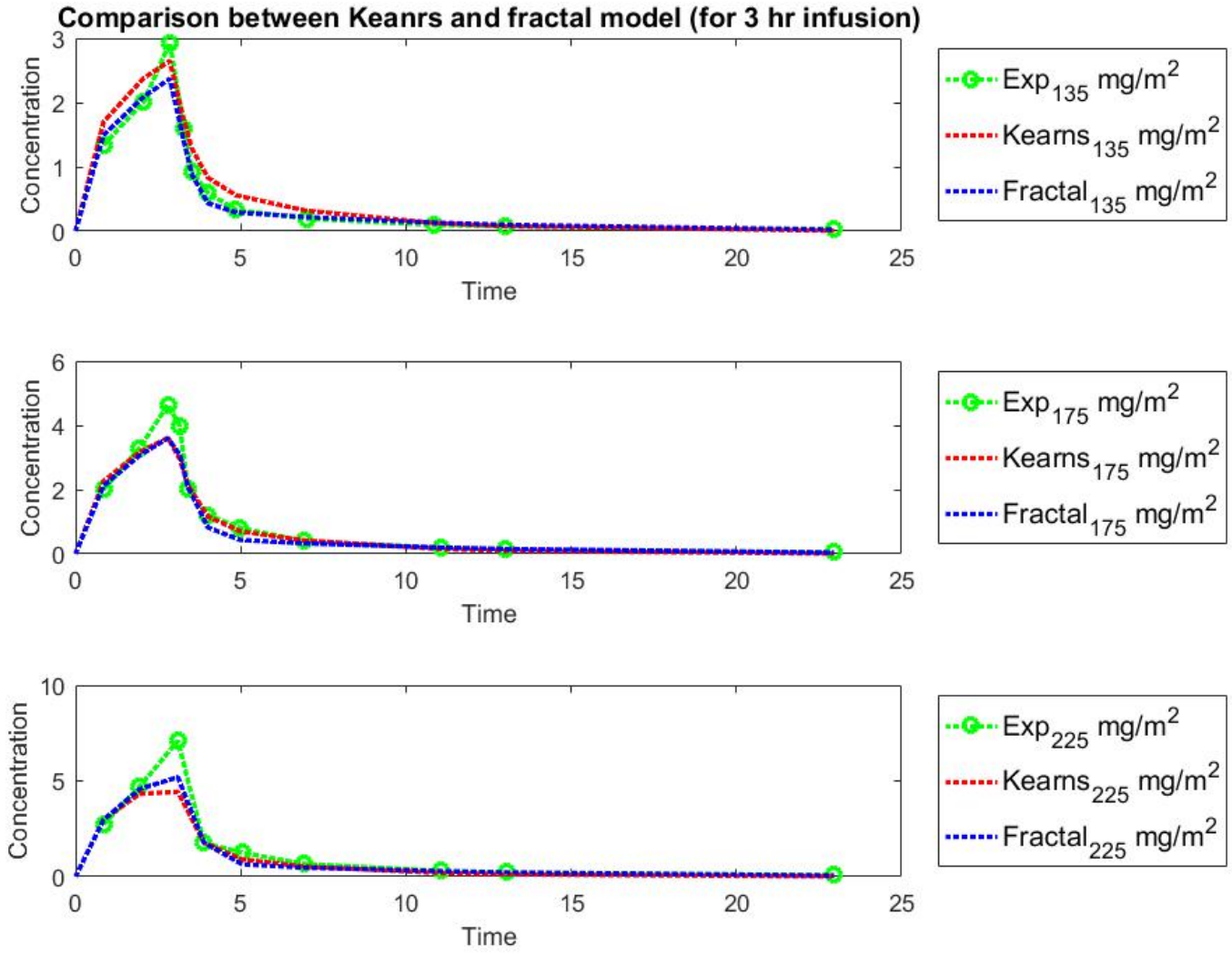

Figure 4.3: Comparing Kearns et al., three compartmental model with the proposed fractal two compartmental model (data from Zuylen et al., [89]).

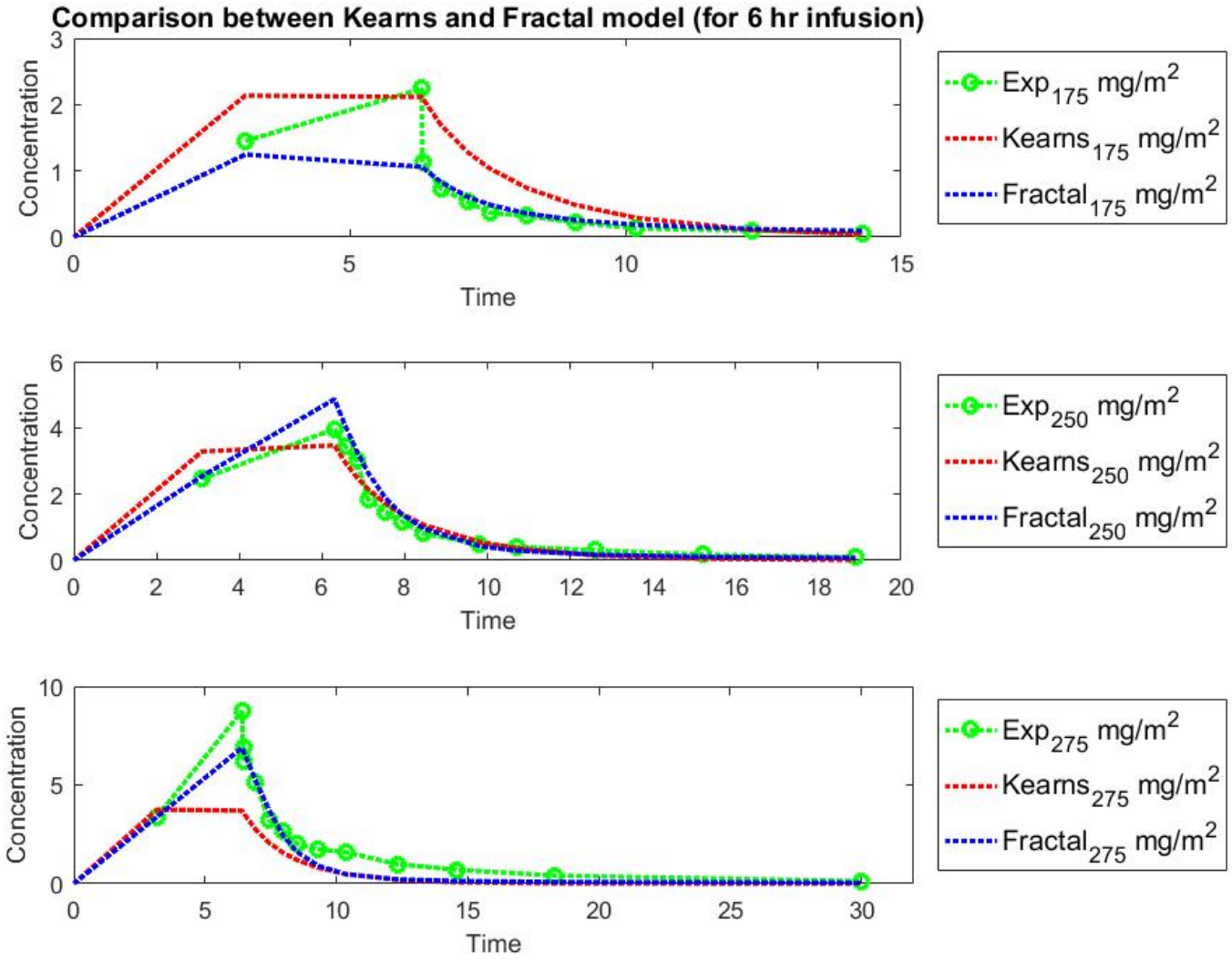

Figure 4.4: Comparing Kearns et al., three compartmental model with the proposed fractal two compartmental model for six hour infusion (data from Brown et al., [9]).

Table 4.3: Optimum parameters values evaluated by using Genetic Algorithm (Matlab) for both Kearns et al. [40] model and the proposed fractal model (data digitized from Brown et al., [9]).

Parameters	Kearns Model	Fractal Model
K_{21} (/h)	1.30	2.72
V_d^{max} (M/h)	14.72	15.39
V_e^{max} (M/h)	14.47	3.38
K_d^M (M)	7.68	2.23
K_e^M (M)	7.77	0.29
V_d (L)	7.16	8.45
K_{13} (/h)	10.24	0.0
K_{31} (/h)	13.19	0.0
p	1	2.05
q	1	2.79
WRSS	6.77	1.69
AIC	36.39	20.96

4.6 Discussion

Figure 4.2 shows that the fractal model appears to fit the experimental data much better than the Kearns model. We also observe this from table 4.1 based on the WRSS and AIC values. The WRSS value of .833 for the fractal model is less than the value of 1.5 for the Kearns model, with a corresponding AIC value of 12.8 for the fractal model compared with an AIC value of 20.34 for the Kearns model. From figure 4.3, it is difficult to distinguish which of the models fits the experimental data better; however, an examination of the WRSS and AIC values for this case (see table 4.2) gives a WRSS value of .51 for the fractal model compared with a value of 1.45 for the Kearns model. Similarly we obtain an AIC value of 9.18 for the fractal model compared to 19.41 for the Kearns model. Hence both WRSS and AIC measures, confirm that the fractal model gives a better fit to the data than the Kearns model. Note that the parameter values in this case for both the models have been calculated using GA.

Figure 4.4 shows that the fractal model fits the experimental data better than the Kearns model except for the dose $175\,mg/m^2$, for which both models fail to capture peak plasma concentration, although they are not too different from the experimental data. However, form table 4.3, the WRSS value of 1.69 compared to 6.77 and AIC values of

20.69 compared to 36.39 again confirm that the fractal model provided a better fit to the data than the Kearns model.

4.7 Conclusion

We extended an existing model (that used Michalis Menten formalism to model the non-linear behavior of the chemotherapeutic drug paclitaxel) by incorporating fractal Michaelis Menten kinetics, to better capture the effects of two competitive saturable processes. We have compared our model with the existing model on three different data sets from three different studies. Although it might appear that one shortcoming of our fractal model and that of Kearns et al., is that a different set of parameter values have to be used in both models for each of the three data sets, a closer examination reveals why it may be, unreasonable to expect that one set of parameter values should be sufficient to predict the three different scenarios. Firstly, the three data sets have been obtained for patients with very different cancers. Secondly, the age groups of the patients, vary significantly for the three data sets. Thirdly, the pre-medication used on the patients are very different for each of the three data sets. Taking into consideration all of these different factors, it is clear that the three data sets obtained are for three very different clinical situations and so clearly we should expect that the parameter values calculated for one data set will not necessarily give the best fit for a data set from a different clinical situation. Naturally, given patients of similar age groups, with the same type of cancer (who received a similar therapeutic drugs), one would expect that parameter values extracted previously from a different patient cohort would still give an effective predictive model, which could be used to evaluate the impact of different infusion times and different doses on a new patient cohort. However, it is clear that the model needs to be validated on a broader range of data before it can be evaluated in a clinical setting. Despite all these challenges, we believe that well validated mathematical compartmental models of this nature are indispensable tools in preclinical studies and play a crucial role in the eventual development of effective clinical therapies.

Chapter 5

Conclusion

Sixty five years have elapsed since F. H. Dost introduced the term pharmacokinetics (PK) in his 1953 paper, Der BliitspiegeI-Kinetic der Konzentrationsablaiife in der KrieslaufJ ssigkeit [83]. By 1979, the number of published articles in clinical pharmacokinetics had exceeded 400 to 500 articles per year, and PK is now an entrenched and integral part of the clinical drug development pipeline. PK is based on four basic processes: absorption, distribution, metabolism and excretion. All these processes are quantified by the various PK parameters. As discussed earlier in chapter 2, there are several frequently used methods to calculate the absorption rate constant, these are the Wagner-Nelson or Loo-Riegelman method, nonlinear least-squares regression analysis and method of residuals. Perrier and Gibaldi [62] stated in their study that these methods can overestimate the absorption rate constant as they do not take into account the variations in absorption rate over time and bioavailability [62].

In Chapter 1 of this thesis, we presented a summary of basic concepts of pharmacokinetics. In general, it is unreasonable to expect that drug concentration as a function of time (for a specific patient) follows a deterministic ODE model. There may be variations as a result of incorrect or inaccurate model specification, as well as due to physiological variations or uncertainty in the distribution, absorption and elimination processes. A means of describing such errors is to develop random differential equation (or stochastic differential equation) models. The simplest one compartmental elimination model:

$$\frac{dx}{dt} = -k_e x, \tag{5.1}$$

(where x is the drug concentration and k_e is the first order elimination rate constant) can

be extended to a random differential equation by writing:

$$dx = -k_e x dt + \sigma_w dw \tag{5.2}$$

where dw is an infinitesimal increment of the Wiener process, and so the model can be described simply as a deterministic ODE perturbed by a normally distributed noise (or random differential equation). The solution of (5.2) is :

$$x(t) = x_0 e^{-k_e t} + \int_0^t \sigma_w e^{-k_e(t-s)} dw. \tag{5.3}$$

Clearly there are some obvious problems with the model (5.2), primarily, it appears that there is no limitation on the drug concentration, and so (even though the model describes a simple drug elimination process) the drug concentration can increase when the increments of the Wiener process are positive. Further more, the model will fluctuate around the mean zero, even after the initial drug dose has been eliminated, and so the model will predict nonphysical negative concentrations. A more realistic model is obtained by adding noise to the rate constant, in this case in the elimination rate constant k_e. Now if we want to make the elimination rate as a random function of t with mean k_e such that:

$$k_e(t) = k_e + \alpha\xi(t), \tag{5.4}$$

where α is the amplitude of the fluctuation and $\xi(t)$ represents the noise.

In this case (5.1) can be written as:

$$\frac{dx}{dt} = -(k_e + \alpha\xi(t))x. \tag{5.5}$$

In the case that $\xi(t)$ is a Wiener process (i.e. in the case of white noise), equation (5.4) can be written as the Ito equation

$$dx = -k_e x dt - \alpha x dw \tag{5.6}$$

In our work, by taking into account randomness in the absorption rate our deterministic model becomes a random differential equation and we make some statistical assumptions concerning the nature of the noise. We consider the noise, to be an Ornstein Uhlenbeck process [78]. It is a Gaussian process, with bounded variance which admits a stationary probability distribution. The stochastic DE of an Ornstein-Uhlenbek process is often written as a Langevin equation. The random differential equation is solved numerically using the Gillespie algorithm [30].

However, in this thesis we consider the more physically realistic case of "colored noise", where the correlation time of the noise is not a delta function. In this case the Ito calculus is not applicable and no exact solution method is available. However, approximation methods have been developed in the physical science for realistic noise (with short correlation times), and in chapters 2 and 3, we examined these approaches and showed that they can be successfully applied to PK models. We started by considering the Bourret approximation to handle random differential equations and then the more amenable Van Kampen approximation applied to the random harmonic oscillations and a one compartment model.

In chapter 3, we examined a stochastic model of a simple compartment model with both absorption and elimination and applied Van Kampen's approximation method to the model, to obtain first and second moments. We also compared Van Kampen's approximation for the first moments to full stochastic simulations for the mean, and the solution of the deterministic equation for small amplitude noise and short correlation times. Our results give us some degree of confidence that Van Kampen's method allows us to determine realistic error bounds on the mean drug concentration levels that allow us to bound the stochastic variability of drug concentration in the body.

In chapter 4, we use the theory of fractal kinetics in the context of pharmacokinetics where saturable reactions may occur in heterogeneous micro environments. Although one compartment models are often oversimplifications, they are able to produce accurate, good fits if drug distribution occurs on a fast time scale and equilibrium is reached rapidly in all tissues. We extended a standard two-compartment PK model to include steady-state fractal Michaelis-Menten kinetics. Transient fractal kinetics is to be expected in well-mixed heterogeneous environments, where as steady-state fractal kinetics is characteristic in poorly mixed heterogeneous environments [54]. Klymko and Kopelman [42] suggest that non-integer values of p and q appearing in equations (4.25) and (4.26), are characteristics of these heterogeneous media which are essentially an assemblage of kinetically independent bundles. In this case, the kinetic rate coefficients are averages taken over regions of varying sizes and varying local concentrations. We applied our two compartmental PK model, incorporating fractal steady-state Micahelis-Menten kinetics to paclitaxel data from the literature. Paclitaxel is a long studied chemotherapeutic drug which has proved effective in the treatment of solid tumors (for example lung, breast, ovarian etc). The plasma concentration time profile of this drug is nonlinear [40], [27], [89]. Our results show that our model best captured the absorption and elimination of paclitaxel, for three different digitized data sets (compared to the Kearns et al., [40] model).

In the thesis we have explored the use of random differential equations as well as fractal kinetics to characterize the PK of therapeutic drugs. In particular, in the latter case (compartmental model of fractal kinetics) the models are deterministic and essentially

characterize macroscopic behavior. It would be fruitful, and a possible future direction of research to investigate the connections and relationship between individual drug molecules, macroscopic drug behavior and the mean, using the theory of stochastic processes. In this context, the incorporation of the idea of Levy flights in PK modeling appears promising. The theory of random walks has been extended to a continuous time random walk formalism, and thus could be used incorporating Levy trapping times to develop a stochastic PK model which includes saturable and fractal kinetics elimination effects with Levy time temporary trapping. These types of models could then be used to infer target doses, using plasma data, as well as to predict the response to different dosing strategies. The approach may avoid assumptions about underlying reasons (e.g., fractal kinetics, heterogeneous cell populations, different cell death mechanism) leading to dispersion in molecule residence times. It might also be possible to understand and explain (using this approach) clinical observations such as delayed reactions in some patients (in terms of this dispersion).

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APPENDICES

Appendix A

Application of Van Kampen's theory to Pharmacokinetics

A.0.1 Numerical method to evaluate mean and variance for random DE

From Langevin to Ornstein-Uhlenbeck process

A particle of mass M, changes its velocity $V(t)$ along the rate follows Newton's second law of motion, which is described as net force $F(t)$. Again the velocity $V(t)$ describes the rate of changes of its position $X(t)$. All these mathematically can be written as:

$$\frac{dV(t)}{dt} = \frac{F(t)}{M} \tag{A.1}$$

and

$$\frac{dX(t)}{dt} = V(t) \tag{A.2}$$

If we consider $V(t)$ and $X(t)$ are random, the idea of Newton's second law is also applicable and can be written in differential form:

$$V(t+dt) - V(t) = \left[\frac{F(t)}{M}\right]dt \tag{A.3}$$

and

$$X(t+dt) - X(t) = V(t)dt \tag{A.4}$$

We can think of that $X(t)$ is a process variable which can be describes by its probability density $p(x,t)$, it means, $X(t)$ can vary in time t and in value x at each time. More precisely speaking, $X(t)$ and $X(t+dt)$ are two distinct random variables and they are presenting different piece of Markov process and are associate with the following dynamical form [46].

$$X(t+dt) - X(t) = G[X(t), dt] \tag{A.5}$$

where $G[X(t), dt]$ is known as a Markov propagator function and it is also a random variable.Equation A.5 is the Einstein's way of defining randomness. The random variable $G[X(t), dt]$ probabilistically determines the other random variables $X(t+dt)$ from $X(t)$ via the relation (A.5). The assumption here is that the time domain and the process variable are continuous, i.e., $G[X(t), dt] \to 0$ as $dt \to 0$, where smoothness is not mandatory [46] . The Markov propagator is described by Wiener as following:

$$G[X(t), dt] = \sqrt{\delta^2 dt} N_t^{t+dt}(0,1) \tag{A.6}$$

where $N_t^{t+dt}(0,1)$ unit normal random variable with mean 0 , variance 1 and connected clearly with the time interval $(t, t+dt)$. δ^2 is a process characterizing parameter. Now the dynamical equation of the process variable $X(t)$ can be written as by substituting A.6 into A.5 and will be of the form:

$$X(t+dt) - X(t) = \sqrt{\delta^2 dt} N_t^{t+dt}(0,1) \tag{A.7}$$

The meaning of the A.7 is that the Wiener process variable $X(t)$ when realizes the sure value $x(t)$ at any time t then the variable $X(t+dt)$ is a normally distributed random variable with mean $x(t)$ and variance $\delta^2 dt$ or we can write the variable as $X(t+dt) = N(x(t), \delta^2 dt)$.

French physicist Paul Langevin (1872-1946) modeled introduced the randomness in Newtons second law A.3, by specifying impulse $\left[\frac{F(t)}{M}\right] dt$ as a viscous drag $-\gamma V(t)dt$ plus the random fluctuation $\sqrt{\beta^2 dt Z_t}$ [46]. Langevin stated that the random variable Z_t has mean 0 and variance 1 and is uncorrelated with the position $X(t)$. If we want to define this random variable as $Z_t = N_t^{t+dt}(0,1)$, then we can write the equation A.3 as following:

$$V(t+dt) - V(t) = -\gamma V(t)dt + \sqrt{\beta^2 dt} N_t^{t+dt}(0,1) \tag{A.8}$$

L. S. Ornstein and G. E. Uhlenbeck [78] are the two who formalized the properties of this continuous Markov process and is known as Langevin equation governed by Ornstein-Uhlenbeck or simply O-U process [46]. The O-U process $V(t)$ (equation A.8)and its time

integral $X(t)$ (equation A.4), together characterize Langevin's Brownian motion.

From the theory of statistics we know that a linear combination of independent normal random variables will also be normal. We are going to use this logic in our evaluation. Here in the sequence of random variables $V(dt), V(2dt), ...V(t)$, each variable is a linear combination of independent normal variables $N_0^{dt}(0,1), N_d t^{2dt}(0,1), ...N_{t-dt}^{t}(0,1)$. From which we can say that $V(t)$ is itself normal and can be written as [46]:

$$V(t) = N_0^t(\text{mean}[V(t), \text{var}[V(t)]]) \tag{A.9}$$

now, we just have to find the mean and variance of the sure function $V(t)$ and then have to substitute into the equation A.9.
Taking the mean on both sides of equation A.8 we will get:

$$< V(t+dt) - V(t) > = < -\gamma V(t) + \sqrt{\beta^2 dt} N_t^{t+dt}(0,1) > \tag{A.10}$$

$$\implies < V(t+dt) > - < V(t) > = -\gamma < V(t) > + \sqrt{\beta^2 dt} < N_t^{t+dt}(0,1) > \tag{A.11}$$

$$\implies \frac{d < V(t) >}{dt} = -\gamma < V(t) > \tag{A.12}$$

where we have used the condition that the mean of $< N_t^{t+dt}(0,1) >$ is 0 and also have used the linearity property for the operator <>. Now we can see the A.12 is an ordinary differential equation and we can solve this to get following expression of mean $V(t)$:

$$mean[V(t)] =< V(t) >= v_0 e^{-\gamma(t-t_0)} \tag{A.13}$$

where the initial condition $V(0) = v_0$ at time $t = t_0$ has been used.

To evaluate the variance of $V(t)$ we can use the definition of variance $< V(t)^2 > - < V(t) >^2$, from where we have $< V(t) >^2 = v_0^2 e^{-2\gamma(t-t_0)}$ and we just have to evaluate $< V(t)^2 >$. We can use the definition as following:

$$d[V(t)^2] = [V(t+dt)]^2 - [V(t)]^2 \tag{A.14}$$

Now using equation A.8 we can get the following:

$$V(t+dt) = V(t) - \gamma V(t) + \sqrt{\beta^2 dt} N_t^{t+dt}(0,1) \tag{A.15}$$

$$\implies V(t+dt) = V(t)(1-\gamma dt) + \sqrt{\beta^2 dt} N_t^{t+dt}(0,1)$$

$$\implies [V(t+dt)]^2 = [V(t)(1-\gamma dt) + \sqrt{\beta^2 dt} N_t^{t+dt}(0,1)]^2 \quad \text{squaring both sides} \tag{A.16}$$

Now using this relation into the right hand side of the equation A.14 we get:

$$\begin{aligned} d[V(t)^2] &= [V(t+dt)]^2 - [V(t)]^2 \\ &= [V(t)(1-\gamma dt) + \sqrt{\beta^2 dt} N_t^{t+dt}(0,1)]^2 - [V(t)]^2 \\ &= V(t)^2(1-\gamma dt)^2 + 2V(t)(1-\gamma dt)\sqrt{\beta^2 dt} N_t^{t+dt}(0,1) + \beta^2 dt [N_t^{t+dt}(0,1)]^2 - V(t)^2 \\ &= -2V(t)^2\gamma dt + 2V(t)\sqrt{\beta^2 dt} N_t^{t+dt}(0,1) + \beta^2 dt [N_t^{t+dt}(0,1)]^2 \end{aligned} \tag{A.17}$$

where we have dropped the terms of order dt^2 and $dt^{3/2}$ who are very small comparing to dt. Taking the mean on the both side of equation A.17 we get:

$$\begin{aligned} d < V(t)^2 > &= -2 < V(t)^2 > \gamma dt + 2 < V(t) N_t^{t+dt}(0,1) > \sqrt{\beta^2 dt} \\ &+ \beta^2 dt < [N_t^{t+dt}(0,1)]^2 > \\ &= -2 < V(t)^2 > \gamma dt + 2 < V(t) N_t^{t+dt}(0,1) > \sqrt{\beta^2 dt} + \beta^2 dt \end{aligned} \tag{A.18}$$

From the statistical condition we have defined before; we can say that $V(t)$ is the linear combination of $N_0^{dt}(0,1), N_d t^{2dt}(0,1), ...N_{t-dt}^{t}(0,1)$ but not of $N_t^{t+dt}(t)$, which means $V(t)$ and $N_t^{t+dt}(t)$ are statistically independent and we can have:

$$< V(t) N_t^{t+dt}(0,1) >=< V(t) >< N_t^{t+dt}(0,1) >= 0 \tag{A.19}$$

By using this equation A.18 becomes:

$$\begin{aligned} d < V(t)^2 > &= -2 < V(t)^2 > \gamma dt + \beta^2 dt \\ \implies \frac{d}{dt} < V(t)^2 > &= -2 < V(t)^2 > \gamma + \beta^2 \end{aligned} \tag{A.20}$$

Now solving the differential equation A.20 with the initial condition $V(0) = v_0$ at time $t = t_0$, we will get:

$$< V(t)^2 >= v_0^2 e^{-2\gamma(t-t_0)} + \left(\frac{\beta^2}{2\gamma}\right)(1 - e^{-2\gamma(t-t_0)}) \tag{A.21}$$

Now using the definition of variance together with the equations A.21 and A.13 we can get the expression for variance of $V(t)$

$$\begin{aligned} \text{var}[V(t)] &= < V(t)^2 > - < V(t) >^2 \\ &= \left(\frac{\beta^2}{2\gamma}\right)(1 - e^{-2\gamma(t-t_0)}) \end{aligned} \tag{A.22}$$

Now using the mean and variance from equations A.13 and A.22 we can have the O-U process as:

$$V(t) = N_0^t\left(v_0 e^{-\gamma(t-t_0)}, \left(\frac{\beta^2}{2\gamma}\right)(1-e^{-2\gamma(t-t_0)})\right) \tag{A.23}$$

From the characteristics of the random variables we know that, two random variables can be determined by their mean, variance and covariance. As we have evaluated the mean and variance for $V(t)$, our next attempt is to evaluate the mean and variance for the time integral of the process, i. e., $X(t)$. Taking the average on A.4 we will get:

$$\begin{aligned}\frac{d < X(t) >}{dt} &= < V(t) > \\ &= v_0 e^{-\gamma(t-t_0)} \quad \text{using equation A.13}\end{aligned} \tag{A.24}$$

Now solving the differential equation A.24 using the initial condition $X(t_0) = x_0$ we will get:

$$< X(t) >= x_0 + v_0/\gamma(1-e^{-(t-t_0)\gamma}) \tag{A.25}$$

Now we are going to multiply equation A.8 with the equation A.4 to evaluate the relation of the covariance between $V(t)$ and $X(t)$ as following:

$$V(t+dt)X(t+dt) = V(t)X(t) - \gamma V(t)X(t)dt + \sqrt{\beta^2 dt}N_t^{t+dt}(0,1)X(t) + V^2(t)dt + o(dt) \tag{A.26}$$

Here $o(dt)$ stands for the order of dt for > 1 in dt. Now taking the average on A.26 and also by using the condition that $N(t)$ and $X(t)$ are two independent random variables means $< N(t)X(t) >=< N(t) >< X(t) >= 0 < X(t) >= 0$ we will get:

$$\frac{d < V(t)X(t) >}{dt} = -\gamma < V(t)X(t) > + < V^2(t) > \tag{A.27}$$

Now using the relation A.22 and A.13 we can solve solve the DE A.27 using the initial condition $< V(t_0)X(t_0) >= v_0 x_0$ and also using the equations A.13 and A.22 we can find the result as following:

$$< V(t)X(t) >= \frac{\beta^2}{2\gamma^2} + (v_0 x_0 + v_0^2/\gamma - \beta^2/\gamma^2)e^{-(t-t_0)\gamma} + \left(\frac{\beta^2}{2\gamma^2} - \frac{v_0^2}{\gamma}\right)e^{-2\gamma(t-t_0)} \tag{A.28}$$

The definition of the covariance for $V(t)$ and $X(t)$ can be written as:

$$\text{cov}(V(t)X(t)) \equiv < V(t)X(t) > - < V(t) >< X(t) > \tag{A.29}$$

and using all these result we can get the relation of the covariance of $V(t)$ and $X(t)$ as following:

$$\text{cov}(V(t)X(t)) = \frac{\beta^2}{2\gamma^2}(1 - 2e^{-(t-t_0)\gamma} + e^{-2(t-t_0)\gamma}) \tag{A.30}$$

Now to evaluate the variance of $X(t)$, we will square the equation A.4 and neglecting the terms of order of $dt > 1$ we will get:

$$\begin{aligned} < X^2(t+dt) > - < X^2(t) > &= 2 < V(t)X(t) > dt \\ \implies \frac{d < X^2(t) >}{dt} &= 2 < V(t)X(t) > \\ \implies < X^2(t) > = x_0^2 + 2\int_{t_0}^{t} < V(t')X(t') > dt' & \end{aligned} \tag{A.31}$$

Now using the result of A.28 in the above A.31 we can solve the equation and then we can use the definition of variance to get the following:

$$\text{var}(X(t)) = \frac{\beta^2}{\gamma^3}\left[\gamma(t-t_0) - 2(1 - e^{-\gamma(t-t_0)}) + \frac{1}{2}(1 - e^{-2\gamma(t-t_0)})\right] \tag{A.32}$$

Exact Updating formula

From the above section we can say that we have a complete solution of the Onrstein Uhlenbeck process of $V(t)$ and its time integral $X(t)$. Now we are going use all of these information to evaluate exact updating formulas for random variables $V(t)$ and $X(t)$. Here we are assumed that the values of $V(t)$ and $X(t)$ are given which will be used to evaluate the random variables $V(t+\Delta t)$ and $X(t+\Delta t)$ for any $\Delta t > 0$ and also we are going to substitute t_0 to t and t to $t + \Delta t$ in the expression of the means, variances and covariance, which will give us the new expressions are as following:

$$\text{mean}(V(t+\Delta t)) = V(t)e^{-\gamma\Delta t} \tag{A.33}$$

$$\text{mean}(X(t+\Delta t)) = X(t) + V(t)/\gamma(1 - e^{-\gamma\Delta t}) \tag{A.34}$$

$$\text{var}(V(t+\Delta t)) \equiv \sigma_V^2 = (\beta^2/2\gamma)(1 - e^{-2\gamma\Delta t}) \tag{A.35}$$

$$\text{var}(X(t+\Delta t)) \equiv \sigma_X^2 = \frac{\beta^2}{\gamma^3}\left[\gamma\Delta t - 2(1 - e^{-\gamma(\Delta t)}) + \frac{1}{2}(1 - e^{-2\gamma\Delta t})\right] \tag{A.36}$$

$$\text{cov} \equiv k_{VX} = \frac{\beta^2}{2\gamma^2}(1 - 2e^{-\gamma\Delta t} + e^{-2\gamma\Delta t}) \tag{A.37}$$

Now we are going to use the theory of the random variable, which stated that if N_1 and N_2 are statistically independent unit normal random variables, then two random variables X_1 and X_2 which have the mean: m_1, m_2; variances σ_1^2, σ_2^2, and covariance k_{12}, can be determined [30]:

$$X_1 = m_1 + \sigma_1 N_1 \tag{A.38}$$

$$X_2 = m_2 + \left(\sigma_2^2 - \frac{k_{12}^2}{\sigma_1^2}\right)^{1/2} N_2 + \frac{k_{12}}{\sigma_1} N_1 \tag{A.39}$$

Now using A.38 and also using the condition that a random variable with mean m and variance σ^2 can be written as:

$$\alpha + \beta N(m, \sigma^2) = N(\alpha + \beta m, \beta^2 \sigma^2) \tag{A.40}$$

it is possible to get expressions for X_1, X_2 and $\mathrm{cov}(X_1, X_2)$ as following [30]:

$$X_1 = m_1 + \sigma N(0,1) = N(m_1, \sigma_1^2) \tag{A.41}$$

$$\begin{aligned} X_2 &= m_2 + \left(\sigma_2^2 - \frac{k_{12}^2}{\sigma_1^2}\right)^{1/2} N(0,1) + \frac{k_{12}}{\sigma_1} N(0,1) \\ &= N\left(m_2, \left(\sigma_2^2 - \frac{k_{12}^2}{\sigma_1^2}\right)\right) + N(0, \frac{k_{12}^2}{\sigma_1^2}) \\ &= N\left(m_2 + 0, \sigma_2^2 - \frac{k_{12}^2}{\sigma_1^2}\frac{k_{12}^2}{\sigma_1^2}\right) \\ &= N\left(m_2, \sigma_2^2\right) \end{aligned} \tag{A.42}$$

$$\begin{aligned} \mathrm{cov}(X_1, X_2) &\equiv < (X_1 - < X_1 >)(X_2 - < X_2 >) > \\ &= < (X_1 - m_1)(X_2 - m_2) > \\ &= \left\langle [\sigma_1 N_1] \left[\left(\sigma_2^2 - \frac{k_{12}^2}{\sigma_1^2}\right)^{1/2} N_2 + \frac{k_{12}}{\sigma_1} N_1 \right] \right\rangle \\ &= \sigma_1 \left(\sigma_2^2 - \frac{k_{12}^2}{\sigma_1^2}\right)^{1/2} < N_1 N_2 > + k_{12} < N_1^2 > \end{aligned} \tag{A.43}$$

By using A.38 and A.39, it is possible to express the dependent normals $V(t+\Delta t)$ and $X(t+\Delta t)$ as a linear combination of independent unit normals. Now by substituting $\mu \equiv e^{-\gamma \Delta t}$ into the moment equations A.33 we will get:

$$\sigma_V^2 = (\frac{\beta^2}{2\gamma})(1-\mu^2) \tag{A.44}$$

$$\sigma_X^2 = \frac{\beta^2}{\gamma^3}[\gamma\Delta t - 2(1-\mu) + (1/2)(1-\mu^2)] \tag{A.45}$$

$$k_{VX} = (\frac{\beta^2}{2\gamma^2})(1-\mu)^2 \tag{A.46}$$

Using all these information and relation it is possible to get the exact updating formula for the Ornstein Uhlenbeck process V and its time integral X as [30]:

$$V(t+\Delta t) = V(t)\mu + \sigma_V n_1 \tag{A.47}$$

$$X(t+\Delta t) = X(t) + \frac{1}{\gamma}V(t)(1-\mu) + \left(\sigma_x^2 - \frac{k_{VX}^2}{\sigma_V^2}\right)n_2 + \frac{k_{VX}}{\sigma_V}n_1 \tag{A.48}$$

where n_1 and n_2 are independent normal numbers, μ, σ_V, σ_X and k_{VX} are characterize by the time step Δt, relaxation time γ and the diffusion constant β

Appendix B

Saturable and fractal kinetics

B.1 Genetic Algorithm

To find an optimal or best solution, optimization techniques have been used in different areas of science and engineering. These techniques are considering the following factors [24]:

- **An objective function:** the function we want to minimize or maximize, for example we want to minimize the cost and maximize the profit in manufacturing.
- **A set of unknown variables:** the variables by which the objective function can be effected.
- **A set of constraints:** which can be used to include certain conditions while evaluating values of the unknown parameters.

So, an optimization technique is a technique which can be used to find the variables that maximize or minimize the objective function while satisfying the constraints. Genetic Algorithm (GA) is a heuristic search algorithm to optimize a problem, inspired by Darwins evolution theory, which uses random search process. The basics of GA can be stated as follows:

- It starts by generating a random population of n chromosome which can be think of the solution of the problem.

- Calculate f(x), the fitness function of x (chromosome) in the population.
- Creates new population by repeating the following processes:
  - (a) Two different parent chromosomes are selected from the population which we can think as **Selection** by comparing with evolution process (when the fitness is better, then the chance to be selected is bigger).
  - (b) Perform a **Crossover probability**. The offspring (children) will be exact same copy of the parents if there is no crossover (but this does not mean that the new generation is same) and the offspring will be made from parts of parents chromosome then crossover probability performed.
  - (c) How often the parts of the chromosome mutated is measured by the **Mutation probability** and offspring can be taken as is after the crossover if there is no mutation.
  - (d) Place the new offspring in the new population which is known as **Accepting** the new population.
- The new generated population is replaced for the next run of the algorithm.
- By testing the constraint conditions it will stop and return the best solution of the current population.
- And it will go to the step 2 to continue the loop as long as the tolerance is achieved.

B.2 Akaike Information Criterion (AIC)

In statistical study we are engaging ourselves to estimate the effects for a given variable using certain parameters. While doing this we certainly may include parameters for which we might loose the physical information we are trying to predict via a mathematical model. And we may also over fit the available data. Form the Occam's razor philosophical principle we know that, if we can describe something with a simple model or with also a more complicated model then we should choose the simple one. Which indicates to rely on the simpler model than to the complicated model. Now when we are fitting some observation how do we know that we are including less or more parameters? In 1973, Akaike H., a Japanese Statistician came with a theory which will compare with the models and that comparison will give the idea which model we should choose among the models are available to choose. By doing so, it restricts us from under or over fit the model. Since this is a

comparison with the available models we have, it will not tell us that this is the best model rather give us the information that this a better one among the models we have. In statistics this means that a model with less parameters is preferable than a model with more parameters. Again a model with too less parameters will be biased and a model with too many parameters will have low precision [10]
The theory is from the information field theory and named as Akaike Information Criterion or AIC. Good model would be the one which will minimize the loss of information. Akaike in 1973 proposed an information criterion as follows:
AIC=-2(log-likely hood)+2K
where K is the number of estimated parameters used in the model. For a given sets of data log-likelihood can be calculated and from there one can tell about the model, is that it is over or under fit or not (smaller value means worse fit) [10]. If the models are based on conventional least squares regression then the assumption is that the error obeys Gaussian distribution. And we can compute the AIC formula as following:

$$AIC = N_{obs} + ln(WRSS) + 2N_{par};$$

where N_{obs}, is the number of observed data point, N_{par} is the number of model parameters, WRSS is the weighted residual sum squares [88]. WRSS can be calculated from the following relation:

$$WRSS = \Sigma_{i=1}^{n} \frac{(C_i - \hat{C}_i)^2}{\hat{C}_i{}^2}$$

where $\hat{C}_i$ is the predicted value and C_i is the true value. A lower AIC value indicate a better fit. Idea about the weighted factor is, if at high concentration i.e., at the beginning of the time plasma profile, data are showing more accuracy than the tail, then the data can be weighted with $WRSS \sim 1$; [88]. On the other hand if the tail end of the profile showing more accuracy then the data might be weighted with $1/\hat{C}^2$ [88]. Following this idea in our model we have used the weighted factor for WRSS is $1/\hat{C}_i$.

Appendix C

Matlab Code for the figures

C.1 Maple Code for chapter 2

Code for Fig. 2.1

```
with(DEtools);

c_1 := 2*tau_c^2/(4*tau_c^2+1);

c_2 := -4*tau_c^3/(4*tau_c^2+1);

coef1 := (1/2)*alpha^2*c_2;

coef2 := 1-(1/2)*alpha^2*c_1;

soln := dsolve({diff(y(tau), tau, tau)
-coef1*(diff(y(tau), tau))+coef2*y(tau) = 0,

y(0) = 1, (D(y))(0) = 0}, y(tau));

tau_c := .1;

alpha := .1;
```

```
p1 := soln;

p2 := evalc(p1);

p3:=1.000000000*exp(-9.615384615*10^(-6)*tau)*cos(.9999519221*tau)

+9.615846928*10^(-6)*exp(-9.615384615*10^(-6)*tau)*sin(.9999519221*tau);

plot(p3, tau = 0 .. 300000, labels = ["tau;", "x(tau;)"]);
```

Code for Fig. 2.2

```
with(DEtools);
eqn1 := (4s^3+4s^2g+s(g^2+1))/(4s^4+4s^3g+s^2(g^2+5)+4sg+g^2+1-a^2);

g := 10; % here g is for gamma

a := .1; % a is for alpha

% tau_c = 1/gamma; relation between tau_c and gamma

eqn2 := convert(eqn1, parfrac, s, complex);

simplify(eqn2);

with(inttrans);

eqn3 := invlaplace(eqn2, s, tau);

simplify(eqn3);

evalc(eqn3)=-0.1022861100e-4*exp(-4.999981833*tau)*cos(4999064302*tau)
-0.3506132442e-4*exp(-4.999981833*tau)*sin(.4999064302*tau)
+(1.000010228*cos(.9999559436*tau)-0.1544872248e
-4*sin(.9999559436*tau))*exp(-0.1816725994e-4*tau)
```

```
+I*(3.801992999*10^(-17)*cos(.9999559436*tau)
-1.*10^(-31)*sin(.9999559436*tau))*exp(-0.1816725994e-4*tau)

eqn4:=-0.1022861100e-4*exp(-4.999981833*tau)*cos(4999064302*tau)
-0.3506132442e-4*exp(-4.999981833*tau)*sin(.4999064302*tau)
+(1.000010228*cos(.9999559436*tau)
-0.1544872248e-4*sin(.9999559436*tau))*exp(-0.1816725994e-4*tau)

plot(eqn4, tau = 0 .. 200000, labels = ["tau;", "y(tau;)"]);
```

C.2 Matlab Code for chapter 3

Matlab files for test case 1:

```
% This is the script file to run the numerical form of the model
% Time set-up for Acetaminophen for maximum dose 4000 mg
% We are checking the simulation by giving the maximum dose
% in every six hours time interval
dt=0.3; % dt=delta_t=time step
t=0:dt:6;% First Dose
tfull=[t,t+6,t+12,t+18];
iteration=5;%100000;

x_mat=zeros(length(tfull),iteration);
A_mat=zeros(length(tfull),iteration);
global tauC D
D = .2;
tauC = .01;
%Initial condition
dose=1000; % dose=x(0)=X_0
y0=[dose;0;0]; % A(0)=0, noise xi(0)=0

for i=1:iteration
    [x1,xi1,A1]=Acetaminophen(t,y0);
```

```
    [x2,xi2,A2]=Acetaminophen(t+6,[x1(end)+dose,xi1(end),A1(end)]);
    [x3,xi3,A3]=Acetaminophen(t+12,[x2(end)+dose,xi2(end),A2(end)]);
    [x4,xi4,A4]=Acetaminophen(t+18,[x3(end)+dose,xi3(end),A3(end)]);


    x_mat(:,i)=[x1';x2';x3';x4'];
    A_mat(:,i)=[A1';A2';A3';A4'];

    disp (i)

end

figure(1);  hold on; plot(tfull,x_mat)
figure(2);  hold on; plot(tfull,A_mat)
figure(3);  hold on; plot(tfull,mean(x_mat,2)','Linewidth',2)
figure(4);  hold on; plot(tfull,mean(A_mat,2)','Linewidth',2)
figure(5);  hold on; e1 = errorbar(tfull,mean(x_mat,2)',std(x_mat')');
figure(6);  hold on; e2 = errorbar(tfull,mean(A_mat,2)',std(A_mat')');
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
% The basic idea of the codes are taken from
% Dr. Mathew Scott's lecture note AMATH 777
% http://www.math.uwaterloo.ca/~mscott/
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

function [x, xi, A]=Acetaminophen(tdom, y0)
% The syntax for this function is 777_jenny([tauC, D],
% [t_start, t_end])
% where tauC is the correlation time of the colored noise,
% D is the standard
% deviation of the noise, t_start is the initial time
% and t_end is the end time
global tauC
x=zeros(1,length(tdom));
xi=zeros(1,length(tdom));
A=zeros(1,length(tdom));
```

```
[t,y] = Eulers(@PKFun, [tdom(1),tdom(end)], y0, min(.01,tauC/10));
    x = x+interp1(t,y(:,1),tdom);
    xi = xi+interp1(t,y(:,2),tdom);
    A = A+interp1(t,y(:,3),tdom);
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function dy=PKFun(~,y,h)

% The vector right-hand sides of the differential equations
% dy(1) is the trajectory of the drug in the absorption site,
% dy(2) is the noise,
% and dy(3) is the drug in the systemic circulation

global tauC D

rho=exp(-h/tauC);
ke=.28; F=.89; ka=1.80*F; p=ke/ka;
% Random form of the model
dy(1)=-(1+y(2))*y(1);
dy(2)=1/h*((rho-1)*y(2)+(1-rho^2)^(1/2)*(D/(2*tauC))^(1/2)*randn);
dy(3)=(1+y(2))*y(1)-p*y(3);
end
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function [tout, yout] = Eulers(FunFcn, tspan, y0, ssize)
%  This function will integrate a system of ordinary
%   differential equations using Euler's method.
% INPUT:
% F     - String containing name of user-supplied
%   problem description.
%         Call: yprime = fun(t,y) where F = 'fun'.
%         t      - Time (scalar).
%         y      - Solution vector.
%         yprime - Returned derivative vector; yprime(i) = dy (i)/dt.
% tspan = [t0, tfinal], where t0 is the initial value of t,
%           and tfinal is the final value of t.
```

```
% y0    - Initial value vector.
% ssize - The step size to be used.
%(Default: ssize = (tfinal - t0)/100).
%
% OUTPUT:
% t  - Returned integration time points (column-vector).
% y  - Returned solution, one solution row-vector per tout-value.

% Initialization
t0=tspan(1);
tfinal=tspan(2);
pm = sign(tfinal - t0);  % Which way are we computing?
if (nargin < 4), ssize = abs (tfinal - t0)/1000; end
if ssize < 0, ssize = -ssize; end
h = pm*ssize;
t = t0;
y = y0(:);
% To compute the number of steps.
dt = abs(tfinal - t0);
N = floor(dt/ssize) + 1;
if (N-1)*ssize < dt
  N = N + 1;
end

% Initialize the output.
tout = zeros(N,1);
tout(1) = t;
yout = zeros(N,size(y,1));
yout(1,:) = y.';
k = 1;

% The main loop

while k < N
  if pm*(t + h - tfinal) > 0
    h = tfinal - t;
    tout(k+1) = tfinal;
  else
```

```
    tout(k+1) = t0 +k*h;
  end
  k = k+1;
  % Compute the slope
  s1 = feval(FunFcn, t, y,ssize); s1 = s1(:); % s1=f(t(k),y(k))
  y = y + h*s1; % y(k+1) = y(k) + h*f(t(k),y(k))
  t = tout(k);
  yout(k,:) = y.';
end
end
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
% This is the script file is to evaluate Van Kampen's
% mean and Variance along with the deterministic solution
%%
% Constants
DoseInterval = 6;   tfinal= DoseInterval*4;  h =.3;
t=0:h:6;% First Dose
t=[t,t+6,t+12,t+18];
dose = 1e3;
ke=.28; F=.89; ka=1.80*F; p=ke/ka; % p is rho in the writing
alpha=.3; tauc=.01;
Cond0 = alpha^2*tauc
Cond1 = 3*(p + 1)/5
Cond2 = (3*p^3+13*p^2+13*p+3)/(22*p^2 + 44*p + 14)
Cond0 < Cond1
Cond0 < Cond2


%% First portion is the solution of the coupled DE
% Deterministic form of the model
fx=@(t,x) (-x);
fA=@(t,x,A)(x-p*A);
%%%Set initial conditions
N = length(t);
A = zeros(N,1);
x = zeros(N,1); x(1)=dose;
for i=2:N
```

```
    if(t(i) == t(i-1))
        x(i) = x(i-1) + dose;
        A(i) = A(i-1);
     else
        % Update x, A
        K1x=fx(t(i-1), x(i-1)                  );
        K1A=fA(t(i-1)        ,x(i-1)             ,A(i-1));
        K2x=fx(t(i-1)+h/2   ,x(i-1)+h/2*K1x);
        K2A=fA(t(i-1)+h/2    ,x(i-1)+h/2*K1x    ,A(i-1)+h/2*K1A);
        K3x=fx(t(i-1)+h/2    , x(i-1)+h/2*K2x);
        K3A=fA(t(i-1)+h/2    ,x(i-1)+h/2*K2x    ,A(i-1)+h/2*K2A);
        K4x=fx(t(i-1)+h     , x(i-1)+h*K3x);
        K4A=fA(t(i-1)+h      ,x(i-1)+h*K3x      ,A(i-1)+h*K3A);
        %
        x(i)=x(i-1)+(h/6)*(K1x +2*K2x +2*K3x +K4x);
        A(i)=A(i-1)+(h/6)*(K1A +2*K2A +2*K3A +K4A);
    end
end
% Deterministic solution
figure (3); hold on ; plot(t,x,'b:','LineWidth',2)
figure (4); hold on;  plot(t,A,'b:','LineWidth',2)

%% Script file to evaluate <x>, <A>, <AX>, <AA> and <XX>
x = zeros(N,1); x(1) = dose;
A = zeros(N,1); A(1) = 0;
Ax = zeros(N,1); Ax(1) = A(1)*dose;
xx = zeros(N,1); xx(1) = dose^2;
AA = zeros(N,1); AA(1) = 0;

%Function handle for mean
fx=@(t,x) (-(1-alpha^2*tauc)*x);
fA=@(t,x,A) ((1-alpha^2*tauc)*x-p*A);
% These are the coefficients for the second moment
coef1=tauc*alpha^2 - p - 1;
coef2=2*tauc*alpha^2 + 2;
=((3*tauc - 2*p*tauc + (p*tauc)/(tauc*(p - 1) ...
+ 1))*alpha^2)/(p - 1) + 1;
coef4=-(alpha^2*(2*tauc - (2*p*tauc)/(tauc*(p - 1) ...
```

```
+ 1)))/(p - 1);
coef5=4*tauc*alpha^2 - 2;
%Function Handle for second moemnt
fAx=@(t,Ax,xx)(coef1*Ax+coef3*xx);
fAA=@(t,Ax,AA,xx) (coef2*Ax-2*p*AA+coef4*xx);
fxx=@(t, xx) (coef5*xx);
% Loop to use for multiple dosage
for i=2:N
     if(t(i) == t(i-1))
        x(i) = x(i-1) + dose;
        xx(i) = xx(i-1) + dose^2 + 2*(x(i-1))*dose;
        Ax(i) = Ax(i-1) + A(i-1)*dose;
        A(i) = A(i-1);
        AA(i) = AA(i-1);
   else
        % Update x, A, Ax, AA, xx
        K1x=fx(t(i-1), x(i-1));
        K1A=fA(t(i-1), x(i-1), A(i-1));
        K1Ax=fAx(t(i-1), Ax(i-1), xx(i-1));
        K1AA=fAA(t(i-1), Ax(i-1), AA(i-1), xx(i-1));
        K1xx=fxx(t(i-1),  xx(i-1));
        K2x=fx(t(i-1)+h/2, x(i-1)+h/2*K1x);
        K2A=fA(t(i-1)+h/2, x(i-1)+h/2*K1x, A(i-1)+h/2*K1A);
        K2Ax=fAx(t(i-1)+h/2, Ax(i-1)+h/2*K1Ax, xx(i-1)+h/2*K1xx);
        K2AA=fAA(t(i-1)+h/2, Ax(i-1)+h/2*K1Ax, AA(i-1)+h/2*K1AA, ...
        xx(i-1)+h/2*K1xx);

        K2xx=fxx(t(i-1)+h/2,    xx(i-1)+h/2*K1xx);
        K3x=fx(t(i-1)+h/2, x(i-1)+h/2*K2x);
        K3A=fA(t(i-1)+h/2, x(i-1)+h/2*K2x, A(i-1)+h/2*K2A);
        K3Ax=fAx(t(i-1)+h/2, Ax(i-1)+h/2*K2Ax, xx(i-1)+h/2*K2xx);
        K3AA=fAA(t(i-1)+h/2, Ax(i-1)+h/2*K2Ax, AA(i-1)+h/2*K2AA, ...
        xx(i-1)+h/2*K2xx);

        K3xx=fxx(t(i-1)+h/2, xx(i-1)+h/2*K2xx);
        K4x=fx(t(i-1)+h, x(i-1)+h*K3x);
        K4A=fA(t(i-1)+h, x(i-1)+h*K3x , A(i-1)+h*K3A);
        K4Ax=fAx(t(i-1)+h, Ax(i-1)+h*K3Ax, xx(i-1)+h*K3xx);
```

```
        K4AA=fAA(t(i-1)+h, Ax(i-1)+h*K3Ax, AA(i-1)+h*K3AA, ...
        xx(i-1)+h*K3xx);

        K4xx=fxx(t(i-1)+h,    xx(i-1)+h*K3xx);
        x(i)=x(i-1)+(h/6)*(K1x +2*K2x +2*K3x +K4x);
        A(i)=A(i-1)+(h/6)*(K1A +2*K2A +2*K3A +K4A);
        Ax(i)=Ax(i-1)+(h/6)*(K1Ax +2*K2Ax +2*K3Ax +K4Ax);
        AA(i)=AA(i-1)+(h/6)*(K1AA +2*K2AA +2*K3AA +K4AA);
        xx(i)=xx(i-1)+(h/6)*(K1xx +2*K2xx +2*K3xx +K4xx);
    end
end

varx=(xx-(x).^2);
varA=(AA-(A).^2);

EnvelopxPlus =  x+sqrt(varx);
EnvelopxMinus = x-sqrt(varx);
EnvelopAPlus = A+sqrt(varA);
EnvelopAMinus = A-sqrt(varA);

figure(5);hold on
plot(t,x,'k--','LineWidth',2)
plot(t,EnvelopxPlus ,'m--','LineWidth',2)
plot(t,EnvelopxMinus ,'m--','LineWidth',2)

figure(6);hold on
plot(t,A','k--','LineWidth',2)
plot(t,EnvelopAPlus ,'m--','LineWidth',2)
plot(t,EnvelopAMinus,'m--', 'LineWidth',2 )
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Matlab files for test case 2:

```
% This code is to solve the Random form of the model
% for the data of subject # 1 of the drug Theophyline
```

```
ka=2.062927706;  dt=0.25; t=0:dt:24*ka;
x_mat=zeros(length(t),iteration);
A_mat=zeros(length(t),iteration);
%Initial condition
Amount=4.02; Weight=79.6; dose=Amount*Weight;
y0=[dose;0;0];
global tauC D
D = .2;
tauC = .01;
% How many times I want to run the simulation
iteration=10000;
for i=1:iteration
    [x,xi,A]=Theophyline(t,y0);
    A_mat(:,i)=A';
    disp (i)
end
figure(1); hold on;
plot(t,A_mat'/dose,'Linewidth',2)
figure(1); hold on;
plot(t,mean(A_mat')'/dose,'k:','Linewidth',2)
figure(1); hold on;
e2 = errorbar(t,mean(A_mat')'/dose,std(A_mat')'/dose);
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function [x, xi, A]=Theophyline(tdom, y0)
% tauC is the correlation time of the colored noise,
% D is the standard deviation of the noise,
%  tdom(1) is the initial time and tdom(2) is the end time

global tauC

x=zeros(1,length(tdom));
xi=zeros(1,length(tdom));
A=zeros(1,length(tdom));

   [t,y] = Euler(@TheoFun, [tdom(1),tdom(end)], ...
          y0, min(.01,tauC/10));
    x = x+interp1(t,y(:,1),tdom);
```

```
    xi = xi+interp1(t,y(:,2),tdom);
    A = A+interp1(t,y(:,3),tdom);

end
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function dy=TheoFun(~,y,h)
global tauC D
rho=exp(-h/tauC);
ke= 0.058333529; ka=2.062927706; p=ke/ka;

dy(1)=-(1+y(2))*y(1);
dy(2)=1/h*((rho-1)*y(2)+(1-rho^2)^(1/2)*(D/(2*tauC))^(1/2)*randn);
dy(3)=(1+y(2))*y(1)-p*y(3);
end
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%
% This is the script file for comapre the theophyline
% Subject # 1 data with the deterministic equation,
% Van Kampan Mean and Variance
ke= 0.058333529; Intercept=1.067449981;
AI=10^(Intercept); ka=2.062927706; p=ke/ka;
Amount=4.02;% mg/kg
Weight=79.6; %kg
dose=Amount*Weight; %mg
F=1;% Bioavalability aproximately 1
V=(ka*F*dose)/(AI*(ka-ke));
alpha=.2; tc=.01; tauc=.01;
%%
% Data for Subject # 1
t_exp1=[0 0.25 0.57 1.12 2.02 3.82 5.1 7.03 9.05 12.12 24.37 ];
C_exp1=[0.74 2.84 6.57 10.5 9.66 8.58 8.36 7.47 6.89 5.94 3.28 ];

figure (1)% FOr the data
plot(t_exp1*ka,C_exp1.*V/dose,'r*','linewidth',2)
hold on
%%
```

```
% Time steps and initial conditions
x(1)=dose; A(1)=0; tfinal=24*ka;  h = .25;  t =0:h:tfinal;
xx(1)=dose^2; AA(1)=0; Ax(1)=0;
N=ceil(tfinal/h);

%% Deterministic form
fx=@(t,x) (-x);
fA=@(t,x,A) (x-p*A);

for i=1:N
% update time
t(i+1)=t(i)+h;
% Update x, A
K1x=fx(t(i), x(i)                  );
K1A=fA(t(i)        ,x(i)             ,A(i));
K2x=fx(t(i)+h/2   ,x(i)+h/2*K1x);
K2A=fA(t(i)+h/2    ,x(i)+h/2*K1x    ,A(i)+h/2*K1A);
K3x=fx(t(i)+h/2    , x(i)+h/2*K2x);
K3A=fA(t(i)+h/2    ,x(i)+h/2*K2x    ,A(i)+h/2*K2A);
K4x=fx(t(i)+h     , x(i)+h*K3x);
K4A=fA(t(i)+h      ,x(i)+h*K3x      ,A(i)+h*K3A);

x(i+1)=x(i)+(h/6)*(K1x +2*K2x +2*K3x +K4x);
A(i+1)=A(i)+(h/6)*(K1A +2*K2A +2*K3A +K4A);

end
figure (1)
plot(t,A/dose,'y:','LineWidth',2)

hold on
%%
% Van Kampen equations for first and second moments:
% By using Runge Kutta method
% Function handle for the mean
fx=@(t,x) (-(1-alpha^2*tc)*x);
fA=@(t,x,A) ((1-alpha^2*tc)*x-p*A);

% These are the coefficients for the second moment
```

```
coef1=tauc*alpha^2 - p - 1;
coef2=2*tauc*alpha^2 + 2;
coef3=((3*tauc - 2*p*tauc + (p*tauc)/(tauc*(p - 1) + 1)) ...
       *alpha^2)/(p - 1) + 1;
coef4=-(alpha^2*(2*tauc - (2*p*tauc)/(tauc*(p - 1) ...
        + 1)))/(p - 1);
coef5=4*tauc*alpha^2 - 2;
%Function Handle for second moemnt
fAx=@(t,Ax,xx)(coef1*Ax+coef3*xx);
fAA=@(t,Ax,AA,xx) (coef2*Ax-2*p*AA+coef4*xx);
fxx=@(t, xx) (coef5*xx);

for i=1:N
% update time
t(i+1)=t(i)+h;
% Update x, A, Ax, AA, xx
K1x=fx(t(i), x(i)                  );
K1A=fA(t(i)         ,x(i)             ,A(i));
K1Ax=fAx(t(i),     Ax(i),             xx(i)     );
K1AA=fAA(t(i)        ,Ax(i)             ,AA(i),   xx(i));
K1xx=fxx(t(i),  xx(i));
%
K2x=fx(t(i)+h/2   ,x(i)+h/2*K1x);
K2A=fA(t(i)+h/2    ,x(i)+h/2*K1x    ,A(i)+h/2*K1A);
K2Ax=fAx(t(i)+h/2   ,Ax(i)+h/2*K1Ax, xx(i)+h/2*K1xx);
K2AA=fAA(t(i)+h/2    ,Ax(i)+h/2*K1Ax, ...
        AA(i)+h/2*K1AA, xx(i)+h/2*K1xx);
K2xx=fxx(t(i)+h/2,    xx(i)+h/2*K1xx);
%
K3x=fx(t(i)+h/2    , x(i)+h/2*K2x);
K3A=fA(t(i)+h/2    ,x(i)+h/2*K2x    ,A(i)+h/2*K2A);
K3Ax=fAx(t(i)+h/2   ,Ax(i)+h/2*K2Ax, xx(i)+h/2*K2xx);
K3AA=fAA(t(i)+h/2    ,Ax(i)+h/2*K2Ax ,AA(i)+h/2*K2AA, ...
         xx(i)+h/2*K2xx);
K3xx=fxx(t(i)+h/2, xx(i)+h/2*K2xx);
%
K4x=fx(t(i)+h     , x(i)+h*K3x);
K4A=fA(t(i)+h      ,x(i)+h*K3x , A(i)+h*K3A);
```

```
K4Ax=fAx(t(i)+h   ,Ax(i)+h*K3Ax, xx(i)+h*K3xx);
K4AA=fAA(t(i)+h    ,Ax(i)+h*K3Ax , AA(i)+h*K3AA, ...
         xx(i)+h*K3xx);
K4xx=fxx(t(i)+h, xx(i)+h*K3xx);
%
x(i+1)=x(i)+(h/6)*(K1x +2*K2x +2*K3x +K4x);
A(i+1)=A(i)+(h/6)*(K1A +2*K2A +2*K3A +K4A);
Ax(i+1)=Ax(i)+(h/6)*(K1Ax +2*K2Ax +2*K3Ax +K4Ax);
AA(i+1)=AA(i)+(h/6)*(K1AA +2*K2AA +2*K3AA +K4AA);
xx(i+1)=xx(i)+(h/6)*(K1xx +2*K2xx +2*K3xx +K4xx);

end
figure (1)% for plot the mean
plot(t,A/dose,'b:','LineWidth',2)
hold on
% Definition of the variance
varA=(AA-(A).^2);
EnvelopAPlus = A+sqrt(varA);
EnvelopAMinus =A-sqrt(varA);

figure(1); %To plot the standard deviation of the mean
plot(t,EnvelopAPlus/dose,'m','LineWidth',2)
plot(t,EnvelopAMinus/dose,'m', 'LineWidth',2 )
hold on
```

C.3 Mtalb code for Chapter 4

Matlab script file for figure 4.2

```
% These data are dizitized from Kearns et.al

Time_135=[0.909 1.939 2.848 3.333 3.636 4.061 5.03 6 8.97
         15.091 24.182 ];
Cnc_135=[1.814 2.95 3.762 1.528 1.199 0.805 0.56 0.396 0.205
         0.081 0.037];
```

```
Time_175=[1.152 1.939 2.091 3.091 3.333 3.576 4.061 5.03 6.061
          9.152 14.97 24.061 ];
Cnc_175=[3.052 4.876 5.23 7.022 3.763 2.398 1.638 0.991 0.666
         0.333 0.141 0.083 ];

Time_225=[0.97 1.939 3.091 3.333 3.576 3.636 3.939 5.273 6.061
         9.152 14.97 24.061 ];
Cnc_225=[4.626 8.061 11.811 8.952 6.441 4.966 3.277 1.697 1.243
         0.523 0.213 0.103 ];

% Plot for experimental data
figure (1)
subplot(3,1,1)
plot(Time_135,Cnc_135,'go:','LineWidth',2)
hold on
figure (1)
subplot(3,1,2)
plot(Time_175,Cnc_175,'go:','LineWidth',2)
hold on
figure (1)
subplot(3,1,3)
plot(Time_225,Cnc_225,'go:','LineWidth',2)
hold on
%% kearns Three compartmental model for dose 135
infusion=3; dose=135;
% Optimum Parameters reported by Kearns et., al., for Kearns model
k21=.68; vdmax = 10.20;
vemax = 18.80; kdm=.32;
kem=5.50; vd=4;
k13=2.20; k31=.65;
gr = @(t,x)[(-vdmax*x(1))/(kdm+x(1)) ...
-(vemax*x(1))/(kem+x(1)) ...
-k13*x(1)+k31*x(3)+k21*x(2) ...
+(t<=infusion)*dose/(infusion*vd); ...
           (vdmax*x(1))/(kdm+x(1))-k21*x(2); ...
           k13*x(1)-k31*x(3)];
[t,yr] = ode45(@(t,x) gr(t,x),[0,Time_135],[0 0 0]);
figure (1)
```

```
subplot(3,1,1)
plot(t, yr(:,1),'r:','LineWidth',2)
hold on
% Calculation for AIC and WRSS
WRSS_yr_135=sum((Cnc_135'-yr(2:end,1)).^2./Cnc_135'.^2);
Number_Of_obs_135=11;
Number_Of_par_MR=8;
AIC_MR_135=(Number_Of_obs_135)*(log(WRSS_yr_135)) ...
+(2*Number_Of_par_MR);
%% kearns Three compartmental model for dose 175
dose=175;
gr = @(t,x)[(-vdmax*x(1))/(kdm+x(1)) ...
-(vemax*x(1))/(kem+x(1))-k13*x(1) ...
+k31*x(3)+k21*x(2)+(t<=infusion)*dose/(infusion*vd); ...
           (vdmax*x(1))/(kdm+x(1))-k21*x(2); ...
           k13*x(1)-k31*x(3)];

[t,yr] = ode45(@(t,x) gr(t,x),[0,Time_175],[0 0 0]);
figure (1)
subplot(3,1,2)
plot(t, yr(:,1),'r:','LineWidth',2)
hold on
% Calculation for AIC and WRSS
WRSS_yr_175=sum((Cnc_175'-yr(2:end,1)).^2./Cnc_175'.^2);
Number_Of_obs_175=12;
Number_Of_par_MR=8;
AIC_MR_175=(Number_Of_obs_175)*(log(WRSS_yr_175)) ...
+(2*Number_Of_par_MR);
%% kearns Three compartmental model for dose 225
dose = 225;
gr = @(t,x)[(-vdmax*x(1))/(kdm+x(1)) ...
-(vemax*x(1))/(kem+x(1)) ...
-k13*x(1)+k31*x(3)+k21*x(2) ...
+(t<=infusion)*dose/(infusion*vd); ...
           (vdmax*x(1))/(kdm+x(1))-k21*x(2); ...
           k13*x(1)-k31*x(3)];

[t,yr] = ode45(@(t,x) gr(t,x),[0,Time_225],[0 0 0]);
```

```
figure (1)
subplot(3,1,3)
plot(t, yr(:,1),'r:','LineWidth',2)
hold on
% Calculation for AIC and WRSS
WRSS_yr_225=sum((Cnc_225'-yr(2:end,1)).^2./Cnc_225'.^2);
Number_Of_obs_225=12;
Number_Of_par_MR=8;
AIC_MR_225=(Number_Of_obs_225)*(log(WRSS_yr_225)) ...
+(2*Number_Of_par_MR);
%% Fractal Two Compartmental model for dose 135
dose=135;
% Optimum Parameters evaluated by GA for Fractal model
k21= 1.9727 ; vdmax = 12.3198 ;
vemax = 13.4051; kdm= 1.6703;
kem=6.3906; vd= 4.9185;
p=1.2019 ; q=1.7010;
k13=0; k31=0;
gf = @(t,x)[(-vdmax*(x(1).^p))/(kdm+(x(1).^p))- ...
(vemax*(x(1).^q))/(kem+(x(1).^q)) ...
-k13*x(1)+k31*x(3)+k21*x(2) ...
+(t<=infusion)*dose/(infusion*vd); ...

(vdmax*(x(1).^p))/(kdm+(x(1).^p))-k21*x(2); ...

k13*x(1)-k31*x(3)];

[t,yf] = ode45(@(t,x) gf(t,x),[0,Time_135],[0 0 0]);

figure (1)
subplot(3,1,1)
plot(t, yf(:,1),'b:','LineWidth',2)
hold on

% Calculation for AIC and WRSS
WRSS_yf_135=sum((Cnc_135'-yf(2:end,1)).^2./Cnc_135'.^2);
Number_Of_obs_135=11;
Number_Of_par_MF=8;
```

```
AIC_MF_135=Number_Of_obs_135*log(WRSS_yf_135) ...
+2*Number_Of_par_MF;
%% Fractal Two Compartmental model for dose 175
dose=175;
gf = @(t,x)[(-vdmax*(x(1).^p))/(kdm+(x(1).^p)) ...
-(vemax*(x(1).^q))/(kem+(x(1).^q)) ...
-k13*x(1)+k31*x(3)+k21*x(2)...
+(t<=infusion)*dose/(infusion*vd); ...
            (vdmax*(x(1).^p))/(kdm+(x(1).^p))-k21*x(2); ...
             k13*x(1)-k31*x(3)];
[t,yf] = ode45(@(t,x) gf(t,x),[0,Time_175],[0 0 0]);
figure (1)
subplot(3,1,2)
plot(t, yf(:,1),'b:','LineWidth',2)
hold on
% Calculation for AIC and WRSS
WRSS_yf_175=sum((Cnc_175'-yf(2:end,1)).^2./Cnc_175'.^2);
Number_Of_obs_175=12;
Number_Of_par_MF=8;
AIC_MF_175=(Number_Of_obs_175)*(log(WRSS_yf_175))...
+(2*Number_Of_par_MF);
%%  Fractal Two Compartmental model for dose 225
dose=225;
gf = @(t,x)[(-vdmax*(x(1).^p))/(kdm+(x(1).^p)) ...
-(vemax*(x(1).^q))/(kem+(x(1).^q)) ...
-k13*x(1)+k31*x(3)+k21*x(2) ...
+(t<=infusion)*dose/(infusion*vd); ...
            (vdmax*(x(1).^p))/(kdm+(x(1).^p))-k21*x(2); ...
             k13*x(1)-k31*x(3)];
[t,yf] = ode45(@(t,x) gf(t,x),[0,Time_225],[0 0 0]);

figure (1)
subplot(3,1,3)
plot(t, yf(:,1),'b:','LineWidth',2)
hold on

% Calculation for AIC and WRSS
WRSS_yf_225=sum((Cnc_225'-yf(2:end,1)).^2./Cnc_225'.^2);
```

```
Number_Of_obs_225=12;
Number_Of_par_MF=8;
AIC_MF_225=(Number_Of_obs_225)*(log(WRSS_yf_225)) ...
+(2*Number_Of_par_MF);
```

Matlab script file for figure 4.3

```
% These are digitized directly from VZ
Time_135=[0.85 2.065 2.854 3.279 3.522 4.008 4.858 6.984 10.87
         12.996 22.955 ];
Cnc_135=[1.338 2.015 2.931 1.59 0.923 0.594 0.328 0.194 0.095
         0.078 0.032 ];
Time_175=[0.85 1.943 2.794 3.158 3.401 4.008 4.98 6.923 11.053
         12.996 22.955 ];
Cnc_175=[2.012 3.298 4.638 3.982 2.018 1.213 0.807 0.396 0.195
         0.141 0.054 ];
Time_225=[0.85 1.943 3.097 3.887 5.04 6.923 11.053 13.057
         22.955  ];
Cnc_225=[2.732 4.713 7.096 1.762  1.256 0.66 0.298 0.22
         0.084 ];

% Plot for experimental data

figure (2)
subplot(3,1,1)
plot(Time_135,Cnc_135,'ko:','LineWidth',2)
hold on
figure (2)
subplot(3,1,2)
plot(Time_175,Cnc_175,'ko:','LineWidth',2)
hold on
figure (2)
subplot(3,1,3)
plot(Time_225,Cnc_225,'ko:','LineWidth',2)
hold on
%% kearns Three compartmental model for dose 135
dose =135; infusion=3;
% Optimum Parameters evaluated by GA for Kearns model
```

```
k21=0.474533333; vdmax=8.297633333;
vemax=22.49566667; kdm=6.160566667;
kem=14.5877; vd=9.526266667;
k13=1.4423; k31=16.63193333;
gr = @(t,x)[(-vdmax*x(1))/(kdm+x(1)) ...
-(vemax*x(1))/(kem+x(1))-k13*x(1)+k31*x(3) ...
+k21*x(2)+(t<=infusion)*dose/(infusion*vd); ...
           (vdmax*x(1))/(kdm+x(1))-k21*x(2); ...
           k13*x(1)-k31*x(3)];

[t,yr] = ode45(@(t,x) gr(t,x),[0,Time_135],[0 0 0]);
figure (2)
subplot(3,1,1)
plot(t, yr(:,1),'r:','LineWidth',2)
hold on
% Calculation for WRSS and AIC
WRSS_yr_135=sum((Cnc_135'-yr(2:end,1)).^2./Cnc_135'.^2);
Number_Of_obs_135=11;
Number_Of_par_MR=8;
AIC_MR_135=(Number_Of_obs_135)*(log(WRSS_yr_135))...
+(2*Number_Of_par_MR);
%% kearns Three compartmental model for dose 175
dose=175;
gr = @(t,x)[(-vdmax*x(1))/(kdm+x(1)) ...
-(vemax*x(1))/(kem+x(1))-k13*x(1)+k31*x(3) ...
+k21*x(2)+(t<=infusion)*dose/(infusion*vd); ...
           (vdmax*x(1))/(kdm+x(1))-k21*x(2); ...
           k13*x(1)-k31*x(3)];

[t,yr] = ode45(@(t,x) gr(t,x),[0,Time_175],[0 0 0]);
figure (2)
subplot(3,1,2)
plot(t, yr(:,1),'r:','LineWidth',2)
hold on
% Calculation for WRSS and AIC
WRSS_yr_175=sum((Cnc_175'-yr(2:end,1)).^2./Cnc_175'.^2);
Number_Of_obs_175=11;
Number_Of_par_MR=8;
```

```
AIC_MR_175=(Number_Of_obs_175)*(log(WRSS_yr_175)) ...
+(2*Number_Of_par_MR);
%% kearns Three compartmental model for dose 225
dose=225;
gr = @(t,x)[(-vdmax*x(1))/(kdm+x(1)) ...
-(vemax*x(1))/(kem+x(1))-k13*x(1) ...
+k31*x(3)+k21*x(2)+(t<=infusion)*dose/(infusion*vd); ...
           (vdmax*x(1))/(kdm+x(1))-k21*x(2); ...
           k13*x(1)-k31*x(3)];

[t,yr] = ode45(@(t,x) gr(t,x),[0,Time_225],[0 0 0]);
figure (2)
subplot(3,1,3)
plot(t, yr(:,1),'r:','LineWidth',2)
hold on
% Calculation for WRSS and AIC
WRSS_yr_225=sum((Cnc_225'-yr(2:end,1)).^2./Cnc_225'.^2);
Number_Of_obs_225=9;
Number_Of_par_MR=8;
AIC_MR_225=(Number_Of_obs_225)*(log(WRSS_yr_225)) ...
+(2*Number_Of_par_MR);
%% Fractal Two Compartmental model for dose 135
dose=135;
k21=0.2043 ; vdmax=9.3617;
vemax=17.3286; kdm=3.7843;
kem=11.8432 ; vd= 9.4833 ;
p=0.8972  ; q=0.6474;


gf = @(t,x)[(-vdmax*(x(1).^p))/(kdm+(x(1).^p)) ...
-(vemax*(x(1).^q))/(kem+(x(1).^q))-k13*x(1) ...
+k31*x(3)+k21*x(2)+(t<=infusion)*dose/(infusion*vd); ...
            (vdmax*(x(1).^p))/(kdm+(x(1).^p))-k21*x(2); ...
             k13*x(1)-k31*x(3)];
[t,yf] = ode45(@(t,x) gf(t,x),[0,Time_135],[0 0 0]);
figure (2)
subplot(3,1,1)
plot(t, yf(:,1),'b:','LineWidth',2)
```

```
hold on
% Calculation for WRSS and AIC
WRSS_yf_135=sum((Cnc_135'-yf(2:end,1)).^2./Cnc_135'.^2);
Number_Of_obs_135=11;
Number_Of_par_MF=8;
AIC_MF_135=Number_Of_obs_135*log(WRSS_yf_135) ...
+2*Number_Of_par_MF;
%% Fractal Two Compartmental model for dose 175
dose=175;
gf = @(t,x)[(-vdmax*(x(1).^p))/(kdm+(x(1).^p)) ...
-(vemax*(x(1).^q))/(kem+(x(1).^q)) ...
-k13*x(1)+k31*x(3)+k21*x(2) ...
+(t<=infusion)*dose/(infusion*vd); ...
            (vdmax*(x(1).^p))/(kdm+(x(1).^p))-k21*x(2); ...
             k13*x(1)-k31*x(3)];
[t,yf] = ode45(@(t,x) gf(t,x),[0 Time_175],[0 0 0]);
figure (2)
subplot(3,1,2)
plot(t, yf(:,1),'b:','LineWidth',2)
hold on
% Calculation for WRSS and AIC
WRSS_yf_175=sum((Cnc_175'-yf(2:end,1)).^2./Cnc_175'.^2);
Number_Of_obs_175=11;
Number_Of_par_MF=8;
AIC_MF_175=(Number_Of_obs_175)*(log(WRSS_yf_175)) ...
+(2*Number_Of_par_MF);

%% Fractal Two Compartmental model for dose 225
dose=225;
gf = @(t,x)[(-vdmax*(x(1).^p))/(kdm+(x(1).^p)) ...
-(vemax*(x(1).^q))/(kem+(x(1).^q)) ...
-k13*x(1)+k31*x(3)+k21*x(2) ...
+(t<=infusion)*dose/(infusion*vd); ...

            (vdmax*(x(1).^p))/(kdm+(x(1).^p))-k21*x(2); ...

             k13*x(1)-k31*x(3)];
[t,yf] = ode45(@(t,x) gf(t,x),[0 Time_225],[0 0 0]);
```

```
figure (2)
subplot(3,1,3)
plot(t, yf(:,1),'b:','LineWidth',2)
hold on
% Calculation for WRSS and AIC
WRSS_yf_225=sum((Cnc_225'-yf(2:end,1)).^2./Cnc_225'.^2);
Number_Of_obs_225=9;
Number_Of_par_MF=8;
AIC_MF_225=(Number_Of_obs_225)*(log(WRSS_yf_225)) ...
+(2*Number_Of_par_MF);
```

Matlab script file for figure 4.4:

```
% This data are dizitized from Brown et.al
Time_175=[3.11 6.31 6.32 6.66 7.14 7.54 8.22 9.09 10.2
         12.3 14.3 ];
Cnc_175=[1.45 2.24 1.14 0.729 0.53 0.37 0.318 0.222 0.13
         0.0964 0.0629 ];
Time_250=[3.1 6.3 6.57 6.84 7.11 7.52 7.92 8.46 9.81 10.7
         12.6 15.2  18.9  ];
Cnc_250=[2.46 3.97 3.43 3.01 1.85 1.47 1.18 0.808 0.506 0.409
         0.303 0.174 0.0913 ];
Time_275=[3.168 6.41 6.464 6.468 6.924 7.44 7.968 8.491 9.287
         10.352 12.338 14.595 18.315 30.026 ];
Cnc_275=[3.398 8.747 6.217 6.916 5.122 3.197 2.69 2.034 1.746
        1.596 0.99 0.697 0.411 0.129 ];

% Plot for experimental data

figure (3)
subplot(3,1,1)
plot(Time_175,Cnc_175,'mo:','LineWidth',2)
hold on
```

```
figure (3)
subplot(3,1,2)
plot(Time_250,Cnc_250,'mo:','LineWidth',2)
hold on
figure (3)
subplot(3,1,3)
plot(Time_275,Cnc_275,'mo:','LineWidth',2)
hold on
%%  kearns Three compartmental model for dose 175
infusion=6; dose=175;
% Optimum Parameters evaluated by GA for Kearns model
k21=1.295266; vdmax = 14.72393;
vemax =14.465566; kdm=7.67703;
kem=7.7655; vd=7.157733;
k13=10.235866; k31=13.187833;
gr = @(t,x)[(-vdmax*x(1))/(kdm+x(1)) ...
-(vemax*x(1))/(kem+x(1))-k13*x(1) ...
+k31*x(3)+k21*x(2) ...
+(t<=infusion)*dose/(infusion*vd); ...
           (vdmax*x(1))/(kdm+x(1))-k21*x(2); ...
           k13*x(1)-k31*x(3)];

[t,yr] = ode45(@(t,x) gr(t,x),[0,Time_175],[0 0 0]);

figure (3)
subplot(3,1,1)
plot(t, yr(:,1),'r:','LineWidth',2)
hold on

% Calculation for WRSS and AIC
WRSS_yr_175=sum((Cnc_175'-yr(2:end,1)).^2./Cnc_175'.^2);
Number_Of_obs_175=11;
Number_Of_par_MR=8;
AIC_MR_175=(Number_Of_obs_175)*(log(WRSS_yr_175))...
+(2*Number_Of_par_MR);

%% kearns Three compartmental model for dose 250
dose=250;
```

```
gr = @(t,x)[(-vdmax*x(1))/(kdm+x(1)) ...
-(vemax*x(1))/(kem+x(1))-k13*x(1)+k31*x(3) ...
+k21*x(2)+(t<=infusion)*dose/(infusion*vd); ...
           (vdmax*x(1))/(kdm+x(1))-k21*x(2); ...
           k13*x(1)-k31*x(3)];
[t,yr] = ode45(@(t,x) gr(t,x),[0,Time_250],[0 0 0]);

figure (3)
subplot(3,1,2)
plot(t, yr(:,1),'r:','LineWidth',2)
hold on

% Calculation for WRSS and AIC
WRSS_yr_250=sum((Cnc_250'-yr(2:end,1)).^2./Cnc_250'.^2);
Number_Of_obs_250=13;
Number_Of_par_MR=8;
AIC_MR_250=(Number_Of_obs_250)*(log(WRSS_yr_250))...
+(2*Number_Of_par_MR);
%% kearns Three compartmental model for dose 275
dose=275;
gr = @(t,x)[(-vdmax*x(1))/(kdm+x(1)) ...
-(vemax*x(1))/(kem+x(1)) ...
-k13*x(1)+k31*x(3)+k21*x(2) ...
+(t<=infusion)*dose/(infusion*vd); ...
           (vdmax*x(1))/(kdm+x(1))-k21*x(2); ...
           k13*x(1)-k31*x(3)];
[t,yr] = ode45(@(t,x) gr(t,x),[0,Time_275],[0 0 0]);
figure (3)
subplot(3,1,3)
plot(t, yr(:,1),'r:','LineWidth',2)
hold on
% Calculation for WRSS and AIC
WRSS_yr_275=sum((Cnc_275'-yr(2:end,1)).^2./Cnc_275'.^2);
Number_Of_obs_275=14;
Number_Of_par_MR=8;
AIC_MR_275=(Number_Of_obs_275)*(log(WRSS_yr_275)) ...
+(2*Number_Of_par_MR);
%% Fractal Two Compartmental model for dose 175
```

```
dose=175;

% Optimum Parameters evaluated by GA for Fractal model
k21=2.7243; vdmax = 15.3931;
vemax = 3.3773;  kdm=2.2279 ;
kem=0.2860; vd=8.4541;
p=2.0532; q=2.7943;
k13=0; k31=0;
gf = @(t,x)[(-vdmax*(x(1).^p))/(kdm+(x(1).^p)) ...
-(vemax*(x(1).^q))/(kem+(x(1).^q)) ...
-k13*x(1)+k31*x(3)+k21*x(2) ...
+(t<=infusion)*dose/(infusion*vd); ...
            (vdmax*(x(1).^p))/(kdm+(x(1).^p))-k21*x(2); ...
             k13*x(1)-k31*x(3)];
[t,yf] = ode45(@(t,x) gf(t,x),[0,Time_175],[0 0 0]);
figure (3)
subplot(3,1,1)
plot(t, yf(:,1),'b:','LineWidth',2)
hold on
% Calculation for WRSS and AIC
WRSS_yf_175=sum(((Cnc_175'-yf(2:end,1)).^2)./Cnc_175'.^2);
Number_Of_obs_175=11;
Number_Of_par_MF=8;
AIC_MF_175=(Number_Of_obs_175)*(log(WRSS_yf_175)) ...
+(2*Number_Of_par_MF);
%% Fractal Two Compartmental model for dose 250
dose=250;
gf = @(t,x)[(-vdmax*(x(1).^p))/(kdm+(x(1).^p)) ...
-(vemax*(x(1).^q))/(kem+(x(1).^q)) ...
-k13*x(1)+k31*x(3)+k21*x(2) ...
+(t<=infusion)*dose/(infusion*vd); ...
            (vdmax*(x(1).^p))/(kdm+(x(1).^p))-k21*x(2); ...
             k13*x(1)-k31*x(3)];
[t,yf] = ode45(@(t,x) gf(t,x),[0,Time_250],[0 0 0]);
figure (3)
subplot(3,1,2)
plot(t, yf(:,1),'b:','LineWidth',2)
hold on
```

```
% Calculation for WRSS and AIC
WRSS_yf_250=sum((Cnc_250'-yf(2:end,1)).^2./Cnc_250'.^2);
Number_Of_obs_250=12;
Number_Of_par_MF=8;
AIC_MF_250=(Number_Of_obs_250)*(log(WRSS_yf_250)) ...
+(2*Number_Of_par_MF);
%% Fractal Two Compartmental model for dose 275
dose=275;
gf = @(t,x)[(-vdmax*(x(1).^p))/(kdm+(x(1).^p)) ...
-(vemax*(x(1).^q))/(kem+(x(1).^q)) ...
-k13*x(1)+k31*x(3) ...
+k21*x(2)+(t<=infusion)*dose/(infusion*vd); ...
            (vdmax*(x(1).^p))/(kdm+(x(1).^p))-k21*x(2); ...
             k13*x(1)-k31*x(3)];
[t,yf] = ode45(@(t,x) gf(t,x),[0,Time_275],[0 0 0]);
figure (3)
subplot(3,1,3)
plot(t, yf(:,1),'b:','LineWidth',2)
hold on
% Calculation for WRSS and AIC
WRSS_yf_275=sum((Cnc_275'-yf(2:end,1)).^2./Cnc_275'.^2);
Number_Of_obs_275=14;
Number_Of_par_MF=8;
AIC_MF_275=(Number_Of_obs_275)*(log(WRSS_yf_275)) ...
+(2*Number_Of_par_MF);
```

Matlab script file to evaluate the optimum parameter values using Van Zuylen data for both Kearns and Fractal model:

```
% Optimization parameter evaluation using VZ data For Fractal Model
function f= OptForDose135VZ_fn(y )
Time_135=[0.85 2.065 2.854 3.279 3.522 4.008 4.858 6.984 10.87
          12.996 22.955 ];
Cnc_135=[1.338 2.015 2.931 1.59 0.923 0.594 0.328 0.194 0.095
         0.078 0.032 ];
infusion=3; dose =135;
%  The parametrs name assigned here to call this function
```

```
%  from mainfem.m
%k21=y(1) vdmax =y(2) vemax =y(3) kdm=y(4) kem=y(5)
%vd=y(6) p=y(7) q=y(8);
%k13=y(9) k31=y(10);
%For Two compartment Fractal model:
k13=0; k31=0;
gf = @(t,x)[(-y(2)*(x(1).^y(7)))/(y(4)+(x(1).^y(7))) ...
     -(y(3)*(x(1).^y(8)))/(y(5)+(x(1).^y(8))) ...
      -k13*x(1)+k31*x(3)+y(1)*x(2) ...
      +(t<=infusion)*dose/(infusion*y(6)); ...
    (y(2)*(x(1).^y(7)))/(y(4)+(x(1).^y(7)))-y(1)*x(2); ...
    k13*x(1)-k31*x(3)];

[~,yf] = ode45(@(t,x) gf(t,x),[0 Time_135],[0 0 0]);
f=sum((Cnc_135'-yf(2:end,1)).^2./Cnc_135'.^2);
end

%%
function f= OptForDose175VZ_fn(y )
Time_175=[0.85 1.943 2.794 3.158 3.401 4.008 4.98 6.923 11.053
         12.996 22.955 ];
Cnc_175=[2.012 3.298 4.638 3.982 2.018 1.213 0.807 0.396 0.195
        0.141 0.054 ];
infusion=3; dose=175;
%For Two compartment Fractal model
k13=0; k31=0;
gf = @(t,x)[(-y(2)*(x(1).^y(7)))/(y(4)+(x(1).^y(7))) ...
-(y(3)*(x(1).^y(8)))/(y(5)+(x(1).^y(8))) ...
-k13*x(1)+k31*x(3) ...
+y(1)*x(2)+(t<=infusion)*dose/(infusion*y(6)); ...
        (y(2)*(x(1).^y(7)))/(y(4)+(x(1).^y(7)))-y(1)*x(2); ...
         k13*x(1)-k31*x(3)];
[~,yf] = ode45(@(t,x) gf(t,x),[0 Time_175],[0 0 0]);
f=sum((Cnc_175'-yf(2:end,1)).^2./Cnc_175'.^2);
end

%%
function f= OptForDose225VZ_fn(y )
```

```
Time_225=[0.85 1.943 3.097 3.887 5.04 6.923 11.053
          13.057 22.955  ];
Cnc_225=[2.732 4.713 7.096 1.762  1.256 0.66 0.298
         0.22 0.084 ];
infusion=3; dose=225;
% For Two compartment Fractal mdeol
k13=0; k31=0;
gf = @(t,x)[(-y(2)*(x(1).^y(7)))/(y(4) ...
+(x(1).^y(7)))-(y(3)*(x(1).^y(8)))/(y(5) ...
+(x(1).^y(8)))-k13*x(1) ...
+k31*x(3)+y(1)*x(2)+(t<=infusion)*dose/(infusion*y(6)); ...
        (y(2)*(x(1).^y(7)))/(y(4)+(x(1).^y(7)))-y(1)*x(2); ...
         k13*x(1)-k31*x(3)];
[~,yf] = ode45(@(t,x) gf(t,x),[0 Time_225],[0 0 0]);
f=sum((Cnc_225'-yf(2:end,1)).^2./Cnc_225'.^2);
end
%%
function f= optwrssVZ_Fractal(y )
f1 = OptForDose135VZ_fn(y);
f2 = OptForDose175VZ_fn(y);
f3 = OptForDose225VZ_fn(y);
f = (f1+f2+f3)/3;
end

%% calling the functions using GA and fmincon
LB=[0 0 0 0 0 0 0 0 ];
x0=[ 0.3537    9.4241   17.2961    3.7221   11.8402
    9.4698    0.8386    0.8880];
UB=[ 100 100 100 100 100 100 100 100];
[x,fval] = fmincon(@optwrssVZ_Fractal,x0,[],[],[],[],lb,ub);
[x,fval] = ga(@optwrssVZ_Fractal,8,[],[],[],[],LB,UB,[],[]);
%% Optimize parameters evaluation using VZ data for Kearns model
function f= OptForDose135VZ_M_fn(y )

Time_135=[0.85 2.065 2.854 3.279 3.522 4.008 4.858 6.984 10.87
         12.996 22.955 ];
Cnc_135=[1.338 2.015 2.931 1.59 0.923 0.594 0.328 0.194 0.095
         0.078 0.032 ];
```

```
infusion=3; dose =135;
% The parametrs name assigned here to call this function
  from mainfem.m

%k21=y(1); vdmax =y(2); vemax =y(3); kdm=y(4); kem=y(5); vd=y(6);
%k13=y(7); k31=y(8);
%For three compartment Kearns model
gf = @(t,x)[(-y(2)*(x(1)))/(y(4)+(x(1))) ...
-(y(3)*(x(1)))/(y(5) ...
+(x(1)))-y(7)*x(1) ...
+y(8)*x(3)+y(1)*x(2)+(t<=infusion)*dose/(infusion*y(6)); ...
        (y(2)*(x(1)))/(y(4)+(x(1)))-y(1)*x(2); ...
         y(7)*x(1)-y(8)*x(3)];
[t,yf] = ode45(@(t,x) gf(t,x),[0 Time_135],[0 0 0]);
f=sum((Cnc_135'-yf(2:end,1)).^2./Cnc_135'.^2);
end
%%
function f= OptForDose175VZ_M_fn(y )
Time_175=[0.85 1.943 2.794 3.158 3.401 4.008 4.98 6.923
         11.053 12.996 22.955 ];
Cnc_175=[2.012 3.298 4.638 3.982 2.018 1.213 0.807 0.396
        0.195 0.141 0.054 ];
infusion=3; dose=175;
%For three compartment Kearns Model
gf = @(t,x)[(-y(2)*(x(1)))/(y(4)+(x(1))) ...
-(y(3)*(x(1)))/(y(5)+(x(1)))-y(7)*x(1) ...
+y(8)*x(3)+y(1)*x(2)+(t<=infusion)*dose/(infusion*y(6)); ...
        (y(2)*(x(1)))/(y(4)+(x(1)))-y(1)*x(2); ...
         y(7)*x(1)-y(8)*x(3)];
[t,yf] = ode45(@(t,x) gf(t,x),[0 Time_175],[0 0 0]);
f=sum((Cnc_175'-yf(2:end,1)).^2./Cnc_175'.^2);
end
%%
function f= OptForDose225VZ_M_fn(y )
Time_225=[0.85 1.943 3.097 3.887 5.04 6.923 11.053
         13.057 22.955  ];
Cnc_225=[2.732 4.713 7.096 1.762  1.256 0.66 0.298
         0.22 0.084 ];
```

```
infusion=3; dose=225;
%For three compartment Kearns Model
gf = @(t,x)[(-y(2)*(x(1)))/(y(4)+(x(1))) ...
 -(y(3)*(x(1)))/(y(5)+(x(1)))-y(7)*x(1) ...
 +y(8)*x(3)+y(1)*x(2)+(t<=infusion)*dose/(infusion*y(6)); ...
        (y(2)*(x(1)))/(y(4)+(x(1)))-y(1)*x(2); ...
         y(7)*x(1)-y(8)*x(3)];
[t,yf] = ode45(@(t,x) gf(t,x),[0 Time_225],[0 0 0]);
f=sum((Cnc_225'-yf(2:end,1)).^2./Cnc_225'.^2);
end
%%
function f= optwrssVZ_M(y )
f1 = OptForDose135VZ_M_fn(y);
f2 = OptForDose175VZ_M_fn(y);
f3 = OptForDose225VZ_M_fn(y);
f = (f1+f2+f3)/3;
end
%%
lb=[0 0 0 0 0 0 0 0 ];
ub=[ 100 100 100 100 100 100 100 100]; ];
x0 = [1E-1, 1E-1, 1E-1, 1E-1, 1E-1, 1E-1 1E-1, 1E-1];
[x,fval] = fmincon(@optwrssBrown,x0,[],[],[],[],lb,ub);
[x,fval] = ga(@optwrssVZ_M,8,[],[],[],[],LB,UB,[],[])
```