UNIVERSITI PUTRA MALAYSIA

STEADY STATE ANALYSIS FOR EFFECTS OF TUMOR MICROENVIRONMENTAL FACTORS ON TUMOR GROWTH DYNAMICS

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FS 2017 23

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By

IBRAHIM MU'AWIYYA IDRIS

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

April 2017

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DEDICATIONS

This work is dedicated to my late father Alhaji Mu'awiyya Idris who died on 20th day of July 2010, may Allah have mercy on his soul and make him together with other departed souls of muslim ummah among the dwellers of jannatul firdaus ameen.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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Chair: Assoc. Prof. Mohd Rizam Abu Bakar, PhD
Faculty: Science

Many biological systems are often subjected to random environmental influences that cannot be understood from the deterministic theoretical approach. Theoretical description of these systems can only be correctly understood from the probabilistic (stochastic) view point, even though the source of randomness may vary depending on the nature of the process and its physical origin. For instance, random processes that evolve with a system intrinsically are best modeled by master equation which is in the form of nonlinear integro-partial differential equation with discrete jump moments at short times. However, for systems subject to external random effects, and for which the jump moments in the transition probability approaches zero, the master equation description approaches the so-called Fokker Planck equation with continuous state space. Tumor growth system subject to random microenvironmental factors effect within the tumor site is the main focus of this thesis. We have considered one-dimensional tumor model in the form of Langevin equation subject to influence from the surrounding tumor microenvironmental factors effect. The tumor microenvironmental factors are the random biological processes existing within the immediate neighborhood of the tumor cells, and whose effects influence tumor growth greatly by either promoting growth, inhibiting growth or sometimes neutral to malignancy. Moreover, the tumor model consist of the logistic model as the deterministic evolution equation for tumor growth, and the stochastic component consisting of additive and multiplicative noise terms respectively. The additive noise term represent the surrounding tumor microenvironmental factors effect which are external to the tumor, while the multiplicative noise term represent tumor response to the surrounding microenvironmental factors effect, and which effects are proportional to the state of tumor growth. In addition, the two noise terms are correlated having originated from the same source.

The tumor model is firstly considered to be driven by correlated additive and multi-

plicative white noises respectively, where the additive noise term represent the non-immunogenic microenvironmental factors effects within the tumor site. The underlying transition probability for the tumor model satisfies the Fokker Planck equation, and of which the steady state distribution corresponding to the long-term limit solution for the tumor growth system is obtained. The study revealed that the surrounding non-immunogenic tumor microenvironmental factors have a diffusive effect on tumor growth as indicated by the tumor response parameter. The tumor model is further considered to be driven by correlated noises with non-zero correlation time (colored noise case), of which consequence yield a non-Markovian tumor model. Consequently, the underlying transition probability for the tumor model does not obey the Markovian Fokker Planck equation, and using the Novikov theorem, Fox approach and the Ansatz of Hanggi, an approximate Fokker Planck equation in the steady state regime is obtained. Further, the steady state properties for the tumor growth system is explored using numerical simulations, where it is observed that the strength of the correlation time has a strong influence on the growth effects exerted by the non-immunogenic component of tumor microenvironment on tumor growth. Finally, the deterministic component of the tumor model is extended to include the tumor-immune interaction potential. This allows us to study the tumor response to the dual effects of immunogenic and non-immunogenic tumor microenvironmental factors within the tumor site. It is observed that in the presence of adequate immune response, the growth effects exerted by the non-immunogenic tumor microenvironmental factors are opposed, and instead the tumor growth is reduced towards extinction.

The research in this thesis is not directly focused on the biological aspect of tumor growth, but rather on the theoretical study of complex properties and behaviors likely exhibited by tumors in response to the surrounding tumor microenvironmental factors effects, which has great influence on tumor evolution and progression. This type of research is particularly important towards understanding the tumor growth process at micro-level for the design of an effective treatment strategy for tumor diagnosis, and for necessary medical precautions.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

ANALISIS KEADAAN MANTAP UNTUK KESAN FAKTOR PERSEKITARAN SECARA MIKRO DALAM TUMOR KE ATAS DINAMIK PERTUMBUHAN TUMOR

Oleh

IBRAHIM MU'AWIYYA IDRIS

April 2017

Pengerusi: Prof. Mady. Mohd Rizam Abu Bakar, PhD
Fakulti: Sains

Kebanyakkan sistem biologi tertakluk kepada pengaruh persekitaran rawak yang gagal difahami melalui pendekatan teori berketentuan. Huraian secara teori bagi sistem ini hanya dapat difahami dengan betul melalui jurus pandang kebarangkalian (stokastik) walaupun punca kerawakan mungkin berubah bergantung kepada proses semula jadi dan keasalan fizikal. Sebagai contoh, proses rawak yang berubah ansur dengan sistem secara intrisik adalah baik dimodelkan dengan persamaan induk dalam bentuk persamaan pembezaan kamilan-separa tak linear dengan lompatan momen diskret pada masa singkat. Untuk sistem yang terkesan secara rawak luaran, dan untuk lompatan momen dalam peralihan kebarangkalian yang menumpu ke sifar, penghuraian persamaan induk akan mirip kepada pendekatan persamaan yang dipanggil persamaan Fokker Planck dengan ruang keadaan selanjar. Sistem pertumbuhan tumor tertakluk kepada kesan rawak faktor persekitaran secara mikro dalam tumor adalah menjadi fokus kajian tesis ini. Kajian memberi tumpuan kepada model tumor satu dimensi dalam bentuk persamaan Langevin tertakluk kepada pengaruh kesan faktor persekitaran tumor secara mikro. Faktor persekitaran tumor secara mikro adalah proses rawak biologi yang wujud bersama kejiranan terdekat bagi sel tumor, dan kesannya yang mempegaruhi secara kuat pertumbuhan tumor sama ada secara pengalakan, perencat atau kadang kala kemaglinan secara neutral. Tambahan, model ini mengandungi persamaan pertumbuhan logistik secara persamaan evolusi berketentuan bagi pertumbuhan tumor, dan komponen stokastik yang mengandungi tempoh hingar masing-masing secara penambahaan dan pendaraban. Tempoh hingar tertambah mewakili kesan faktor keadaan sekeliling di persekitaran tumor secara mikro yang dianggap luaran terhadap tumor. Tempoh hingar secara pendaraban mewakili tindak balas tumor kepada kesan faktor keadaan sekeliling persekitaran secara mikro, dan memberi kesan secara kadaran terhadap tahap pertumbuhan tumor. Tambahan, kedua-dua tempoh hingar adalah berkorelasi oleh kerana terbit dari unsur yang sama.

Model tumor mula diberi perhatian hasil dorongan hingar putih Gaussian berkolerasi positif penambahan dan pendaraban, dengan tempoh hingar penambahan positif mewakili kesan faktor persekitaran secara mikro tak immunogenik dalam tumor. Kebarangkalian transisi pendasar untuk model tumor mematuhi persamaan Fokker Planck, dan dengan taburan keadaan mantap mewakili penyelesaian had jangka panjang bagi sistem pertumbuhan tumor dapat dihasilkan. Dapatan kajian menunjukkan faktor sekeliling persekitaran secara mikro tak immunogenik memiliki kesan resapan terhadap pertumbuhan tumor seperti ditunjukkan oleh parameter respons tumor. Model tumor seterusnya dianggap terdorong oleh hingar berkorelasi dengan korelasi masa bukan sifar (kes berwarna) yang mengakibat terhasilnya model tumor tak Markovan. Akibatnya, model tumor ini tidak mematuhi persamaan Markovan Fokker Planck, dan mengunakan teori Novikov, pendekatan Fox dan Ansatz Hanggi, penghampiran persamaan Fokker Planck dalam regim keadaan mantap terhasil. Seterusnya, sifat keadaan mantap bagi sistem pertumbuhan tumor diteroka menerusi simulasi berangka, dimana didapati kekuatan korelasi masa mempengaruhi secara kuat keatas kesan pertumbuhan yang dipengaruhi oleh komponen tak immunogenik persekitaran secara mikro keatas tumor. Akhirnya, komponen berketentuan bagi model tumor dikembangkan untuk merangkumi potensi interaksi imun-tumor. Ini membolehkan kajian terhadap tindak balas tumor keatas faktor kesan dual bagi immunogenik dan tak immunogenik dalam tumor dilakukan. Ia dapat diperhatikan dengan kehadiran respons imun yang cukup, kesan pertumbuhan yang disebabkan oleh faktor persekitaran mikro tak immunogenik dalam tumor yang terhalang, dan sebaliknya pertumbuhan tumor dikurangkan sehingga terhapus. Penyelidikan dalam tesis ini tidak fokus secara terus pada aspek biologi pertumbuhan tumor, tetapi menjurus kepada pengajian secara teori kekomplekan ciri-ciri dan perilaku yang terjana oleh tumor yang terkesan dari persekitaran secara mikro, dan yang memberi pengaruh besar kepada evolusi dan progressi tumor. Penyelidikan sebegini adalah amat penting dalam memahami proses pertumbuhan tumor pada peringkat mikro bagi membentuk strategi pemulihan yang berkesan dalam mendiagnosis tumor, dan keperluan amaran awal dalam perubatan.

ACKNOWLEDGEMENTS

All thanks, praise and appreciation be to Allah and his messenger Prophet Muhammad (P.B.U.H) for sparing my life and enriching me with health, wisdom and perseverance to accomplish this thesis.

Firstly, I would like to express my gratitude and sincere appreciation to my supervisor Assoc. Prof. Mohd Rizam Abu Bakar for guiding me through the doctoral studies. I am indeed grateful to all his advise, his patience and support throughout the period of my study.

Deep and sincere gratitude goes to Assoc. Prof. Ibragimov Gafurjan for his immense guidance, advises and for the opportunity to attend his postgraduate students class on game theory, I have learn't a lot than I could have imagined, and also for the many inspiring discussions we had during the period of my study.

I would like to sincerely acknowledged the contribution of Dr. Maizurwatul Ahlam Binti Mohd Jaffar especially her constructive criticism and good suggestions.

I would also like to acknowledge the support of the entire staff and my colleagues in the department of mathematics Universiti Putra Malaysia, indeed the cordial relationships we had during the period of my studentship in the department was an unforgettable experience.

Finally I wish to express my deepest gratitude to my family especially my wife Saratu and my three loving children's Amina (Ummi), Hafsat and Aliyu (New born) for their patience, love and understanding throughout the tiresome period of my study.

This research was financially sponsored by Umaru Musa Yar'adua University katsina under the Tertiary Education Trust Fund (TETFUND) government of Nigeria.

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy.

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CHAPTER 1

INTRODUCTION

1.1 Introduction

Tumor growth and cancer pandemic in both developed and developing countries have become a great deal of concern in the recent decades. A global surveys conducted in 20 world regions (Figure 1.1) indicated an estimate of about 7.6 million cancer related death in 2008, and about 8.2 million death in 2012, Ferlay et al. (2010, 2015). Over the

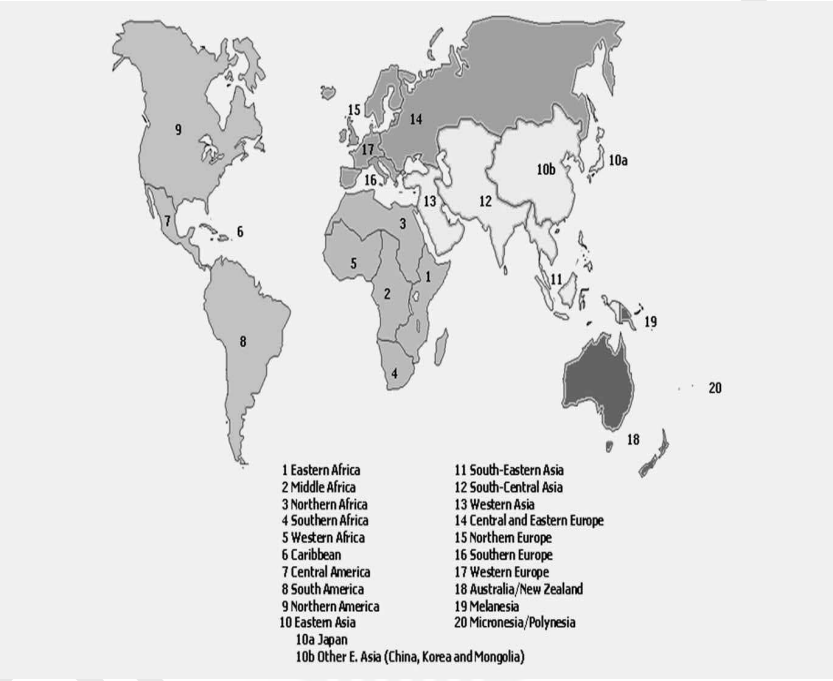

Figure 1.1: Global map showing 20 world regions where the survey study for cancer related death were conducted, (Source Ferlay et al. (2010)).

years, various models have been developed and papers were published in which each systematically contributes towards better understanding of the evolutionary dynamics of tumor growth, Kuznetsov et al. (1994); Boondirek et al. (2006); Roose et al. (2007); Durrett et al. (2011). Moreover, the study of tumor growth have attracted the attention of researchers from across many disciplines such as in clinical, experimental, mathematical biology and mathematical biophysics, Kirschner and Panetta (1998); de Pillis et al. (2006); Bose and Trimper (2009); Sahoo et al. (2010); Yang et al. (2014b); Gutiérrez-Sanchez et al. (2014); Guo et al. (2016). Tumor growth from the microscopic point of view is an open biological process in which the growth pattern

exhibited is non-linear, and interaction between the tumor cells and the surrounding tumor microenvironmental factors induce random effect on the tumor growth system that cannot be understood from the clinical, experimental and deterministic mathematical investigations. It is therefore absolutely indispensable in the theoretical study of tumor growth system to consider impacts from the surrounding tumor microenvironmental factors, and of which stochastic methods provide a powerful tool for theoretical study.

The study of random (stochastic) systems have been of interest since the seminal presentation of Einstein (1905). Prior to the Einsteins theory on Brownian motion, many complex systems were studied deterministically which gave a unique solution neglecting influence from the random perturbations of nature. In addition, the complex biological, physical and chemical systems were then studied deterministically which in turn result to insufficient understanding of the systems under study. In most cases, biological systems are subject to internal and external random environmental influences that can only be correctly understood from the probabilistic view point, Ai et al. (2003); Bao-Quan et al. (2003); Zhang and Ai (2010); Liu and Ning (2016); Idris and Bakar (2016). Theoretical description of these systems inevitably involves the notion of randomness and uncertainty, thereby establishing a link between deterministic theory and stochastic process. Even though, the source of randomness may vary depending on the nature of the process and its physical origin. It is therefore imperative at this juncture to make a distinction between the internal and external fluctuations before proceeding further. Internal fluctuations are self originating, it evolves with the system intrinsically with no external parameter measuring its effect on the system. Further, internal fluctuations are best modeled or described by the master equation

$$\begin{aligned}\frac{\partial}{\partial t}p\,(x,t) = \omega(x,x-1;t)\,p\,(x-1,t) + \omega(x,x+1;t)\,p\,(x,t)\\ -[\omega(x+1,x;t)+\omega(x-1,x;t)]p\,(x,t),\end{aligned} \tag{1.1}$$

where $p(x,t)$ is the probability of the system being at position x at time t, and $\omega(x,x\pm 1;t)$ is the transition probability of moving from state $x\pm 1$ to state x at time t, the condition of detailed balance is satisfied in Eq. (1.1). However for long-time macroscopic systems, internal fluctuations usually scale with the system size and often vanish in the thermodynamic limit. In the limit, the master equation description reduces to deterministic model equation generating the system, Sancho and Miguel (1984); Horsthemke (1984)

$$\frac{dx}{dt} = f(\mu,x,t), \tag{1.2}$$

where Eq. (1.2) represent an arbitrary deterministic model equation describing an evolution of some system, x and t are the system and time variables respectively, while μ is some parameter. On the other hand, external noise which is the central focus of this thesis is not self originating, its effect on system lies on the existence of an external body of statistical fluctuations that induce stochastic effect on either the system variable(s) and or parameter(s), depending on the type of noise and its physical origin. Theoretical study of random systems subject to external noise effect involves incorporating a stochastic term to the deterministic model equation generating the system [such as Eq. (1.2)], and which consequence yields the non-trivial stochastic

differential equation.

Theoretical study of tumor growth is such a heuristic approach where some mathematical equations that closely captures the general features of tumor growth, and as well their ability to fit experimental data are considered as deterministic models. The most popularly used deterministic models for microbial cell growth, and particularly tumor cell growth in literature are the logistic and Gompertz equations, Marušic et al. (1994); Forys and Marciniak Czochra (2003). An experimental data obtained from

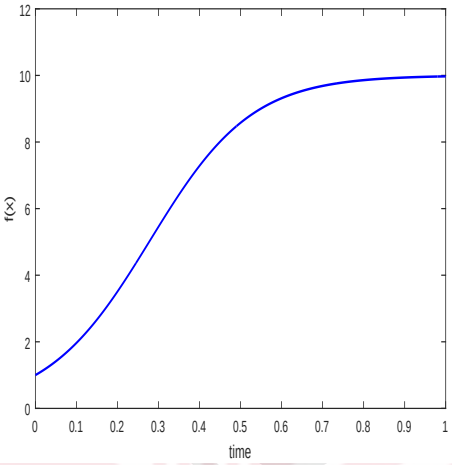

Figure 1.2: Logistic growth equation with carrying capacity $k = 10$.

tumor cell cultivation in vitro were shown to fit the logistic growth equation, Bose and Trimper (2009), with characteristic of exponential growth at the initial stage of growth, and eventually approaching a maximum size on the long-run known as the carrying capacity (Figure 1.2). The logistic growth equation is given by

$$f(x) = a(1 - \frac{x}{k})x, \tag{1.3}$$

where $x = x(t)$ is the population of tumor cells at time t, a is the positive growth constant $(a > 0)$ and $k = (a/b)$ is the carrying capacity, and $b > 0$ is the decay constant. In other word, k is the growth limit allowed for the state variable x.

In literature, tumor models are formulated in terms of differential equation that link the rate of growth of the tumor to its instantaneous state of growth. The evolution and progression of tumor from the microscopic point of view is a random biological process which is due to stochastic effects from the surrounding microenvironmental factors, and which understanding requires the knowledge of probability distribution and indeed a stochastic approach. The power of stochastic methods have over the years proven proficiency especially in the study of properties and behaviors of random systems, Quan et al. (2003); Zhong et al. (2005); Boondirek et al. (2006); Lo (2009); Li and Li (2010a); Wang et al. (2011). In addition, the term random refers

to the fluctuations that engulfs the state of a dynamical system and which requires a probabilistic theoretical framework for its description and analysis.

1.2 Motivation

There is a growing concern over the compelling evidence that tumors are resisting therapy thereby given rise to complications with regards to tumor diagnosis, Albini and Sporn (2007); Balkwill et al. (2012); Gao et al. (2014). The recent complications in tumor growth as evident from many clinical research findings necessitated the need for further research especially on tumor response to the surrounding tumor microenvironmental factors effect from the theoretical view point, and which proper understanding will help towards developing an effective treatment strategy for tumor diagnosis.

1.3 Problem Statement

The main problem this thesis intends to investigate is the tumor response to the random influence of internal tumor microenvironmental factors effect within the tumor site using applied stochastic method. Tumor microenvironment is an integral part of tumorigenesis, it has a strong influence on tumor initiation, progression and as well as in therapeutic control, Cheng and Weiner (2003); Whiteside (2008); Räsänen and Vaheri (2010). An extensive review of literatures on tumor microenvironment and its role on tumor growth were reported in Abbott et al. (2008); Lorusso and Rüegg (2008); Witz (2009); Hanna et al. (2009); Strell et al. (2012), and references therein. In other words, tumor microenvironment is a complex body of interacting microscopic biological degrees of freedom that varies and interact with tumor cells constantly and independently, each with a specific biological function. Such biological degrees of freedom include among others the signal transduction in cellular activity, nutrients, fibroblast cells, extracellular matrix proteins and immune cells. Figure 1.3 shows a schematic diagram of some components of tumor microenvironment. In addition, tumor microenvironment is divided into two components of factors:

1. Immunogenic tumor microenvironmental factors
2. Non-immunogenic tumor microenvironmental factors

Indeed, careful study of literatures on tumor microenvironment, especially its influence on tumor growth shows that application of stochastic method in the study of tumor response to the surrounding tumor microenvironmental factors effect has not been exactly reported to our knowledge. Meanwhile, application of stochastic methods in the study of random systems especially biological and physical systems have been quit successful. It is with this view that we intend to expand the scope of research in tumor microenvironment from clinical and experimental approach to include stochastic theoretical approach. This is with the hope that applied stochastic method in the study of tumor response to the surrounding tumor microenvironmental factors effect within the

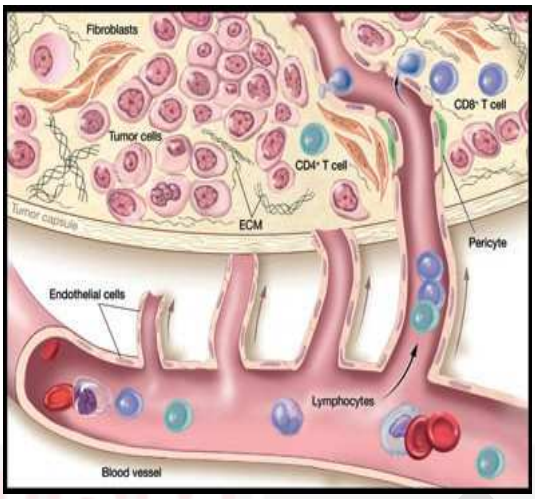

Figure 1.3: Schematic Diagram showing components of tumor microenvironment, (Source Hanna et al. (2009)).

tumor site will give some additional insight into the complex dynamical properties and behaviors likely exhibited by tumor growth.

1.4 Objectives

The main aim of this thesis is to study the steady state properties for the effect of tumor microenvironmental factors on tumor growth system using stochastic method with the following objectives:

1. To derive the steady state distributions and analyze the steady state properties for the tumor response to non-immunogenic microenvironmental factors effect modeled by correlated additive and multiplicative white noises (zero correlation time).

2. To derive the steady state distributions and analyze the steady state properties for the tumor response to non-immunogenic microenvironmental factors effect modeled by correlated additive and multiplicative colored noises (non-zero correlation time).

3. To derive the steady state distribution and analyze the steady state properties for the effect of non-immunogenic microenvironmental factors effect in the presence of immune response.

4. To verify the theoretical results obtained by numerical computer simulations.

1.5 Limitation

This thesis is limited to the biophysical properties likely exhibited by tumor growth in response to its surrounding random tumor microenvironmental factors effect modeled as stochastic process, and based on some specified assumptions. The biochemical component of the tumor is not within the interest of this research.

1.6 Thesis Organization

The subsequent chapters of this thesis are organized as follows:

Chapter 2 - Consist of historical background of the study area as contained in the works of some prominent scientist, and other related works with particular emphasis on systems where similar methodological approach were applied.

Chapter 3 - Consist of the basic mathematical background and concept in the field of applied stochastic process needed to analyze a stochastic model. This chapter provides an introduction to stochastic process (random function), the Brownian motion or otherwise Wiener process as a mathematical idealization and other important concepts. The general methodological framework for the analysis of stochastic differential equation expressed in terms of Langevin equation and the corresponding Fokker-Planck equation are highlighted. Moreover, Langevin equation driven by Ornstein-Uhlenbeck noise (colored noise) with associated correlation time cannot be described by the Fokker-Planck equation with Markovian assumption, for such situation an Approximate Fokker Planck equation is also discussed in the chapter.

Chapter 4 - This chapter investigates the steady state properties for the effect of non-immunogenic microenvironmental factors within the tumor site. The tumor model is formulated in the form of Langevin stochastic equation driven by correlated additive and multiplicative noises with zero correlation time (white noise limits).

Chapter 5 - This chapter considers the case of non-zero correlation times (Ornstein-Uhlenbeck noise) for the tumor model in chapter 4. In addition, the self-correlation times for the additive and multiplicative noises respectively and the cross-correlation time between noises are non-zero (colored noise).

Chapter 6 - This chapter considers the tumor model in chapter 5 in the presence of immune response.

Chapter 7 - The main contribution of this thesis to the complex dynamical properties of tumor growth system are summarized in this chapter. Suggestions for further research are also highlighted. This chapter is followed by bibliography, list of publications and biodata of the author to this thesis.

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