Discrete Mathematical Analysis of Vascular Tumor Growth

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It is certified that **Muhammad Awais (CIIT/FA16-RMT-007/LHR)** has carried out all the work related to this thesis under my supervision at the Department of Mathematics, COMSATS University Islamabad, Lahore Campus, and the work fulfills the requirement for award of MS degree.

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DEDICATION

This thesis is dedicated to my Father Ch. Liaqat Ali Azhar (Late), my Mother Riffat Parveen, who taught me that the best kind of knowledge to have is that which is learned for it's own sake. I also dedicated it to my wife (Somia kanwal), who taught me that even the largest task can be accomplished if it is done one step at a time.

Muhammad Awais

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In the name of Allah, the Most Gracious and the Most Merciful

The Prophet (S.A.W) said:

"Seeking knowledge is obligatory for every Muslim"

First, I recognize the creator and finisher of my faith and in memorial of my life, I say thank ALLAH Almighty and Prophet Muhammad (S.A.W) for everything. I am grateful to Almighty ALLAH, without whose endowments it was difficult to finish this proposal.

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Abstract

In this thesis, the growing field of mathematical oncology is discussed in a discrete manner. The discrete mathematical modeling of cancer has remained a topic of debate during the past decade. In the proposed research, we aim to discuss the effects of chemotherapy, on angiogenesis and on the associated tumour microenvironment with the help of a computational tool. Different combination of drug applications will be analyzed in order to predict the best dose candidate to eliminate the tumour. During this research, we will demonstrate, with the help of mathematical tools, the importance discrete agent based approach to model cancer invasion.

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Chapter 1

Introduction

1 Introduction

In this chapter, we will discuss the role of cancer invasion at the inter-scale as well as at the intra-scale.

1.1 Cancer Dynamics

Cancer is mainly caused by changes in tumor defenselessness genes, which have oncogenesis, tumor suppressor genes (TSGs) and ability to cause hereditary insecurity. There are more than 200 types of cancer and it is mainly caused due to "Age", "Alcohol", "Cancer-Causing Substances" , "Chronic Inflammation", "Diet Hormones", "Immunosuppression", "Infectious Agents", "Obesity", "Radiation", "Sunlight", "Tobacco" and many more.

1.2 Computational Oncology

A quantitative comprehension of cancer biology requires a scientific system to depict the key standards of population hereditary qualities and development that represent tumor initiation and movement. Transformation, determination and tissue association decide the flow of tumorigenesis and ought to be explored quantitatively, by examination and hypothesis. The mathematical investigation of tumor began in 1950's, when Nordling [4], Armitage and Doll [5], Lombard and Potter [6] and Fisher [7] clarified age subordinate occurrence curve of human cancer. These original examinations suggested that few probabilistic occasions may enhance somatic advancement of cancer.

In mid 1970's, Knudson [8] utilized statistical examination of occurrence of retinoblastoma in youngsters to clarify part of TSGs in sporadic and genetics tumors. Latter on this legendary work received much attention to design the stochastic models for the tumour invasion [9], the epigenomics of cancer [10], sta-

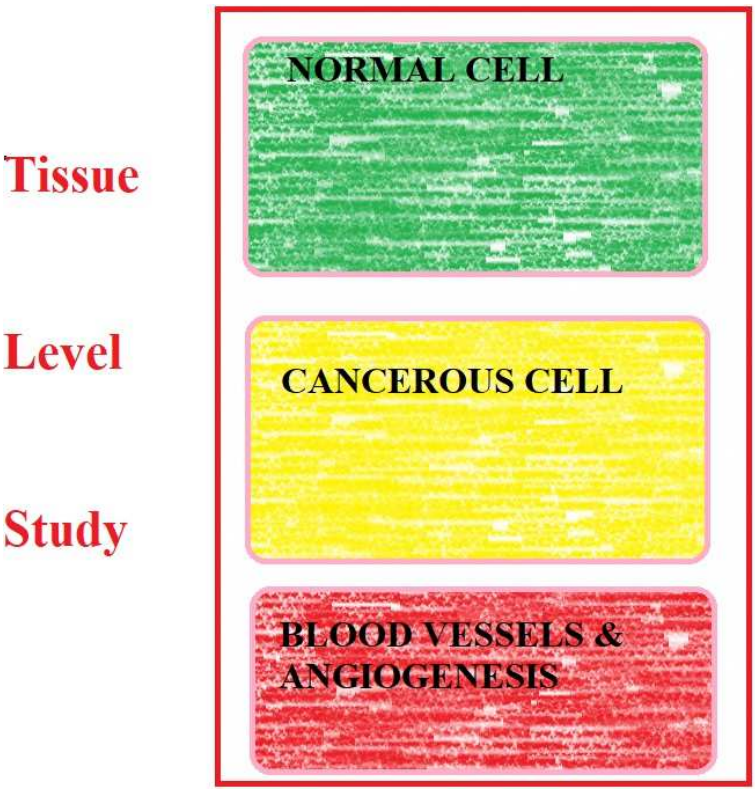

Figure 1: Computational oncology "tissue level study".

tistical approaches [11] and the pathology and genetics of tumours of soft tissue and bone [12].

The mathematical models depict procedure of tumor initiation, movement and give a quantitative comprehension of elements of tumorigenesis as for transformation, choice, hereditary unsteadiness and tissue design. Mathematical & statistical models have been developed for the improvement of particular speculations for drug resistance [13], angiogenesis [14], invulnerable reactions against tumors [15, 16] and hereditary dangers [17, 18]. These models have contributed extensively in the field of oncology [19, 20], and have remained helpful to understand the causes of different types of cancers and the invasion, the possible means of avoidance, and different treatment strategies of resulting malignancies [21].

Cancer mortality data by age, race, and sex has been analyzed by different researchers to provide a detailed geographical description of cancer related deaths

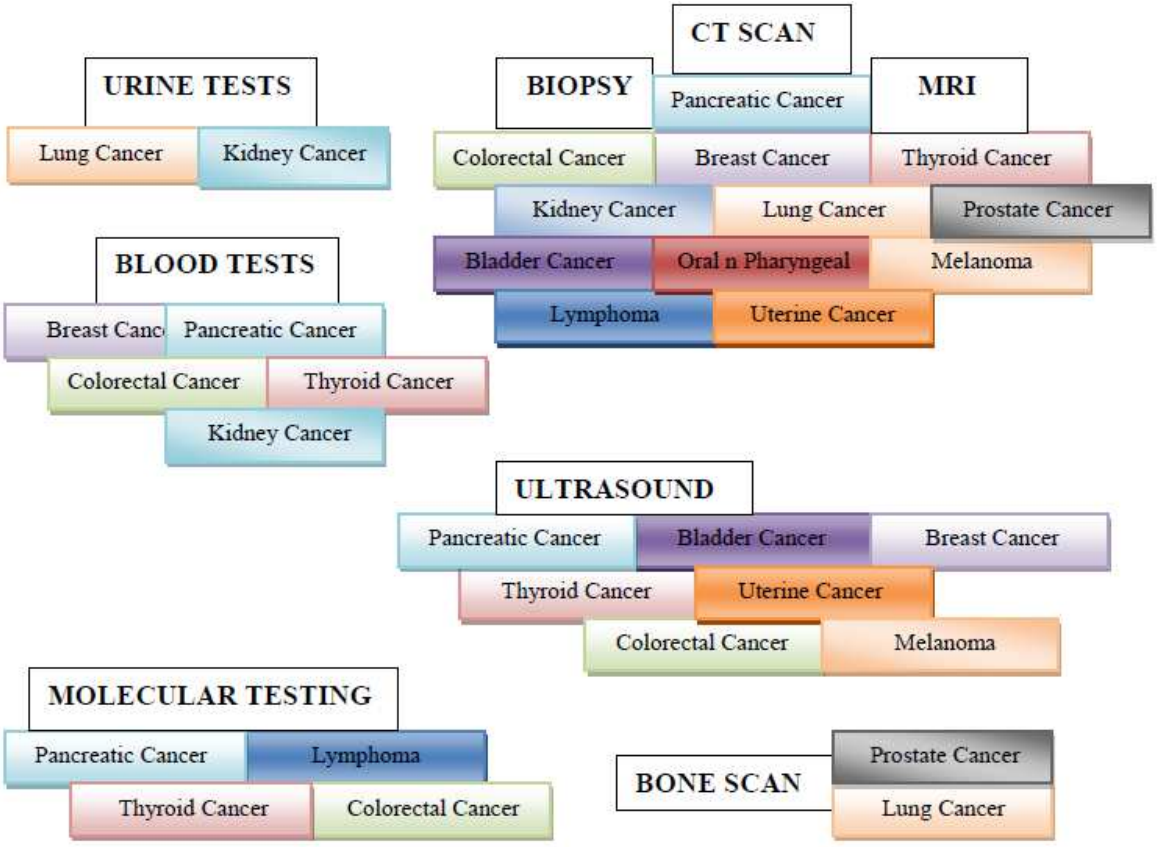

Figure 2: Different types of cancers and their respective treatment strategies.

over a certain period, from different parts of the world. A clear direction toward increasing spatial convergence in cancer mortality trends can be drawn from such studies [22, 23].

In this thesis we aim to present the population dynamics of cancer. In the next section we have collected some important mathematical techniques used to understand the population dynamics of cancer cells. In next section, we have summarised the epidemiology of cancer and have elaborated with the help of examples. In last section, some useful conclusions are drawn.

1.3 Dynamics of Cancer Cells

Cancerous cells are characterized by three properties; diminished or unrestricted control of growth, capability of invasion of local tissues and capable of spreading to distinct parts of body by metastasis. Therefore, a cancer's staging is based on size and extension of the primary tumor in accordance to the cancerous cells behavior. It has five stages named as 0,I,II,III and IV.

Stage 0: Cancers are still located in the place they started and have not spread to nearby tissues in this stage. This type of cancer is often highly curable, usually by removing the entire tumor with surgery.

During the progression of cancer the accumulation of driver and passenger mutations are found and this accrual can also be examined by a discrete time branching process. Bozic *et'al* [24] presented a model that described the relationship of drivers and passengers mutation in tumor growth. Initially it starts with a single driver mutation and then its clonal expansion accrues more mutations, showing that the death rate is reducing slightly in each mutation and therefore the clonal expansion rate is increased by each new driver mutation. Moreover, in the growth of tumor this model provides a relatively simple formulation for the number of driver mutations as a component of the aggregate number of mutations.

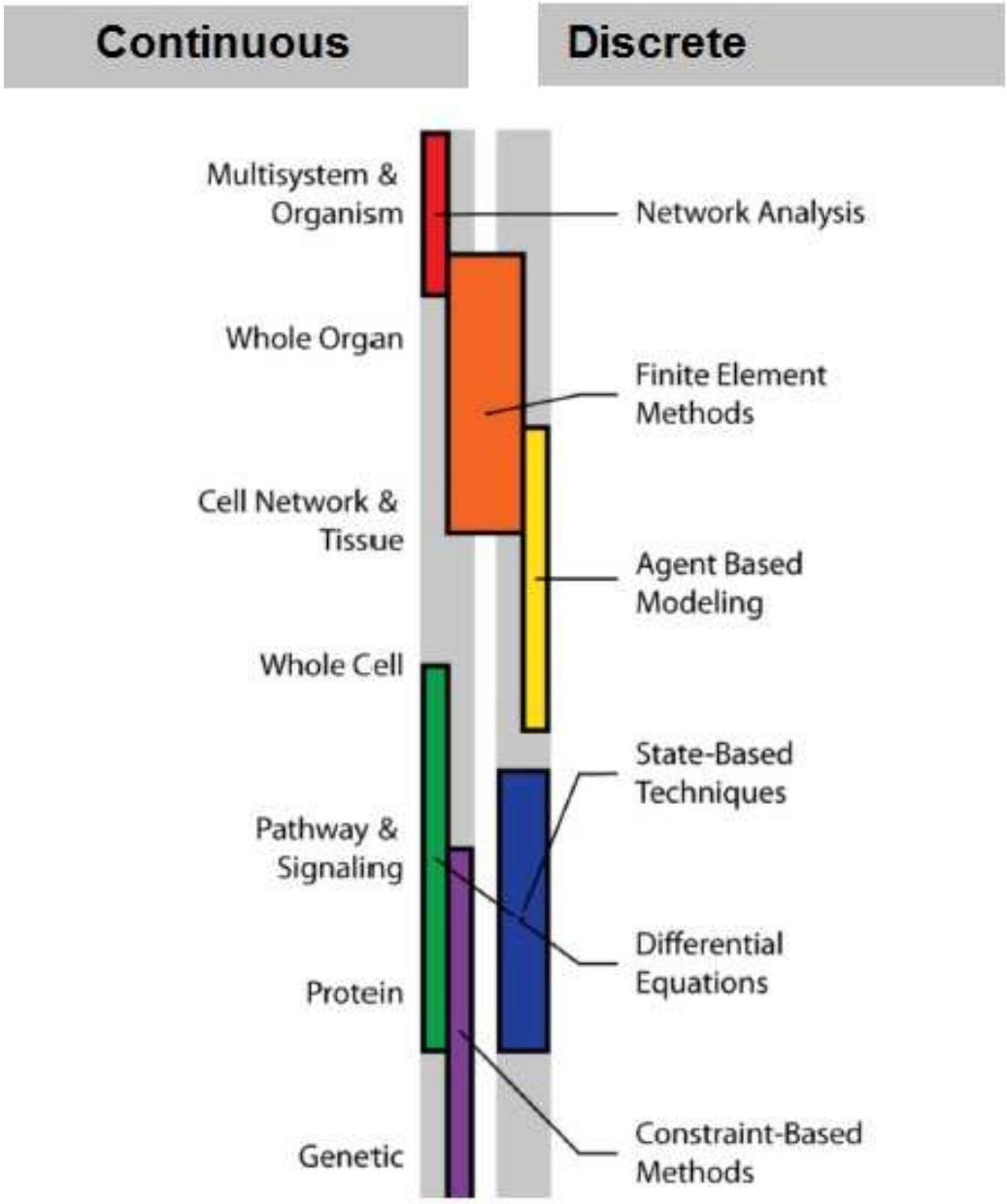

Figure 3: Continuous vs discrete models.

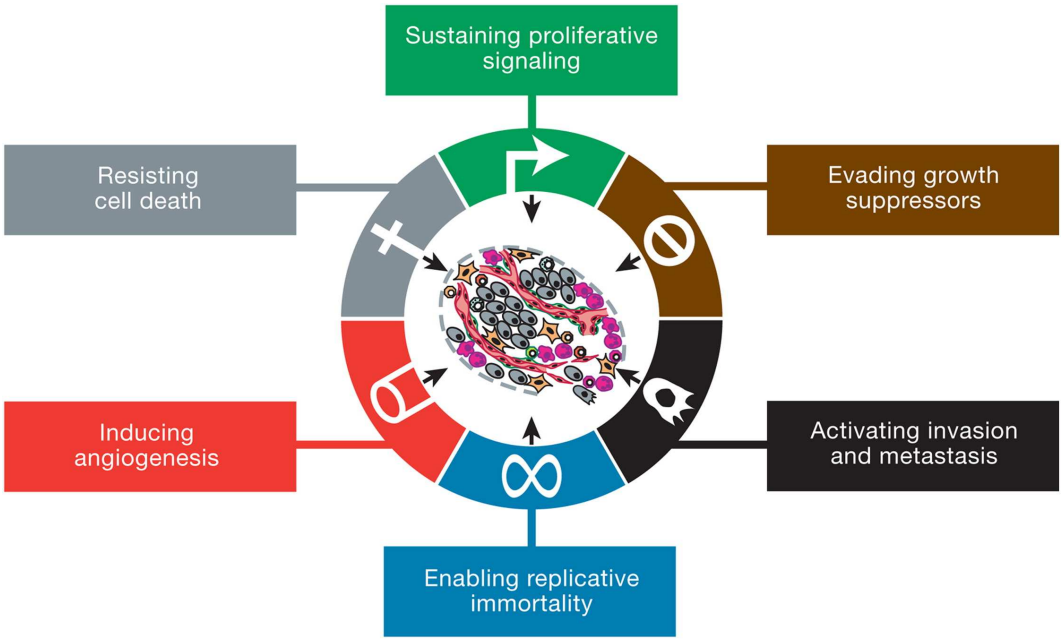

Figure 4: The cycle of cancer evolution and destruction.

The actual selective advantage which is given by regular somatic mutation in human tumors is that its location is calculated by this model when applied to the experimental data. Selective advantage though exceptionally small steps proceeds to have great potential for experimental cancer analysis.

Tumor cell growth and events related to it can be analyzed by using a stochastic branching process model. The related events include death, mutation accumulation and dissemination events. A relevant model in this regard has been proposed by Haeno *et'al* [25]. The principal contribution of this model is to forecast the probability of metastasis formation before tumor diagnosis. Additionally the model in [25] analyses the size of main lesion to predict the size and number of distribution of metastasis. In a study of patients with pancreatic cancer, this model proved useful in identifying the therapeutic interventions. The findings of the stochastic branching process model in this case indicated that early growth rate reduction can be more effective than tumor restriction.

1.4 Mutation and Modelling

Despite the assumption that the assurance of some of the somatic mutations that are present in tumors might be before tumor inception, unfortunately there is a sparsity of experimental and conceptual details regarding this concern. For the intuitive study of accuracy, Tomasetti et'al [26] devised a mathematical model for the progression of somatic mutation staking incorporating all the relevant stages of the tissues history. Verified by their empirical evidences, they deduced that the number of somatic mutations in tumors of self- renewing tissues is directly proportional to the age of the respective patient. This evaluation suggests that half or more of the somatic mutations in specific tumors of self-renewing tissues transpire prior to the start of the formation of a new abnormal growth of tissues. This model further gives a distinctive method to instantly approximate the in-vivo tissue-specific somatic mutation rates in normal tissues using the sequencing data of tumors. Cell dynamics in skin tissue can be studied by a descriptive method termed a two-type branching process. Antal and Krapivsky [27] have conducted a study using this approach. This method uses experimental data and works on a single type of progenitor cell only and therefore support from a self-renewed population of stem cells is not required. This method provides an exact solution for the function and number of different post-mitotic cells which were generated by the division of the progenitor cell. This process is also used for the deduction of large time asymptotic behaviors and it draws accurate results.

The tumour micro-environment is a heterogeneous tissue and it not only contains the tumour cells but also the stromal & immune cells. The effect of micro-environmental heterogeneity on the drug resistance's progression in cancerous cells can also be studied via branching processes. Mumenthaler *et'al* [28] designed a mathematical model for pre-existing drug resistance to illustrate multiple cellular compartments each of which demonstrates a particular tumor environmental

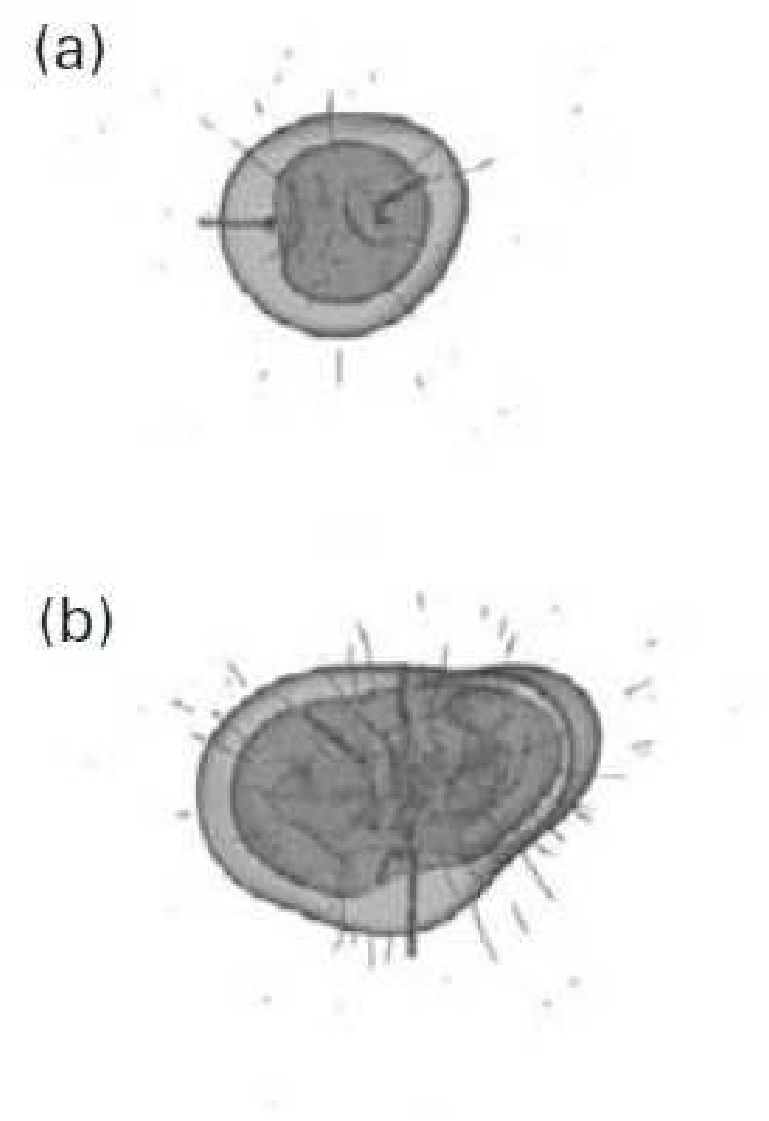

Figure 5: Earlier stages of brain cancer growth.

cavity. The model was utilized to estimate the influence of nutrient gradient and drug concentration on tumor structure and at the times of its reappearance after removal and it was shown that these extreme points are effectively dependent on the micro-environment. This collaborative strategy generates a model system that helps to measurably determine the impact of micro-environment effects on the progressive dynamics of tumor cells.

The purpose of using moran process in cancer progression modeling is to describe the probabilistic evolution of the finite population with two different geno-

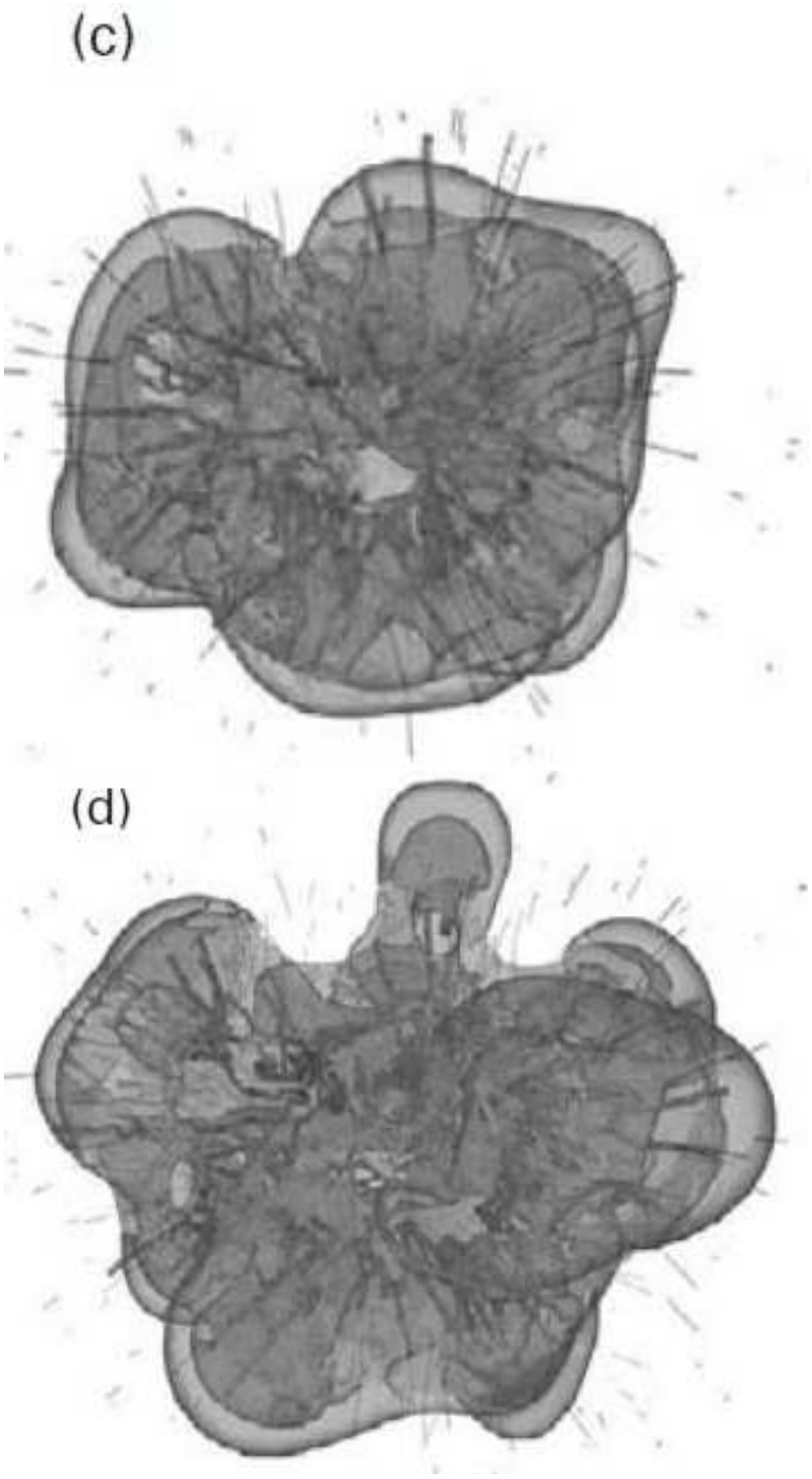

Figure 6: Simulation of brain cancer cells.

types and they are competing for their dominance. To define Moran process, consider a population having constant size (say N) with two types of individuals (e.g. N_1 and N_2), at each time step a random individual (which is of either type N_1 or N_2) is chosen to reproduce or to die so that the population size remains constant, the reproduction rate depends on fitness and both the types can have different fitness. If the fitness of type N_1 is set to 1 and the fitness of type N_2 is set to r then probability that type N_1 or N_2 is chosen to reproduce are respectively,

$$P(N_1) = \frac{ri}{ri + (N - i)} \tag{1}$$

$$P(N_2) = \frac{N - i}{ri + (N - i)} \tag{2}$$

In 2006 Michor et'al [29] proposed a model based on stochastic moran process, which scrutinize the evolution of mutation of cells which leads to metastasis (it is the process by which cancer spreads from one place to anther distant from primary tumor), furthermore they studied weather all the cells in the main tumor have the property of metastatic potential or it is only of a small portion. Their work presented how the expected number of metastases that are formed by a tumor can be calculated.

The Monte Carlo simulation is one of the example of stochastic modeling.

Chotard-Ghodsnia at'al [30] used Monte Carlo simulation in adhesion dynamics in cancer to model bond formation and breakage. During radiation therapy of cancer, it is very important to estimate the dose accuracy, for the standard of treatment planning. Monte-Carlo simulation has proved to be the most suitable to evaluate dose accuracy for cancer in radiation therapy as well as in other dose calculation algorithms. In 2014 Zhao et'al [31] presented a study in which they evaluated the accuracy of dose in lung cancer radiation therapy by using Monte-Carlo simulation. They concluded that it is the most accurate calculation

of dose in lung cancer and it has proved to be an effective tool for benchmarks the performance of other dose distribution algorithms.

Cancer originates from a single cell so it become essential to have a thorough study of cells. In this context Drasdo *et'al* [32] developed a model of Monte-Carlo simulation in which they studied growth population of tissue cells. The investigation of growth properties and pattern formation of the different types of cells are made in the laboratories.

Having complete knowledge of tumor micro-environment is emphasized to understand the complexity of tumor. Therefore, Jiang *et'al* [33] presented a multi-scale model for avascular tumor growth and progression based on three different levels. At cellular level, they used Monte-Carlo simulation to model the dynamics in cell such as its growth, ability to do work, intracellular adhesion and death. Based on their simulation, they predicted the conditions of micro-environment needed for tumor cell survival and the diffusion coefficients range of cell growth inhibitors and promoters. Radiotherapy for cancer after surgery get influenced by uncertainty in stages and wrong assessment of staging. Due to this, patients have come across inappropriate treatment. Therefore, Ekaette et'al [34] developed a Bayesian Monte-Carlo simulation model which reflected the typical process of assessing patients for radiation therapy after surgery followed by cohort of hypothetical patients for the true stage and required RT technique where defined a prior. In 2012 Maiti [35] developed a Monte-Carlo simulation to analyze the size and number of metastatic tumors. In which they evaluated the size and the total number of tumor as a function of time to demonstrate the accuracy of this approach on a specific growth and metastatic model. To apply this approach, it is needed to validate the accuracy of it and to check the validity of Monte-Carlo approach is the main purpose of their paper. Monte-Carlo approach has the ability to accommodate the real-life complexities and variations from patient to patient.

Human body is negatively influenced by radiation; however, it is needed for certain medical treatments. The side effects can be avoided using recent techniques, for example, Seo et'al [36] presented a study on this crucial aspect to avoid the negative influence as a result of medical radiation exposure. They used Monte-Carlo simulations for the close calculation of thyroid and neighboring organs, they also calculated the lifetime attribute risk of thyroid cancer due to radiation exposure and concluded that the risk of cancer was lower in males than in females and the risk was found to be variable relative to age.

Chapter 2

Research Methodology for Inter-Tumour Study

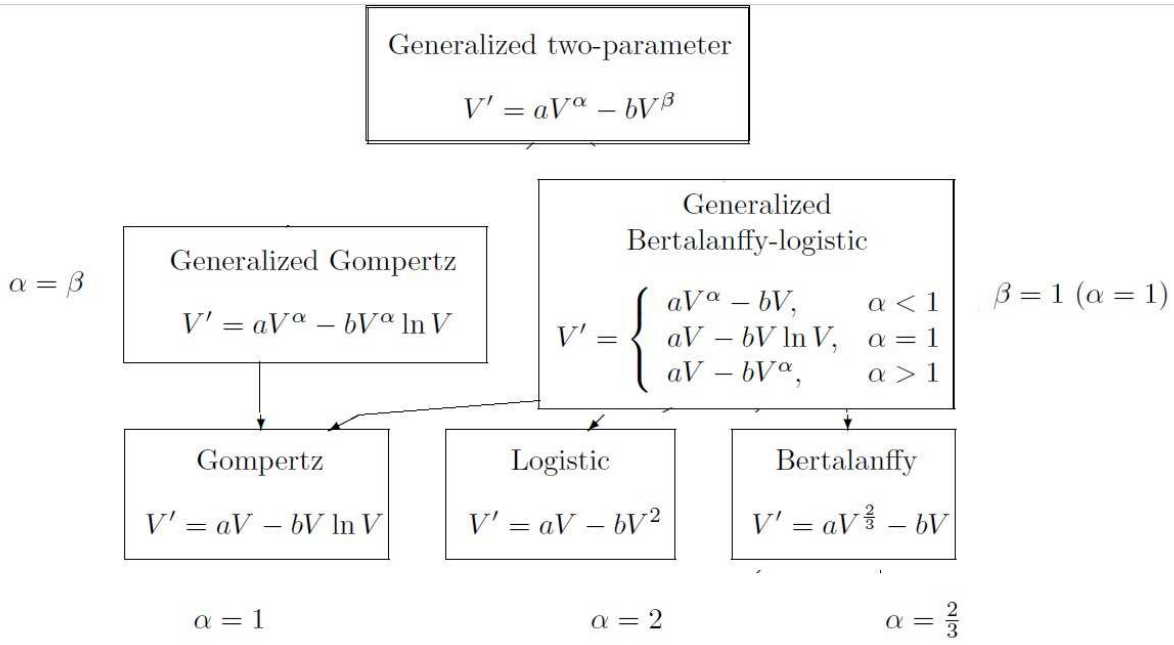

Figure 7: Different logistic growth models relative to different values of α.

2 Research Methodology for Inter-Tumour Study

2.1 Mathematical Formulation

In this chapter, we will setup a heterogenous method, after explaining the role of heterogenous effects involved in cancer invasion. This is an inter-cancer study.

2.2 Heterogeneous Effects

For most of the cancer studies, the word "heterogeneity" is used to express the variability with respect to attributes of individuals that affect their mortality [37].

While conducting cancer studies, detailed understanding of heterogeneity is necessary, since a false assumption (that observed patterns for the entire population are true for the sub-population or at individual level) may lead to wrong inference. The difficulty in this field of research is that there is lot of heterogeneity, and this may lead to wrong conclusions and thus incomplete hypothesis.

Heterogeneous studies are more challenging, the pathway for the groups under

consideration is some times similar and confusing, and thus heterogeneous patter identification is difficult and sometimes impossible. In 1970's [38] mathematical models were used to simplify the analysis of heterogeneous populations.

The death and birth rate of every population (of animals or human beings) contributes in its epidemiology. The entire population of a specific study can further be divided into subgroups based on their age groups. Let G_i be the group name for i population subgroups. In population dynamics the mortality is calculated with respect to the force of the spread. At age x and time t. $\phi(x,t)$ is the proportion of the subgroup born x years ago that is surviving at time t and t_0 the birth year. In equation 3, the variables are continuous. In a homogeneous population, all individuals of age x during one year of study face the same hazard rate $p(x,t)$, on the other hand, the heterogeneity can be seen in depth as a collection of sub-homo-populations. In the extreme case, when the population size is small, or the disease studied is rare, each homogeneous sub-population consists of a single individual. Consider the system of equations:

$$\phi(x,t) = \frac{\frac{dp(x,t)}{dt}}{p(x,t)} \quad , \qquad t = t_0 + x \tag{3}$$

$$\xi(0) = \frac{n_1}{n_1 + n_2} \tag{4}$$

$$\xi(x) = n_1 \frac{p_1(x)}{n_1 p_1(x) + n_2 p_2(x)} \quad , \qquad x > 0 \tag{5}$$

and after simplification leads to:

$$\xi(x) = \xi(0) \frac{p_1(x)}{\xi(0) p_1(x) + [1 - \xi(0)] p_2(x)} \tag{6}$$

$$\phi(x) = \xi(x)\phi_1(x) + [1 - \xi(x)]\phi_2(x) \tag{7}$$

suppose first sub-group is weaker $\phi_1(x) > \phi_2(x)\ \forall\ x$

$$p_i(x) = e^{-\int_0^x \phi_i(t)dt} \quad , \qquad i = 1, 2 \tag{8}$$

For cancer studies, we have considered an example to elaborate the technique used in the literature for the heterogeneous population. These hazard lines produce the apparent crossover in mortality rates shown in Figures 8 and 9: the calculations are based on Eqs. (3-8). The data is based on information provided by Cancer Research UK.

2.3 Epidemiological evidence

The variation in the cancer statistics, drawn from different parts of the world makes its understanding and cure more challenging. This dynamic response linked with experimental exposure and the population spread. Cancer enlargement motility has been an individual of biological modification for other than 60 years (foremost studies) and has been analytically examined broadly (see for a watchful assessment and for further current work). One of the mainly frequent conclusion for animal and human tumors alike is that their virtual development rates decrease with time; or consistently, that their recurrence period enlarge.

Cancer is, in France, the first reason of death . Despite the reliable development of medical investigation, cancer is in silent a sickness which is inefficiently silent in a many aspects. Cancer is a infection which is started when a few cells of the living being split free from the hereditary system and experience endless mitosis. This experience to the arrangement of a mass of cells with unmanageable enlargement inside the organs, which have no usefulness at all for the organism: the primary

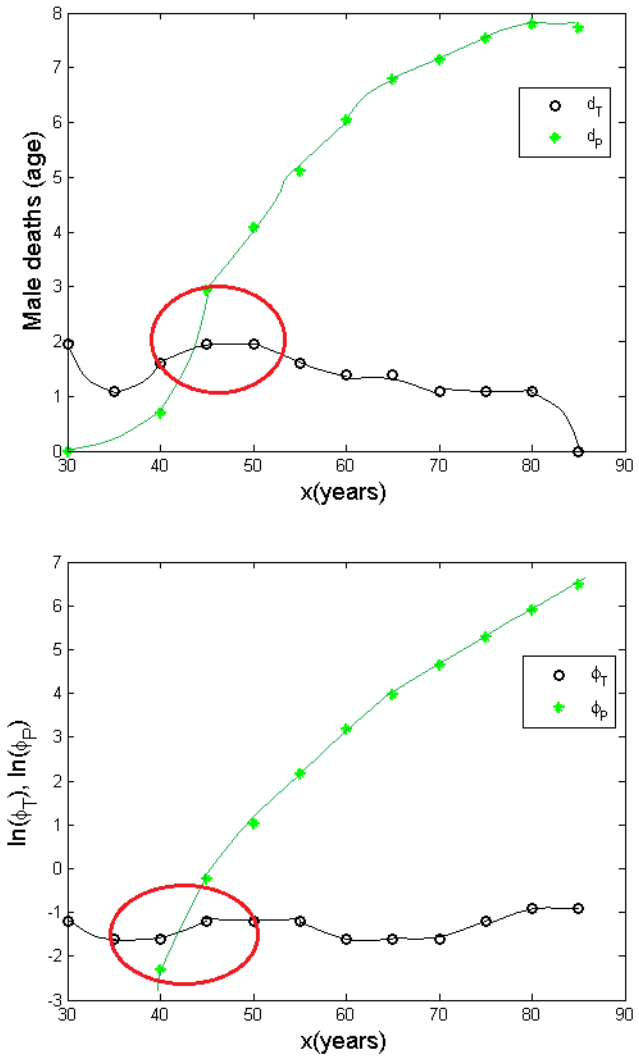

Figure 8: Observed mortality rates for two causes of death may appear to intersect (red). Left, d_T & d_P shows the number of deaths caused by testicular-cancer & prostate cancer respectively. Right, the death rates calculated from system of Eqs. (1-4)

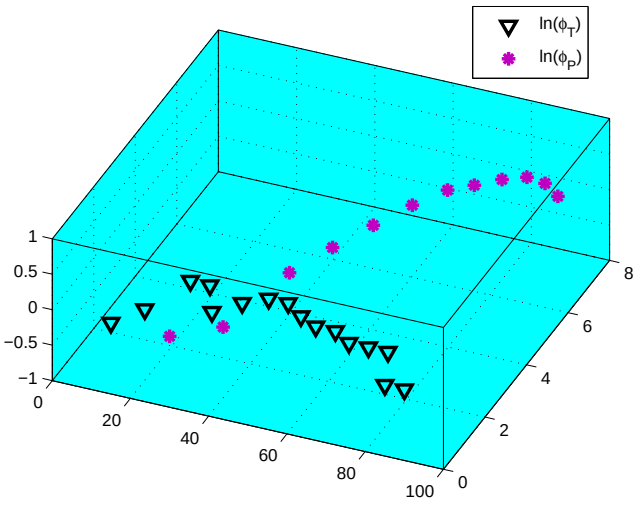

Figure 9: 3D visulization of mortaitly rate elaborated in figure 8

tumor. At various stage, the tumor cannot yield further owing to the be shortness of of nutrients. But some primary tumors find themselves capable to persuade that is called angiogenesis, which permits to stimulate its own vascularization. By this way, the tumor can access more nutrients and grow up yet extra. A number of tumor cells may be capable to break the organ, throughout the blood or the lymph nodes, give the choice of a spread of cancer cells within the entire person. Cancer cells later colonized in new organs and breed inside the that new organ and form a tumor name secondary tumor. This newest procedure is called metastatic progression, and is the least implicit and the most fatal part in the majority of cancers. Block Angiogensis is one of the most possible ways to treat tumor, in sort to get rid the tumor from its nutrients, thus weakening it. Amongst the mainly famous Antiangiogenic medicines, we can reference the Sutent (or sunitinib, for the name of the particle).

The occurrence rates of PCa (prostrate cancer) and BC (breast cancer) are higher around the world; and lowest incidence in Asia and Africa. In more developed countries, there were 5.9 million women who had survived breast cancer for at least 5 years; the figure for less developed countries was 3.7 million. In tables 2.3

Table 1: Annual incidence rates of Prostate and Breast Cancer in different areas of world [1].

High-risk areas		Low-risk areas	
Prostate Cancer			
France	227-234	USA	98-102
Sweden	119-123	Denmark	90-97
Australia	115-121	Belgium	89-92
Ireland	114-123	Estonia	88-94
Breast Cancer			
Belgium	110-115	USA	92-97
Denmark	105-109	Ireland	92.3-92.4
Iceland	96-99	Italy	91-94
UK	95-97	Malta	85-88

Table 2: Annual incidence rates of prostate cancer and testicular cancer in different parts of the world per 100,000 men [2, 3]

High-risk areas		Low-risk areas	
Testicular Cancer			
Germany	10-14	Lithuania	2.1-3.4
Hungary	9-12	Ukraine	2.0-3.9
Ireland	9.6-13.4	Spain	1.7-3.6
Norway	8-13	Moldova	1.7-3.1
Slovenia	8-12	Greece	1.5-4.2
Prostate Cancer			
France	227-234	USA	98-102
Sweden	119-123	Denmark	90-97
Australia	115-121	Belgium	89-92
Ireland	114-123	Estonia	88-94

& 2.3, we have provided some statistics for three types of cancer. The variation portrays the epidemiological effects.

Genomic cancer evolution studies have been reported in the literature [39] (and the references therein), the resulting computational models are promising to help in developing therapeutic strategies which cause delay in tumour evolution [40].

Cancer can arise not only as effect of a "mutant phenotype" [41], but actually of a "mutator phenotype" [42]. The selective pressure over mutants and, even more, mutator cells, is likely to be crucial in explaining the role of environmental

exposures.

Darwin's research on different species of the world was based on the phenotypes of different species. The clear understanding of "responses to somatic selection" (including clonal adaptation, diversification and extinction) was made possible with the advancement in the mathematical theory of Darwinian dynamics. This theory can be implemented to analyze the cancer initiation and progression [41]. As the selection of certain genotypes was favorable in specific environments and not in others, similarly, the selection of cells carrying certain mutations can lead to a greater incidence of cancer under specific environmental circumstances. Comparative analysis of cancer cell phylogenies could reveal which molecular changes occurring during neoplastic progression facilitate the development of invasive, metastatic and resistant cell phenotypes. Incorporation of biological markers into epidemiological research and development of genetic epidemiology may lead to better understanding of this evolving subfield of oncology.

2.4 Discussion

Genetic and epigenetic variability among people lead to differences in susceptibility, and makes cancer diagnosis and therapies difficult and sometimes ineffective. Tumors develop in different organs and tissues of the body, and cancers deriving from the same tissue can be stratified into disease subtypes based on differences in gnomic measurements [20]. Therefore, the cancer research and its population dynamics at cellular, subcellular and genomic level is a vast field of research. We have made an attempt to highlight some important features of this field of research. This article provides:

- An insight of important mathematical techniques to obtain population dynamics of cancer cells.

- It also explains the epidemiology of cancer, in a simple way with useful examples.

- It outlines the role of genomic cancer evolution studies, in the field of oncology.

With advancement in the field of oncology, the percentage of cancer survivors has increased all over the world. Nevertheless cancer survivors from one particular cancer type are at increased risk to other diseases including different cancers, cardiovascular disease, diabetes, osteoporosis and many more. Lifestyle factors, such as a healthy diet, regular exercise, stress control, and smoking cessation may prevent these conditions. More research is necessary to develop interventions that can effectively promote cancer awareness and accelerate robust cures.

Chapter 3

Research Methodology for Intra-Tumour Study

3 Research Methodology for Intra-Tumour Study

3.1 An Overview

Cancers can be considered as compound vibrant systems since they have lots of interrelate parts that can change over time and space. Possibly the mainly renowned compound vibrant system is the weather and, comparable to weather predicting, investigators in the Integrated Mathematical Oncology Department at the Moffitt Cancer Center are used mathematical methods to report for lots of variables in the appearance for novel ways to be thankful and control cancer. Their new knowledge, which look like as the appearance article in the May issue of Cancer Research, view that mathematical models could be use to expect how diverse enlargement cell society correlate with each other and respond to a changeable atmosphere. They originate that, by using math models to recognize the compound dynamics inside cancers, they might employ little changes in the environment to sustain the enlargement of cells that are fewer aggressive and thereby reduce cancer enlargement. A solitary cancer is possessed of several different lineage of cells. With a combination of new and mathematical knowledge, the Moffitt analyzers recognized two dissimilar cell lineage that they exist together in numerous different cancer types; a hostile cell lineage that can assault the close space and move to form metastases, and a non-persistent cell population that is smooth to settle in one position and assist formulate blood vessels. They illustrate that in characteristic tumor emergent in mice, the persistent cells are extra abundant and have a vitality benefits over non- persistent cells in a cancer. But evolutionary principles state that the observance and proceedings of any living thing (whether plants, animals or cancer cells) appear with reward and lack. Yet although the persistent cells have a reward as of their ability to assault neighboring tissues, that persistent character also has its flaws: increased deficency to changes in inadequate reserves

and their surroundings. The evolutioners use computer models to predict that tiny changes of the pH inside the cancer might tilt the stability, lessening the endurance benefit of the persistent cells in support of the non- persistent cells.

Mathematical model, that demonstrate the dynamics of a tumor cell population growing out of the human body (in vitro) in abandoned microenvironment conditions, are vigilant. Tumor cells in vitro make and break greatly quicker than tumor cells in the human body, as a result, the effects of different tumor treatments useful to them can be predictable much faster. These cell inhabitants, when not profess to any tumor treatment applying, display differential enlargement that we pass on to as the Balanced Exponential Growth (BEG) condition. This surveillance has lead to numerous efficient methods of guessing dimensions that there after are not mandatory to be resolute practically. We present beginning of the age-structured model and its theoretical examination of the endurance of the result. Besides, we have acquired the circumstance for BEG endurance using the Perron-Frobenius theorem. A mathematical explanation of the cell-cycle control is revealed for one-compartment and two-compartment population, where a compartment recommended to a cell population contained of cells that reveal alike kinetic properties. We have incorporated into our mathematical model the mandatory emergent/aging period in every stage of the cell cycle for the biological possibility. Furthermore, we have resulting logical formulae for imperative parameters in cancer examine, such as population repetition time, the normal cell-cycle age, and the normal elimination age from all phases, which we gave reason is the normal cell-cycle time of the population. An estimate of the standard cell-cycle time is of a demanding interest for biologists and clinicians, and for diseased person endurance diagnosis as it is measured that short cell-cycle times correlate with poor endurance diagnosis for diseased person.

3.2 Mathematical Kinetics of Mutation

Presence of several types of natural noises in biological systems has gained the attention of many scientists, recently. This phenomena leads to the fact that such systems are not purely deterministic and involve some randomness, mainly consisting of internal (thermal fluctuations) or external (mainly conformational) noises. Such noises have a vicious part in natural processes and lead system towards abnormalities or sometimes entirely random behavior. For better perceptive of biological systems it is thus necessary to add stochastic effects in mathematical models of biological and biochemical systems. Kramer's seminal paper [43] has been a prototype for a thermal activation process continually. Lately, activation in the presence of time varying fields has become a topic of vast significance because of the findings of many counterintuitive noise supported special effects, such as stochastic resonance [44] or movement in Brownian motors [45]. A relevant mesoscopic approach in which the time evolution of a collective coordinate is overseen by stochastic differential equations may be used to study the dynamics of such complex biological systems [46]. In such an approach, system kinetics resembles to Kramer's situation with a Brownian particle wandering over an effective free energy potential. The Brownian particle may experience a potential that is influenced by some random oscillations with characteristic time scale which is comparable with one of the time scales governing the passage over the potential barrier separating basins of the stationary points of the biological system [47, 48, 49, 50, 51, 44]. According to the stochastic model, tumor cells are biologically equivalent but their behavior is influenced by intrinsic and extrinsic factors and is therefore both variable and unpredictable. One of the major roles of the immune system is to recognize and eradicate the tumor cells on the basis of their expression of tumor specific-antigens or molecules provoked by cellular stress. Such process is named as tumor immune surveillance in which cancerous

and/or precancerous cells are killed by immune system before they can cause harm. Many experiments on mouse model of cancer and human with cancer have provided a convincing evidence about tumor extinction i.e., particular immune cell types, effector molecules, and pathways can sometimes mutually function as extrinsic tumor suppressor mechanism [52, 53, 54]. Immune system recognizes the tumor cells because of the antigens the cells bear; such antigens are strange for the system. The immune response against these antigens may be mediated by so called effector cells such as T-lymphocytes, macrophages or natural killer cells (see figure 10).

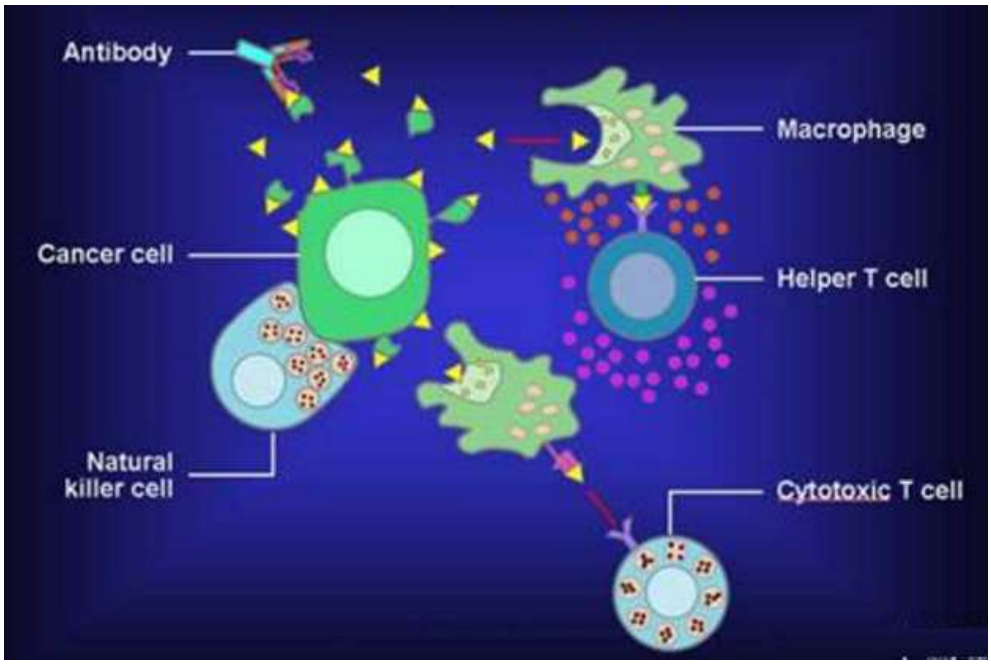

Figure 10: Motion and dynamics.

The process of damage to tumor proceeds via infiltration of the latter by the specialized cells which subsequently develop a cytotoxic activity against the cancer cell population (as shown in figure 11).

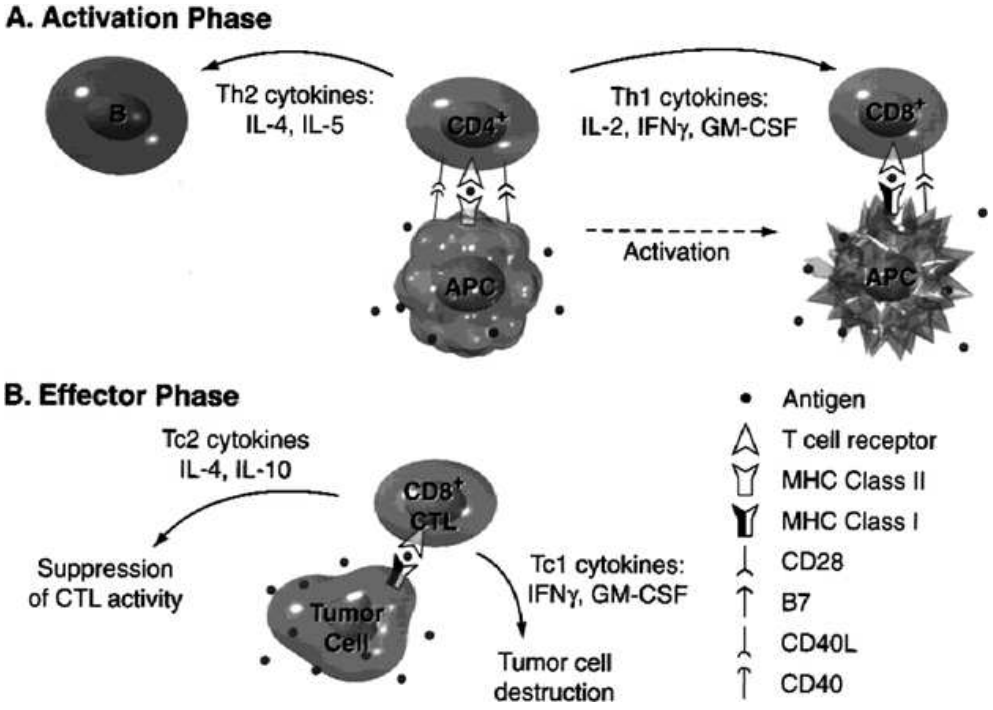

Figure 11: Schematic of kinetic model.

3.3 Kinetic Model

In biochemistry, 'Michaelis–Menten' kinetics is one of the best-known models of enzyme kinetics. The model takes the form of an equation describing the rate of enzymatic reactions, by relating reaction rate to the concentration of a substrate. A basic model can be defined as follows:

$$S + E[k_{-1}]k_1 S \cdot E - > [k_2]P + E \tag{9}$$

where S is the substrate, E is the enzyme, SE is the substrate-enzyme complex, P is the product, and k_1, k_{-1} and k_2 are constants. Let W, G, X and p be the corresponding concentrations of the substrates S, E, SE and P, respectively. According to the Law of Mass Action (LMA) "the rate of a reaction is proportional to the product of the concentration of the reactants". The enzyme reaction illustrated

above based on LMA forms the following system of differential equations:

$$\frac{dW}{dt} = -k_1 GW + k_{-1} X, \tag{10}$$

$$\frac{dG}{dt} = -k_1 GW + (k_{-1} + k_2) X, \tag{11}$$

$$\frac{dX}{dt} = k_1 GW - (k_{-1} + k_2) X, \tag{12}$$

$$\frac{dR}{dt} = k_2 X, \tag{13}$$

where k_1, k_{-1}, k_2,s_0 and e_0 are positive constants [55]. The cell-mediated immune surveillance against cancer is as well one of the effects which may be described in terms of a "predator-prey" system and be approximated by a saturating, enzymatic like process whose time evolution equations are similar to the standard Michaelis-Menton kinetics. The population of tumor cells plays the role of "preys" and immune cells act as "predators".

where X, Y, Z and P represent the population of tumor cells, active cytotoxic cells, bound cells and dead tumor cells, respectively [56]. A lot of work has been done to analyze the effect of noise in the cancer dynamics. In [56] such studies have been discussed in detail to elaborate the kinetic modelling approach. Random fluctuations of the environmental conditions may disturb the enzyme activities which in return may deviate to rate of formation from the mean value in the biochemical reactions. The role of such fluctuations might be critical for whole system. Many environmental factors like, the supply of oxygen, the supply of nutrients, chemical agents, gene expression, degree of vascularization of tissues, the immunological state of the host, temperature, radiations, protein synthesis and antigens influence cancer tissues and tumor growth. As a consequence of this, the system faces some inescapable stochastic effects [57, 58, 59, 60, 60, 61].

3.4 Discussion

Tumor cell growth and events related to it can be analyzed by using a stochastic models. A branching model has been proposed by Haeno et'al [62] to forecast the probability of metastasis formation before tumor diagnosis and to analyze the size of main lesion to predict the distribution of metastasis. In a study of patients with pancreatic cancer, this model proved useful in identifying the therapeutic interventions. The findings of the stochastic branching process model in this case indicated that early growth rate reduction can be more effective than tumor restriction. Despite the assumption that the assurance of some of the somatic mutations that are present in tumors might be before tumor inception, unfortunately there is a sparsity of experimental and conceptual details regarding this concern. For the intuitive study of accuracy, Tomasetti et'al [63] devised a mathematical model for the progression of somatic mutation staking incorporating all the relevant stages of the tissues history. Verified by their empirical evidences, they deduced that the number of somatic mutations in tumors of self- renewing tissues is directly proportional to the age of the respective patient. This evaluation suggests that half or more of the somatic mutations in specific tumors of self-renewing tissues transpire prior to the start of the formation of a new abnormal growth of tissues. This model further gives a distinctive method to instantly approximate the in-vivo tissue-specific somatic mutation rates in normal tissues using the sequencing data of tumors. The outcome of the model presented in [63] proved to have significant conclusions which have clarified the large number of genome wide cancer studies that are now being tackled.

Chapter 4

Numerical Algorithm and Simulations

4 Numerical Algorithm and Simulations

4.1 Discrete Models

Mathematical representation of biological method is extensively used to improve quantifiable understanding of bio-medical development. This quantifiable understanding could be functional,mutually in scientific and investigational framework. A significant submission of modeling actions is in the part of tumor biology model [12, 13]. For explaining some aspects of cancer many mathematical models are developed. [14–17]. Those models be different from a simple representation annoying to emulate the enlargement of tumor size to stylish models with a lot of biologically important most trivial developments [18, 19]. Perceptible models be able to reproduce clinically related development for anti-cancer treatment. Since the complexity of the biology, need to be linked molecular techniques to that of macroscopic ones such we observed in the clinic. . As solving the difficulty of the biology we need multiscale models quite than macroscopic ones.

4.2 Matlab Programming for Invasion

During this research, we have employed the following strategy to simulate the cancer cells invasion.

```
function [c,b,s] = andereqn(x,t,u,DuDx)
%WE HAVE CONSIDERED THE SYSTEM OF DIFFERENTIAL EQUATIONS
%WE HAVE CONSIDERED THE PARAMETRIC VALUES
c = [1;1;1];D1 = 1;chi = 1;.....
    ....rho = 1;beta = 1; gamma = 1; eta = 1;
dd = [1;0;0] .* D1.*DuDx......
    ....-[0;0;u(1)./(1+u(3))] .* chi.*DuDx-[0;u(1);0] .* D1.*DuDx;
b = [dd(1)+dd(2)+dd(3);0;0];
```

```
s = [0;beta.*u(1)-.....
    .....gamma.*u(1).*u(2);-eta.*u(1).*u(3)];
```

```
m = 0;
x = linspace(0,1,10);
t = linspace(0,1,10);
sol = pdepe(m,@andereqn,@initialAnder,@anderbc,x,t);
u1 = sol(:,:,1);



surf(x,t,u1);
title('u1(x,t)');
xlabel('Distance x');
ylabel('Time t');
```

```
function value = initialAnder(x);
%FOR THE SECOND CASE,
%WE HAVE CONSIDERED THE INITIAL VALUES
%FOR THE THREE VARIABLES.
%THIS TIME, THERE ARE THREE
%PERIODIC WAVES
value = [sin(2.*pi.*x);sin(2.*pi.*x);sin(2.*pi.*x)];
```

```
function value = wazinitial(x);
%IN THIS MFILE WE HAVE CONSIDERED
%A SINUOSOIDAL WAVE LIKE INITIAL CONDITION
%SUCH CONDITION IS GOOD FOR ACCURACY.
value = [sin(x)];
```

```
function [pl,ql,pr,qr] = wazbc(xl,ul,xr,ur,t)
%IN THIS CODE
%WE HAVE USED
%THE BOUNDARY CONDITIONS


pl = [ul(1)];
%THE LEFT BOUNDARY


ql = [0];
%THE LEFT BOUNDARY AT SECOND VARIABLE
pr = [ur(1)];
% THE RIGHT BOUNDARY
qr = [0];
% THE RIGHT BOUNDARY AT SECOND VARIABLE.
```

From the Matlab codes presented above, we explored the cancer cells invasion, based on two important variables, the cancerous cells and the healthy cells. In next section, we will discuss the C++ code to explore invasion.

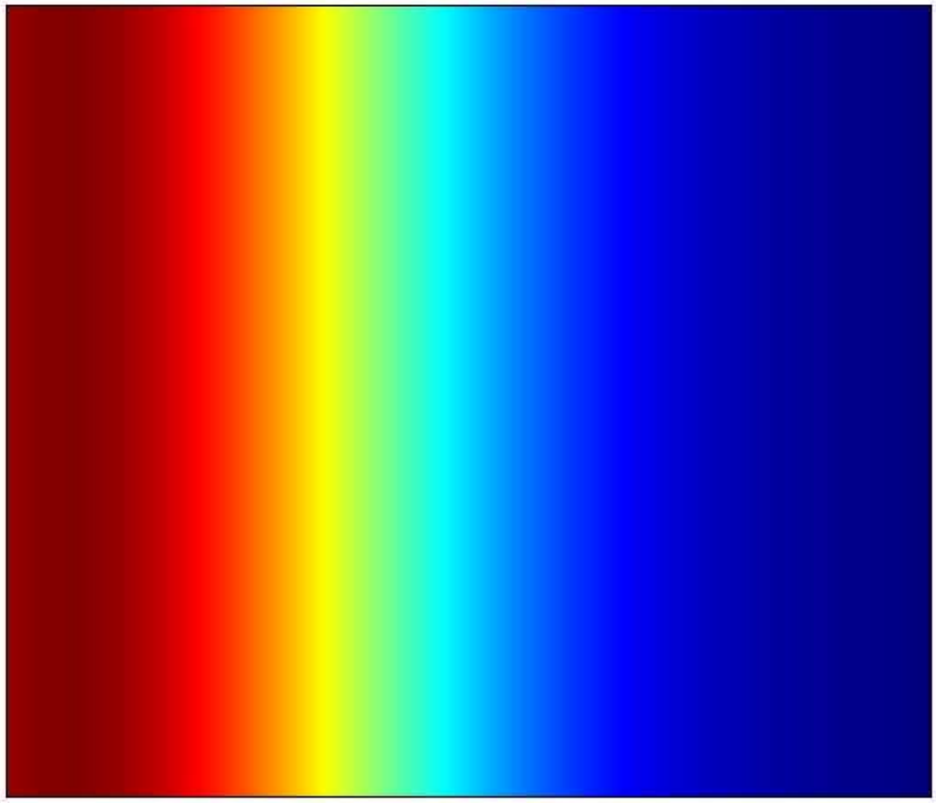

Figure 12: Diffusion chart for the cancer spread.

```
void simulate(int nSteps) {
        vector<cell> cellsTmp;
        int newSite;
        cell currCell, newCell;
        for (int i = 0; i<nSteps; i++) {
                random_shuffle(cells.begin(), cells.end()); //shuffling cells
                while (!cells.empty()) {
                        currCell = cells.back(); //pick the cell
                        cells.pop_back();
                        newSite = returnEmptyPlace(currCell.place);

                        if (newSite) {//if there is a new spot
                                newCell = currCell;
                                newCell.place = newSite;
                                if ((double)rand() / (double)RAND_MAX < pDiv) {
                                if (currCell.is_stem) {
                                lattice[newSite] = true;
                                cellsTmp.push_back(currCell);
                                if ((double)rand() / (double)RAND_MAX > ps) {//asymmetric division
                                                                        newCell.is_stem = false;
                                        }
                                        cellsTmp.push_back(newCell);
                                }
                                else if (currCell.p > 0 && (double)rand() / (double)RAND_MAX >
```

Figure 13: C^{++} code for the execution of cancerous cells in four directions.

4.3 C++ Code for Tumour Invasion and Lattice Development

In this section, specific libraries are used to model and analyze the cancer cells dispersion. We can see that the forward, backward, top and down movement of cancer cells is monitered by the loop. We have also presented the code for the better understanding of lattice. We have applied this code and have obtained the results presented in figure 16. Figures 17 & 18 shows the invasion using numerical solver.

```
        lattice[N / 2 * N + N / 2] = true; //initial cell in the middle
        cell initialCell = { N / 2 * N + N / 2,pmax,true };//initial cell definition
        cells.push_back(initialCell);}
int returnEmptyPlace(int indx) {
        int neigh[8], nF = 0;
        for (int j = 0;j<8;j++) {//searching through neighborhood
                if (!lattice[indx + indcNeigh[j]]) {//if free spot
                        neigh[nF] = indx + indcNeigh[j]; //save the index
                        nF++; //increase the number of found free spots}}
        if (nF) {//selecting free spot at random                return neigh[rand() % nF];
        }
        else {//no free spot
                return 0;
        }
}
void simulate(int nSteps) {
        vector<cell> cellsTmp;
        int newSite;
        cell currCell, newCell;
        for (int i = 0; i<nSteps; i++) {
                random_shuffle(cells.begin(), cells.end()); //shuffling cells
                while (!cells.empty()) {
                        currCell = cells.back(); //pick the cell
                        cells.pop_back();
                        newSite = returnEmptyPlace(currCell.place);
```

Figure 14: C^{++} code for the execution of cancerous cells location on the lattice.

```
#include <vector>
#include <algorithm>
#include <stdlib.h>
#include <time.h>
using namespace std;
struct cell {//defining cell
        int place;  char p;
        bool is_stem;};
static const int N = 2000; //lattice size
bool lattice[N*N] = { false }; //empty lattice
vector<cell> cells; //vector containing all cells present in the system
static const int indcNeigh[] = { -N - 1, -N, -N + 1, -1, 1, N - 1, N,
N + 1 };//neighborhood
char pmax = 10; //proliferation capacity
double pDiv = 1. / 24.; //division probability
double alpha = 0.05; //spontaneous death probability
double ps = 0.05; //probability of symmetric division
double pmig = 10. / 24.; //probability of migration
void initialize() {
        for (int i = 0; i<N; i++) { lattice[i] = true; };//filling left
        for (int i = 0; i<N*N; i = i + N) { lattice[i] = true; };//filling top
        for (int i = N - 1; i<N*N; i = i + N) { lattice[i] = true; };//filling bottom
        for (int i = N*(N - 1); i<N*N; i++) { lattice[i] = true; };//filling right
```

Figure 15: C^{++} code for the execution of cancerous cells adhesion and cohesion.

4.4 Agent Based Modelling for the Drug Therapy

With the help of a schematic, we can explain the stages of the cancer and the effect of tumour, as well as the technique to present its mathematical modelling, with the help of agent based modelling. Figures 12-18 shows the application (and resulting growth) of numerical codes using C++ and Matlab. The cells growth is shown in figure 19. From figures 20 and 21, a reader can see that the supply of oxygen is necessary for the tumour growth. Similarly the nutrients are provided with the aid of angiogenesis. The cells will metastasize. Now, with the aid of the drug delivery, we can control the cancer spread. We can see from the frequency graphs that the effect of the drug on the cancer treatment is correlated with the frequency. This factor is depicted in figure 22.

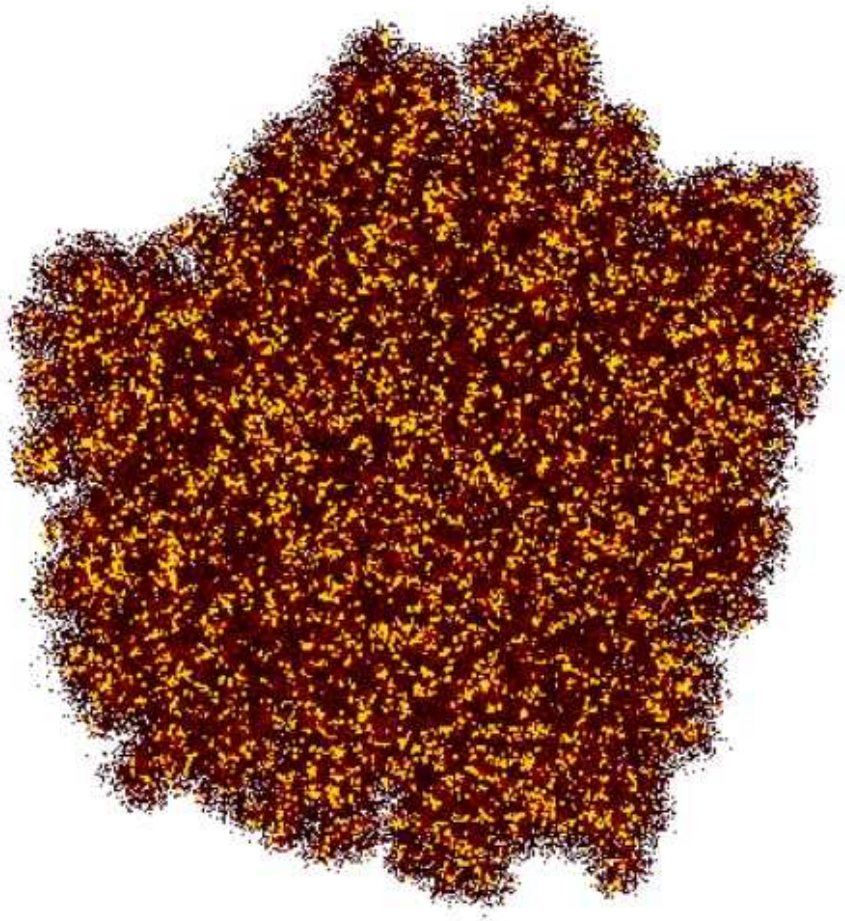

Figure 16: The lattice.

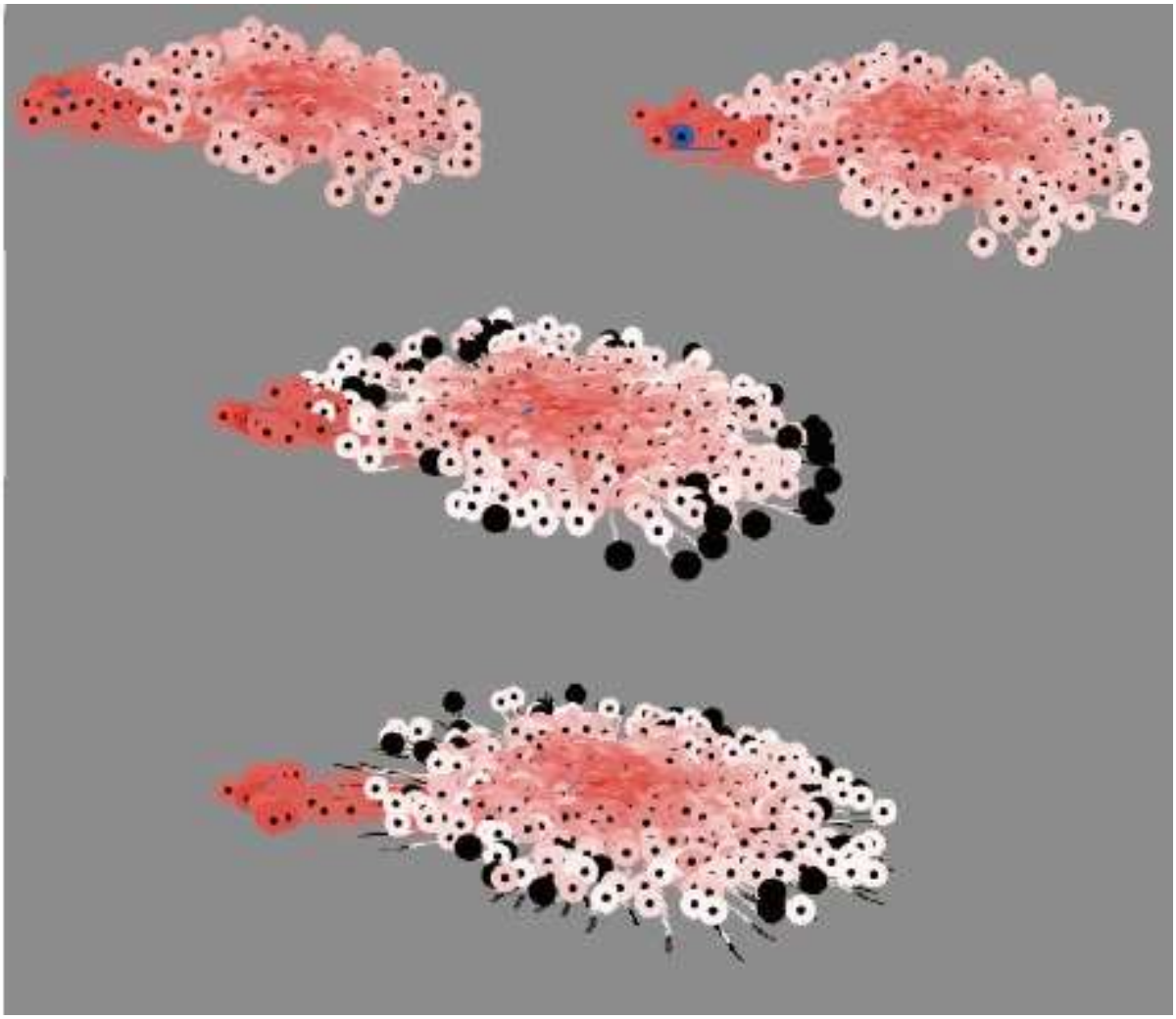

Figure 17: Schematic of cancer cells growth using AGB.

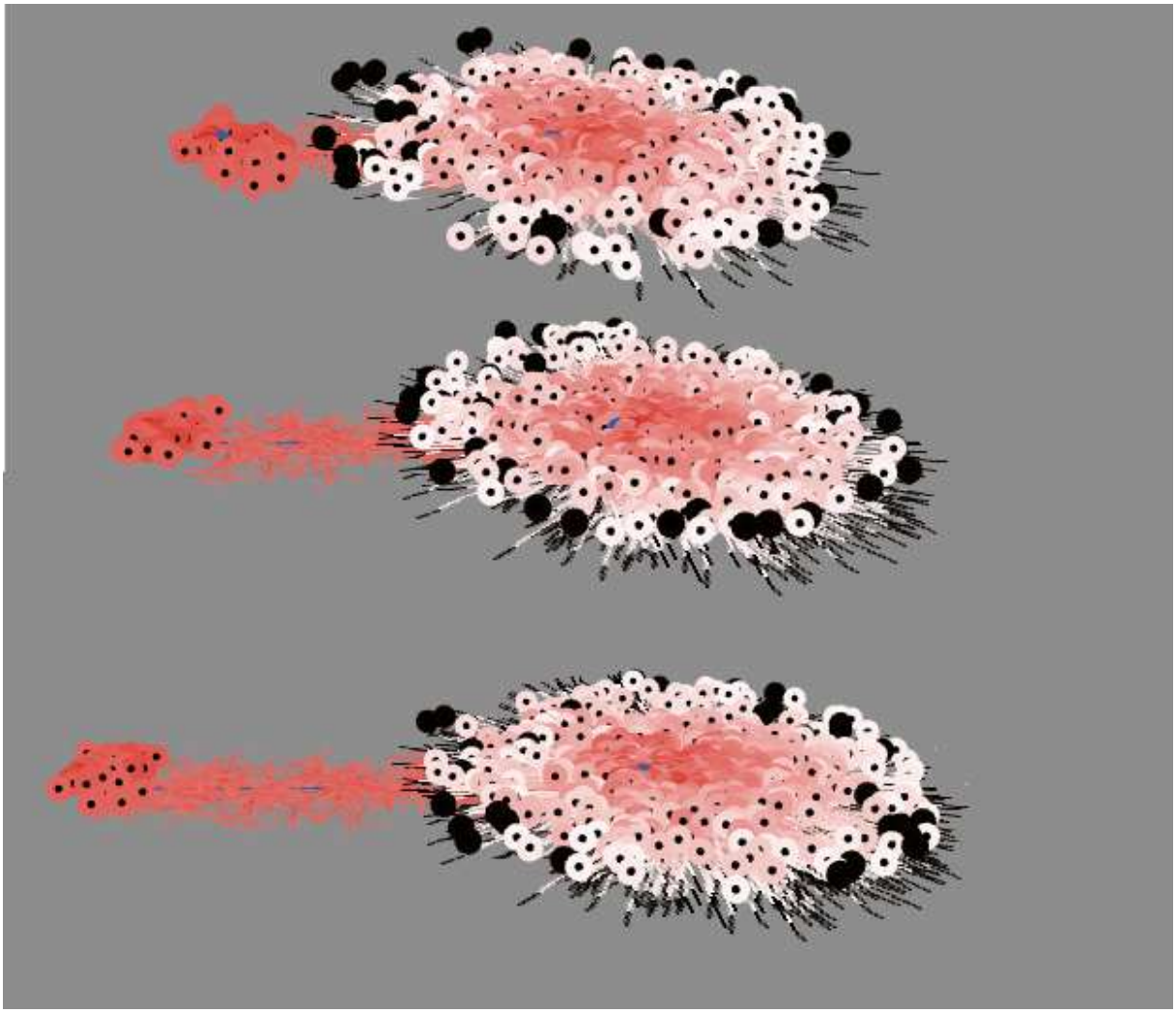

Figure 18: Vascular growth of cancer cells using AGB.

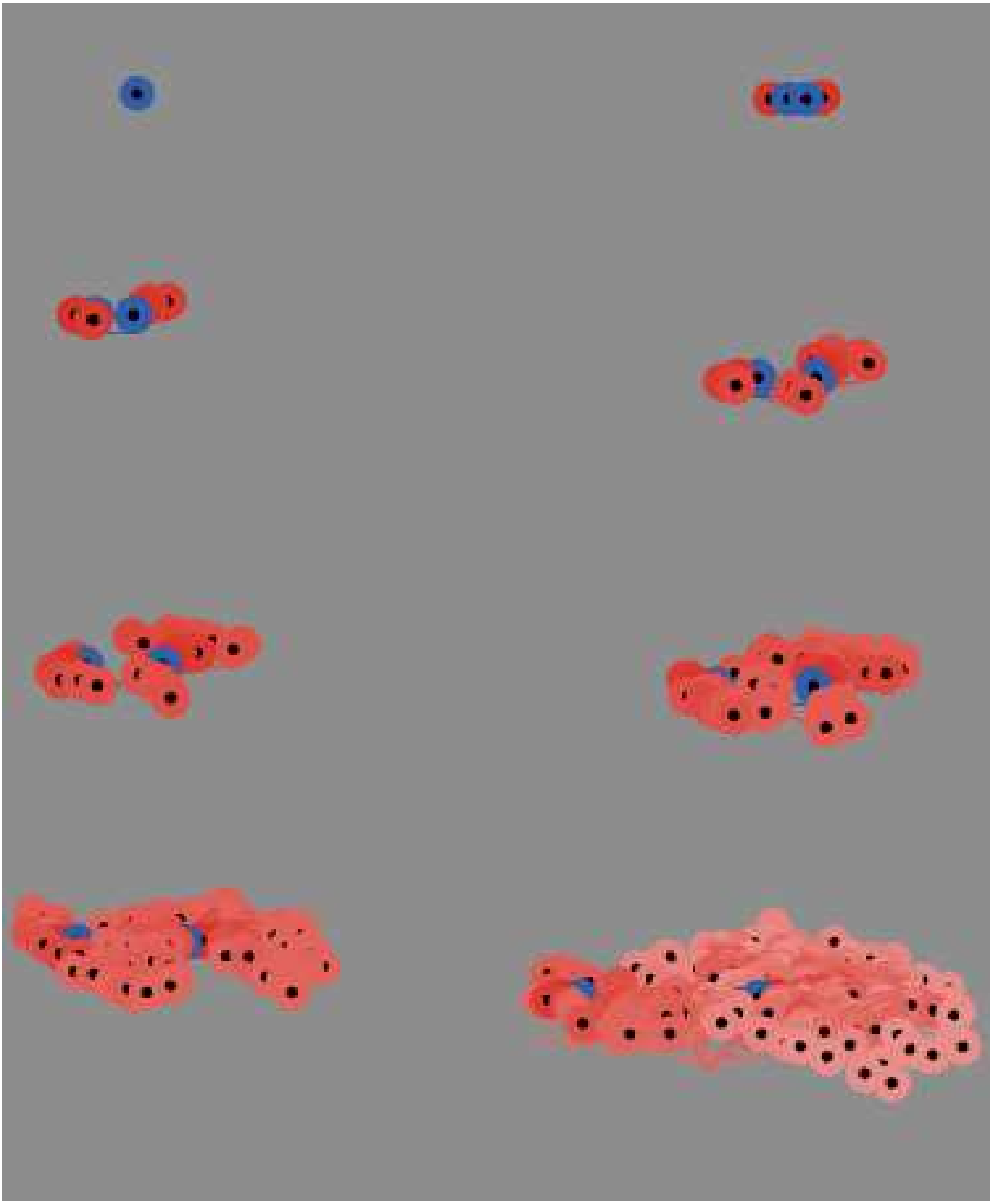

Figure 19: Cells growth (top to bottom).

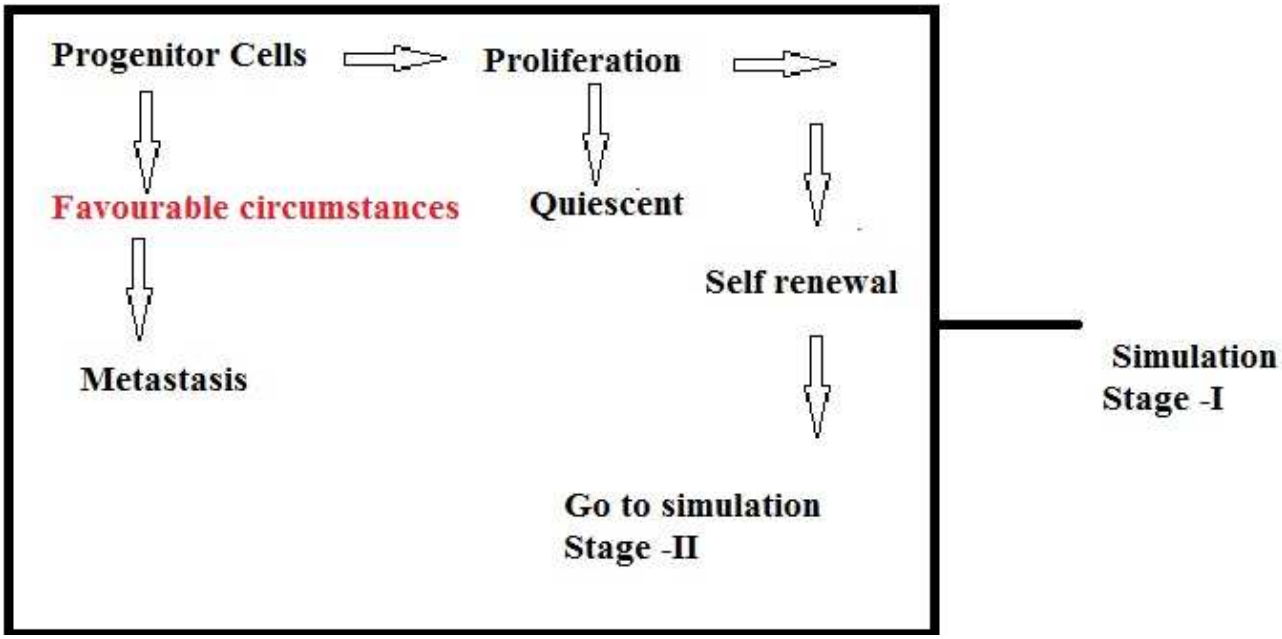

Figure 20: Schematic of numerical algorithm.

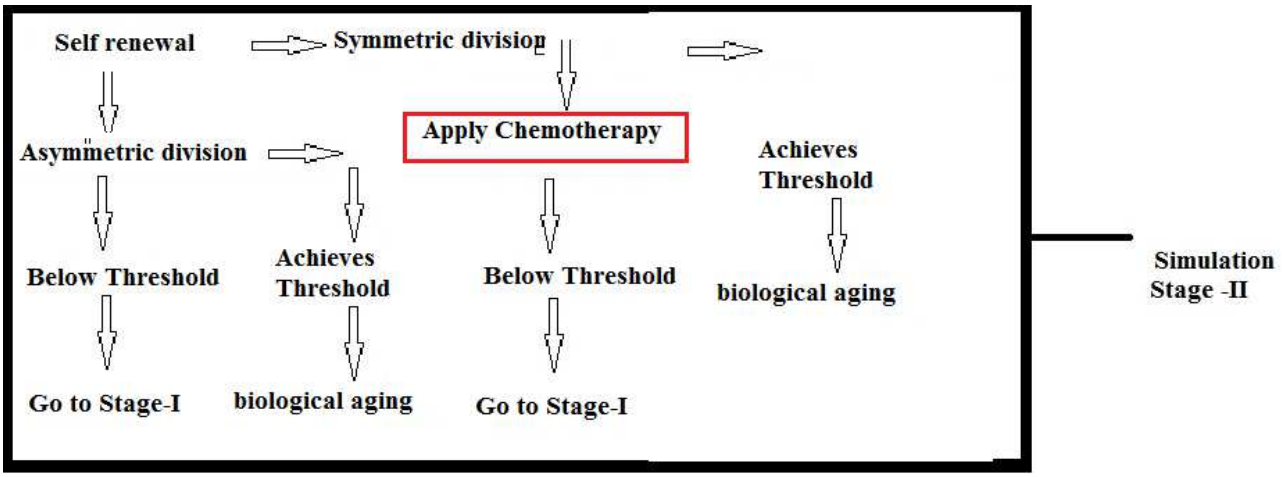

Figure 21: The next stage of cancer dynamics and numerical algorithm.

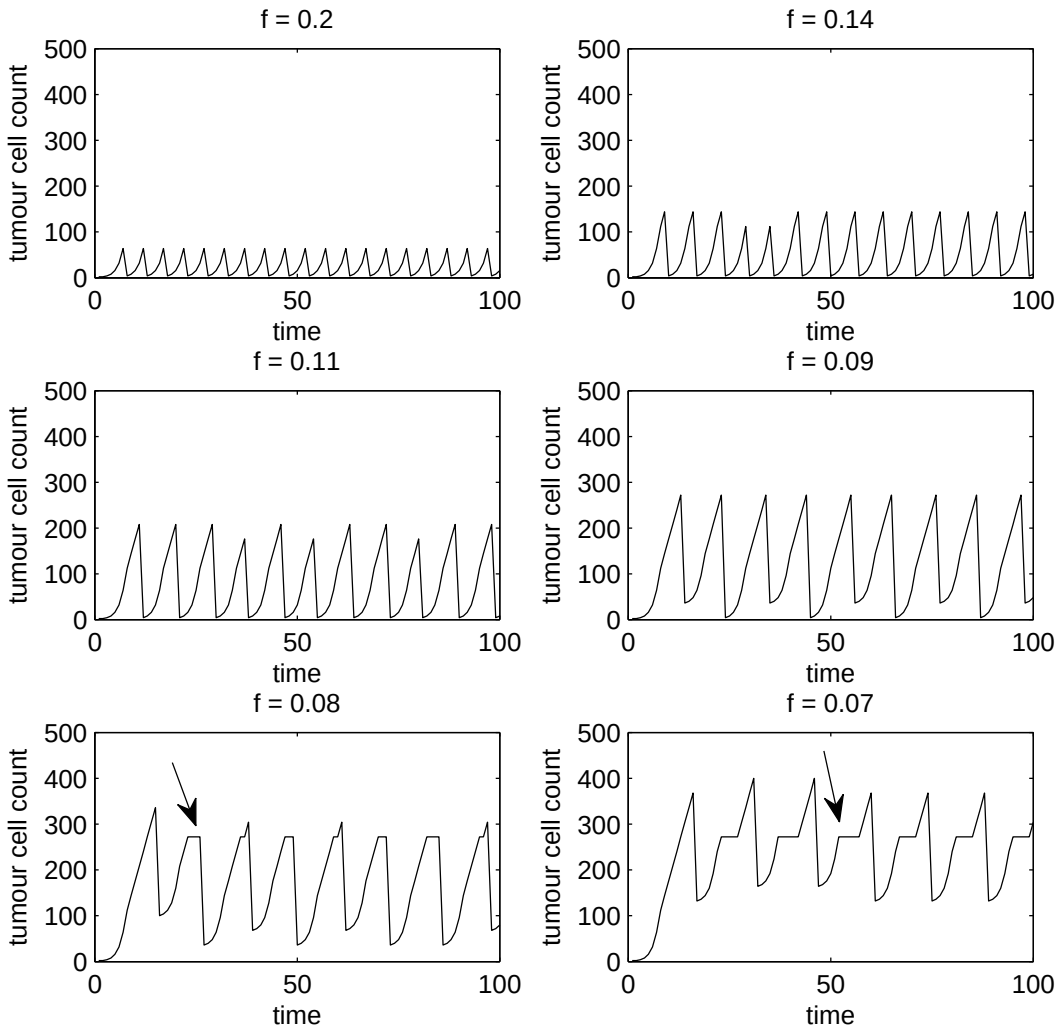

Figure 22: Different drug frequencies.

Chapter 5

Conclusions

5 Conclusions

The cancer cells are malignant in nature and are difficult to be treated, even this field of research has acquired certain benchmarks. In this thesis different levels are discussed using the discrete modelling approaches. Cancer treatment is successful in avascular cases. In the case of vascular cancers, cancer treatment is really vague. Angiogenesis plays a crucial role. The cancer treatment research is a growing field. Computational methods are promising. These techniques can help the clinicians to explore the effects and rapidness of the drugs in a more safe and reliable manner. The invivo studies are thus getting fame. In this thesis the techniques used can be further extended for future progress.

6 References

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