KWAME NKURMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY

APPROXIMATING THE SOLUTION OF AN SDE MODEL FOR CANCER CELL GROWTH WITH A PDE USING THE FEYNMAN-KAC THEOREM

By

MUNTARI UMAR FARUK

A THESIS SUBMITTED TO THE DEPARTMENT OF MATHEMATICS, KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY IN PARTIAL FUFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF M.PHIL APPLIED MATHEMATICS

October 11, 2015

Declaration

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

Muntari Umar Faruk (PG8104412)	.....	.....
Student	Signature	Date

Certified by:

Dr. Amoako-Yirenkyi Peter	.....	.....
Supervisor	Signature	Date

Certified by:

Prof. S.K. Amponsa	.....	.....
Head of Department	Signature	Date

Dedication

I dedicate this work to God almighty and my family.

Abstract

In this work the Feynman-Kac theorem was used to derive a Partial Differential Equation (Kolmogorov Equation) from an SDE model for cancer cell growth.Two Numerical schemes specifically for Stochastic Differential Equations were used to solve for the time it takes for the cancerous cells to be extinct (Persistence Time) and the resulting deterministic PDE so derived was solved using the Finite Difference approach.Tabular and Graphical results are presented and discussed. The results obtained showed that the Stochastic Numerical schemes; the Euler Maruyama and the Milstein Method employed for the SDE gave fairly consistent results while the Finite difference method employed for the deterministic PDE gave a very close approximate results to that of the SDEs.

Acknowledgment

My profound gratitude goes to Almighty Allah for haven seen me through successfully.I wish to express my most heart felt gratitude and thanks to my supervisor, Dr. Peter Amoako-Yirenkyi for the valuable and useful discussion which invaluably improved this thesis. I am further grateful to my precious family, the Umaru Maifata family and to my parents Mr. Mukhtar Umar and my late lovely mother Lardi Ali. And to my uncles; Mr. Jafaru, Mr. Basiru Umar, my siblings; Ayinawu Mukhtar, Sa'adatu Mukhtar, Aziz Mukktar, Abdul Rashid Ahmed, Ali Ahmed and Mr. Bashiru Shehu for the motivation and support they gave me. May the Almighty Allah continue to bless them in all their endeavors. Special thanks go to my friends Chenyuo Boniface and Daniel Opare and my godfather Mr. Dan.

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

Contents

List of Tables

List of Figures

Chapter 1

Introduction

Cancer is used to describe diseases where cells grow uncontrollably and tumours develop to invade normal tissues. It is considered as the second most deadly disease after cardiovascular diseases in the European countries. About a third of people diagnosed with breast cancer die annually in Ghana,Hunter and Anita (2003). Unfortunately, most treatment plans administered to patients are based on only empirical data such as clinical examinations and imaging studies. It is not uncommon to find the cancer redeveloping even after successful treatment. A possible reason is that the treatment might have been stopped prematurely while the cancer cells still persist. In some situations the treatments, (i.e. radiotherapy, chemotherapy or a combination of both) may be continued even when there are no more cancerous cells left. Another reason could also be attributed to the fact that the cancer is said to be caused by only cancer stem cells neglecting differentiated cancer stem cells which have high rates of proliferation. Like many other biological processes, population growth of cells have been modeled using deterministic models which unfortunately assume that the processes are influenced by only internally deterministic factors. However, most biological processes are influenced by noise emanating from hormonal oscillations, blood pressure, enzymatic actions, cellular metabolism, etc. Some attempts have however been made to use more realistic models which include the noise factor to describe biological processes. Example, Stochastic Differential Equations (SDEs) have been used to model pharmacodynamics and pharmacokinetics as well as population growth of cells etc. Yet such SDEs proved some difficulties in term of their solution. This thesis seeks to use a Partial Differential Equation (PDE) to approximate the solution of an SDE model describing cancer cells through their persistence

time.

1.1 Problem Statement

Cancer continuous to be a life threatening disease in most countries world wide. The cancerous cells may still persist even after what is described as successful treatment. Stochastic Differential Equations (SDEs) are mostly used to model cancer cell growth and their persistent time. However most Stochastic Differential Equations cannot be easily solved. Even with numerical methods the choice of initial conditions may sometimes make solutions of SDE unrealistic. In this work the Feynman-Kac theorem was used to derive a Partial Differential Equation (PDE) to approximate the solution of an SDE model for cancer cell growth through their persistent time.

1.2 Objectives of the study

- To review the Feynman-Kac theorem and use it to derive a Kolmogorov Equation (PDE) from an SDE model for cancer cell growth.
- To solve the derived PDE for the Average Persistence Time of the cancer cells.
- To analyze and compare the solution of the derived PDE with that of the SDE model.

1.3 Methodolgy

This thesis looked at how to use the Feynman-Kac theorem to obtain a Kolmogorov Equation(PDE) from a system of SDEs describing cancer growth dynamics. The Stochastic Differential Equation was used to obtain an approximate solution to the system of Stochastic Differential Equation. First

a Stochastic Differential Eqaution that describes cancer stem cells and Differentiated cancer cells was considered. The Feynman-Kac theorem was then proven and in conjunction with the Ito's Lemma, the Feynman-Kac theorem was used to derive a PDE for the SDE model. The SDE model was simulated for the population of the cancer cells and average Persistence using two Numerical methods specifically for SDEs, i.e. The Euler Maruyama and the Milstein Methods. The resulting PDE was also solved numerically using the Finite Difference Method for the average Persistence Time. The results of the average Persistence Time derived from both the SDE and the PDE were compared. The simulations and graphs were done using MatLab. Information for this study was gathered from the Internet and the published articles and books that are related to the study.

1.4 Justification of the Work

In Ghana, about 1000 women die annually due to cancer related ailments, the cancer has unfavorable prognostic features and unlikely to respond to hormonal manipulation, Solomon (2010). This number makes up to 70% of th women diagnosed with the disease Clegg-Lamptey (2007). Recovery rates of the disease vary depending on cancer type, treatment plan and schedule etc. example, for testicular cancer, the rate is 97.3% but as low as 10.9% for lung cancer, Kroos (2014). So far the treatment has mostly been based on only clinical examinations. However, the fight against cancer is far from over. It becomes very prudent to try to tackle the problem also from a theoretical point of view. It must be emphasized that, looking at the high mortality rates of cancer, any research that aims at improving the success rates of cancer treatment becomes crucial.

1.5 Organization of Thesis

The Chapter one of this study will contain Introduction of study, Problem statement, Objectives of study, Methodology, Justification of the study, and Organization of thesis. Chapter two will contain the literature review, where studies already carried out and are related to our study, methods and applications of SDE and PDE will be looked at. The Feynman-Kac theorem, Ito's Lemma as well as the SDE and PDE models will be considered under chapter three. Chapter four will contain results of their analysis,based on methods outlined in chapter three. In Chapter five, a conclusion will be drawn based on our findings and analysis to check if the goals of this study are achieved.Recommendations will be given with respect to the results obtained that are based on the methods used in the analysis.

Chapter 2

Literature Review

In this section, we reviewed relevant studies which have been conducted and are relevant to our work. The review was focused on various stochastic differential equations models and some proposed methods of solutions. Some of the methods included the use of Ito calculus and Stratonovich Integrals. The Ito calculus for instance creates a way of extending methods of calculus to stochastic processes. We also looked at how important stochastic processes are in the field of Physics, finance and in the medical field.

2.0.1 Brownian Motion

Brownian motion otherwise called pedesis is a random motion of particles suspended in a fluid due to collisions and pressure build up between liquid or gas molecules and between them and the walls of their containing vessels. Mathematically, the term "Brownian motion" is used to refer to mathematical models used to describe random movements often referred to as particle theory, Brown (1866). While looking through microscope at particles of pollen grains in water, Robert Brown noted that the particles move through the water, but was unable to describe the mechanism of the movement immediately. Einstein (1956) explained how the motion Brown had observed occurs. He noted that the pollen grains were moved by individual water molecules. This definition went on to establish the existence of atoms and molecules. According to him the direction of the force of atomic bombardment is constantly changing, and at different times a particle is hit more on one side than the other, leading to what seams to be the random nature of the motion.

2.0.2 Stochastic Calculus

Brownian motion or the Wiener Process was discovered to be exponentially complex, mathematically. The Wiener Process is no where differentiable. This meant that it required it own form of calculus. This led to the two dominating versions of stochastic calculus called the Ito Stochastic calculus by Kiyoshi Ito and the Stratonovich Stochastic calculus. Whether to apply the Ito calculus or the Stratonovich calculus to a particular problem can be very tricky. Oksendal (2003) provided guidelines of which of the two versions is preferable at a given instance. He provided guidelines as to how to switch between Ito Stochastic Calculus and Stratonovich Stochastic Calculus. It must be noted however that for a given stochastic problem, one has to be careful as to which of the two versions to employ.

Ito calculus

Kiyoshi Ito extended the methods of calculus to stochastic processes, such as Brownian Motion (Wiener Process) David and Kevin (2012). It has very important applications in financial mathematics and stochastic differential equation. The central concept in Ito Calculus is about the Ito integral and consequently, the Ito's Lemma. The Ito's Integral is a generalization of the ordinary concepts of a Riemann-Stiltjes integral. The generalization is in two parts. The first is the fact that for stochastic differential equations, we are dealing with random variable. Secondly, we are integrating with respect to a non-differentiable function(technically; a stochastic process). The Ito integral allows us to integrate one stochastic process with respect to another stochastic process. It must be noted also that an important result of the Ito calculus include the integration by parts formula and the Ito's Lemma, which is a change in variable formula. These differ slightly from the formulas of standard calculus due to quadratic variation.

Stratonovich Stochastic Process

Ruslan L. Stratonovich and D.L.Fisk developed the Stratonovich Stochastic Process simultaneously. These processes are basically Stochastic Itegrals which are considered as alternative to the more popular Ito Stochastic calculus. Ito calculus are mostly employed in problems in Applied Mathematics while Stratonovich Integrals are mostly used in prblems that emanate from Physics. Both methods are mathematically correct and one could be converted into the other form. Mostly it is a matter of choice based on the problem at hand. For instance, in areas of physics, it is realized that the stratonovich is better suited as opposed to the Ito calculus. In certain areas, the stratonovich integrals are easier to manipulate. For example, unlike Ito calculus, Stratonovich Stochastic calculus are defined such that the chain rule of ordinary calculus holds. According to E.Platen and Kloeden (1995), Stochastic Integrals and differentials can rarely be solved analytically making stochastic numerical integration an important tool in all uses of stochastic integrals. They also realized that various numerical approximations converge to the stratonovich integral and variations of these are used to solve stratonovich SDEs. It must be noted however that, most widely used Euler Scheme(The Euler Maruyama method) for the numerical solution of the Langevin equations requires the equation to be in Ito form.

2.0.3 Application of Ito Integrals and Stratonovich Integrals

As mentioned earlier, the method to be employed in solving a particular Stochastic Differential Equation could be very tricky. From purely mathematical point of view both the Ito and Stratonovich Calculi are correct. The question as to whether one employs which method relies on the context of particular application. Ito SDE is appropriate when the continuous approximation of a discrete system is concerned (many examples occur in biological sciences). The stratonovich in-

tegral lacks the important property of the Ito integral which does not "look into the future". In many real world applications, such as modeling stock prices, one only has information about past events and hence the Ito interpretation is more natural. In financial mathematics, the Ito interpretation is mostly employed. Stratonovich SDE or integral process is more appropriate when the idealization of a smooth real noise is concerned (many examples are found in engineering and in physical sciences). In Physics for example, Stratonovich integrals occurs as the solution of Langevin Equations (In Statistical Physics) a Langevin Eqaution is a stochastic differential equation describing the time evolution of a subset of the degree of freedom Langevin (1908). These degree of freedom are collective or macroscopic varaiable changing only slowly in comparison to the other (microscopic) variable of the system. The fast (microscopic) variables are responsible for the stochastic nature of the Langevin Equation. The original Langevin eqaution describes Brownian motion- the apparently random movement of particles in a fluid due to collisions with the molecules of the fluid. The degree of freedom here is the position of the particles. The noise term in the Langevin equation in Physics is what is described as stochastic processes in SDEs. The Wong-Zakai theorem states that physical systems with non-white noise spectrum characterized by a finite correlation time, T can be correlated by a Langevin Eqaution with the noise in Stratonovich interpretation in the limit where T tends to zero. Because the Stratonovich calculus satisfies the ordinary chain rule, Stochastic Differential Equations in the Stratonovich sense can be meaningfully defined on arbitrary differential manifolds, rather than just on R^n. This is not possible in Ito calculus since here, the coordinate system would affect the SDE's solution.

2.0.4 SDE models

SDE models are used in the field of Applied Sciences, Mathematics, Financial Mathematics and in some Physical Science such as Physics. In Physics, SDEs are written in the Langevin equation. This form is basically based on the notion that

there are standard techniques for transforming higher order equations into several first order equations, by bringing in new unknowns. In Physics, the main method of finding solution is to find the probability distribution function as a function of time using the relevant Fokker-Plank Equation. It is similar to the Schodinger Equation which results in the time evolution of the quantum wave function or the diffusion equation. The Fokker-Plank Equation (FKE) shows how the probability distribution evolves in time.In the field of Financial Mathematics, the SDEs are used to model stock prices of commodities. It has also been used to model interest rates, inflation and sometimes electricity prices. Examples of the models used here is the famous Black Scholes SDE model, the Cox-Intergrosol Model (CIR) mean reverting models, Geometric Brownian Motion model, Ohrnstein-Uhlenbeck processes etc.

2.0.5 Principal Funtions of Financial Institutions

Among the chief functions of financial institutions is to act as a risk-reducing intermediary among customer engaged in production. For example, the insurance industry draws premiums of several customers and is suppose to pay off only the few who actually incur losses. But risk comes in situations for which pooled-premium insurance is available. For example, as a hedge against higher fuel costs an airline may want to buy a security whose value may increase if oil prices rise. But who will want to sell such a security? The role of a financial institution is to design such a security, determine a "fair" price for it and sell it to the airlines.The security thus sold becomes a "derivative" i.e. it value is dependent on other securities. "Fair" in this context means that the financial institution earns enough money from selling the security to enable it to trade in other securities whose relation with oil prices is such that, if oil price do indeed rise up, the firm can pay off it increased obligation to the airlines.An efficient market thus is one in which risk-hedging securities are widely available at "fair" prices. Here is where the stochastic models normally fit in. The Black-Scholes Option pricing

formula for instance, provided for the first time, a theoretical method of fairly pricing a risk-hedging security.If an investment bank offers a derivative security at a price that is higher than "fair" it may be under bid. If it offers the security at less than "fair" price, it runs the risk of substantial loss. This makes the bank reluctant to offer many of the derivative securities that could contribute to market efficiency.In particular, the bank only likes to offer derivative securities whose "fair" price can be obtained in advance. Moreover, If the bank sells such a security, it must subsequently address hedging problems. How must it manage the risk associated with its new position? The mathematical theory ensuing out of the Black-Scholes Option Pricing model gives the solutions for both the pricing and hedging problems. It thus has made the creation of many specializing derivative securities.

2.0.6 SDE models in Financial Mathematics

The Brownian motion models for financial markets are based on the work of Robert C. Merton and Paul A. Samuelson, as extensions to the one-period market models of Harold Markowitz and William F. Sharpe, and are concerned with defining the concepts of financial assets and markets, portfolios, gains and wealth in terms of continuous-time stochastic processes.Under this model, these assets have continuous prices evolving continuously in time and are driven by Brownian motion processes.This model requires an assumption of perfectly divisible assets and a frictionless market (i.e. that no transaction costs occur either for buying or selling). Another assumption is that asset prices have no jumps, that is there are no surprises in the market. This last assumption is removed in jump diffusion models. The theory of finance tries to explain how financial markets work, how to make them more efficient, and how they should be regulated. It explains and enhances the important role these markets play in capital allocation and risk reduction to facilitate economic activities.Without loosing it practical aspects of trading and regulation, theory of finance has become increasingly mathematical,

to the point that problems in finance are new driving research in mathematics. Markowitz (1952) laid the ground work for the mathematical theory of finance. He developed an idea of mean return and covariances for common stocks that allowed him to quantify the concept of "diversification" in a market. He showed how to compute the mean return and variance for a given portfolio and argued that investors should hold only these portfolios whose variance is minimal among all portfolio with a given mean return. Although the language of finance now involves 'Ito Calculus', management of risk in a quantifiable manner is the underlying theme of the modern theory and practice of quantitative finance. Merton (1971) introduced Stochastic Calculus into the study of finance. Merton was motivated by the desire to understand how prices are set in financial markets which is the classical economics question of "equilibrium" and in later papers he used the machinery of Stochastic Calculus to begin investigation of this issue. While Merton's work was in progress, Fisher Black and Myron Scholes were simultaneously developing their popular Option pricing formula. It gave a satisfying solution to a prudent practical problem, that is, finding a price that is fair for an European call option (i.e. the right to buy one share of a given stock at a particular price and time). Pliska (1981) used the general theory of continuous time stochastic process to put the Black-Scholes option pricing formula on a solid theoretical basis and a result, showed how to price numerous other "derivative" securities.Many of the theoretical developments in finance have found immediate application in finance markets. In general, to understand how the Black-Scholes formula and for that matter other Stochastic Differential Eqautions' models, we will need to investigate on the role of financial institutions.

2.0.7 Other SDE models in finance

A lot of SDE models have been developed in the past to describe concepts in the financial sector. Some of such projects are as follows;

Ho-Lee model

HO and Lee (1986) provided a short rate model widely used in the pricing of bond options, captions and other interest rate derivatives and in modeling future interest rates. It was the first arbitrage free model of interest rates. The model can be calibrated to market data. This calibration, and subsequent valuation of bond options, swaptions and other interest rate derivatives, is typically performed via a binomial lattice based model. Closed form valuations of bonds, and "Black-like" bond option formulae are also available.

Hull-White Model

The Hull (2006) model as applied in financial is a Stochastic model that describes future interest rates. In its most generic formulation,it belongs to the class of non-arbitrage models that are able to fit today's term structure of interest rates. It is relatively straightforward to translate the mathematical description of the evolution of future interest rates onto a tree of lattice and so interest rate derivatives such as bermudan swaptions can be valued in the model.

Cox-Ingersoll-Ross model (or CIR model)

Cox et al. (1985) developed the CIR model as an extension of the Vasicek model.In mathematical finance, the Cox-Ingersoll-Ross model describes the evolution of interest rates. It is a type of "one factor model" (short rate model) as it describes interest rate movements as driven by only one source of market risk. The model can be used in the valuation of interest rate derivatives.

Black-Derman-Toy model

The Black-Derman-Toy model (BDT)by Black et al. (1990) is a popular short rate model used in the pricing of bond options, swaptions and other interest rate derivatives.It is a one factor model; that is , a single stochastic factor-the short rate- determines the future evolution of all interest rates. It was the first

model to combine the mean-reverting behaviour of the short rate with lognormal distribution, and is still widely used. The model was introduced by Fischer Black, Emanuel Derman, and Bill Toy. It was first developed for in-house use by Goldman Sachs in the 1980s and was published in the Financial Analysts Journal in 1990. Under BDT, using a binomial lattice, one calibrates the model parameters to fit both the current term structure of interest rates (yield curve), and the volatility structure for interest rate caps (usually as implied by the Black-76-prices for each component caplet) Using the calibrated lattice one can then value a variety of more complex interest-rate sensitive securities and interest rate derivatives.

2.1 SDE Models in Medicine

Continuous time processes are often modeled as a system of ordinary differential equations. These models assume that the dynamics observed are exclusively driven by internal, deterministic processes. However, real biological systems are always prone to influences that are not understood completely or not feasible to model explicitly, and thus, there is the need to extend the deterministic models to models that encompasses more complex variations in the dynamics. A way of modeling these elements is by including random influences or noise. A natural extension of a deterministic differential equations model is a system of stochastic differential equations, where relevant parameters are modeled as suitable stochastic processes, or stochastic processes are added to the driving system equations. This procedure assumes that the dynamics are to some extent driven by noise. All biological dynamical systems develop under stochastic forces, if we define stochasticity as the aspects of the dynamics that we either cannot predict or understand or the part we choose not to include in the explicit modeling. To best mimic the real world, models of biological systems should include random influences, since they involve subsystems of the real world that cannot be sufficiently separated from external effects to the model. The physiological justi-

fication to include erratic behaviors in a model can be seen in the many factors that cannot be controlled, like blood pressure variations,hormonal oscillations, respiration, variable neural control of muscle activity, energy requirements, the cellular metabolism,enzymatic processes, sympathetic nerve activity, or individual characteristics like body mass index, genes, smoking, stress impacts, etc. Also external influences, like temperature, small differences in the experimental procedure, differences in preparation and administration of drugs, if these are added to the experiment, or maybe the experiments are conducted by different scientist that inevitably will lead to small differences in procedures within the protocols. Different sources of errors will need different modeling of the noise, and these factors should be considered as carefully as the modeling of the deterministic part, in order to make the model predictions and parameter values possible to interpret. It is thus, very important to understand and investigate the influence of noise in the dynamics. In many cases the noise simply blurs the underlying dynamics without qualitatively affecting it, as is the case with measurement noise or in many linear systems. However, in nonlinear dynamical systems with system noise, the noise will usually drastically cause some changes in the corresponding deterministic dynamics. In general, stochastic effects influence the dynamics, and may promote, diminish or even completely change the dynamic behavior of the system. The following are sample works that have been done in the past in medicine.

SDE models in system Biology

? used a type of Stochastic Differential Equation called Reflected Stochastic Differential Equations to model ion channels. Ion channels are membrane proteins that open and close at random and play a vital role in the electrical dynamics of excitable cells. The stochastic nature of the conformational changes these proteins undergo can be significant, however ordinary stochastic modeling methodologies limit make it difficult to study such systems. Some of the limitations

are as follows: Discrete-state Markov chain models are seen as the "gold standard," but are computationally intensive, restricting investigation of stochastic effects to the single-cell level. Continuous stochastic methods that use stochastic differential equations (SDEs) to model the system are more efficient but can lead to simulations that have no biological meaning David and Kevin (2012) In their paper they showed that modeling the behavior of ion channel dynamics by a reflected SDE ensures biologically realistic simulations, and further argued that this model follows from the continuous approximation of the discrete-state Markov chain model.They compared Open channel and action potential statistics from simulations of ion channel dynamics using the reflected SDE with those of a discrete-state Markov chain method. Their results proved that the reflected SDE simulations are in good agreement with the discrete-state approach. The reflected SDE model therefore provides a computationally efficient method to simulate ion channel dynamics while preserving the distributional properties of the discrete-state Markov chain model and also ensuring biologically realistic solutions. This framework could easily be extended to other biochemical reaction networks. Variability in the action potential of isolated myocytes and tissue samples is observed in experimental studies. Variability is manifested as both differences in the action potential (AP) morphology between cells (extrinsic variability), and also 'intrinsic' or beat-to-beat variability of repolarization (BVR) in the AP duration of each cell Zaza (2015) used Stochastic Differential Equations to study the the relative contributions of experimentally recorded intrinsic and extrinsic variability to dispersion of repolarization in tissue. We developed four cell-specific parameterizations of a phenomenological stochastic differential equation AP model exhibiting intrinsic variability using APs recorded from isolated guinea pig ventricular myocytes exhibiting BVR. They performed simulations in tissue using the four different model parameterizations in the presence and the absence of both intrinsic and extrinsic variability. They further altered the coupling of the tissue to determine how inter-cellular coupling affected the dispersion of

the AP duration in tissue. Both intrinsic and extrinsic variability were gradually revealed by reduction of tissue coupling.

2.1.1 Comparison between SDEs and PDEs

Since it is not always possible to obtain closed form solutions for both stochastic and Ordinary differential equation and for that matter partial differential equations, the usual practice would be to resort to numerical procedures. Nonetheless, even the numerical procedures might sometimes prove some difficulty. Another way out would be to find a means of switching between the two types of equations with the hope of finding solutions much easier. Some of the related works are as follows; Geib and Manthey (1998) proved the comparison theorems of ordinary stochastic differential equations as well as for stochastic partial differential equations. Comparison theorems are useful in the theory of deterministic and stochastic differential equations. In their paper they proved such a theorem for systems of ordinary stochastic differential equations with the main interest focused on Stochastic Partial Differential Equations (SPDEs). Independently, the authors proved a similar assertion in a more particular case (cf. Manthey and Stiewe, 1992). Melnikova and Parfenenkova (2012) introduced a generalization of the Feynman-Kac theorem in Hilbert spaces. Connection between solutions to an abstract stochastic differential equation and solutions to a derived deterministic partial differential (with derivatives in Hilbert spaces) equation for probability characteristic was proven. Interpretation of objects in the equations was also given.

Chapter 3

Methodology

In this section we consider a Stochastic Differential Equation (SDE) model that describes cancer growth dynamics and that which takes into consideration both cancer stem cells and differentiated cancer cells. We will also use the Feynman-Kac theorem to derive a Kolmogorov Equation that models the persistent time of our cancerous cells.

3.1 Stochastic Differential Equation

Stochastic Process

A stochastic process is a collection of random variables. Formally, given a probability space (Ω, Λ, P) and a measurable space (S, υ). An s - valued stochastic process is a collecition of s - valued random variables, Ω indexed by the ordered set T (time).

Probability Space

The set of possible outcomes in a random experiment is called sample space and is denoted with Ω. A possible combination of outcomes is called an event and the set of all events is denoted with Λ

Definintion 3.2.1

A σ-algebra, Λ is a family of subsets of Ω so that:

1. $\Omega \in \Lambda$
2. A $\in \Lambda \Rightarrow A^c \in \Lambda$
3. $A_1, A_2, ... \in \Lambda \Rightarrow \cup_{i \geq 1} A_i \in \Lambda$

Defininition 3.2.2 (Probability Measure)

: Let Λ be a σ-algebra over Ω, a mapping $P : \Lambda \longrightarrow [0, 1]$ is a probability measure if it satifies the following two axioms;

1.$P(\phi) = 0$

2. $A_1, A_2, ... \in \Lambda$ and $A_i \cap A_j = \phi$ for $i \neq j \Rightarrow P(\cup_{i\geq 1} A_i) = \Sigma_{i\geq 1} P(A_i)$

The tripplet (Ω, Λ, P) is called probability space.

Definition 3.1.3 (Stochastic Process, trajectory)

: A stochastic process is a mapping
$X : [0, T] \times \Omega \longrightarrow R^n$ so that;

- $X(t) = X(t, .) : \Omega \longrightarrow R^n$ is a random variable for every t $\in [0, T]$
- $X(., \omega)$:[0, T]$\longrightarrow R^n$ is called a path, a realization or a trajectory of the stochastic process for every $\omega \in \Omega$.

For each patient we are always going to represent the patient by a trajectory.

3.1.1 Wierner Process

It is the most important stochastic process in continuous time. The Wiener Process is also called the Brownian Motion named after Robert(1828).The precise mathematical formulation of the Brownian motion was given by Norbert Wiener (1923)

Definition 3.3.1 (Wiener Process :)

A stochastic process $\{W(t)\}_{t\geq 0}$ is called a Wiener Process or a Brownian Motion if;

- $W(0) = 0$

- $\{W(t)\}_{t\geq 0}$ has independent increment i.e $W_{t_1}, W_{t_2}, ...W_{t_k} - W_{t_{k-1}}$ are independent random variables for all $0 \leq t_1 < t_2 < ... \leq t_k$
- $W(t+s) - W(s) \sim N(0,t)$ for all $t > 0$

Here, $N(\mu, \sigma^2)$ denotes the normal distribution with mean μ and variance σ^2. Thus, the Wiener process is a Gaussian process. From the works of Albert Eistein (1905) and Marian Smoluchowski (1906), it is established that the displacement of Brownian particles is not protportional to the elapsed time, but rather it's square root. The brownian motion thus is expressed mathematically us

$$\Delta W(t_k) = \varepsilon(t_k)\sqrt{\Delta t}$$

where $\varepsilon(.)$ is a discrete-time Gaussian white noise i.e. with mean zero and standard deviation of 1. The Wiener process is continuous with mean zero and variance proportional to the elapsed time:$E(W(t)) = 0$ and $Var(W(t)) = t$. If $X(t)$ is a stationary stochastic process, then $X(t)$ has the same distribution as $X(t+h)$ for all $h > 0$. Thus, the Wiener process cannot be stationary since the variance increases with t. The autocovariance function is given by $Cov(W_t, W_s)$ =min(s,t) The sample paths of a Wiener process behave "widly" in that they are nowhere differentiable. To see what that means define the total variation of a real-valued function f on an interval $[a,b] \subset R$ by the quantity

$$V_a^b(f) = sup \sum_{k=1}^{n} |f(t_k) - f(t_{k-1})|$$

where the supremum is taken over all finite partitions $a \leq t_0 < ... < t_n \leq b$ of $[a,b]$. When $V_a^b < \infty$ we say that f is of bounded variation on $[a,b]$. Functions that behave sufficiently "nice" are of bounded variation, if for example f is differentiable, it is of bounded variation. It turns out that the Wiener process is of unbounded variation everywhere. This happens because the increments $W(t+\Delta t) - W(t)$ is on the order of $\sqrt{\Delta t}$ instead of Δt since the variation is Δt.

Therefore

$$\begin{aligned} V_a^b(W) &= sup \sum_{k=1}^{n} |W(t_k) - W(t_{k-1})| \\ &\geq \lim_{n \longleftrightarrow \infty} \sum_{k=1}^{n} \left| W\left(a + \frac{k}{n}(b-a)\right) - W\left(a + \frac{k-1}{n}(b-a)\right) \right| \\ &\approx lim_{n \longrightarrow \infty} \sum_{k=1}^{n} \sqrt{\frac{1}{n}(b-a)} = lim_{n \longrightarrow \infty} \sqrt{n(b-a)} = \infty \end{aligned}$$

for any interval $[a, b]$. Trying to differentialte we see how this affects the limit

$$\lim_{\Delta t \longrightarrow 0} \frac{|W(t + \Delta t) - W(t)|}{\Delta t} \approx \lim_{\Delta t \longrightarrow 0} \frac{|\sqrt{\Delta t}|}{\Delta t} = \infty$$

Now we define the quadratic variation of a real-valued function f on $[a, b] \subset R$ by

$$|f|_a^b = sup \sum_{k=0}^{n} (f(t_k) - f(t_{k-1}))^2$$

where the supremum is taken as before. For functions of bounded variation the quadratic variation is always 0, and thus,if $|f|_a^b > 0$ then $V_a^b(f) = \infty$.The quadratic variation of a Wiener process over an interval$[a, b]$ equals $t - s$ and in the limit we therefore expect

$$\lim_{\Delta t \longrightarrow 0} (W(t + \Delta t) - W(t))^2 \approx \Delta t$$

Definintion 3.2.3: History of the Wiener Process

The σ-algebra

$$U(s) := U(W(r)) : 0 \leq r \leq s$$

is called the history of the Wiener process $(W(t))$ till time s. This implies that $U(s)$ records all information of our observations of $W(r)$ for all times $0 \leq r \leq s$.

Definition 3.2.4. (n-dimensional Wiener proces). A stochastic process $(W(t))_t$, $W : R_+ \longrightarrow R^n$ is an n-dimensional Wiener process(also called

n-dimensional Brownian motion), if it satifies the following;

- For all $i = 1, ...n$ the stochastic process $(W^i(t))_t$ is a one-dimensional Wiener process with $W(t) = (W^1(t), ..., W^n(t))$
- The σ-algebra $W^i := B(W^i(t)) : t \geq 0$ are independent, where B is the σ-algebra generated by the random variable $W^i(t), t \geq 0$

3.1.2 Evolution of SDE from a PDE

The method employed here is the semi-group technique for PDEs. Roughly speaking, the semi-group approach is to consider a time-dependent partial differential equation as an ordinary differential equation on a function space. We begin by formulating the SDE from a diffusion equation. Consider the diffusion equation below;

$$\frac{\partial \mu(t,x)}{\partial t} = \frac{\partial^2 \mu(t,x)}{\partial x^2}, x \in (0,1), t > 0 \tag{3.1}$$

$$\begin{aligned} \mu(t,x) &= 0, x \in \{0,1\}, t > 0 \\ \mu(t,x) &= U_0(x), x \in (0,1), t = 0 \end{aligned}$$

If we define D as the second order derivative operator, that is $D = \frac{\partial^2}{\partial x^2}$ eqn(3.1) becomes

$$\frac{d\mu(t)}{dt} = D\mu(t) \tag{3.2}$$

Next we set $D\mu(t) = f(t,x)$ and $\mu(t) = X(t)$ we obtain the ODE in the form

$$\frac{dX(t)}{dt} = f(t,x) \tag{3.3}$$

with the initial condition $X(0) = x_0$. The equation can also be written in the

integral form as follows

$$X(t) = x_0 + \int_0^t f(s, x(s))ds \tag{3.4}$$

where $X(t) = X(t, x_0, t_0)$ is the solution of eqn(4) with the initial condition $X(0) = x_0$ In eqn(3.4) above if we assume that f(t,x) is the product of two functions $a(t)$ and $x(t)$ i.e $f(t, x) = a(t)x(t)$ eqn(3.4) becomes

$$\frac{dX(t)}{dt} = a(t)x(t), X(0) = x_0 \tag{3.5}$$

In the ODE (3.5), if we further assume that $a(t)$ is not deterministic parameter but rather a random parameter, we get a stochastic differential equation(SDE).Thus a natural extension of ordinary differential equation model is a stochastic differential equation model where the relevant parameters are randomized or modeled as random process of some suitable form, or simply by adding a noise term to the driving equations of the system. This approach assumes some degree of noise is present in the dynamics of the process. The random process will be using for the purposes of this paper is the Weiner Process with all its properties defined earlier. Thus we assume that

$$a(t) = f(t) + h(t)\varepsilon(t)) \tag{3.6}$$

where $\varepsilon(t)$ denotes a white noise process. Thus we obtain the equation;

$$\frac{dX(t)}{dt} = f(t)X(t) + h(t)X(t)\varepsilon(t) \tag{3.7}$$

If we further assume that $\varepsilon(t)$ is a certain change in a stochastic process (Weiner process) with respect to time, i.e. $dW(t) = \varepsilon(t)dt$, where $dW(t)$ represents the differential form of a the Brownian motion, we obtain

$$dW(t) = f(t)X(t)dt + h(t)X(t)dW(t) \tag{3.8}$$

3.1.3 Stochastic Differential Equations

Let $(W(t))_{t\geq 0}$ be an m-dimensional Wiener process and X_0 an n-dimensional random vector that is independent from $(W(t))_{t\geq 0}$. Further we let $F(t) := U(X_0, W(s)), 0 \leq s \leq t$ be the σ-algebra generated by X_0 and the history of the Wiener process till time t. A stochastic differential equation on the interval [0,T], has the form

$$dX(t) = f(t, X(t))dt + g(t, X(t))dW(t) \tag{3.9}$$

$$\text{for} \quad t \in [0, T] \quad \text{and with} \tag{3.10}$$

$$X(t) = (X_1(t), ..., X_d(t))^t \tag{3.11}$$

$$W(t) = (X_1(t), ..., X_m(t))^t \tag{3.12}$$

$$f : [0, T] \times R^d \longrightarrow R^d \tag{3.13}$$

$$g : [0, T] \times R^d \longrightarrow R^{d\times m} \tag{3.14}$$

$$\tag{3.15}$$

where $W(t)$ denotes an n-dimensional Wiener process and $X(t)$ a stochastic process. The function, f is called the drift coefficient of the stochastic differential equation and g is its diffusion coefficient.

3.1.4 Numerical Solutions for Stochastic Differential Equations

In equation (3.9) above, the coefficients of the functions f and g may not be linear or constants all the time in which situations, exact solutions may be obtained. However, in more realistic problems, such functions may have non-linear coefficients. They may be square root processes. In such situations we apply numerical methods or procedures just like the ones in ODEs and PDEs. The two

most famous numerical schemes applied in this regards for Stochastic Differential Equations (SDEs) are the Euler-Maruyama method which is an extension of the classical Euler method for ordinary differential equations and the second method is the Milstein method, which is a scheme for higher order.

3.1.5 The Euler-Maruyama Method

The Euler-Maruyama method for a stochastic differential equation (9) is defined by: $X_{n+1} = X_n + f(t_n, X_n) + g(t_n, X_n)\Delta W_n$ with

$n = 0, ..., N-1, X_n \approx X(t_n), \Delta t = \frac{T}{N}, t_i = i\Delta t$ and $\Delta W_n = W(t_{n+1}) - W(t_n) \sim \aleph(0, \Delta t)$. For each component this implies that:

$$X_{i,n+1} = X_{i,n} + f(t_n, X_n)\Delta t + \sum_{j=1}^{m} g_{ij}(t_n, Xn)\delta W_{j,n} \tag{3.16}$$

for $i = 1, ..., d$ with $\Delta W_{j,n} \sim \aleph(0, \Delta t)$ for all $j = 1, ..., m$ and $n = 0, ..., N$

3.1.6 The Milstein Method

The implicit Milstein method is defned for each component of X_n by:

$$X_{i,n+1} = X_{i,n} + f_i(t_{n+1}, X_{n+1})\Delta t + \sum_{j=1}^{m} g_{ij}(t_n, X_n)\Delta W_{j,n} + \sum_{j1=1}^{m}\sum_{j2=1}^{m}\sum_{l=1}^{d} g_{lj_1}\frac{\partial g_{ij2}}{\partial x_l} I_n(j_1, j_2) \tag{3.17}$$

for $i = 1, ..., d$ and the other parameters defined as in 3.5.1. Also, we have

$I_n(j_1, j_2) = \int_{t_n}^{t+\Delta t}\int_{t_n}^{s} dW_{j_1}(r)dW_{j_2}(s)$ For $j_1 = j_2$ this double ito integral can be written as $I_n(j_1, j_1) = \frac{1}{2}((\Delta W_{j_1,n})^2 - \Delta t)$ The double Ito-integral does not have a closed analytical form for $j_1 \neq j_2$. Nevertheless, in order to compute it, we can approximate this integral by: $I_n(j_1, j_2) \sim \jmath_n(j_1, j_2) = \sum_{j=0}^{M-1}(W_{j_1}(t_{j,n}) - W_{j_1}(t_{0,n}))(W_{j_2}(t_{j+1,n}) - W_{j_2}(t_{j,n}))$ with $t_{j,n} = t_n + j\frac{\Delta t}{M}$ for $j = 0, ...M$

3.1.7 The Finite Difference Method

When solving PDEs it is not always possible to obtain a closed form formula for the solution, in such cases we resort to numerical method to compute approximate values of the solution. An example is the Monte Carlo computation and the deterministic Finite Difference method.

A finite difference is a quotient that approximates a derivative. For example consider Kolmogorov Backward Equation (PDE) given by;

$$0 = \partial_t f(x,t) + a(x,t)\partial_x f(x,t) + \frac{b^2(x,t)}{2}\partial_x^2 f(x,t) \tag{3.18}$$

The FDM uses the grid points (x_j, t_k) with $x_j = j\delta x$ and $t_k = k\delta t$ also $T = t_n = n\delta t$ and $t_k - \delta t = t_{k-1}$ Next we compute the following approximations;

$$\begin{aligned}
\partial_t f(x_j,t_k) &\approx \frac{f(x_j,t_k) - f(x_j,t_{k-1})}{\delta} \approx \frac{f_{j,k} - f_{j,k-1}}{\delta t} \\
\partial_x f(x_j,t_k) &\approx \frac{f_{j+1,k} - f_{j-1,k}}{2\delta x} \\
\partial_x^2 f(x_j,t_k) &\approx \frac{f_{j+1,k} - 2f_{j,k} + f_{j+1,k}}{\delta x^2}
\end{aligned}$$

by substituting the following approximations into eqn(3.18) we obtain the following

$$0 = \frac{f_{j,k} - f_{j,k-1}}{\delta t} + a(x_j,t_k)\frac{f_{j+1,k} - f_{j-1,k}}{2\delta x} + \frac{1}{2}b^2(x_j,t_k)\frac{f_{j+1,k} - 2f_{j,k} + f_{j+1,k}}{\delta x^2}$$

Now, the purpose of all this was to compute the numbers $f_{j,k-1}$ from the numbers $f_{j,k}$. For this, you only need to put $f_{j,k-1}$ on the other side of the equation and solve:

$$f_{j,k-1} = f_{j,k} + \frac{\delta t}{2\delta x}a(x_j,t_k)(f_{j+1,k} - f_{j-1,k}) + \frac{\delta t}{2\delta x^2}b^2(x_j,t_k)(f_{j+1,k} - 2f_{j,k} + f_{j+1,k}) \tag{3.19}$$

This is the Forward Euler Method, also called explicit Euler for finding the approximations eqn (3.18)

3.2 An SDE model for Cancer Stem Cells and Differentiated Cancer cells

In this section, we consider a stochastic differential equation which models cancer growth dynamics by Julia Maria Kroos (August,2014), then in subsequent discussions apply the Feynman-Kac theorem to it.

3.2.1 A brief on Cancer Stem Cells and Differentiated Cancer cells

Until the year 1997, the monoclonal model was used to describe tumour growth dynamics. In this model, the tumour is supposed to be composed of only differentiated cancer cells. In contrast to this model is the one proposed by Bonnet and Dick in 1997 while they were investigating the oringin of leukemia. They introduced the concept of cancer stem cells. In their proposition they suggested that cancer stem cells could be the origin of cancer and possibly bring about the resistance of malignant tumours and recurrence. In their model, the tumour is said to be composed of both differentiated cancer cells and a few cancer stem cells that have the typical characteristics of stem cells. The cancer stem cells are able to generate differentiated cancer cells that in turn enlarge the tumour by frequent proliferation. These cancer stem cells could be an explanation for the fact that after therapy the tumor first disappears and after some time reappears: as stem cells proliferate less often than differentiated tumor cells most therapies do not harm the stem cells as much as they harm the differentiated cancer cells. Nevertheless, the origin of the cancer stem cells is not solved yet. They may develop when self-renewing normal stem cells acquire mutations and are transformed by altering only proliferative pathways. It is also possible that the cancer stem cells

originate by multiple mutations in progenitor cells which acquire the capability of self-renewal.

3.2.2 The Model

We begin by first defining some few parameters. let c(t)= population of differentiated cancer cells and s(t)= population of cancer stem cells at any time, t. We also make the following assumptions:

- Cancer stem cells are immortal and have unlimited replicative potential.
- Cancer stem cells are able to divide in various ways
  - into two stem cells (with a probability , a_1)
  - into one differentiated cancer cell and once cancer stem cell (with probability, a_2)or
  - into two differentiated cancer cells(with probability, a_3), with $a_i \in [0,1], i = 1,2,3, \sum_{i=1}^{3} a_1 = 1$
- Differentiated cancer cells are mortal and have finite potential to divide.
- During proliferation, differentiated cancer cells divide into cells each of them being again a differentiated cancer cell.

we further define the following parameters: b_c, b_s : proliferation rate (birth rates) for differentiated cancer stem cells and cancer stem cells respectively d_c, d_s : death rates for differentiated cancer stem cells and cancer stem cells respectively

m_{12}: transfer rate from differentiated cancer stem cells to cancer stem cells

m_{21}: transfer rate from cancer stem cells to differentiated cancer stem cells

The assumptions above thus lead to the following

$d_s = 0$, $m_{12} = 0$ and $d_c \geq 0$

For small interval of time, Δt the respective transition probabilities for the random variable $X = (c, s)^t$ is as summarized in the table below.

Changes	Probability
$\Delta X^{(1)} = (1, 0)^t$	$p_1 = b_c c\Delta t + b_s a_2 s\Delta t$
$\Delta X^{(2)} = (-1, 0)^t$	$p_2 = d_c c\Delta t$
$\Delta X^{(3)} = (0, 1)^t$	$p_3 = b_s a_1 s\Delta t$
$\Delta X^{(4)} = (0, 1)^t$	$p_4 = 0$(cancer stem cells are immortal)
$\Delta X^{(5)} = (2, -1)^t$	$p_5 = b_s a_3 s\Delta t$
$\Delta X^{(6)} = (-1, 1)^t$	$p_6 = m_{12}\Delta t = 0$(cancer cells cannot become cancer stem cells)
$\Delta X^{(7)} = (0, 0)^t$	$p_7 = 1 - \sum_{i=1}^{6} p_i$

Next we compute the expectation and the covariance matrix for a given time t:

$$
\begin{aligned}
E(\Delta X) &= \sum_{i=1}^{7} p_i \Delta X^{(i)} \\
&= \begin{pmatrix} b_c c + b_s a_2 s - d_c c + 2 b_s a_3 s \\ b_s a_1 s - b_s a_3 s \end{pmatrix} \Delta t \\
E(\Delta X(\Delta X)^t) &= \sum_{i=1}^{7} p_i \Delta X^{(i)} (\Delta X^{(i)})^t \\
&= k_1 \begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix} \Delta t + k_2 \begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix} \Delta t + k_3 \begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix} \Delta t + k_4 \begin{pmatrix} 4 & -2 \\ -2 & 1 \end{pmatrix} \Delta t \\
&= \begin{pmatrix} b_c c + b_s a_2 s + d_c c + 4 b_s a_3 s & -2 b_s a_3 s \\ -2 b_s a_3 s & b_s a_1 s + b_s a_3 s \end{pmatrix} \Delta t
\end{aligned}
$$

$k_1 = (b_c c + b_s a_2 s), k_2 = d_c c, k_3 = b_s a_1 s, k_4 = b_s a_3 s$

It can be shown that

$$V = \frac{E((\Delta X(\Delta X)^t)}{\Delta t}$$

is positive-definite. Hence the square root of the matrix V exists which we now define as $B := V^{\frac{1}{2}}$. Further we define and compute the following:

$$\mu := \frac{E(\Delta X)}{\Delta t} = \begin{pmatrix} b_c c + b_s a_2 s - d_c c + 2 b_s a_3 s \\ b_s a_1 s - b_s a_3 s \end{pmatrix}$$

$$V := \frac{E(\Delta X (\Delta X)^t}{\Delta t} = \begin{pmatrix} b_c c + b_s a_2 s + d_c c + 4 b_s a_3 s & -2 b_s a_3 s \\ -2 b_s a_3 s & b_s a_1 s + b_s a_3 s \end{pmatrix}$$

This gives an indication that B is a (2×2)matrix, which we can explicitly define as follows;

$$B = V^{\frac{1}{2}} = \begin{pmatrix} u & v \\ v & w \end{pmatrix}^{1/2} = \frac{1}{\eta} \begin{pmatrix} u + \tau & v \\ v & w + \tau \end{pmatrix}$$

with $\tau = \sqrt{uv - v^2}$ and $\eta = \sqrt{u + w + 2\tau}$. With the previously computed matrix V we obtain the following values for the matrix B

$$\begin{aligned} u &= b_c c + b_s a_2 s + d_c c + 4 b_s a_3 s \\ v &= -2 b_s a_3 s \\ w &= b_s a_1 s + b_s a_3 s \\ \tau &= \sqrt{b_s s (a_1 (b_s a_2 s + 4 b_s a_3 s + c(b_c + d + c)) + a_3 (b_s a_2 s + c(b_s a_2 s + c(b_c + d_c)))} \end{aligned}$$

$$\begin{aligned} \eta = (&2\sqrt{b_s s (a_1 (b_s a_2 s + 4 b_s a_3 s + c(b_c + d + c)) + a_3 (b_s a_2 s + c(b_s a_2 s + c(b_c + d_c)))} \\ &+ b_s a_1 s + b_s a_2 s + 5 b_s a_3 s + c(b_c + d_c))^{1/2} \\ = &\sqrt{2\tau + b_s a_1 s + b_s a_2 s + 5 b_s a_3 s + c(b_c + d_c)} \end{aligned}$$

The stochastic differential equation for the dynamics of the two cancer cell populations is then given by

$$d\mathbb{X} = \mu(t, c, s) dt + B(t, c, s) d\mathbb{W}(t)$$

with the initial condition $X(0) = X_0$ and $\mathbb{W}(t) = ((W_1)(t), W_2(t))^t$, $W_1(t)$ and $W_2(t)$ denote independent Wiener process. For each population, we obtain the following differential equation

$$\begin{aligned} dc(t) &= \mu_1(t,c,s)dt + B_{11}dW_1(t) + B_{12}dW_2(t) \\ &= (u + v - 2d_c c)dt + \frac{1}{\eta}(u+\tau)dW_1(t) + \frac{v}{\mu}dW_2(t) \\ ds(t) &= \mu_2(t,c,s)dt + B_{21}dW_1(t) + B_{22}dW_2(t) \\ &= (w+v)dt + \frac{v}{\eta}dW_1(t) + \frac{1}{\eta}(w+\tau)dW_2(t) \end{aligned} \tag{3.20}$$

Thus we obtain stochastic processes such that each trajectory describes the tumor growth dynamics for a specific patient.

3.3 The Feynman-Kac Theorem

In this section, we establish the Feynman-Kac theorem and use it to obtain differential Equation out of the Stochastic Differential Equation we derived earlier. To review the Feynman-Kac theorem, we need the Ito Calculus, Ito's Lemma, and Markov Process.

3.3.1 Ito Calculus

Ito Calculus named after Kiyoshi Ito extends the methods of calculus to stochastic processes such as Brownian motion (Weiner Process). It has a very important application in mathematical finance. The central concept in ito calculus is the Ito Integral. This is the generalization of the ordinary concepts of Riemann-Stieltjes integral. The generalization is in two parts; first we are dealing with stochastic process and secondly, we are integrating with respect to a non-differentiable function(technically;a stochastic process). The Ito calculus enables us to integrate one stochastic process with respect to another (Brownian motion). Consider the

stochastic process given by the equation

$$d\mathbb{X}(t,w) = f(t,x(t,w)dt + g(t,x(t,w))d\mathbb{W}(t,w) \tag{3.21}$$

where w denotes that $\mathbb{X} = \mathbb{X}(t,w)$ is a random variable and initial condition $\mathbb{X}(0,w) = \mathbb{X}_{\not\vdash}$ with probability one.

In the integral form equation (3.21) could be written as follows

$$X(t,w) = X_0 + \int_0^1 f(s,X(s,X(s,w)))ds + \int_0^t g(s,X(s,X(s,w)))dW(s,w) \tag{3.22}$$

The second term in equation (3.22) is an ordinary Lebesgue integration while the third term

$$\int_0^t g(s,x)dW$$

represents the Ito integration. Let us define the ito integration as follows

$$Y_t = \int_0^t g(s,X(s,w))dW(s,w) \tag{3.23}$$

where $W(.)$ is a Brownian motion (Weiner process)and $g(s,X(s,w)$ is a square integrable process. The standard rules of calculus fails to evaluate the integral (3.23) because of the path of the Weiner process. In particular the Weiner process is no where differentiable and at any time is of unbounded variation. Thus the integral cannot be defined in the general sense of the Reinmann-Stieltjes integral. The idea of the Ito calculus is thus hinged on the fact that $g(.)$ be adapted. Loosely speaking, it means that the value of $g(.)$ at any time ,t can only depend on information until that time.

3.3.2 Integration with respect to Brownian Motion

The ito integral can be defined in a manner similar to the Reimann-Stieltjes integral, that is as a limit of a Reimann sums. Suppose $W(t,w)$ is a Weiner

process and that $g(t, X(s, w))$ is continuous and locally bounded. Suppose also that $\{\Pi_n\}$ is a sequence of partitions of $[0T]$ with the mesh going to zero, then the Ito integral of $g(t, X(s, w))$ with respect to $W(t, w)$ up to t is a random variable S given by

$$S = \int_0^t g(t, w) dW(t, w) \tag{3.24}$$

thus S can be written as a Reimann Sum

$$S_n = \sum_{i=0}^{N} g(t_{i-1}, w)(W(t_i, w) - W(t_{i-1}, w) \tag{3.25}$$

with $N \longrightarrow \infty$

A random variable S is called the Integral of a stochastic process $g(t, w)$ with respect to the Brownian motion $W(t, w)$ on the interval $[0, T]$ if

$$\lim_{N \longrightarrow \infty} \mathbb{E}\left[\left(S - \sum_{i=1}^{N} g(t_{i-1}, w)(W(t_i, w) - (W(t_{i-1}, w)))\right)\right] = 0 \tag{3.26}$$

for each of the partitions $(t_0, t_1 \cdots t_N)$ of interval [0, T] such that $max_i(t_i - t_{i-1}) \longrightarrow 0$. The limit in the above definiton converges in the mean square sense. Thus the stochastic process is a random variable , the samples of which depends on the individual realizations of the path $W(t, w)$.

To establish the difference between Lebesgue integration and the Ito calculus , we consider the example below.

E.g. Let $g(t, w) = W(t, w) = W(t, w)$ from equation (4)

$$\begin{aligned}
\int_0^T W(t, w) dW(t, w) &= \lim_{N \longrightarrow \infty} \sum_{i=1}^{N} W(t_{i-1}, w)(W(t_i, w) - W(t_{i-1}, w)) \\
&= \lim_{N \longrightarrow \infty} \left[\frac{1}{2} \sum_{i=1}^{N} (W^2(t_i, w) - W^2(t_{i-1}, w) - \frac{1}{2} \sum_{i=1}^{N} (W(t_i, w) - W(t_{i-1}, w))^2\right. \\
&= -\frac{1}{2} \lim_{N \longrightarrow \infty} \sum_{i=1}^{N} (W(t_i, w) - W(t_{i-1}, w))^2 + \frac{1}{2} W^2(T, w)
\end{aligned} \tag{3.27}$$

Equation (7) can be achieved as follows, first

$$\sum_{i=1}^{N}\left[W^2(t_i,w)-W^2(t_{i-1},w)\right]=W^2(t_1,w)-W^2(t_0,w)+W^2(t_2,w)-W^2(t_1,w)+\cdots W^2(t_N,w$$

$$=W^2(t_N,w)-W^2(t_0,w)$$

$$=W^2(T,w)$$

(i.e as $N\longleftrightarrow\infty$ and using the initial condition $W(t_0,w)=0$) Note the use of the substitution below;

$y(x-y)=yx-y^2+\frac{1}{2}x^2-\frac{1}{2}x^2=\frac{1}{2}x^2-\frac{1}{2}y^2-\frac{1}{2}(x-y)^2$

Now from eqn (7) we take a critical look at

$$\lim_{N\longrightarrow\infty}\sum_{i=1}^{N}(W(t_i,w)-W(t_{i-1},w))^2$$

$$\lim_{N\longrightarrow\infty}\sum_{i=1}^{N}(W(t_i,w)-W(t_{i-1},w))^2=\lim_{N\longrightarrow\infty}\sum_{i=1}^{N}\left[(W^2(t_i,w)-W^2(t_{i-1},w)+2W(t_i,w)W(t_{i-1},w\right. \tag{3.28}$$

Next according to the rules of Brownian motion,

$$\begin{aligned}W(t_i,w).W(t_{i-1},w)&=0\\W^2(t_i,w).W^2(t_{i-1},w)&=\Delta W^2(t,w)\\&=\Delta t\end{aligned}$$

Thus eqn (3.28) reduces to $\lim_{N\longrightarrow\infty}\sum_{i=1}^{N}(t_{i+1}-t_i)=t_1-t_0+t_2-t_1+\cdots+t_N-t_{N-1}=t_N-t_0=T$ therefore

$$\lim_{N\longrightarrow\infty}\sum_{i=1}^{N}(W(t_i,w)-W(t_{i-1},w))^2=T \tag{3.29}$$

Hence our SDE

$$\int_0^T W(t,w)dW(t,w) = \frac{1}{2}W^2(T,w) - \frac{1}{2}T \tag{3.30}$$

This contrasts to our knowledge of Standard Calculus.In which case for the derterministic integral

$$\int_0^T x(t)dt = \frac{1}{2}x^2(T)$$

whereas the Ito integral differs by the term $-\frac{1}{2}T$.This example shows that the rules of differentiation (in particular chain rule)and integration need to be reformulated in the stochastic calculus.

3.4 Properties of the Ito Integral

i) $\mathbb{E}\left(\int_0^T g(t,w)dW(t,w)\right) = 0$

ii) $\mathrm{v}ar\left[\int_0^T g(t,w)dW(t,w)\right] = \int_0^T \mathbb{E}\left[g^2(t,w)\right]dt$

3.4.1 Proof of properties

i) $\mathbb{E}\left(\int_0^T g(t,w)dW(t,w)\right) = 0$

Proof

$$\begin{aligned}\mathbb{E}\left(\int_0^T g(t,w)dW(t,w)\right) &= \mathbb{E}\lim_{N\longrightarrow\infty}\sum_{i=1}^{N} g(t_{i-1},w)(W(t_i,w)-W(t_{i-1},w)) \\ &= \lim_{N\longrightarrow\infty}\sum_{i=1}^{N}\mathbb{E}\left[g(t_{i-1},w)\right]\mathbb{E}\left[(W(t_i,w)-W(t_{i-1},w)\right] = 0\end{aligned} \tag{3.31}$$

The result in (3.31) is because from the rules of Weiner process, we know that a Weiner process $W(t)$ has independent increment and that $\mathbb{E}\left[W(t) - W(s)\right] = 0$ and $var\left[W(t) - W(s)\right] = (t - s)$, for times $t \geq s \geq 0$.

ii) $\text{v}ar\left[\int_0^T g(t,w)dW(t,w)\right] = \int_0^T \mathbb{E}\left[g^2(t,w)\right]dt$

Proof:

$$\begin{aligned}
\text{v}ar\left[\int_0^T g(t,w)dW(t,w)\right] &= \mathbb{E}\left[\left(\int_0^T g(t,w)dW(t,w)\right)^2\right] \\
&= \mathbb{E}\left[\lim_{N\longrightarrow\infty}\sum_{i=1}^{N} g(t_{i-1},w)\left(W(t_i,w) - W(t_{i-1},w)\right)^2\right] \\
&= \lim_{N\longrightarrow\infty}\sum_{i=1}^{N}\sum_{j=1}^{N}\mathbb{E}\left[g(t_{i-1},w)g(t_{j-1},w)\right]\left(W(t_i,w) - W(t_{i-1},w)\right) \\
&= \lim_{N\longrightarrow\infty}\sum_{i=1}^{N}\mathbb{E}\left[g^2(t_{i-1},w)\right]\mathbb{E}\left[\left(W(t_i,w) - W(t_{i-1},w)\right)^2\right] \\
&= \lim_{N\longrightarrow\infty}\sum_{i=1}^{N}\mathbb{E}\left[g^2(t_{i-1},w)\right]\left(t_i - t_{i-1}\right) \\
&= \int_0^T \mathbb{E}\left[g^2(t,w)\right]dt
\end{aligned} \tag{3.32}$$

The result in eqn (3.32) is achieved by employing the property of Weiner process ;

$$(\Delta W^2 = \Delta t)$$

3.4.2 The Ito's Lemma

Ito's Lemma is the most important aspect of the Ito Calculus. It serves as the most important tool employed in establishing the Feyman-Kac Theorem. It states that any twice differentiable function of the Stochastic diffusion process can also be expressed as a diffusion process. Given the SDE below;

$$dX(t) = f(t,X(t))dt + q(t,X(t))dW(t) \tag{3.33}$$

as a diffusion process, we define a function $Y(t) = g(t, X(t))$ we differentiate $Y(t)$ as follows using chain rule

$$\frac{dY(t)}{dt} = \frac{\partial g(t,x)}{\partial t} + \frac{\partial g(t,x)}{\partial x}\frac{dX(t)}{dt} \tag{3.34}$$

This can also be written as

$$dY(t) = \frac{\partial g(t,x)}{\partial t}dt + \frac{\partial g(t,x)}{\partial x}dX(t), \quad (NB \quad X(t) = x) \tag{3.35}$$

Next we apply the Taylor series expansion to eqn (3.35) to obtain

$$dY(t) = g_t(t,x)dt + \frac{1}{2}g_{tt}(t,x)(dt)^2 + g_x(t,x)dX(t) + \frac{1}{2}g_{xx}(t,x)(dX)^2 + \Theta(h^3) \tag{3.36}$$

We now substitute equation (3.33)into eqn (3.36)

$$\begin{aligned} dY(t) = g_t(t,x)dt + \frac{1}{2}g_{tt}(t,x)(dt)^2 + g_x(t,x)\left[f(t,x)dt + q(t,x)dW\right] \\ + \frac{1}{2}g_{xx}(t,x)\left[f(t,x)dt + q(t,x)dW(t)\right]^2 + \Theta(h^3) \end{aligned} \tag{3.37}$$

This implies that

$$\begin{aligned} dY(t) = g_t(t,x) + \frac{1}{2}g_{tt}(t,x)(dt)^2 + g_x(t,x)f(t,x)dt + g_x(t,x)q(t,x)dW \\ + \frac{1}{2}g_{xx}(t,x)\left[f^2(t,x)(dt)^2 + q^2(t,x)dW^2(t) + 2f(t,x)q(t,x)dtdW(t)\right] + \cdots \end{aligned} \tag{3.38}$$

Next we note the following under Weiner process

1. Higher order derivatieves of dt and $dW(t)$ becomes zero

2. $(dt)^2 \longrightarrow 0$ and $dtdW(t) \longrightarrow 0$

3. $dW^2(t) = dt$

Eqn (3.38) becomes

$$\begin{aligned} dY(t) = & \left[\frac{\partial g(t,x)}{\partial t} + \frac{\partial g(t,x)}{\partial x} f(t,x) + \frac{1}{2}\frac{\partial^2 g(t,x)}{\partial x^2} q^2(t,x)\right] dt \\ & + \left[\frac{\partial g(t,x)}{\partial x} q(t,x)\right] dW(t) \end{aligned} \tag{3.39}$$

Eqn (3.39) is a diffusion equation of the form

$$dY(t) = \mho(t,x)dt + \eth(t,x)dW(t) \tag{3.40}$$

where;

$$\mho(t,x) = \left[\frac{\partial g(t,x)}{\partial t} + \frac{\partial g(t,x)}{\partial x} f(t,x) + \frac{1}{2}\frac{\partial^2 g(t,x)}{\partial x^2} q^2(t,x)\right] \tag{3.41}$$

$$\eth = \left[\frac{\partial g(t,x)}{\partial x} q(t,x)\right] \tag{3.42}$$

The expression below

$$\frac{\partial g(t,x)}{\partial t} + \frac{\partial g(t,x)}{\partial x} f(t,x) + \frac{1}{2}\frac{\partial^2 g(t,x)}{\partial x^2} q^2(t,x)$$

is called the Ito correction factor. Now we allow $X(t) \in \mathbb{R}^n$ and let $W(t)$ be an m-dimensional standard Brownian motion and $f(t, X(t)) \in \mathbb{R}^n$ and $q(t,x) \in \mathbb{R}^{n\times m}$. Let $Y(t)$ be a scalar process defined by $Y(t) = \phi(t, X(t))$, where $\phi(t, X(t))$ is a scalar function which is continuously differentiable with respect to time, t and twice continuously differentiable with respect to X.

The Ito's formula can be written in the vector notation as follows

$$dY(t) = \mho(t,x)dt + \eth(t,x)dW(t)$$

where

$$\mho(t, X(t)) = \phi_t(t, X(t)) + \phi_x(t, X(t))f(.) + \frac{1}{2}tr\left(\frac{\partial^2\phi(t, X(t))}{\partial x^2}q(t, X(t))X(t)q^T(t, X(t))\right) \quad (3.43)$$

$$\eth(t, X(t)) = \phi_x(t, X(t))g(t, X(t)) \quad (3.44)$$

Where the operator "tr" denotes the trace operator and $f(.) = f(t, X(t))$

3.4.3 Markov Chain

A stochastic Process is said to be a Markov Chain if it has the Markov property. This means that

$$\mathbb{E}\left(h(X(t+s))|F_t\right) = \mathbb{E}\left[h(X(s))\right] \quad (3.45)$$

$t, s \in R$ and $t \leq s$ and F_t is called the filtration such that $\forall t \leq s \quad F_t = \{X_t | t \in I\}$

Proof of Markov property

Consider the stochastic Diffusion Process below

$$dX(t) = \delta(X(t))dt + \sigma(X(t))dW(t) \quad (3.46)$$

$X(0) = y \quad and \quad t \in [0, T]$ We consider the diffusion process for which the existence and uniqueness of the solution to the Cauchy Problem for eqn (3.46) are fulfilled. Let $X^{t,x}, t \in [0, T], X(t) = x$ be the solution of eqn (3.46), by the uniqueness of the solution to the Cauchy problem for (3.46) we have $X(r) = X^{t,X(t)}(r), r \geq t$ almost surely. Define $F(x, t; \tau, w) = X^{t,x}(\tau)$. We prove the property, through the equality below;

$$\mathbb{E}\left[h(F(X(t), t, t+s, w))|F_t\right] = \mathbb{E}\left[h(F(t), 0, s, w)\right] \quad (3.47)$$

Next we introduce

$$V^{t,x}(t+s,w) = h(F(x,t,t+s,w)) \tag{3.48}$$

and then fix

$$t_k = t + \frac{k(T-t)}{m}, k = 0,1,2\cdots m$$

Let

$$V_m^{t,x(t)} = \sum_{k=0}^{m} V^{t,x(t)}(t_{k+1},w)\mathbb{X}_{\tau\in[t_k,t_{k+1})} \tag{3.49}$$

where $\mathbb{X}_{\tau\in[t_k,t_{k+1}]}$ is a characteristic function of the semi-open interval $\mathbb{X}_{\tau\in[t_k,t_{k+1}]}$ Then we can write

$$\mathbb{E}[V_m^{t,x(t)}(\tau,w)|F_t] = \mathbb{E}\left[\sum_{k=0}^{m} V^{t,x(t)}(t_{k+1},w)\mathbb{X}_{\tau\in[t_k,t_{k+1}]|F_t}\right] \tag{3.50}$$

We observe that $\mathbb{X}_\tau(\cdot)$ does not depend on w, hence eqn (30) will be as follows

$$\mathbb{E}[V_m^{t,x(t)}(\tau,w)|F_t] = \sum_{k=0}^{m} \mathbb{X}_{\tau\in[t_k,t_{k+1})\mathbb{E}(V^{t,x(t)}(t_{k+1},w)|F_t)} \tag{3.51}$$

$= \sum_{k=0}^{m} \mathbb{X}_{\tau\in[t_k,t_{k+1}]}\mathbb{E}(V^{t,x(t)}(t_{k+1},w))$, F_t has vanished because $t_{k+1>t}$, thus $V^t(t_{k+1},w)$ does not depend on F_t hence

$$\begin{aligned}\mathbb{E}[V_m^{t,x(t)}|F_t] &= \mathbb{E}\left[\sum_{k=0}^{m} \mathbb{X}_{\tau\in[t_k,t_{k+1})V^{t,x(t)}}(t_{k+1},w)\right] \\ &= \mathbb{E}[V_m^{t,x(t)}(\tau,w)]\end{aligned} \tag{3.52}$$

Now we let $V_m^{t,x(t)}(\tau,w) \longrightarrow V^{t,x(t)}(\tau,w) \quad as \quad m \longrightarrow \infty$ Thus as $\tau = t+s$ it can

be concluded that

$$\mathbb{E}[h(F(x(t), t, t+s, w)|F_t] = \mathbb{E}[h(x(t), t, t+s, w)] \tag{3.53}$$

This yields the needed result.

3.5 Martingale Process:

In probability theorem, a martingale is a model of a fair game, where knowledge of past events never helps predict the mean of the future winnings

Definition: A sequence of random variables $X_1, X_2, \cdots, X_n$ is said to be a martingale if ;

$$\mathbb{E}[X_{n+1|X_1,\cdots,X_n}] = X_n$$

That is, the conditional expectation of the next observation, given all the past observations is equal to the last observation. Thus for the function $g(t, X(t))$ to be a Martingale, then

$$\mathbb{E}[g(t, X(t)|F_s)] = g(s, X(s)), \quad 0 \leq s \leq t \tag{3.54}$$

3.6 The Feynman-Kac Theorem

The Feynman-Kac theorem relates the solution of the Stochastic Differential Equation with the Brownian motion (Weiner Process) , $W(t), t \geq 0$

$$dX(t) = AX(t)dt + BdW(t), \quad t \in [0, T] \quad and \quad X(0) = y \tag{3.55}$$

with the solution of the Cauchy Problem for the deterministic Partial Differential Equation;

$$g_t(t,x) + \beta(t,x)g_x(t,x) + \frac{1}{2}\gamma^2(t,x)g_{xx}(t,x) = 0$$
$$g(T,x) = h(x) \tag{3.56}$$

for the probability characteristic, $g(t,x) = \mathbb{E}^{t,x}h(X(T))$ Here, $\mathbb{E}^{t,x}$ means the mathematical expectation of a solution to eqn (35) with the initial condition $X(t) = x, 0 \leq t \leq T$.

Study of the relationship between the two equations (3.55) and (3.56) was initial caused by the needs of Physics. Example: while the process $X(t)$ describes the random motion of particles in liquids or gas, $g(t,x)$ is a probability characteristic such as temperature determined by the Kolmogorov Equation, Melnikova and Parfenenkova (2012).
Similarly, in financial mathematics for instance, $X(t)$ may describe stock price at time t, while $g(t,x)$ is the value of stock options, determined by the famous Black Scholes equation.

3.6.1 Proof of the Feynman-Kac Theorem

Theorem

Consider the Stochastic Differential Cauchy problem (3.55). Fix some $T \geq 0$ and suppose that

$\mathbb{E}^{t,x}[h(X(T))] < \infty$ for all pairs t and s. Then $g(t,x) = \mathbb{E}^{t,x}h(X(T))$ is a Martingale process and it is a solution to the Kolmogorov (backward) Equation (3.56).

Proof of Theorem

We start by applying the Ito's lemma on $g(t,x)$ to obtain

$$\begin{aligned} dg(t,x) = &\left[\frac{\partial g(t,X(t))}{\partial t} + \frac{\partial g(t,X(t))}{\partial x}AX(t) + \frac{1}{2}\frac{\partial g(t,X(t))}{\partial x^2}B^2\right]dt \\ &+ \frac{\partial g(t,X(t))}{\partial t}BdW(t) \end{aligned} \tag{3.57}$$

In the integral form eqn (3.57) can be written as

$$\begin{aligned} g(t,X(t)) = g(0,y) &+ \int_0^t \frac{\partial g(s,X(s))}{\partial x}BdW(s) \\ &+ \int_0^t \left[\frac{\partial g(s,X(s))}{\partial s} + \frac{\partial g(s,X(s))}{\partial x}AX(s) + \frac{1}{2}\frac{\partial g(s,X(s))}{\partial x^2}B^2\right]ds \end{aligned} \tag{3.58}$$

Next we take the expectations of both sides of eqn (3.58)

$$\begin{aligned} \mathbb{E}[g(t,X(t))] = \mathbb{E}[g(0,y)] &+ \mathbb{E}\left[\int_0^t \frac{\partial g(s,X(s))}{\partial x}BdW(s)\right] \\ &+ \mathbb{E}\left[\int_0^t \left[\frac{\partial g(s,X(s))}{\partial s} + \frac{\partial g(s,X(s))}{\partial x}AX(s) + \frac{1}{2}\frac{\partial g(s,X(s))}{\partial x^2}B^2\right]ds\right] \end{aligned} \tag{3.59}$$

Since $g(t,X(t))$ is a Martingale process, thus

$$\mathbb{E}[g(t,X(t))] = \mathbb{E}[g(t,X(t))|F_0] = g(0,y)$$

It can also easily be seen that $g(0,y)$ is not a random variable thus $\mathbb{E}[g(0,y)] = g(0,y)$. Further more, the expectation of an Ito integral as proved earlier is zero i.e.

$$\mathbb{E}\int_0^t \frac{\partial g(s,X(s))}{\partial x}BdW(t) = 0$$

Equation (3.59) now becomes

$$g(0,y) = g(0,y) + \mathbb{E}\left(\int_0^t \left[\frac{\partial g(s,X(s))}{\partial s} + \frac{\partial g(s,X(s))}{\partial x}A(s) + \frac{1}{2}\frac{\partial^2 x g(s,X(s))}{\partial x^2}B^2\right]\right)ds \tag{3.60}$$

Which implies that

$$\mathbb{E}\left(\int_0^t \left[\frac{\partial g(s,X(s))}{\partial s} + \frac{\partial g(s,X(s))}{\partial x}A(s) + \frac{1}{2}\frac{\partial^2 g(s,X(s))}{\partial x^2}B^2\right]\right)ds = 0 \tag{3.61}$$

Applying Tonelli-Fubini's Theorem to (3.61) we get the equality below.

$$= \left(\int_0^t \mathbb{E}\left[\frac{\partial g(s,X(s))}{\partial s} + \frac{\partial g(s,X(s))}{\partial x}A(s) + \frac{1}{2}\frac{\partial^2 g(s,X(s))}{\partial x^2}B^2\right]\right)ds = 0 \tag{3.62}$$

thus

$$\mathbb{E}\left[\frac{\partial g(s,X(s))}{\partial s} + \frac{\partial g(s,X(s))}{\partial x}A(s) + \frac{1}{2}\frac{\partial^2 g(s,X(s))}{\partial x^2}B^2\right] = 0 \tag{3.63}$$

Subsequently we rewrite equation (3.63) at the origin and employ the linearity of expectations ($\mathbb{E}$) to obtain

$$\mathbb{E}\left[\frac{\partial g(0,y)}{\partial s}\right] + \mathbb{E}\left[\frac{\partial g(0,y)}{\partial x}A(s)\right] + \mathbb{E}\left[\frac{1}{2}\frac{\partial^2 g(0,y)}{\partial x^2}B^2\right] = 0 \tag{3.64}$$

since each of the terms in eqn (3.64) is not random, we finally get the following;

$$\frac{\partial g(s,X(s))}{\partial s} + \frac{\partial g(s,X(s))}{\partial x}A(s) + \frac{1}{2}\frac{\partial^2 g(s,X(s))}{\partial x^2}B^2 = 0 \tag{3.65}$$

So far the Cauchy problem given by eqn (3.55) is such that $t \in [0,T]$. Consider this problem for the same equation with the initial condition at the moment $\tau \in [0,T]$:

$$dX(t) = AX(t)dt + BdW(t), \quad t \in [\tau,T] \quad and \quad X(\tau) = x \tag{3.66}$$

Then by the arguments similar to that conducted previously the equality

$$\frac{\partial g}{\partial t}(\tau, x) + \frac{\partial g}{\partial x}(\tau, x)Ax + \frac{1}{2}\frac{\partial^2 g}{\partial x^2}(\tau, x)B^2 = 0 \tag{3.67}$$

holds. Varying $\tau \in [0, T]$ we obtain eqn (3.67) for $x = X(\tau)$. We therefore would conclude that

$$g(T, x) = \mathbb{E}^{T,x} h(X(T)) = h(X(T))|_{x=X(T)} = h(x) \tag{3.68}$$

This completes the proof. The Feynman-Kac theorem thus establishes the interrelation between the stochastic and the deterministic problems on both sides. In numerical methods this relationship is indeed important to both sides: numerical methods obtained for stochastic equations are used for solving differential equations in partial derivatives, and basic methods for partial differential equations allow to obtain the characteristics of solutions to stochastic problems Melnikova and Parfenenkova (2012). We must emphasize that equation (3.68) is called the Kolmogorov Equation. This means that the Feynman-Kac theorem 'give birth' to a Kolomogorov equation (in particular, the Kolmogorov Backward Equation). For more details of the proof especially in Hilbert spaces refer to Melnikova and Parfenenkova (2012).

3.7 The Kolmogorov Equations

These are two Partial Differential Equations (PDE) that arise in the theorem of continuous-time stochastic Markov Process. i.e. the Kolmogorov Forward and the Kolmogorov Backward Equation. Both were published in the year 1931 by Andrey Kolmogorov. It became evident however that the Kolomogorov Forward Equation was already in existence under the name Fokker-Planck Equation; but the Kolmogorov Backward Equation(KBE) was an entirely new concept. The

KFE arises as follows; assuming we have information (probability distribution, $p_t(x)$)of the state x we want to find the probability distribution of the state at later time $s > t$. Here the adjective 'forward' stresses the fact that $p_t(x)$ serves as the initial condition and the PDE is integrated forward in time. In contrast to the KFE, the KBE is used if we are interested in knowing for every state x at time t, $(t < s)$ what is the probability of ending in a given subsets of states $\mathbb{B}$ at time s. If we describe the target set by the given function $\mu_s(x)$, then $\mu_s(x)$ serves as the final condition of the PDE, which is integrated backwards in times from s to t. The Kolmogorov Backward Equation (3.69) for our system of Stochastic Differential Equations derived for the cancer stem cells and differentiated cancer cells can be written as follows:

$$\frac{\partial F}{\partial t} = \sum_{k=1}^{2} \mu_k(t, y_1, y_2) \frac{\partial F}{\partial y_k} + \frac{1}{2} \sum_{k,j=1}^{2} \sum_{m=1}^{2} B_{km}(t, y) B_{jm}(t, y) \frac{\partial^2 F}{\partial y_k \partial y_j} \tag{3.69}$$

where μ and B are in eqn (3.20) and $(c, s) = (y_1, y_2)$ In following we reformulate the KBE so derived to calculate the persistent time for our two interacting populations.

3.8 Persistent Time

The Persistent Time is the period or time it takes for one of the interacting populations, c(t) and s(t) to become zero or become extinct. This is first preceded by a decrease in rate of cell growth usually in the advent of therapy or as the population rises to its carrying capacity. The rate of cell growth here is used to describe the proportion of the cancer cells within the tumour which are growing and dividing to form new cancer cells. We will employ two approaches to calculate the persistent time.

- First is to simulate the PDE (The kolmogorov Backward Equation) directly for the persistent time. To this end we will adjust the KBE to suit the intended purpose.

- We will also solve the system of SDEs till one of our two interacting populations i.e. $c(t)$ or $s(t)$ goes to zero or becomes extinct.

3.8.1 Simulation of the KBE

First we let C_1 and C_2 be the respective carrying capacities of $c(t)$ and $s(t)$. This represents the maximum population of differentiated cancer cells and cancer stem cells respectively. We let: $C_1 = C_2 = R$, $K \in \mathbb{R}$

$W = W(y)$ be a random variable, where $y = (c_0, s_0)^t$ represents the initial populations. Then $T = \mathbb{E}(W((y))$ denote average persistent time $F(t, y_1, y_2) = P((W(y)) > t)$, represent the probability that the persistent time exceeds time, t. Also F is as in the KBE (3.69) this implies that we can define $pW(y) = \frac{-\partial F}{\partial t}(y, t)$

where $pW(y)$ is the probability density of $W(y)$ and finally

$$T(y) = \int_0^\infty F(y, t)dt \tag{3.70}$$

Now KBE (3.62) when simplified can be represented by

$$\frac{\partial F}{\partial t} = (u + v - 2d_c c_0)\frac{\partial F}{\partial c_0} + (w + v)\frac{\partial F}{\partial s_0} + \frac{1}{2}(u\frac{\partial^2 F}{\partial c_0^2} + w\frac{\partial^2 F}{\partial s_0^2} + 2v\frac{\partial^2 F}{\partial c_0 \partial s_0}) \tag{3.71}$$

Next we integrate both sides of eqn (3.71) and taking (3.70) into consideration we obtain the following.

$$\begin{aligned}\int_0^\infty \frac{\partial F}{\partial t}(X(0), t) &= F(X(0), \infty) - F(X(0), 0) = 0 - 1 \\ &= ((b_c - d_c)c_0 + b_s(a_2 + 2a_3)s_0)\frac{\partial T}{\partial c_0} + (b_s(a_1 - a_3)s_0)\frac{\partial T}{\partial s_0} \\ &+ \frac{1}{2}\left(((b_c + d_c)c_0 + b_s(a_2 + 4a_3)s_0)\,\frac{\partial^2 T}{\partial c_0^2}\right. \\ &\left. + (b_s(a_1 + a_3)s_0))\frac{\partial^2 T}{\partial s_0^2}\right) - 2b_s a_3 s_0 \frac{\partial^2 T}{\partial c_0 \partial s_0}\end{aligned} \tag{3.72}$$

with the following initial conditions

$$T(0, s_0) = 0 \quad s_0 \in (0, K)$$

$$T(c_0, 0) = 0 \quad c_0 \in (0, K)$$

$$\frac{\partial T}{\partial c_0}(K, s_0) = 0, \quad s_0 \in (0, K)$$

$$\frac{\partial T}{\partial c_0}(c_0, K) = 0, \quad c_0 \in (0, K)$$

Now we solve our new KBE above using the finite difference method as discussed earlier.

Chapter 4

Analysis

This chapter contains the results from our study on comparison of Stochastic Differential Equation for Cancer growth dynamics with Derived Partial Differential Equation using the Feynman-Kac theorem.....

This chapter contains the various results of the comparison between the SDEs for Cancer Cell growth and the derived PDE (Kolmogorov Equation) as derived by the Feynman Kac theorem.

4.1 Initial Conditions

To solve our system of SDE (3.20) we need initial conditions that describe the size of each population at time $t = 0$. As in Kroos (2014) we refer to Hillen and Backman (March 2013) on the study of Oncology and Powathil (2007) and MA Kroos for our choice of initial condition and model parameters. The initial condition thus becomes $(c_0, s_0)^t = (0.5, 0.4)^t$. This implies that we consider the area that is very close to the center of the tumour. The proliferation rates are also set as follows. $b_c = b_s = \ln(2)/5$, slightly different from that in Hillen and Backman (March 2013). The motive is that high birth and death rates in stochastic differential equations lead to higher fluctuations and thus a lot of the trajectories become zero after a small period of time. We assume that the death rate is equal to the mitosis rate for the differentiated cancer cells, meaning that $d_c = \ln(2)/5$. The different probabilities of the cancer stem cells to differentiate are defined as $a_1 = p > 0.215$ for the symmetric division into two cancer stem cells and $a_3 = 1 - p$ for the division into two differentiated cancer cells. As proved by Hillen and Bachmann (March 2013), the model without asymmetric division of the cancer cells is as good as when its included in the model, thus we set $a_2 = 0$.

Table 4.1: Initial Condition and Parameters

$parameters$	$(c_0, s_0)^t$	b_c, b_s, d_c	a_1	a_2	a_3
$value$	$(0.5, 0.4)$	$\ln(2)/5$	0.7	0	0.3

4.2 Numerical Simulations

A naive approach would be to try to solve to perform the simulations using the classical Euler-Maruyama method as described in the earlier section. This algorithm may yield values which are negative for the popultions of cancer stem cells and differentiated cancer cells. Such values occur because the incremental change of the Gaussian Process is not bounded from below. To deal with such a problem we cut of all such trajectories that give negative values by setting them to zero when they intercept the horizontal axis. The moment a trajectory becomes zero it will maintain this status. Figure 4.2. shows some realizations of our system of stochastic differential equations and the mean value of 10^4 trajectories solved with the Euler-Maruyama method. The figure also includes the magnification to see the impact of the stochastic part of our differential equation, the typical fluctuations of stochastic processes. We further solve our system numerically with a higher order methods i.e. the implicit Milstein method given in detail also in the earlier section. We use the supplementary term in the Milstein method to determine the random term $g(t_n, \mathbb{X}_n)\Delta\mathbb{W}_n$. Figure 4.3. shows the trajectories computed with the implicit Milstein Method. When we make a comparison of the two solutions we realize that the results are almost in the same order of magnitude except that the Euler-Maruyama method gives slightly smaller values for the population sizes.One great problem however for the Milstein method is that it has a long program execution time, resulting from the approximations of the derivatives and the double Ito-integral in equation (3.3).

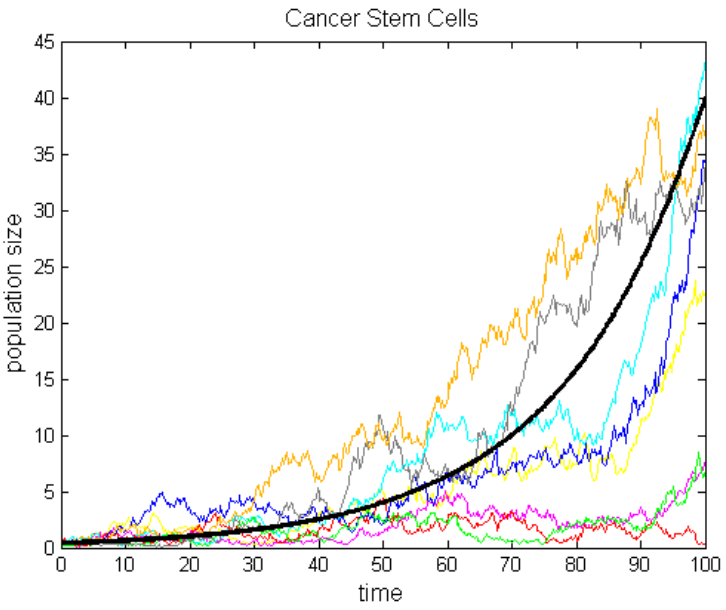

Figure 4.1: (a) Cancer Stem Cells as simulated by Euler Maruyama Method, mean value in black.

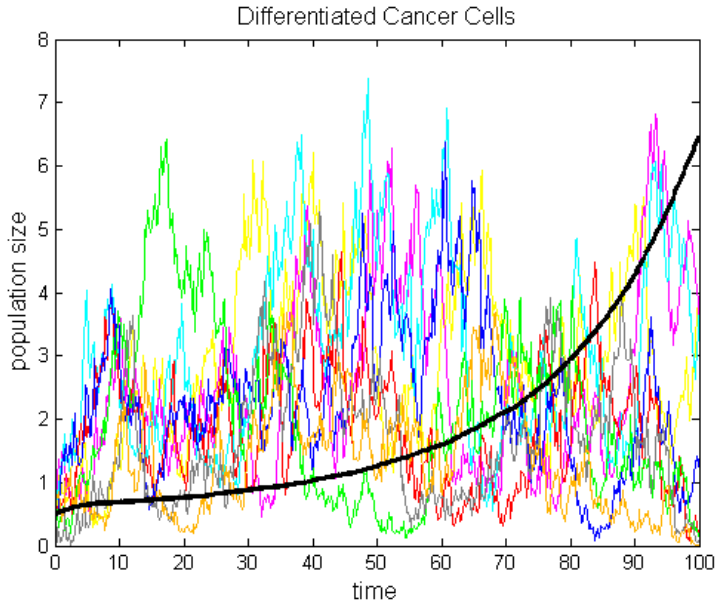

Figure 4.2: (b) Differentiated Cancer Stem Cells as simulated by the Euler Method, mean value in black.

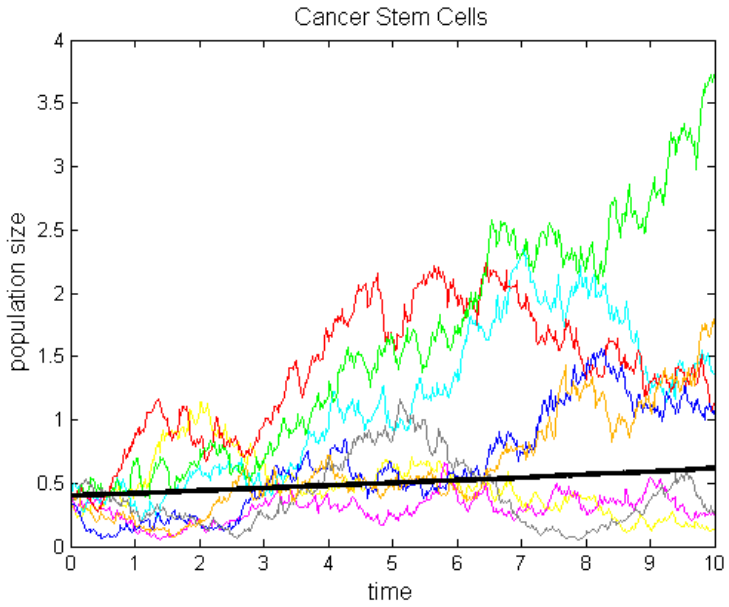

Figure 4.3: (c)-amplified version of (a):Cancer Stem Cells as simulated by Euler maruyama Method, mean value in black.

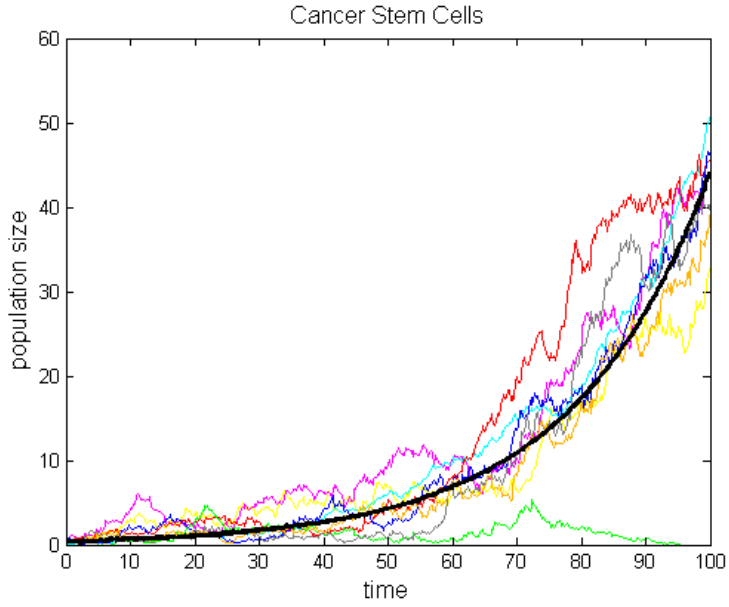

Figure 4.4: (a):Cancer Stem Cells as simulated by the Milstein Method, mean value in black.

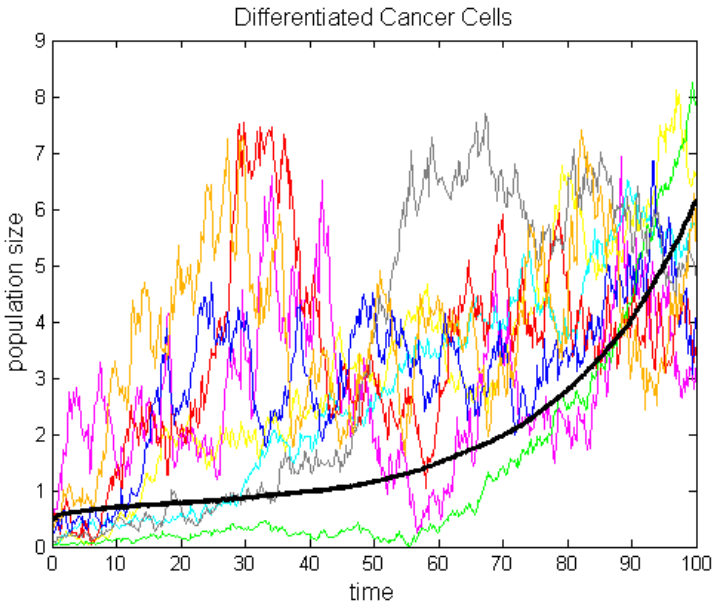

Figure 4.5: (b):Differentiated Cancer Stem Cells as simulated by the Milstein Method, mean value in black.

Table 4.2: Solution of KBE at different points

Populations $(c, s)^t$	Persistent Time from FDM
$(0.02, 0.02)^t$	0.17889
$(0.1, 0.1)^t$	0.90253
$(0.2, 0.2)^t$	0.81561
$(0.2, 0.3)^t$	0.93564
$(0.3, 0.1)^t$	1.23700
$(0.3, 0.2)^t$	0.94212
$(0.3, 0.3)^t$	1.07602
$(0.5, 0.4)^t$	1.00233
$(0.4, 0.5)^t$	0.87678
$(0.5, 0.5)^t$	0.99905
$(0.5, 0.6)^t$	2.26509
$(0.5, 0.7)^t$	0.99338
$(0.8, 0.2)^t$	0.96579
$(0.8, 0.8)^t$	0.99745
$(1.0, 0.8)^t$	0.78871
$(1.0, 1.0)^t$	1.03908

Table 4.3: Numerical Simulation of Average Time of Persistence

$Populations \quad (c,s)^t$	$Av.Persitent \quad Time(EMM)$	$Av.Persistent \quad time(MM)$
$(0.02, 0.02)^t$	0.18385	0.17828
$(0.1, 0.1)^t$	0.15847	0.57750
$(0.2, 0.2)^t$	0.76467	0.76621
$(0.3, 0.1)^t$	0.86595	0.86007
$(0.3, 0.2)^t$	0.87392	0.87482
$(0.3, 0.3)^t$	0.99701	0.96859
$(0.5, 0.4)^t$	0.87661	0.88329
$(0.4, 0.5)^t$	0.92550	0.92460
$(0.5, 0.5)^t$	0.98805	0.98891
$(0.5, 0.6)^t$	0.98905	0.97891
$(0.5, 0.7)^t$	0.99805	0.98991
$(0.8, 0.2)^t$	0.96859	0.96995
$(0.8, 0.8)^t$	0.97807	0.97897
$(1.0, 0.8)^t$	0.98721	0.98662
$(1.0, 1.0)^t$	1.07359	1.08359

4.3 Simulation of our system of Stochastic Differential Equations

The procedure used here is to compute the average persistent time numerically. We carry out simulations of population behavior of our system of Stochastic Differential Equation (3.13) several times till one of the populations is extinct. Then the average time of persistence is calculated. We thus generate for example 1000 trajectories with the Euler Maruyama Method and the Milstein Methods . The trajectories are stopped whenever $c \leq 0$ or $s \leq 0$ and we note the exact time of this event. table 4.3 gives the respective average persistent time for our system of Differential Equations from the Euler Maruyama Method (E.M.M) and the Milstein Methods(M.M)

4.4 Analysis of the Results

Upon careful observation, we realize that most of the values of the persistent time computed for the Euler Maruyama Method and the Milstein Methods deviate

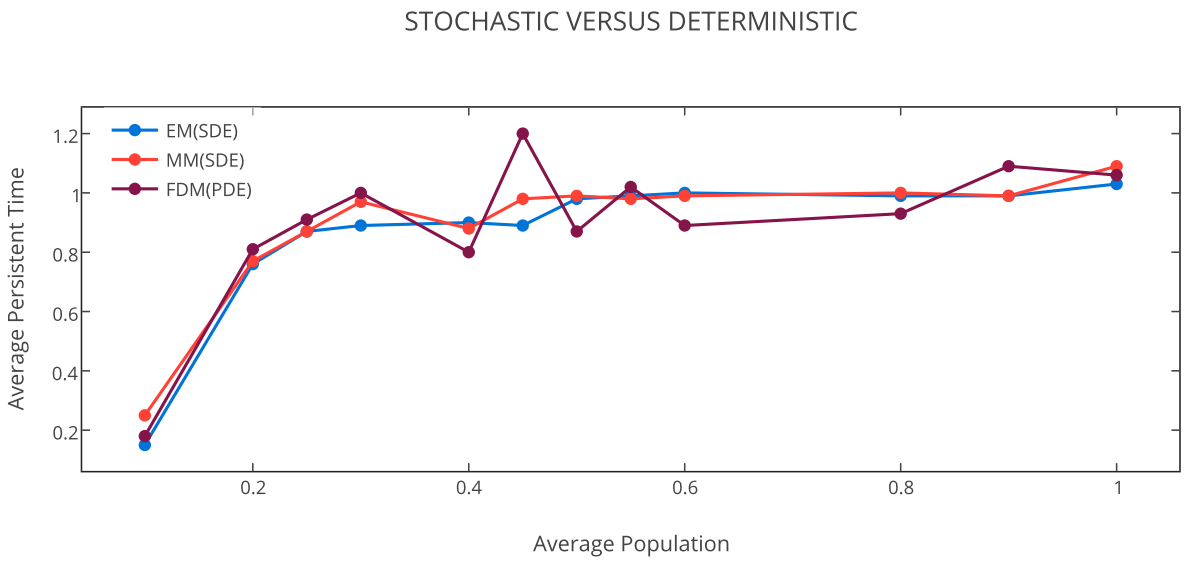

Figure 4.6: Comparison of Average Persistent Time (a)

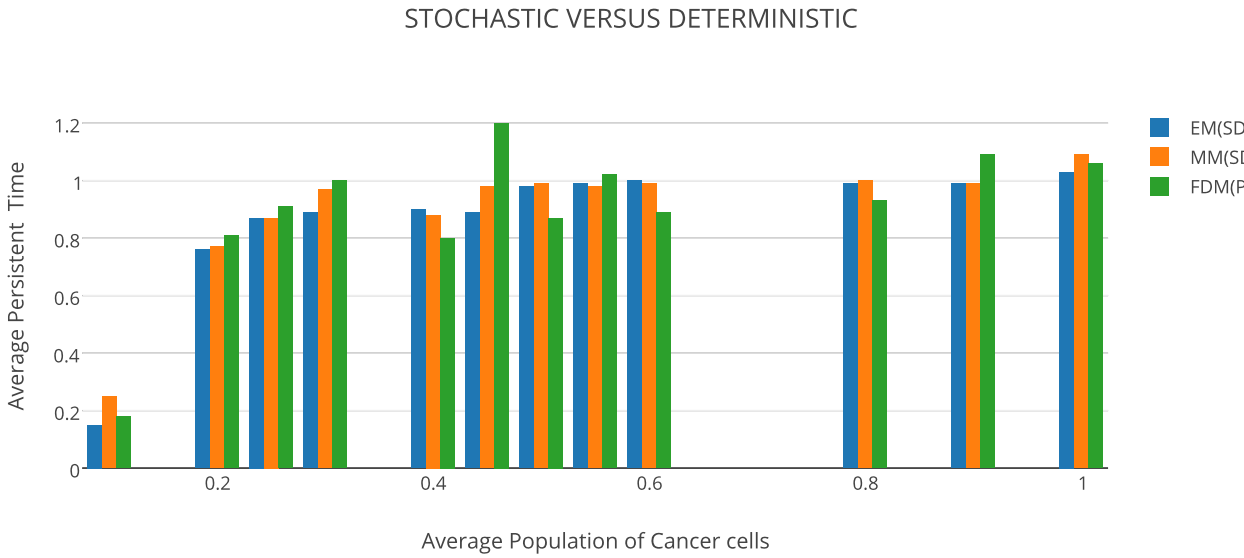

Figure 4.7: Comparison of Average Persistent Time (b)

only slightly from each other. Some of the values of the persistence time are almost the same for The Euler Maruyama Method, Milstein Method as well as the Finite difference method for the PDE. A clear example can be seen at $T(0.8, 0.2)$ and $T(1.0, 1.0)$ The reasons for the above observations can be attributed to the following:

- The first obvious reason is that the methods are not exactly the same even though they are intended for the same purpose. The Milstein Method for instance is a higher order method relative to the Euler Maruyama Method both of which are used for the approximations of the system of SDEs while the Finite Difference method is adopted for a non-stochastic equation i.e. a PDE. These analysis can easily be verified from the graphs depicted in fig 4.6 and fig 4.7 above.

- Another reason may also be due to the fact that we computed up to 1000 trajectories. An attempt to increase the number of trajectories proved difficult as it by far exceeded the run-time of the program computing the values with the Milstein method.

Relatively speaking, the Euler Maruyama and the Milstein method showed slight deviations in terms of their persistent time values as obtained from our system of Stochastic Differential Equations. When you make a comparison between any of the persistent times i.e. from the Euler Maruyama or the Milstein method or their average with the Finite difference method used to compute for the persistent time in case of the kolmogorov backward equation (i.e. PDE), it is realized that the KBE deviated slightly higher but not so significant. The three methods are thus almost consistent with one another but the Euler and the Milstein methods were more consistent to each other. The reason is that the Kolmogorov Equation does not take into accounts, the randomness of the population growth behaviour of the cancer cells, i.e. it does not factor uncertainties. To stress on the analysis

we made above,we use the Frobenius norm to compute the relative and absolute errors made by the Kolmogorov Backward Equation as compared with the approximations with the simulations of the SDEs.(i.e. their average persistent time) For the exact values x and the approximation $\bar{x}$ we compute the errors for $N = 100$ discretization as follows.

$$error_{relative} = \left\| x - \bar{x} \right\|$$

$$error_{absolute} = \frac{\left\| x - \bar{x} \right\|}{\left\| x \right\|}$$

$$E_{rel} = \left\| x - \bar{x} \right\| = 0.20052$$

$$E_{abs} = \frac{\left\| x - \bar{x} \right\|}{\left\| x \right\|} = 3.3673$$

Judging from the examples given above we realize that the Kolmogorov Backward Equation basically slightly overestimates the persistence time but the error made is rather very small. In principle, the numerical simulations for the SDEs tend to be more accurate and thus offer more realistic values for the persistence time. However this work has proven that such systems of stochastic Differential Equations can be changed to an equivalent Partial Differential Equation and obtain solutions which are very close to that of the SDE. It is worth noting that, for very small initial populations sizes the numerical simulations of the SDEs tend to be less accurate. This is caused by the factor $\frac{1}{\eta}$ in equation (3.20), which becomes problematic for the values of s and c close to zero and thus an η that is close to zero. In the Kolmogorov backward equation this problem does not exist as this approach to compute the persistence time only uses the deterministic part of

equation (3.9) leaving out the stochastic part that includes the factor $\frac{1}{\eta}$. We again realize that the Stochastic Differential Equation model considered in this thesis does not capture cancer treatment. This is due to the assumption that $d_s = 0$. However some treatments that are employed in the treatment of cancer include chemotherapy and Radiotherapy and sometimes a combination of both methods. Their overall effect is that they speed up the death rates of the cancerous cells. In such situations $d \neq 0$ and that will mean that the Stochastic differential equations we solved earlier on will be changed slightly for the populations of the cancer stem cells and the differentiated cancer cells. This will also affect the values we found for the average persistence time. However cancer treatment is outside the scope of this thesis. Nevertheless, the Stochastic Differential Equation model is almost sure to give a very good estimate of persistence time and so is the Kolmogorov Backward Equation(a PDE) derived through the Feynman Kac theorem.

Chapter 5

Conclusion

In conclusion we note that Feynman-Kac theorem can be used to obtain a PDE (Kolmogorov Equation) from an equivalent SDE model to describe the average persistent time of the cancer cells. The PDE is able to provide an approximate solution to the usual SDE models used to describe cancer cell growth and thus provides an alternative method of solution.

5.1 Recommendation

Judging from our results, we make two recommendations;

- The SDE model used in this work should be developed to include cancer treatment such as chemotherapy and radiotherapy. In addition the model should be improved to deal with situations when initial populations of the cancer cells are relatively small as this led to fluctuating results.

- Other Numerical schemes for PDE should be used to solve the Kolmogorov equation derived for the SDE and to compare the results.

REFERENCES

Black, Derman, F., and Toy, W. (1990). A one-factor model of interest rates and its application to treasury bond options. *Financial Analyst Journal*, pages 24–32.

Brown, R. (1866). The miscellaneous botanical works of robert brown. 1.

Clegg-Lamptey (2007). A study of bresast cancer in korle bu teaching hospital,accessing impact of health education. *Ghana Medical Journal*, 4(2):72–77.

Cox, J., Ingersoll, J., and Ross, S. (1985). A theory of the term structure of interest rates. econometrica. 53:385–407.

David, K. and Kevin, B. (2012). Modelling ion channel dynamics through reflected stochastic differentail equations. *Statistical, Nonlinear and Soft Matter Physics*, 85(5).

Einstein, A. (1956). Investigations on the theory of the brownian movement. *Dover Publications.*

E.Platen and Kloeden, P. (1995). *Numerical Solution of Stochastic Differential Equations.*

Geib, C. and Manthey, R. (1998). Stochastic process and their applications. 78(2):155–171.

HO, T. and Lee, S. (1986). Term structure movements and pricing rate contingent claims. *Journal of Finance*, 41.

Hull, J. C. (2006). Interest rate derivatives:models of the short rate, options, futures and other derivatives.

Hunter, M. and Anita, H. (2003). Fatalism towards breast cancer among the women of ghana. *Healthcare for Women Internatioanl*, 24(7):608–615.

Kroos, J. M. (2014). An sde approach to cancer therapy including stem cells. *International Journal of Mathematics and mathematical sciences*, 1:1–29.

Langevin, P. (1908). Sur la thÃ©orie du mouvement brownien [on the theory of brownian motion. *C. R. Acad. Sci. (Paris)*, 146:530–533.

Markowitz, H. (1952). Portfolio selection. *Journal of Finance*, 7:77–91.

Melnikova, I. and Parfenenkova, V. (2012). Relations between stochastic and partial differential equations in hilbert spaces. *International Journal of Statistical Analysis*, 2012:1–9.

Merton, R. (1971). Theory of rational option pricing. *World Journal of Modelling and Simulation*, 1:132.

Oksendal, B. (2003). *Stochastic Differential Equations.An introduction with Application*. springer.

Pliska, S. (1981). Martingales and stochastic integrals in the theory of continuous trading in stochastic process and their applications. *Communications in Nonlinear Science and Numerical Simulation*.

Solomon, Q. (2010). African ancestry and higher prevalence of triple-negative breast cancer. *Ghana Medical Journal*, 116(21):4926–4932.

Zaza, H. (2015). Application of stochastic phenomenological modeling to cell-to-cell and beat-to-beat electrophysiological variability in cardiac tissue. *Journal of Theoretical Biology*, 365:325–336.