Some Stochastic Models For Cancer Cell Growth

This book is designed to provide the stochastic models for cancer cell growth as an alternative of non-parametric approach of assessing the cancer severity. Much emphasis of modeling is focused to formulation of mathematical models with probabilistic measures on the pathophysiology and genetic properties of cancer. The study is stressed more on stochastic modeling of cancer growth as modeling with deterministic environment is far from the reality. Bivariate stochastic model for normal and mutant cell growth was developed under the assumption of the growth and loss processes of mutant and normal cells are Poisson. Approach of difference differential equations is adopted to obtain the probability functions and several statistical measures. Another stochastic model for mutant and normal cell growth under chemotherapy is developed by taking similar assumptions. Two stage stochastic models for a cancer cell growth with the assumption of (i) every malignant tumor will have the premalignant and malignant clones and (ii) the growth of premalignant cell, mutation and loss of premalignant and malignant cells are random and follows Poisson processes, were developed.

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Dedications

In Loving Memory of My Beloved Father

(Late) ***Padi. Narayana Master***

Preface

In this study the author has attempted to present some stochastic models for cancer cell growth. Research evidences reveals that Non-parametric approach of assessing the cancer severity is the age old practice in which these studies have many limitations as they are far from the accuracy and beyond the reach of real quantification. Further, it allows much ambiguity in assessment of disease behaviour. Whereas Mathematical studies in Biological applications are gaining more importance due to their significant advantages. Hence assessment of real situation through mathematical simulations is a suitable alternative for handling biological problems. Applying the mathematical models for measuring the cancer growth is one of such useful approaches. Modeling on genetics and Pathophysiology of cancer cell growth through mathematical techniques is attracting much attention of researchers due to its multi disciplinary approaches with Biologists, Mathematicians, Statisticians, Computing Experts, etc.

As stochastic models are providing the basic frame work for analyzing the natural phenomena of cancer growth, this study is stressed on modeling the biological aspects of cancer disease with mathematical approaches. Studies on tumor growth models have gained interest due to their utility for optimal drug administration. The vital processes of tumor growth related with spontaneous mutation, proliferation process, loss process, etc of the cells have to be assessed through suitable modeling. This study focused on developing and analyzing some stochastic models for cancer cell growth in different environments of tumor.

The cell kinetics plays a vital role in the growth of tumors. Usually the spontaneous mutation and proliferation process of cells are random in nature. Therefore the growth of a tumor has to be analyzed through the mentioned behaviour of cells in the tumor. Many studies have proposed that the stochastic Models for the growth of mutant cell population based on the assumption of growth rates of normal and mutant cells are homogeneous. However, it is interesting to note that the growth rates of normal and mutant cells are not homogeneous as their proliferation processes are not same. Hence, the proliferation of normal and mutant cells is considered to be stochastic rather than deterministic.

The second chapter of the study consists of a Bivariate stochastic model for normal and mutant cell growth under the assumption of the growth and loss processes of mutant and normal cells are Poisson with different growth rates and loss rates. Difference

differential equations are used to derive several statistical measures based on the probability functions. This model is extended with the assumption of mutant cell's growth is much faster than the normal cell. Another stochastic model for mutant and normal cell growth when the patient is under chemotherapy is developed by assuming the loss process of normal and mutant cells is the sum of natural loss and loss due to chemotherapy. These models are very useful for analyzing the tumor growth and to administer the chemotherapy more effectively.

Third chapter of the book consists of two stage stochastic model for a cancer cell growth with the assumption of every malignant tumor will have the premalignant and malignant clones. A premalignant cell may either extinct without becoming a malignant cell or it may take mutation and become a malignant cell. The size of the malignant tumor is heavily influenced by these growth kinetics of malignant cells, that make up the foci within the foci. This situation in the tumor growth is also modeled as another two stage stochastic model with the assumption that the growth of premalignant cell, mutation and loss of premalignant and malignant cells are random and follows Poisson processes.

Chapter four of the book is on a stochastic model for the mutant cell growth under chemotherapy. The situations of drug administration and drug vacations are modeled by assuming the growth and loss processes of the cancer cells are Poisson with different parameters for two stages of the patient. The probability of extinction of the tumor is derived so as the average size and variances of cancer cells in the tumor are analyzed. It is observed that the efficiency of the drug is directly linked with the extinction of the malignant cells in the tumor. This model will have significant utility for administering the chemotherapy. Summary presentation was given in the last chapter.

The models with this study have lot of importance to the health caretakers for implementing the optimal chemotherapy protocols. The complexity of the model and its application in real time data with cumbersome data sets demands the speedy and accurate calculations, which in turn increase the demand of computer technologists to prepare suitable software. User friendly computer automation may be developed by combining the developed mathematical models and suitable computer programs.

The author is indebted to his research supervisor, teacher and philosopher Prof. K. Srinivasa Rao, Dept. of Statistics, Andhra University, Vishakhapatnam, A.P., India for his scintillating support, encouragement and continuous follow up on the refinements of this study.

Tirupathi Rao Padi

CONTENTS

CHAPTER -1

Introduction

1.1. OVERVIEW:

Mathematical studies in Biological applications is gaining its importance due to its sharp edged advantage. The assessment of real situation with mathematical simulation is the suitable alternative without disturbing the basic biological issues. Applying the mathematical models for measuring the cancer growth is one of such useful approaches. It is more useful in understanding the cancer dynamics. Several nonparametric approaches are in practice to assess the problem severity. However, they have many limitations as they are far from the accuracy and beyond the reach of real quantification. Further it allows much ambiguity in assessment of disease behaviour. Many significant works were reported in quantifying the qualitative traits for measuring the eventual phenomena. Modeling the genetical issues and Pathophysiology of the cancer cell growth through mathematical techniques has attracted the attention of the multi disciplinary approaches with Biologists and Mathematicians, Statisticians, Computing Experts. This study has dedicated to modeling the biological aspects cancer disease with mathematical approaches. The stochastic processes involved in growth and loss of cancer cells are obtained through suitable assumptions and postulates.

Cancer Pathophysiology:

Pathophysiology of cancer describes that most of the cancers are due to the genetic structures and the disease processes characterized by uncontrolled growth and spread of cells. Causing of cancer may be attributed with several unexplained reasons. Healthy and normal behaved cells having specific size, growth pattern, function and structure may be exposed to spontaneous mutation and ultimately they will be converted in to cancer causing cells. These cancer cells differ from normal cells in several factors with respect to their size, structure, function, growth rate, etc. These malignant cells will be beyond the normal regulating control as observed with healthy cells. Further the cancer cells will invade to adjacent structures and affect the related tissues and organs.

The mutant cells may form metastasis in other areas of the body through the blood circulation systems and further they will lose their ability to act like normal and healthy cells. This inability leads to transform them as either benign cells or malignant cells. Benign neoplasm is made up of the same cell type as the original parent cell and they do

not invade to the adjacent tissues. Whereas the malignant cells will be more vibrant in forming their secondary cells and grow with faster rate by continuous and unending proliferation. There are considerable differences in the growth rates of malignant tumors. Some tumors are very slow-growing, even in a malignant state, and are therefore removed easily. Other tumors may grow slowly at first and then undergo change and continue to grow at a rapid pace. Others tumor types may grow very rapidly throughout their entire existence. Tumor growth is influenced by the factors like individual's immune system, growth rate of tumor, number of actively spreading tumor cells, etc. Hence, we may describe that uncontrolled cell growth is a characteristic of cancer.

Understanding the causing factors of cancer occurrence is a complex process. It is linked with many factors to name a few, professional hazardous, unhealthy lifestyles and practices, medical interventions, genetic traits, etc. The initiation of carcinogenesis occurs will be observed when DNA is damaged or altered. Genetic cancer is a susceptibility to a small percentage of cancers and a primary cause of cancer is damage to a specific gene. If the damaged gene is part of the genetic line, then the cancer can be inherited by succeeding generations. Cancer also can be caused by Oncogenic viruses can affect DNA or RNA, which infect normal cells and cause alterations in the cell's genetic material. These genetic alterations can cause specific types of malignant and benign cancers in susceptible individuals by allowing uncontrolled growth in cells. Cancer causing due to genetic reasons require the attention of the researchers as the biological relations and Pathophysiology issues can be understood with well defined scientific principles.

Inherited cancers tend to occur earlier in life and typically cause multiple growths in the same organ. Disorganization of cells shall indicate dysplasia. Dysplasia is a result of chronic un healing among the organs. The initial level of dysplasia is referred as Metaplasia and it is reversible. Epithelium of the respiratory tract where columnar epithelial cells change into squamous epithelial cells is the most common type of metaplasia. Increase in the number of cells in a tissue or in a part of a tissue is referred as Hyperplasia, and results in increased tissue size. Normal hyperplasia is observed in the tissue and increases during the healing of wound, bone fracture, formation of callus, etc.

Tumors are classified according to tumor node metastasis (TNM) Clinical Classification System. Tumor (T) is classified as Carcinoma in situ, increasing size, local extent, or both, of primary tumor, etc. Regional lymph nodes include no metastasis and increasing involvement of regional lymph nodes. The spread of cancer cells from the primary site, or site of origin, is called metastasis. Cancer cells can spread throughout the

body through the bloodstream, the lymphatic system, or through local invasion and infiltration into surrounding tissues. Metastasis includes no distant metastasis and distant metastasis. A multi step process in the progression of sequential accumulation of mutations within tissue cells is referred as tumor genesis. The cancer stem cell hypothesis has enormous implications for cancer therapeutics and will target the rapidly dividing differentiating cells that comprise the major bulk of tumors, often leading to significant reduction in tumor size.

If occurrence of cancer is as an epidemiology, it may be due to the reasons of environmental issues and individual life styles. These cancers are usually observed during the transitions of people from countries with low cancer rates migrated to countries with high cancer rates. we may observe variations in cancer rates in different geographical locations of the same nation. The staging of cancer is decided with the rate of growth and the extent of the disease. It will help to know the treatment options to expect the life span of the patient and to determine the severity of the disease. the factors that decide the stage of cancer includes Location and size of the primary tumor; Extent of lymph node involvement; Presence or absence of metastasis and Type of tumor and the tumor-host relationship

Cancer Measuring Models:

Several mathematical models for measuring the spread and intensity of cancerous growths have been developed, especially on solid tumors, in which growth primarily comes from cellular proliferation. The invasiveness of gliomas, however, requires a change in the concept to include cellular motility in addition to proliferative growth. Stochastic models provide the basis frame work for analyzing the natural phenomena. In many biological systems it is important to study the development and growth of tumors. A tumor a is mass of tissues formed as a result of abnormal, excessive and inappropriate (purposeless) proliferation of cells. Owing to the complex nature of growth process of tumor it is necessary to formulate and integrate models that attempt to describe the growth process at different levels. Mayneord (1932) has pioneered the systematic mathematical study of tumors. Later several authors have developed various models for cancer cell growth with various assumptions in order to analyse the growth kinetics of tumors. One of the potential string in developing these models is replacing some of the homogeneity assumptions, where a more realistic nature can be employed.

Tumor growth models gained interest due to their ready utility for optimal drug administration. So as to incorporate the natural phenomena, we have to consider the growth process as stochastic rather than deterministic. The vital processes of tumor growth are spontaneous mutation, proliferation process and loss process of the cells. Along with several other assumptions, it is customary to assume that the mutation and proliferation processes of normal and mutant cells are homogeneous. This assumption is valid only when we analyse the models under the single environmental for both normal and mutant cells. However in tumors, once the tumor is formed (in particular with cancer cells) the growth and loss processes of normal and mutant cells are non-homogeneous (heterogeneous). In this study an attempt is made to fill the gap in this area of research by developing and analyzing some stochastic models for cancer cell growth in different environments of tumor.

1.2 RESUME ON CANCER CELL GROWTH MODELS

This section has provided a brief review on some contributions on the modeling of cancer cell growth in chronological order. Several models have been developed for understanding the origin and development of tumors.

Mayneord (1932) Pioneered the study on growth of the tumor in volume through the application of a differential equation model for the rat sarcoma. Rashevsky (1945) developed the mathematical models involving differential equations that deal with the dynamic or time course variation of the cancer. Iverson et al. (1950) studied the mechanism of experimental carcinogenesis. The probability distribution of latent period, the lethality of applied carcinogenesis etc. were estimated through the stochastic theory. Arley et al. (1952) developed a model based on the one stage mutation hypothesis. The dose response relation in any one series characteristics by a fixed time pattern was fitted by this model. Kendall (1952) has developed a quantitative model for carcinogenesis based on phenotypically delayed mutation. Armitage et al. (1957) developed a model for two stage theory of carcinogenesis in relation to the age distribution of tumor cancer. This model is characterized by a deterministic assumption that the clone of first order mutants grow in exponential form. Neyman (1958) discussed the biological situations of cell growth as a stochastic model and phenotypical delayed mutation process for a quantitative theory of carcinogenesis.

Kendall (1960) investigated the biological situation of cell growth as a birth and death model considering a large population of normal cells subject to carcinogenic action.

The carcinogenic action was categorized in to four states. He assumed that the birth and death rates are constants. Armitage et al.(1961) developed a stochastic model for carcinogenesis and reviewed various mathematical models, which discussed the induction period of carcinogenesis transition probability density per unit time for each tissue. Laird (1964) discussed the dynamic of growth of a tumor using Gompertz law. Burton (1966) studied the growth rate of solid tumors as a diffusion process. Neyman et al. (1967) used a linear birth and death process to describe tumor growth. They considered the probabilities of birth and death are constant and hence it is also density dependent.

Simpson et al. (1970) investigated the experimental tumor system with cell kinetics and growth curves. They have computed the time required for tumor to pass from the initial size referred as the first passage-time formula. Sullivan et al. (1972) described the kinetics of tumor growth and regression relations in Ig. G multiple myolema through Gompertz law. Wette et al. (1974) developed a stochastic model for growth of solid tumors based on physical characteristics of the tumor. This model leads to density dependent stochastic process for the mean size of the tumor. Bahrami et al. (1975) dealt with the applications of engineering optimal control theory to investigate the drug regimen for reducing an exponential tumor cell populations. Dubin (1976) formulated a density dependent birth and death process to describe tumor growth subject to immunological response. The density dependence is due to a non-linear factor in the transition probability of the death of a tumor cell. The deterministic part of Dubin's model is similar to the logistic growth law.

Swan et al. (1977) has utilized engineering optimal control theory for chemotherapy problems involving a human tumor. Steel (1977) studied various growth kinetics of tumor through the logistic model and demonistrated the applicability of Gompertz growth law of tumor growth. Swan (1977) reviewed various mathematical models regarding the tumors. He described a method for obtaining the exact solution to Dubin's (1976) model. Schwartz. (1978) developed a mathematical model for breast cancer to evaluate the benefits of screening for breast cancer, the hypothesis concerning the age-specific incidence of the disease was considered. The rate of disease progression, the tendency of the disease, etc. were studied.

Hanson et al. (1981) derived an asymptotic approximation to the first passage time problem for singular diffusion population. They have obtained a solution for density dependent stochastic population. Bartosynski (1981) developed a model on the appearance times of metastases s a non-stationary poisson process and developed

algorithm using probability density estimation, mortality measurements and discrete maximum penalized likelihood approach. Kang et al. (1982) considered a continuous bilinear model in state space cell kinetics of a tumor cell population under the effects of chemotherapy. the time course behaviour of a Chinese – Havster Overy (CHO) cell population is simulated and an optimal strategy for cancer treatment is derived to balance the effects on cancerous as well as normal tissues. Hanson et al. (1982) derived a stochastic model for tumor growth based on diffusion approximation of continuous time, density dependent branching process with a Gompertz growth law as the deterministic part.

Coldman et al. (1983) developed a mathematical model of tumor resistance to chemotherapy. the probability of no resistant cell is utilized as a fundamental quality of interest, and the effects of various therapeutic strategies on it are explored. After observing the application of various drugs, it was inferred that the simultaneous administration of all available active agents is optimal where this is permissible. Steven et al. (1983) described a mathematical model of growth based on the kinetics of cell cycle. Intrinsic growth rate equations were derived and behaviour of model was characterized based on animal tumor cell cycle kinetics data.

Atkinson (1983) studied the growth rate of a cancerous tumor as a function of its age. An estimator for the growth function from data on size at detection is obtained and applied to data on large series of cases of breast cancer, which indicates that the growth function can be adequately described by exponential growth. Chiang (1983) discussed the theory of multistage carcinogenesis with a time dependent stochastic model. He derived the distribution of the time required for a given number of mutations and the probability of developing neoplastic cells in a given interval of time.

Serio (1984) studied a two-state stochastic model for carcinogenesis with time – dependent parameters. Epidemiological characteristics of the cancer to the biological evolution of the tissue are also studied. Forbes et al. (1984) reviewed various mathematical models of carcinogenesis, which provide an insight in to the consequences of making certain biological assumptions. They have suggested that it is appropriate to select the simplest model. Marco et al. (1984) developed a mathematical model, which consists of a system of first order partial differential equations. They investigated the evolution of a homogeneous cell population under the action of mutagenic agents.

Birkhead et al. (1984) studied a mathematical model relating tumor response under repeated doses of a single cytotoxic agent to the presence and accumulation of phenotypic

drug resistance. They have presented an analytic expression for quantities like the fractional tumor reduction effected by dose, the minimum tumor size achieved under therapy etc. Dibrov et al. (1984) studied the development of chemotherapeutic protocols with increased selectivity in killing malignant cells as opposed to normal cells. They considered the dynamics of a proliferating cell population under periodic treatment by a phase – specific agent.

Kendal (1984) developed a model which relates the growth of tumors to the degree of their cellular heterogeneity. The growth rate is proportional to the logarithms of the number of combinations of cellular states. when the number of combinations of states is inversely proportional to the total number of inter cellular interactions then tumor's growth is Gompetzian.

Jushuachover et al. (1985) compared two types of stochastic models for the initial growth of cancereous tumors. In the first type, the random element enters via the initial time of growth (or) via the initial size of the growth of clone. Where as in second type tumor differ from one another essentially via these growth rates. Tan et al. (1985) derived the probability distribution for the number of tumors and the incidence rates at the experiments using two stage model, when an individual is continuously exposed to environmental agents of cancer.

Hiep (1985) derived a stochastic model of evolution of mutant sub populations from stem cells in human tumor system. The growth of mutants (both stem cell mutants and overall mutation) due to mutation of tumor stem cells during growth is explored. This model relates the mutant stem cells and overall tumor mutant cell population sizes.

Coldman et al. (1985) studied a stem cell compartment model to simulate the growth of human tumors, which is used to explore the effects of cell differentiation and loss on the development of spontaneous drug resistance. According to them, the probability that the resistant cell is independent of rate of cellular differentiation for one drug and the probability, that the cell resistance is proportional to the rate of cellular differentiation for more than one drug. Kranz (1985) studied the effects of demographic and environmental stochasticity on the qualitative behavior of mathematical model from tumor immunology. A stochastic differential equation whose solution is a limiting diffusion process to a branching process with random environments is used.

Birkhead (1986) derived the transient solution of the simple linear birth and death process subject to random mutation. He investigated the curability of cancer under drug treatment through this solution. He also derived the expression relating to curability of the

disease to increasing tumor size. Jackson (1986) reviewed some applications of kinetic simulation of multi enzyme networks to the study of antimetabolic drugs used as anticancer agents. Kinetic models consists of system of nonlinear differential equations which describe changes in concentrations of cellular metabolites with respect to time. Drug sensitivity, drug resistance and drug intervals were estimated with the above networks. Coldman et al. (1986) presented a stochastic model for the chemotherapy of experimental tumors. They have derived the equations for the joint probability generating function for the number of chemo-sensitive and chemo-resistant cells. This model is extended to two drugs and they have shown now the model can be used to make deduction regarding the optimum scheduling of therapy.

Marek et al. (1986) described a mathematical model to estimate the cell cycle phase specific action of a new anticancer drug CI-921. The estimate obtained is in the form of a sequence of fraction of the cell flow blocked in successive sub compartments of the cell cycle. Adam (1986) developed a one-dimensional model of tumor tissue growth in which the source of mitotic inhibitor is non0uniformly distributed within the tissue.

Flehinger et al. (1987) developed a mathematical model of progression kinetics of lung cancer in a periodically screened population. They assumed that the development of adenocarcinoma of lung is a stochastic process with two stages, say early stage and advanced stage. Various parameters like mean times, detection probabilities, confidence region etc., were also estimated. Kinsella (1987) fitted a linear multiple regression model to a tumor time series. The slope parameters are used to estimate the expected life time extension / reduction as an unambiguous index of treatment effects.

Moolgavkar et al. (1988) described the evolution of malignant cells in the tissue and those malignant cells that arise from direct mutation from premalignant cells. Premalignant cells are generated from normal cells as a non homogeneous poisson process which ignore birth and death of malignant cells. Dinse (1988) described a regression analysis that adjust for survival and allows different conditional death rates. The methods proposed provide a frame work for incorporating covariates, as well as for estimating the tumor's relative risk are illustrated with liver tumor data from the EDOI study.

Abundo et al. (1989) developed a stochastic model to study the problem of inherent resistance by cell population. When chemotherapeutic agents are used to control tumor growth. They have introduced stochastic differential equations and numerically integrated to simulate expected response to the chemotherapeutic strategies as a function of different parameters. Dewanji et al. (1989) developed mathematical expressions for the

number and size distribution of intermediate regions. He defined a type-I premalignant cells as one that has arisen by direct mutation from one of the normal cells, and a premalignant clone as the collection of premalignant cells descended from a single type-I premalignant cell, not counting the dead or differentiated cells.

Michelson et al. (1989) developed a stochastic analogue to a deterministic model describing sub population emergence in heterogeneous tumors. They have also described a finite element approach for the numerical solution to the Fokker – plank or forward kolmogorov equation. The results of the simulation supported the stochastic model, as the basic dynamics of its deterministic counterpart.

Chiang et al. (1989) studied a stochastic model of survival distributions, where the mortality intensity is a function of the accumulated affect of an individual's continuous exposure to toxic materials in the environment and his biological reaction to toxin absorbed. They have given the formulae for the density function, the distribution function and expectation of life time. Tan et al. (1989) developed a non-homogeneous stochastic model for drug resistance in Chemotherapy that permits killing resistant cells with immunostimulation. The probability of distribution of the number of resistant tumor cells, the probability of nonresistant cells, the expected value and cumulants of the number of resistant tumor cells are derived.

Adam et al. (1989) studied two mathematical models for the control of the growth of a tumor by diffusion of mitotic inhibitor. The inhibitor production rate is taken to be uniform in a necrotic core for the first model and in the non-necrotic region for the second model. Regions of stable and unstable growths are determined and conclusions are drawn about the limiting peripheral widths of stable tissue growth for both models.

Martin et al. (1990) discussed an optimal parameter selection model of cancer chemotherapy which describes the treatment of tumor over a fixed period of time by the repeated administration of a single drug. The model constructed a regimen that minimize the tumor population by satisfying the constrains of the drug toxicity and intermediate tumor size. Murray (1990) investigated some models of cancer chemotherapy problems where the normal cell population must be maintained above a lower limit and a measure of total drug used is bounded as a limit of toxicity. Swan (1990) reviewed various ways in which optimal control theory interacts with cancer chemotherapy. he classified the models into three broad areas, namely (i) miscellaneous growth kinetic models (ii) cell cycle models and (iii) the other models. Designs of better chemotherapy strategies are also suggested.

Dewanji et al. (1991) developed two-mutation model for carcinogenesis which postulated two-state limiting events for malignant transformation as a generalization of the recessive oncogenesis hypothesis. As per this model, inactivation of homogeneous tumor suppresser genes leads to cancer. This model has been used for the analysis of altered heptic foci in rodents.

Martin (1992) investigated three types of tumor growth models namely, gompertz, Logistic and Exponential. They observed that the tumor burden during therapy have a little impact on survival time for exponential and logistic growth tumors. Tusnday (1992) discussed various mathematical methods of cancer research as (i) understanding the description of processes leading to cancer such as investigation of non-erogodic sequence of stochastic automate (ii) diagnostic methods for estimating the growth factors by algorithms and (iii) follow up studies using the Keplan – Meier estimator and Cox regressions for one dimensional and multi-dimensional survival distributions.

Dewanji et al. (1993) developed a new method of estimating tumorgenic potency that takes into account information on survival and cause of death. They described the time to tumor occurrence (X) the time to death as a result of tumor occurrence (Y) and the time to death from causes other than tumor occurrence (Z) through the Weibull distribution.

Asselain et al. (1994) studied a biological based parametric model of tumor latency with an evidence of the contra lateral breast cancer recurrence is most likely to originate from subclinical tumor foci that pre exist at the time of treatment. Biswas et al. (1994) measured the relative risks and longevity of a group of cancer patients using Weibull model whose parameters are the functions of the covariates based on randomly censored data. Mathisca et al. (1994) developed a mathematical theory based on a two-mutation model for carcinogenesis, which is used for the quantitative analysis of premalignant clones induced by specific carcinogenesis.

Byrne et al. (1995) derived a model for the evolution of spherically symmetric and non necrotic tumor. They have studied the effect of nutrients and inhibitors on the existence and stability of time dependent solution. They have also discussed the implications of the model for the treatment of cancer and suggested that non-trivial solution is stable and the trivial solution is non stable. Duffy et al. (1995) developed a two parameter markov chain model to explicitly estimate the preclinical incidence rate (λ_1) and the rate of transition from preclinical to clinical state (λ_2). They have also proposed an

estimate of sensitivity based on the estimated parameters of the markoiv process. Carriere (1995) studied an identifiability theorem in the theory of dependent competing risks. He has discussed the modeling of dependence with copila functions and they have also calculated the survival probabilities after cancer is removed by solving a system of non linear differential equations.

Little (1995) studied some generalizations of the two mutation carcinogenesis model of Moolgavkar, Venzon & Knudson and the multi stage model of Armitage & Doll. He has shown that process of cell division is governed by the parameters death or additional mutation of the penultimate stage are subjected to perturbation and there are relatively large fluctuations in the hazard function for carcinogenesis for the model. Morell et al. (1995) used a non-linear mixed effects model to describe longitudinal changes in prostate specific antigen (PSA) in men before their prostate cancers were detected clinically through a piece wise model. The time at which the PSA levels change from non-linear to exponential could be estimated by including random terms that allow each subject to have his own transition time.

Milklavcic et al. (1995) developed a mathematical model in which the pharmacokinetic model was extended and transformed to the level of macroscopic biologically detectable effect. They have used Gompertz equation for modeling. The effect of bleomycin on tumor growth was obtained by introducing the influential parameters.

Ying et al. (1995) studied a model for tumor development and discussed the identifiability of parameters in the model. They have combined the results of tests for each marginal tumor incidence rate to develop stimulataneous tests of all marginal tumor incidences. Jam et al. (1995) developed a stochastic model for one, two and three stage malignant transformations for embryonic and adult mice to study the influence of mutation rate, number of stages required for transformations and number of stem cells at risk on the kinetics of spontaneous appearance of malignant tumors.

Little et al. (1996) fitted a two mutation carcinogenesis model of Moolgavkar's Venzon & Knudson and generalized to lymphatic leukemia incidence data. Both Acute Lymphatic Leukemia (ALL) and Chronic Lymphatic Leukemia (CLL) were fitted by the model of mutation. These two mutation models are such that first mutation rate and the susceptible stem cell population vary rapidly with age.

Alexander et al. (1997) developed a stochastic model of spontaneous carcinogenesis to allow for a simple pattern of tumor growth kinetics. They have

discussed a method of estimating numerical characteristics of unobservable stage of carcinogenesis from data on tumor size at detection. They assumed that a tumor becomes detectable when its size attain some threshold level, which treated as a random variable. The model yields a parametric family of joint distribution for tumor size and age at detection. Hanin et al. (1997) discussed the distribution of tumor size at detection derived within the frame work of a stochastic model of carcinogenesis. They have considered two versions of the model with reference to (i) spontaneous and (ii) induced carcinogenesis having the asymptotic behaviour.

Chen et al. (1997) derived a mover-stayer mixture of markov chain models with the complication that movers were unobservable because tumors were excised on diagnosis. They have used a Quasi likelihood method for estimation.

Zheng (1998a, 1998b) suggested a method to compute the hazard function for the multistage carcinogenesis model, based on the Kolmogorov forward equation, which highlights the interplay of the forward equation, the backward characteristic method. He also discussed the advantages and disadvantages of the forward and backward equations are equivalent. He also reports that as far as the survival and hazard functions are concerned, all three models given by Kendall (1960). He also discussed some of the implications within the context of the two stage models.

Xu et al. (1998) developed a model by making the hazard function for detecting a metastatic cancer a constant. Two quantities were considered to study the relationship between the size of primary cancers and the occurrence of metastages, they are (i) the distribution of tumor size at the point of metastatic transition, and (ii) the probability that detectable metastases are present when cancer comes to medical attention. They have proposed an estimator of the tumor size distribution at metastases and the result is applied to a set of colorectal cancer data. Chen et al. (1998) considered a stochastic model with exponential components to describe the phase-III cancer clinical trials data. They presented the relationship between the hazard ratio of disease free survival (DFS) for an active treatment versus a control treatment and the cumulative hazard ratio of survival for the same two treatments.

1.3 FOCUS OF THE STUDY

With the brief review given in the section 1.2, it is clear that stochastic models are more powerful in the study of cancer cell growth. Starting from the pioneering work in 1932, by Meyneard much work has been reported in the literature regarding the tumor

growth and its origin. The works of Laird (1964).Burton (1966), Simpson-Hersen and Llyod (1970). Sullivon and Salmon (1972) and Steel (1977) demonstrated the applicability of the Gompertz growth law to tumor growth. Their results are based upon curve fitting with actual data.

The Gompertz model is deterministic. In real situations, tumor cells are subject to irregular growth due to random events. The irregular growth can result in tumor sizes that are different from those predicted by the deterministic model. The irregular growth of tumor appears to be the rule rather than exception.

To account for the irregular growth stochastic models of tumor growth have been introduced particularly in the models of cancer cells. Iverson and Arley (1950) described the growth of transformed cell, a progenitor of a tumor, by a pure linear birth process. In this model, the probability of a birth is a constant, which is analogous to a constant specific growth rate and hence a density independent model. Kendall (1960), Neyman and Scott (1967) used a linear birth and death process to describe tumor growth. Their model used constant birth and death probabilities and hence also density independent. Wette, Katz and Rodin (1974) developed a stochastic model for growth of solid tumors based upon the physical characteristics of the tumor. This leads to a density dependent stochastic process for the mean tumor sizes. Dubin (1976) formulated a density dependent birth and death process to describe the tumor growth subject to immunological response. He used various approximations to obtain information about the process. Swan (1977) described a method for obtaining the exact solution to Dubin's model. Hanson and Charles Tier (1982) developed a stochastic model for tumor growth which is the diffusion limit of a continuous time density dependent branching process.

Dewanji et al. (1989, 1991) have developed stochastic model for cancer risk assessment through the number and size of the malignant clones with the assumption that once a malignant was generated, it gave rise with probability 1 to a malignant tumor after a suitable lag time. However to take the explicit account of growth kinetics of malignant cells, that are of cells that makeup the foci within the foci. They have also developed another stochastic model by incorporation a birth-death process for malignant cells. Birkhead (1986) developed a stochastic model using the linear birth and death process with random spontaneous mutation by considering tumor cells are assumed to proliferate by division and may lost to the population.

A close look into the cell kinetics of tumor reveals that the spontaneous mutation, proliferation and loss processes play a dominant role for the growth and development of

tumor. The mutation and proliferation process can be described as follows. The normal cell can be divided into two normal cells (or) a normal cell can be divided into a normal and mutant cell (or) a mutant cell may be divided into two mutant cells (or) a normal cell may be lost (or) a mutant may be lost in a small time interval. It is also evident that the growth rates of normal and mutant cells are not homogeneous due to recessive oncogenesis hypothesis, according to which inactivation of both alleles of a specific genes leads to cancer. So in order to analyse the tumor growth more close to reality, it is needed to develop a density dependent stochastic model with heterogeneous (non-homogeneous) growth and loss rates for normal and mutant cells.

In this study, an attempt is made to fill this gap in this area of research. The First part of the study deals with development of a bivariate stochastic model for a cancer cell growth with the assumption that the growth and loss processes of normal and mutant cells are all poisson with different rates. This model is extended to incorporate the receissive oncognesis hypothesis by assuming that the growth processes of mutant cells is a sum of natural growth and growth due to inactivation of both alleles due to specific genes. In order to analyse the drug efficiency in cancer chemotherapy, another stochastic model is developed with the assumption that the loss process of both normal and mutant cells is a sum of two processes namely, due to natural loss and loss due to chemotherapy. Using the difference differential equations, the joint probability density function of the normal and mutant cells is obtained at any given time 't'. The mean number of normal and mutant cells, the variability of the number of normal and mutant cells and the covariance between the number of normal cells and number of mutant cells are obtained explicitly as function of time. Another variation in these models is considered by developing a two stage stochastic model for malignant cells. Once a malignant cell was generated, the malignant cell may become extinct without mutation or may divide into mutant cells and then it become extinct. So there are two stages attributable to the malignant cells. The joint distribution of the number of malignant cells in both stages is derived in order to obtain the mean tumor size. The variability at a given time 't', the probability of a malignant cell duration in the tumor are also obtained and analysed. The various characteristics of this model are derived and analysed.

Cancer chemotherapy is generally prescribed on cyclic basis. When an anti cancer drug is induced to the body, both normal and mutant cells are killed. The white blood cells count falls to low levels and care is needed to evaluate the status of the patient. If the outcome is not favorable, life threatening fever can develop. An interval of time is

specified, during which the patient can (hopefully) recover. But, the tumor will also grow. At the end of this recovery period the cycle of chemotherapy is usually begins again. In order to have affective administration of chemotherapy, this situation is modeled through developing a stochastic model for mutant cell growth under chemotherapy. using the difference differential equation, the Laplace transformations of the tumor size probabilities in both states of the patients namely, under recovery and under chemotherapy are obtained. Assuming the recovery period follows an exponential distribution, the mean and variance of the tumor size and the probability of extinction of the tumor are obtained under the equilibrium conditions.

These models are very useful for understanding the origin and development of malignant tumors and also useful for effective administration of chemotherapy. These models also include some of the earlier models as particular cases for specific or limiting values of the parameters. The study also focused on development of stochastic models for cancer growth. The statistical measures like average number of normal cells, average number of mutant cells, variances of normal and mutant cells, covariance between number of normal and mutant cells are derived through the developed model.

1.4 ORGANIZATION OF THE BOOK

This study is presented into five chapters. The chapter wise outline of the book is as follows. Chapter one of the book is to give a brief resume on previous research on cancer cell growth models. A brief introduction of the problem, the motivation of the present work are also given. The short description on the organization of the chapters is presented. Chapter two is on the development and analysis of stochastic models with heterogeneous growth rates and loss rates for normal and mutant cells under spontaneous mutation, proliferation and loss processes. The recessive oncogenesis hypothesis is also incorporated in the model. Another bivariate model for normal and mutant cells is developed and analyzed with the assumption that the loss due to drug administration. The various characteristics of the models are derived and analyzed under transient conditions. Chapter three is devoted to study the two stage stochastic models for malignant cells. The joint probability generating functions of number of malignant cells in both states are derived and analyzed. The duration of the malignant cell in the tumor is analysed through deriving the survival probability. The mean and variance of the tumor size are also obtained and analysed. Chapter four is concerned with the development and analysis of the stochastic model for malignant cell growth under chemotherapy. The Laplace

transformations of the tumor size distribution when the patient is under recovery and chemotherapy are derived and analysed. The mean and variance of the tumor size and the probability of extinction of the tumor are derived under equilibrium conditions. Chapter five is to summarized the results obtained in the earlier chapters with conclusions. The scope for further study in this area of research is also mentioned.

Chapter – 2

Stochastic Model for Tumor Growth with Spontaneous Mutation and Proliferation

2.1 INTRODUCTION

The cell kinetics plays a vital role in the growth of tumors. The spontaneous mutation and proliferation process of cells are random in nature. The growth of a tumor can be analyzed through the nature of spontaneous mutation and proliferation of cells in the tumor. Several authors have developed stochastic Models for the growth of mutant cell population with the assumption that the growth rates of normal and mutant cells are homogeneous. However it is interesting to note that the growth rates of normal and mutant cells are not homogeneous, since the proliferation of normal and mutant cells are not homogenous, since the proliferation of normal and mutant cells is effected by various factors. In order to analyse the tumor growth, a Bivariate stochastic model for normal and mutant cell growth with heterogeneous growth and loss rates is needed.

In this chapter, a Bivariate stochastic model for normal and mutant cell growth is developed with an assumption that the growth and loss processes of mutant and normal cells are Poisson with different growth rates and loss rates. Using the difference differential equations and the cumulant generating functions, the expected number of normal and mutant cells at time t, the variability of the normal and mutant cells and the covariance between normal and mutant cells are also derived and analyzed. In section 3, this model is extended by considering that the growth of mutant cells is much faster than the normal cells, because of the fact that the growth of mutant cells is a sum of natural growth and the growth due to inactivation of allele gene. The Joint probability generating function of normal and mutant cells at time 't' is derived. The tumor behaviour is analysed by deriving the various characteristics of the model. In section 4, a stochastic model for mutant and normal cell growth when the patient is under chemotherapy is developed by assuming that the loss process of normal and mutant cells is the sum of natural loss and loss due to chemotherapy. The Joint probability generating function for the mutant and normal cells is derived by using the difference differential equations and the drug sensitivity is also analyzed. These models are very useful for analyzing the tumor growth and to administer the chemotherapy more effectively.

2.2 STOCHASTIC MODEL FOR NORMAL AND MUTANT CELL GROWTH WITH HETEROGENEITY

In this section, the author has considered the proliferation of both mutant and normal cells can be approximated by stochastic processes. It is assumed that the growth process of the normal cell is Poisson with parameter b_2. The growth process of the mutant cell is Poisson with parameters 'α' and 'b_1' for normal cell to mutant cell and mutant cell to mutant cell respectively. The loss process of normal and mutant cells are also Poisson with parameters d_1 and d_2 respectively. Also considered that the proliferation of cells are independent. With these assumptions, the postulates of the model are.

1. The probability that the normal cell divides in to two normal cells during a small interval of time 'h' is $b_2h+o(h)$.
2. The probability that a normal cell divides into one normal and one mutant cell during the small interval of time 'h' is $\alpha h+o(h)$.
3. The probability that a mutant cell is divides into two mutant cells during a small interval of time 'h' is $b_1h+o(h)$.
4. The probability that a normal cell is lost during a small interval of time 'h' is $d_1h+o(h)$.
5. The probability that the loss of a mutant cell during a small interval of time 'h' I $d_2h+o(h)$.
6. The probability that there is no growth or loss of either normal cell or mutant cell during a small interval of time 'h' is $1-(b_1+b_2+\alpha+d_1+d_2)h+o(h)$.
7. The probability that the occurrence of other than the above events during a small interval of time 'h' is o (h) and
8. The events in non-overlapping intervals of time are stochastically independent.

Let $P_{n,\,m}(t)$ be the probability that there are 'n' normal cells and 'm' mutant cells at time 't'. with the above postulates, the differential equations of the model are:

$$\begin{aligned}P_{n,m}(t+h) &= P_{n,m-1}(t)(m-1)b_1h + P_{n,m-1}(t)n\alpha h + P_{n-1,m}(t)(n-1)b_2h \\ &+P_{n+1,m}(t)d_1(n+1)h + P_{n,m+1}(t)d_2(m+1)h \\ &+P_{n,m}(t)\left[1-(mb_1+n\alpha+nb_2+nd_1+md_2)h\right]+o(h);\ m,n\geq 1 \qquad (2.2.1)\end{aligned}$$

$$P_{1,0}(t+h) = P_{2,0}(t)2d_1h + P_{1,1}(t)d_2h + P_{1,0}(t)\left[1-(b_2+\alpha+d_1)h\right]+o(h) \qquad (2.2.2)$$

$$P_{0,1}(t+h) = P_{1,0}(t)d_1h + P_{0,2}(t)2d_2h + P_{0,1}(t)\left[1-(b_1+d_2)h\right] + o(h) \tag{2.2.3}$$

$$P_{0,0}(t+h) = P_{1,0}(t)d_1h + P_{0,1}(t)d_2h + P_{0,0}(t) + o(h) \tag{2.2.4}$$

Therefore the difference differential equations of the model are

$$\begin{aligned}\frac{d}{dt}P_{n,m}(t) = &-(mb_1 + n\alpha + nb_2 + nd_1 + md_2)P_{n,m}(t) + (m-1)b_1P_{n,m-1}(t) \\ &+ n\alpha P_{n,m-1}(t) + b_2(n-1)P_{n-1,m}(t) + d_1(n+1)P_{n+1,m}(t) \\ &+ (m+1)d_2P_{n,m+1}(t); \qquad m \geq 1, n \geq 1\end{aligned} \tag{2.2.5}$$

$$\frac{d}{dt}P_{1,0}(t) = -(b_2 + \alpha + d_1)P_{1,0}(t) + 2d_1P_{2,0}(t) + d_2P_{1,1}(t) \tag{2.2.6}$$

$$\frac{d}{dt}P_{0,1}(t) = -(b_1 + d_2)P_{0,1}(t) + d_1P_{1,1}(t) + 2d_2P_{0,2}(t) \tag{2.2.7}$$

$$\frac{d}{dt}P_{0,0}(t) = d_1P_{1,0}(t) + d_2P_{0,1}(t) \tag{2.2.8}$$

With the initial condition $P_{N_0,M_0}(0) = 1$

i.e. initially when the tumor is identified there are N_0 normal cells and M_0 mutant cells in the tumor.

Let $P(x,y;t)$ be the Joint probability generating function of $P_{n,m}(t)$. i.e.

$$P(x,y;t) = \sum_{m=0}\sum_{n=0} x^n y^n P_{n,m}(t) \tag{2.2.9}$$

Multiplying the equations (2.2.5) to (2.2.8) with $x^n y^n$ and summing over all m and n_1 we have

$$\begin{aligned}\frac{d}{dt}P(x,y;t) = \sum_{m=1}\sum_{n=1} &\left[-(mb_1 + n\alpha + nb_2 + nd_1 + md_2)x^n y^m P_{n,m}(t)\right. \\ &+ (m-1)b_1x^n y^m P_{n,m-1}(t) + n\alpha x^n y^m P_{n,m-1}(t) \\ &+ b_2(n-1)x^n y^m P_{n-1,m}(t) + d_1(n+1)x^n y^m P_{n+1,m}(t) \\ &\left.+ (m+1)d_2x^n y^m P_{n,m+1}(t)\right] + 2d_1xP_{2,0}(t) + d_2xP_{1,1}(t) \\ &- (b_2 + \alpha + d_1)xP_{1,0}(t) + d_1yP_{1,1}(t) + 2d_2yP_{0,2}(t) \\ &- (b_1 + d_2)yP_{0,1}(t) + d_1P_{1,0}(t) + d_2P_{0,1}(t)\end{aligned} \tag{2.2.10}$$

Reorgansing the terms and after simplification the equation (2.2.10) becomes,

$$\frac{d}{dt}P(x,y;t)=b_1\left[y^2\sum_m\sum_n(m-1)x^n y^{m-2}P_{n,m-1},(t)-y\sum_m\sum_n mx^n y^{m-1}P_{n,m}{}^{(t)}\right]$$

$$+d_1\left[\sum_m\sum_n(n+1)x^n y^m P_{n+1,m}{}^{(t)}-x\sum_m\sum_n nx^{n-1}y^m P_{n,m}{}^{(t)}\right]$$

$$+b_2\left[x^2\sum_m\sum_n(n-1)x^{n-2}y^m P_{n-1,m}{}^{(t)}-x\sum_m\sum_n nx^{n-1}y^m P_{n,m}{}^{(t)}\right]$$

$$+d_2\left[x\sum_m\sum_n(m+)y^{m-2}P_{n,m-1}{}^{(t)}-y\sum_m\sum_n mx^n y^{m-1}P_{n,m}{}^{(t)}\right]$$

$$+\alpha\left[xy\sum_m\sum_n nx^{n-1}y^{m-1}P_{n,m+1}{}^{(t)}-x\sum_m\sum_n nx^{n-1}y^m P_{n,m}{}^{(t)}\right] \qquad (2.2.11)$$

Further simplification of the equation (2.2.11), will give

$$\frac{d}{dt}P(x,y;t)=b_1\left[y^2\frac{\partial}{\partial y}P(x,y;t)-y\frac{\partial}{\partial y}P(x,y;t)\right]$$

$$+d_1\left[\frac{\partial}{\partial x}P(x,y;t)-x\frac{\partial}{\partial x}P(x,y;t)\right]$$

$$+b_2\left[x^2\frac{\partial}{\partial x}P(x,y;t)-x\frac{\partial}{\partial x}P(x,y;t)\right]$$

$$+d_2\left[\frac{\partial}{\partial y}P(x,y;t)-y\frac{\partial}{\partial y}P(x,y;t)\right]$$

$$+\alpha\left[xy\frac{\partial}{\partial x}P(x,y;t)-x\frac{\partial}{\partial x}P(x,y;t)\right] \qquad (2.2.12)$$

This implies that

$$P(x,y;t)=\left[x^2b_2+x(\alpha y-d_1-b_2+\alpha)+d_1\right]\frac{\partial}{\partial x}P(x,y;t)$$

$$+\left[b_1y^2-(b_1+d_2)y+d_2\right]\frac{\partial}{\partial y}P(x,y;t) \qquad (2.2.13)$$

We can obtain the characteristics of the model by using the joint cumulant generating function of $P_{n,m}(t)$. Taking $x=e^u$ and $y=e^v$ and denoting $K(U,V;t)$ as the Joint Cumulant generating function of $P_{n,m}(t)$, the equation (2.2.13) gives

$$\frac{\partial}{\partial t}K(u,v;t)=\left[b_2e^u-(d_1+b_2+\alpha)+\alpha e^v+d_1e^u\right]\frac{\partial}{\partial u}K(u,v;t)$$

$$+\left[b_1e^v-(b_1+d_2)+d_2e^{-v}\right]\frac{\partial}{\partial v}K(u,v;t) \qquad (2.2.14)$$

Let $m_{i,j}(t)$ denote the moments of order (i,j) of normal and mutant cells at time 't'. Then the differential equations governing $m_{i,j}(t)$ are obtained as

$$\frac{\partial}{\partial t} m_{1,0}(t) = (b_2 - d_1) m_{1,0}(t) \tag{2.2.15}$$

$$\frac{\partial}{\partial t} m_{0,1}(t) = \alpha m_{1,0}(t) + (b_1 - d_2) m_{0,1}(t) \tag{2.2.16}$$

$$\frac{\partial}{\partial t} m_{2,0}(t) = (b_2 + d_1) m_{1,0}(t) + 2(b_2 - d_1) m_{2,0}(t) \tag{2.2.17}$$

$$\frac{\partial}{\partial t} m_{1,1}(t) = (b_2 - d_1 + b_1 - d_2) m_{1,1}(t) + \alpha m_{2,0}(t) \tag{2.2.18}$$

$$\frac{\partial}{\partial t} m_{0,2}(t) = 2\alpha m_{1,1}(t) + \alpha m_{1,0}(t) + (b_1 + d_2) m_{0,1}(t) + 2(b_1 - d_2) m_{0,2}(t) \tag{2.2.19}$$

From the equation (2.2.15) we have

$$m_{1,0}(t) = N_0 e^{(b_2 - d_1)t} \tag{2.2.20}$$

Substituting (2.2.20) in the equation (2.2.16), we get

$$\frac{d}{dt} m_{0,1}(t) + (d_2 - b_1) m_{0,1}(t) = \alpha N_0 e^{(b_2 - d_1)t} \tag{2.2.21}$$

Solving the equation (2.2.21), we get

$$m_{0,1}(t) = \frac{\alpha N_0 e^{(b_2 - d_1)t}}{(d_2 + b_2 - b_1 - d_1)} + \frac{\alpha N_0 e^{(b_1 - d_2)t}}{(d_1 + b_1 - b_2 - d_2)} + M_0 e^{(b_1 - d_2)t} \tag{2.2.22}$$

On simplification the equation (2.2.22) become

$$m_{0,1}(t) = A\left[e^{(b_2 - d_1)t} - e^{(b_1 - d_2)t}\right] + M_0 e^{(b_1 - d_2)t} \quad ; \quad \text{Where } A = \frac{\alpha N_0}{d_2 + b_2 - (b_1 + d_1)} \tag{2.2.23}$$

Consider the equation (2.2.17) and substituting the equation (2.2.20) in (2.2.17), we have

$$\frac{d}{dt} m_{2,0}(t) + 2(d_1 - b_2) m_{2,0}(t) = (b_2 + d_1) N_0 e^{(b_2 - d_1)t} \tag{2.2.24}$$

Solving the equation (2.2.24), we get

$$m_{2,0}(t) = \left(\frac{b_2 + d_1}{d_1 - b_2}\right) N_0 e^{-(d_1 - b_2)t} + \left(\frac{b_2 + d_1}{b_2 - d_1}\right) N_0 e^{-2(d_1 - b_2)t} \tag{2.2.25}$$

On simplification, the equation (2.2.25) become

$$m_{2,0}(t) = B e^{(b_2 - d_1)t}\left[1 - e^{(b_2 - d_1)t}\right]; \text{ where } B = \left(\frac{b_2 + d_1}{d_1 - b_2}\right) N_0 \tag{2.2.26}$$

Consider the equation (2.2.18) and substituting the value of $m_{2,0}(t)$ as in the equation (2.2.26), we have

$$\frac{d}{dt}m_{1,1}(t)+(d_1+d_2-b_1-b_2)m_{1,1}(t)=\alpha Be^{(b_2-d_1)t}\left[1-e^{(b_2-d_1)t}\right] \quad (2.2.27)$$

Solving the equation (2.2.27), we get

$$m_{1,1}(t)=\frac{\alpha(b_2+d_1)}{(d_1-b_2)}N_0e^{(b_2-d_1)t}\left[\frac{1}{d_2-b_1}-\frac{e^{(b_2-d_1)t}}{b_2+d_2-b_1-d_1}\right]$$

$$+\frac{\alpha(b_2+d_1)N_0}{(d_2-b_1)(b_2+d_2-b_1-d_1)}e^{(b_1+b_2-d_1-d_2)t} \quad (2.2.28)$$

On simplification the equation (2.2.28), gives

$$m_{1,1}(t)=De^{(b_2-d_1)t}\left[\frac{(b_2+d_2-b_1-d_1)-(d_2-b_1)e^{(b_2-d_1)t}}{d_1-b_2}+e^{(b_1-d_2)}\right]$$

where $D=\frac{\alpha(b_2+d_1)N_0}{(d_2-b_1)(b_2+d_2-b_1-d_1)}$ (2.2.29)

consider the equation (2.2.19) and substituting the values of $m_{1,0}(t), m_{0,1}(t)$ and $m_{1,1}(t)$ as in the equations (2.2.20), (2.2.23) and (2.2.28) and solving it, we get

$$m_{0,2}(t)=e^{2(b_1-d_2)t}\left[(E+H+I)\left(e^{(b_2-d_1)t}-1\right)+F\left(e^{2(d_1-b_2)t}-1\right)\right.$$

$$\left.+G\left(e^{(b_2+b_1-d_1-d_2)t}-1\right)-(J-K)\left(e^{(b_1-d_2)t}-1\right)\right]$$

Where $A=\frac{\alpha N_0}{d_2+b_2-d_1-b_1}$; $B=\left(\frac{b_2+d_1}{d_1-b_2}\right)N_0$

$D=\frac{\alpha(b_2+d_1)N_0}{(d_2-b_1)(d_2+b_2-d_1-b_1)}$; $E=\frac{2\alpha D(b_2+d_2-b_1-d_1)}{(d_1-b_2)(b_2-d_1)}$

$F=\alpha D\left(\frac{d_2-b_1}{(d_1-b_2)^2}\right)$; $G=\frac{2\alpha D}{b_1+b_2-d_1-d_2}$; $H=\frac{\alpha}{b_2-d_1}$;

$I=\frac{A(b_1+d_2)}{(b_2-d_1)}$; $J=\frac{A(b_2+d_2)}{(b_1-d_2)}$; $K=\frac{M_0}{b_1-d_2}$

…(2.2.30)

From equations (2.2.20), (2.2.23), (2.2.26), (2.2.29) and (2.2.30) the values of $m_{10}(t)$, $m_{01}(t)$, $m_{20}(t)$, $m_{11}(t)$ and $m_{02}(t)$ are computed for various values of the parameters $\alpha, b_1, b_2, d_1, d_2; N_0, M_0$ and presented in Table (2.1.)

TABLE – 2.1:
The values of m_{10} (t), m_{01} (t), m_{20} (t), m_{11} (t), m_{02} (t) for various values of the parameters

α	b_1	b_2	d_1	d_2	M_0	N_0	t	$m_{10}(t)$	$m_{01}(t)$	$m_{11}(t)$	$m_{20}(t)$	$m_{02}(t)$
0.05	0.38	0.021	0.932	1.43	5	10	5	0.105	0.042	0.005	0.109	0.039
0.29									0.132	0.028		1.484
0.64									0.265	0.064		7.529
0.98									0.392	0.098		17.65
0.05	0.03	0.43	0.32	0.93	5	10	5	73.155	2.631	17.617	536.309	$7.168\text{x}10^{-7}$
	0.42								4.051	24.053		0.008
	0.53								4.816	26.704		0.13
	0.68								6.408	31.189		0.192
0.95	0.08	0.43	0.172	0.23	5	10	5	36.328	75.504	338.64	223.168	154.774
		0.584						78.46	126.287	$1.306\text{x}10^{3}$	985.612	275.125
		0.693						135.312	186.218	$3.385\text{x}10^{3}$	$2.815\text{x}10^{3}$	388.831
		0.945						477.033	485.929	$3.105\text{x}10^{4}$	$3.219\text{x}10^{4}$	899.71
0.95	0.08	1.945	0.342	0.23	2	5	2	123.401	66.04	$1.986\text{x}10^{4}$	$4.169\text{x}10^{3}$	370.97
						10		246.802	130.601	$3.972\text{x}10^{3}$	$8.330\text{x}10^{3}$	872.742
						15		370.203	195.162	$5.957\text{x}10^{3}$	$1.251\text{x}10^{4}$	$1.375\text{x}10^{3}$
						20		493.603	259.723	$7.943\text{x}10^{3}$	$1.668\text{x}10^{4}$	$1.876\text{x}10^{3}$
0.46	0.08	0.945	0.099	0.23	2	5	2	4.953	1.874	0.08	1.91	6.223
						10		9.906	2.269	0.16	3.82	13.027
						15		14.86	2.664	0.239	5.73	19.83
						20		19.813	3.059	0.319	7.64	26.634
0.95	0.08	1.945	0.342	0.23	2	5	2	123.401	66.04	$1.980\text{x}10^{3}$	$4.169\text{x}10^{-3}$	370.97
							4	$3.046\text{x}10^{3}$	$1.642\text{x}10^{3}$	$1.414\text{x}10^{0}$	$2.642\text{x}10^{0}$	$3.557\text{x}10^{3}$
							6	$7.516\text{x}10^{4}$	$4.054\text{x}10^{4}$	$8.69\text{x}10^{8}$	$1.612\text{x}10^{9}$	$2.964\text{x}10^{4}$
							8	$1.855\text{x}10^{0}$	$1.001\text{x}10^{0}$	$5.296\text{x}10^{11}$	$9.819\text{x}10^{11}$	$2.143\text{x}10^{5}$
0.05	0.08	0.945	0.099	0.23	2	5	2	4.953	1.874	0.08	1.91	6.223
							4	4.907	1.777	0.287	3.766	7.175
							6	4.861	1.701	0.583	5.571	6.144

α	b_1	b_2	d_1	d_2	M_0	N_0	t	$m_{10}(t)$	$m_{01}(t)$	$m_{11}(t)$	$m_{20}(t)$	$m_{02}(t)$
							8	4.815	1.642	0.941	7.324	4.642
0.05	0.08	0.095	0.099	0.23	3	2	2	1.981	2.376	0.032	0.764	1.198
							4	1.963	1.913	0.115	1.507	1.749
							6	1.944	1.57	0.233	2.228	1.736
							8	1.926	1.314	0.376	2.929	1.45
0.95	0.08	1.945	0.342	0.23	5	10	5	3.026×10^{4}	1.632×10^{4}	7.03×10^{7}	1.306×10^{8}	2.745×10^{4}
			0.562					1.007×10^{4}	6.211×10^{3}	1.128×10^{7}	1.837×10^{7}	1.34×10^{4}
			0.834					2.585×10^{3}	1.937×10^{3}	1.229×10^{6}	1.665×10^{6}	5.869×10^{3}
			0.992					1.173×10^{3}	1.004×10^{3}	3.501×10^{5}	4.206×10^{5}	3.792×10^{3}
0.05	0.08	0.095	0.099	0.23	5	10	5	9.768	3.943	0.852	9.35	11.48
				0.49					1.636	0.609		0.28
				0.69					0.947	0.487		0.024
				0.74					0.842	0.462		0.013
0.95	0.08	1.945	0.342	0.23	2	5	2	123.401	66.04	1.986×10^{3}	4.169×10^{3}	370.19
					4				67.518			369.083
					6				68.997			367.195
					8				70.476			365.308
0.05	0.08	0.095	0.099	0.23	2	5	2	4.953	1.874	0.08	1.91	6.222
					4				3.352			4.336
					6				4.831			2.449
					8				6.31			0.562
0.05	0.38	0.021	0.932	1.43	50	10	5	0.105	0.271	0.005	0.109	0.037
0.29									0.36	0.028		1.483
0.64									0.493	0.064		7.528
0.98									0.62	0.098		17.649

From the equations (2.2.20), (2.2.23) and Table (2.1) it is observed that the average number of mutant cells at any given time is an increasing function of 'α' when other parameters are fixed. We also observe that $m_{0,1}(t)$ at any given time is a decreasing function of 'd_2' and $m_{1,0}(t)$ in a decreasing function of 'd_1' when other parameters remain fixed. It is further observed that $m_{0,1}(t)$ at any given time is an increasing function of b_1 and b_2 when the other parameters are fixed. It is also observed that $m_{10}(t)$ is independent of b_1. The expected number of both mutant and normal cell populations are increasing functions of time 't' when $(\alpha + b_1 + b_2) > (d_1 + d_2)$. It is further observed that the expected number of both mutant and normal cell populations are decreasing functions of 't' when $(\alpha + b_1 + b_2) < (d_1 + d_2)$. The expected number of mutant cells is an increasing function of M_0 when $(\alpha + b_1 + b_2) > d_1 + d_2;\ d_1 > d_2$. The expected number of both mutant cells and normal cells are increasing functions of N_0 when other parameters remains fixed. The average number of normal and mutant cells are increasing function of 't' for $b_2 > d_2$ and $b_1 + \alpha > d_2$ respectively. Similarly it is observed that the average number of mutant cell is a decreasing function of t when $b_1 + \alpha < d_2$ for fixed values of d_1 and d_2.

From the equation (2.2.26), (2.2.30) and Table (2.1), the variance of the number of the mutant cells is an increasing function of 'α' as the other parameters remain fixed. It is also observed that the variance of the number of mutant cells is a decreasing function of d_2 when other parameters remain fixed. The variances of number of both normal and mutant cells are increasing functions of b_2 when other parameters are fixed. The variances of number of both normal and mutant cells are decreasing functions of 'd_1' when the other parameters remain fixed. The variance of number of normal cells is an increasing function of b_1 as the other parameter are fixed. It is further observed that the variances of both normal and mutant cells are increasing functions of 't' when $b_1 + b_2 + \alpha > d_1 + d_2$. The variance of number of mutant cells is a decreasing function of 't' when $b_2 < d_2$ and the variance of number of normal cells is an increasing function of time 't' when $b_2 < d_2$. The variances of number of both normal cells and mutant cells are increasing functions of 'N_0' when the other parameters remain fixed. The variance of the number of mutant cells is decreasing function of 'M_0' when other parameters remain fixed.

From the equation (2.2.29) and table (2.1) we observe that the covariance between the number of Normal and mutant cells is an increasing function of α, b_2 and b_1 as the other parameters remain fixed. It is also observed that $m_{11}(t)$ is a decreasing function of d_1

and d_2 as the other parameters remain fixed. It is also observed that there is a positive dependence between the number of normal and mutant cells. It is further observed that the covariance between the number of normal and mutant cells is an increasing function of 't' when $b_1 + b_2 + \alpha > d_1 + d_2$. It is also observed that the covariance between the number of the mutant cells and normal cells is an increasing function of N_0as $M_0 < N_0$.

2.3 STOCHASTIC MODEL FOR MUTANT CELL GROWTH WITH INACTIVATION OF ALLELE GENES

In this chapter, the author has analyzed a stochastic model for normal and mutant cell growth after the tumor is formed. Once the tumor in formed, the proliferation of mutant cells is much faster than the proliferation of normal cells. Hence the proliferation process of normal and mutant cells are not homogenous. This can be modeled by incorporating the additional proliferation process for the growth of the mutant cells which may be due to inactivation of allele genes. In this section we assume that the proliferation processes of (i) the normal cell to two normal cells (ii) normal cell to one normal and one mutant cell (iii) mutant cell to two mutant cells and (iv) the additional proliferation due to inactivation of the allele are all poisson with parameters b-α, α, b and β respectively. The loss processes of the normal and mutant cells are also poisson with parameter 'd' with these options, the postulates of the model are

1. The probability that a normal cell is divided into two normal cells during a small time interval 'h' is (b-α) h + o (h).
2. The probability that a normal cell divided into one normal and one mutant cell during a small time interval 'h' is α h +o (h).
3. The probability that one mutant cell divided into two mutant cells during a small time interval 'h' is b h + o (h).
4. The probability that one normal cell is divided into one normal and one mutant cell due to inactivation of allege gene during a small time interval 'h' is β h + o (h).
5. The probability that one mutant cell is divided into two mutant cells due to inactivation of allele during a small time interval 'h' is βh + o (h).
6. The probability that one normal cell is dead during a small interval of time 'h' is d h + o (h).
7. The probability that one mutant cell is dead during a small interval of time 'h' is d h + o (h).

8. The probability that the occurrence of other than the above events during a small interval of time 'h' is o (h) and
9. The occurrence of the events in non-over lapping interval of time are stochastically independent.

Let $P_{n,m}(t)$ be the probability that there are 'n' normal cells and 'm' mutant cells at time 't'. With this structure the difference equations of the model are

$$\begin{aligned}P_{n,m}(t+h) &= P_{n,m-1,}(t)(b+\beta)(m-1)h + P_{n,m-1}(t)(\alpha+\beta)nh \\ &+P_{n-1,m}(t)(b-\alpha)(n-1)h \\ &+P_{n+1,m}(t)d(n+1)h + P_{n,m+1}(t)d(m+1)h \\ &+P_{n,m}(t)\left[1-(m+n)(b+\beta+d)h+o(h)^2\right] \\ &+\sum_{i\neq 0,1} P_{n\pm i,m\pm i}(t)o(h), \qquad m,n\geq 1 \end{aligned} \tag{2.3.1}$$

$$P_{1,0}(t+h) = P_{2,0}(t)2dh + P_{1,1}(t)dh + P_{1,0}(t)\left[1-(b+\beta+d)h+o(h)^2\right] \tag{2.3.2}$$

$$P_{0,1}(t+h) = P_{1,1}(t)dh + P_{0,2}(t)2dh + P_{0,1}(t)\left[1-(b+\beta+d)h+o(h)^2\right] \tag{2.3.3}$$

$$P_{0,0}(t+h) = P_{1,0}(t)dh + P_{0,1}(t)dh + P_{0,0}(t)+o(h) \tag{2.3.4}$$

Therefore the difference differential equations of the model are

$$\begin{aligned}\frac{d}{dt}P_{n,m}(t) &= -(m+n)(b+\beta+d)P_{n,m}(t)+(m-1)(b+\beta)P_{n,m-1}(t) \\ &+(\alpha+\beta)nP_{n,m-1}(t)+(b-\alpha)(n-1)P_{n-1,m}(t) \\ &+d(n+1)P_{n+1,m}(t)+(m+1)dP_{n,m+1}(t) \text{ for } m\geq 1, n\geq 1 \end{aligned} \tag{2.3.5}$$

$$\frac{d}{dt}P_{1,0}(t) = -(b+\beta+d)P_{1,0}(t)+2dP_{2,0}(t)+dP_{1,1}(t) \tag{2.3.6}$$

$$\frac{d}{dt}P_{0,1}(t) = -(b+\beta+d)P_{0,1}(t)+dP_{1,1}(t)+2dP_{0,2}(t), \text{ and} \tag{2.3.7}$$

$$\frac{d}{dt}P_{0,0}(t) = dP_{1,0}(t)+dP_{0,1}(t) \tag{2.3.8}$$

Let $P(x,y;t)$ be the Joint probability generating function of $P_{n,m}(t)$,

i.e $P(x,y;t) = \sum_{m=0}\sum_{n=0} x^n y^m P_{n,m}(t)$ (2.3.9)

Multiplying the equations (2.3.5) to (2.3.8) by x^n and y^m and summing over all n and m, and after simplification we have

$$\frac{d}{dt}P(x,y;t) = -(b+\beta+d)\left[\sum_m\sum_n (m+n)x^n y^m P_{n,m}(t)\right]$$

$$+d\left[\sum_m\sum_n (n+1)x^n y^m P_{n+1,m}(t)+\sum_m\sum_n (m+1)x^n y^m P_{m+1,n}(t)\right]$$

$$+(b+\beta)\left[\sum_m\sum_n (m-1)x^n y^m P_{n,m-1}(t)\right]$$

$$+(b-\alpha)\left[\sum_m\sum_n (n-1)x^n y^m P_{n-1,m}(t)\right]$$

$$+(\alpha+\beta)\left[\sum_m\sum_n nx^n y^m P_{n-1,m}(t)\right] \qquad (2.3.10)$$

This implies

$$\frac{d}{dt}P(x,y;t)=-(b+\beta+d)\left[y\frac{\partial}{\partial y}P(x,y;t)+x\frac{\partial}{\partial x}P(x,y;t)\right]$$

$$+d\left[\frac{\partial}{\partial y}P(x,y;t)+\frac{\partial}{\partial x}P(x,y;t)\right]$$

$$+(b+\beta)\left[y^2\frac{\partial}{\partial y}P(x,y;t)\right]+(b-\alpha)\left[x^2\frac{\partial}{\partial x}P(x,y;t)\right]$$

$$+(\alpha+\beta)\left[xy\frac{\partial}{\partial x}P(x,y;t)\right] \qquad (2.3.11)$$

On simplification the equation (2.3.11) become

$$\frac{d}{dt}P(x,y;t)=\left[(b+\beta)y^2-(b+\beta+d)y+d\right]\frac{\partial}{\partial y}P(x,y;t)$$

$$+\left[-(b-\alpha)x^2-\left\{(b+\beta+d)-(\alpha+\beta)y\right\}x+d\right]\frac{\partial}{\partial x}P(x,y;t) \qquad (2.3.12)$$

The equation (2.3.12) can be solved by using lagrange's method we have the following auxiliary equations.

$$-\frac{dt}{1}=\frac{dx}{x^2(b-\alpha)+x\left[(\alpha+\beta)y-(b+\beta)-d\right]+d}=\frac{dy}{y^2(b+\beta)-y(b+\beta+d)+d}$$

(i) (ii) (iii)

$$=\frac{dp(x,y;t)}{\theta} \qquad (2.3.13)$$

(iv)

Consider the relation (iv) in the equation (2.3.13), and on simplification, we have

$\theta_1=P(x,y;t)$ where θ_1 is an integrating constant (2.3.14)

Considering (i) and (iii) of the equations (2.3.13), we have.

$$-\frac{dt}{1}=\frac{dy}{y^2(b+\beta)-y(b+\beta+d)+d}$$

Which implies that

$$-\int dt=\int \frac{1}{\left[(b+\beta)y-d\right](y-1)}dy$$

The solution of this equations is

$$-t=\log\left[\left(\frac{(b+\beta)y-d}{b+\beta}\right)^{\frac{b+\beta}{d-(b+\beta)}}(y-1)^{\frac{1}{b+\beta-d}}\right] \tag{2.3.15}$$

On simplification the equation (2.3.15) become

$$\theta_2=\left(\frac{(b+\beta)y-d}{1-y}\right)e^{-(b+\beta-d)t}$$

Where, θ_2 is the integrating constant. (2.3.16)

Consider the relations (ii) and (iii) in the equations (2.3.14) then

$$\frac{dx}{x^2(b-\alpha)+x\left[(\alpha+\beta)y-(b+\beta+d)\right]}=\frac{dy}{y^2(b+\beta)-(b+\beta+d)y+d} \tag{2.3.17}$$

The equation (2.3.17) can be rewritten as

$$\frac{dx}{dy}=\frac{x^2(b-\alpha)}{\left[y(b+\beta)-d\right](y-1)}+\frac{x\left[(\alpha+\beta)y-(b+\beta+d)\right]}{\left[y(b+\beta)-d\right](y-1)}$$

$$+\frac{d}{\left[y(b+\beta)-d\right](y-1)} \tag{2.3.18}$$

The equation (2.3.18) is in the form of the Ricatti first order differential equation [Piaggio (1950)]. x =y is a particular solution and the substitution of $x=y+\frac{1}{V(y)}$ in equation (2.3.18) leads to

$$\frac{dV}{dy}=\frac{\left[2(b+\beta)-(\alpha+\beta)\right]y-(b+\beta+d)}{\left[y(b+\beta)-d\right](y-1)}V+\frac{(\alpha-b)}{\left[y(b+\beta)-d\right](y-1)} \tag{2.3.19}$$

Solving the equation (2.3.19), we get

$$V(y)=\left[(b+\beta)y-d\right]^{\frac{-A}{b+\beta}}(1-y)^{-B}\left[(b+\beta-d)\int\left\{(b+\beta)y-d\right\}^{\frac{A}{b+\beta}-1}(1-y)^{B-1}dy+\theta_3\right] \tag{2.3.20}$$

Where, θ_3 is the integrating constant. Rearranging the equation (2.3.20), we have

$$V(y)=\frac{(b-\alpha)(b+\beta+z)}{(b+\beta-d)A}F\left(1-B,1,\frac{A}{b+\beta}+1,\frac{-z}{b+\beta}\right)+\theta_3(by-d)^{\frac{-A}{b+\beta}}(1-y)^{-B}$$

Where $A=\dfrac{(b+\beta)^2-(b+\beta+d)+(\alpha+\beta)d}{b+\beta-d}$

$$B=\frac{b-\alpha-d}{b+\beta-d};\qquad z=\frac{(b+\beta)y-d}{1-y}$$

and F is the hypergeometric function (2.3.21)

Using the initial condition that at t=0 there are 'N_0' normal cells and 'M_0' mutant cells in the tumor and eliminating the integration constants from (2.3.15), (2.3.16) and (2.3.21), then the general solution of the equation (2.3.9) after simplification is

$$P(x,y;t)=\left(\frac{d+z\ e^{-\delta t}}{b+\beta+ze^{-\delta t}}\right)^{M_0}\left[\frac{d+z\ e^{-\delta t}}{b+\beta+ze^{-\delta t}}+\left\{\left(\frac{b+\beta+ze^{-\delta t}}{b+\beta+z}\right)\left(\phi(z)e^{-\delta t}\right)\right.\right.$$

$$\left.\left.+\left(\frac{1}{x-y}-\phi(x)\right)\left(\frac{b+\beta+z}{b+\beta+ze^{-\delta t}}\right)^{\frac{-A}{b+\beta}-B}e^{\frac{A\delta t}{b+\beta}}\right\}^{-1}\right]^{N_0}$$

Where $\delta=b+\beta-d$ and $\phi(z)=\dfrac{(b+\beta+z)(b-\alpha)}{(b+\beta-d)A}F\left(1-B,1,\dfrac{A}{b+\beta}+1,\dfrac{-z}{b+\beta}\right)$ (2.3.22)

using the equation (2.3.22) we can analyse the model behaviour. The probability that there are 'n' normal cells and 'm' mutant cells at time 't' in the tumor can be obtained by expanding the equation (2.3.22) and collecting the coefficient of x^n and y^m.

The expected number of normal cells in the tumor at time 't' is

$$m_{1,0}(t)=\frac{\partial}{\partial x}P(x,y;t)\Big|_{x=1,y=1}$$

From equation (2.3.22), we have

$$m_{1,0}(t)=N_0e^{(b+\alpha-d)t} \qquad (2.3.23)$$

The expected number of mutant cells in the tumor at time 't' is

$$m_{0,1}(t)=\frac{\partial}{\partial y}P(x,y;t)\Big|_{x=1,y=1}$$

From equation (2.3.23), we have

$$m_{0,1}(t)=A\left[e^{(\alpha-d)t}-e^{((b+\beta)-d)t}\right]+M_0e^{(b+\beta-d)t}\quad \text{where, } A=\left(\frac{\alpha+\beta}{\alpha-\beta}\right)N_0 \qquad (2.3.24)$$

The variability of the normal cells in the tumor at time 't' is

$$m_{2,0}(t) = B.e^{(b+\alpha-d)t}\left(1-e^{(b+\alpha-d)t}\right) \text{ where, } B = \left(\frac{b+\alpha+d}{d-b-\alpha}\right)N_0 \qquad (2.3.25)$$

The covariance between the normal and mutant cells at time 't' is

$$m_{1,1}(t) = De^{(b+\alpha-d)t}\left(1-e^{(b+\beta-d)t}\right)+Ee^{(2b+\alpha-2d)t}\left(e^{\alpha t}-e^{\beta t}\right)$$

Where $D = \frac{B(\alpha+\beta)}{d-\beta-b}; E = \frac{B(\alpha+\beta)}{\beta-\alpha}$ and B is as given in the equation (2.3.25) (2.3.26)

The variability of the mutant cells in the tumor at time 't' is

$$m_{0,2}(t) = e^{2(b+\beta-d)t}\left[\left(e^{(\alpha-\beta)t}-1\right)(F+H)+\left(e^{(\alpha+d-2\beta-b)t}-1\right)(L+1)\right.$$
$$\left.+J\left(e^{(\alpha+d-2b-2\beta)t}-1\right)+G\left(e^{2(\alpha-b-\beta)t}-1\right)+(M-K)\left(e^{(d-b-\beta)t}-1\right)\right]$$

Where

$$L = \frac{2(\alpha+\beta)D}{\alpha+d-2\beta-b}; \qquad F = \frac{2(\alpha+\beta)}{\beta-\alpha}D$$

$$G = \left(\frac{\alpha+\beta}{\alpha-\beta}\right)E; \qquad H = \frac{2(\alpha+\beta)}{\beta-\alpha}E$$

$$I = \frac{(\alpha+\beta)N_0}{\alpha-2\beta+d-b}; \qquad M = \frac{(b+\beta+d)M_0}{(-b-\beta+d)}$$

$$J = \left(\frac{b+\beta+d}{\alpha+d-2b-2\beta}\right)A; \qquad K = \left(\frac{b+\beta+d}{d-b-\beta}\right)A$$

A is as given in the equation (2.3.24), B is a given in the equation (2.3.25) and D, E are as given in the equation (2.3.26). (2.3.27)

From equations (2.3.23) to (2.3.27) the values of $m_{1,0}(t), m_{0,1}(t), m_{2,0}(t), m_{0,2}(t)$ and $m_{1,1}(t)$ are computed for given values of $\alpha, \beta, b, d, M_0, N_0$ and t are presented in table (2.2).

TABLE – 2.2

The values of $m_{10}(t)$, $m_{20}(t)$, $m_{11}(t)$, $m_{02}(t)$ for various values of the parameters

α	β	b	d	M_0	N_0	t	m_{10}	m_{01}	m_{20}	m_{11}	m_{02}
0.043	0.986	0.134	0.46	2	3	5	0.743	145.456	1.269	19.235	$9.466x10^{3}$
0.253							2.125	193.747	7.574	108.755	$1.402x10^{4}$
0.684							18.33	462.318	329.696	$3.362x10^{3}$	$5.403x10^{4}$
0.753							25.88	575.798	615.218	$5.825x10^{3}$	$6.049x10^{4}$
0.653	0.196	0.124	0.86	2	3	5	2.021	1.775	13.633	14.671	91.791
	0.484							2.053		28.094	990.77
	0.749							33.999		52.441	$4.763x10^{3}$
	0.932							45.588		83.637	$2.009x10^{3}$
0.275	0.384	0.124	1.86	2	3	5	0.305	2.542	0.753	0.935	11.101
		0.321					0.818	8.472	3.322	5.11	93.577
		0.392					1.166	12.506	5.744	9.518	222.245
		0.424					1.368	14.848	7.371	12.621	342.715
0.275	0.384	0.124	0.86	2	3	5	0.305	16.172	0.753	4.028	258.478
		0.438					1.468	78.824	8.225	71.595	$4.302x10^{3}$
		0.746					6.846	369.293	99.826	$1.293x10^{3}$	$7.411x10^{4}$
		0.983					22.39	$1.209x10^{3}$	761.005	$1.243x10^{4}$	$7.084x10^{5}$
0.175	0.847	0.845	0.32	2	3	5	97.87	$6.161x10^{3}$	$5.963x10^{3}$	$1.275x10^{5}$	$1.064x10^{7}$
			0.46				49.58	$3.121x10^{3}$	$2.03x10^{3}$	$3.986x10^{4}$	$3.231x10^{6}$
			0.63				20.98	$1.321x10^{3}$	533.718	$9.136x10^{3}$	$7.221x10^{5}$
			0.84				7.566	476.286	115.45	$1.608x10^{3}$	$1.243x10^{5}$
0.128	0.184	0.135	0.32	2	3	5	2.21	11.904	5.575	4.527	384.976
			0.46				1.12	6.031	2.569	1.832	49.5
			0.63				0.474	2.552	0.966	0.578	9.637
			0.84				0.171	0.92	0.309	0.149	2.173
0.128	0.184	0.135	0.84	2	3	1	1.691	2.899	1.412	0.203	15.23
						3	0.538	1.95	0.845	0.302	6.035

α	β	b	d	M_0	N_0	t	m_{10}	m_{01}	m_{20}	m_{11}	m_{02}
						5	0.171	0.917	0.309	0.149	2.164
						7	0.054	0.381	0.102	0.056	0.85
0.175	0.847	0.845	0.32	2	3	1	6.023	21.865	11.695	8.556	49.44
						2	12.09	98.037	70.623	153.408	$1.985x10^{3}$
						3	24.28	395.838	331.821	$1.66x10^{3}$	$3.899x10^{4}$
						4	48.75	$1.565x10^{3}$	$1.432x10^{3}$	$1.512x10^{4}$	$6.605x10^{5}$
0.175	0.847	0.845	0.32	1	3	5	97.87	$5.222x10^{3}$	$5.96x10^{3}$	$1.279x10^{5}$	$9.339x10^{6}$
				2				$6.161x10^{3}$			$1.064x10^{7}$
				3				$7.1x10^{3}$			$1.193x10^{7}$
				4				$8.039x10^{3}$			$1.323x10^{7}$
0.128	0.149	0.135	0.84	1	3	5	0.171	0.842	0.309	0.149	2.007
				2				0.917			2.164
				3				0.993			2.321
				4				1.069			2.478
0.128	0.185	0.135	0.84	2	1	2	0.318	1.332	0.415	0.109	4.147
					2		0.636	1.952	0.83	0.218	7.267
					3		0.954	2.572	1.245	0.327	10.387
					4		1.272	3.191	1.66	0.436	13.507
0.175	0.847	0.845	0.32	2	1	2	4.031	53.287	23.541	51.36	$1.1x10^{3}$
					2		8.062	75.662	47.082	102.272	$1.542x10^{3}$
					3		12.09	98.037	70.623	153.408	$1.985x10^{3}$
					4		16.12	120.412	94.165	204.544	$2.427x10^{3}$

From the equations (2.3.23), (2.3.24) and from Table (2.2), we observe that expected number of both normal and mutant cells at any given time are increasing functions of 'b' when other parameters remain fixed. It is further observed that the average number of both normal and mutant cells at any given time are decreasing functions of 'd' when other parameters remain fixed. The expected number of mutant cells at a given time is an increasing function of β. It is also observed that both $m_{01}^{(t)}$ and $m_{10}^{(t)}$ are increasing functions of 'α' when other parameters remain fixed. We further observe that the average number of mutant cells and normal cells are increasing functions of t, when $(b+\beta+\alpha) > d$ and they are decreasing functions of time t when $(\alpha+\beta+b) < d$. The average number of mutant cells is an increasing function of M_0. The average number of normal cells is an increasing function of N_0 when other parameters remains fixed for the given period 't'. It is also observed that the expected number of normal cells in the tumor are not influenced by β. The value of $m_{01}^{(t)}$ can be reduced by activating the allele gene in the tumor.

From the equations (2.3.25), (2.3.27) and table (2.2) we observe that the variances of number of normal and number of mutant cells are increasing functions of 'd', when other parameters remain fixed. It is also observed that $m_{02}(t)$ is a decreasing function of b and $m_{20}(t)$ is an increasing function of 'b' when other parameters remain fixed. The variance of number of mutant cells is an increasing function of 'β' and variances of number of both normal and mutant cells are increasing functions of 'α' at given time 't' when other parameters remain fixed. It is further observed that the variances of number of both normal and mutant cells are increasing functions of 't' when α+β+b>d and they are decreasing functions of 't' when (α+β+b)<d. the variance of number of mutant cells is an increasing function of M_0 and the variances of number of both mutant and normal cells are increasing functions of N_0 at a given time 't' for other parameters being fixed.

From the equations (2.3.36) and table (2.2) we observe that the covariance between number of mutant and normal cells is positive and increasing function of 'd', $m_{11}(t)$ is positive and decreasing as 'b' is increasing. The dependence between normal and mutant cells is positively increasing as the time increases for the given values of other parameters. We also observe that $m_{11}(t)$ is an increasing function of α and β $m_{11}(t)$ is a decreasing function of 't' as (α+β+b)<d and an increasing function of t as (α+β+b)>d. It is further

observed that the covariance between the number of normal cells and mutant cells is an increasing function of N_0 and not influenced by M_0 when other parameter are fixed. This model includes the model given by Birkhead)1986) when $\beta \to 0$.

2.4 STOCHASTIC MODEL FOR NORMAL AND MUTANT CELL GROWTH UNDER CHEMOTHERAPY

In this section we develop a stochastic model for the growth of normal and mutant cells when the patient is under chemotherapy. In addition to the assumptions made in section 3, here we assume that the loss process of the normal and mutant cells is a sum of two loss processes, one is due to natural loss and the other is due to drug induction. It is also further assumed that the loss processes due to natural and due to drug are also poisson with parameters 'd' and 'θ' respectively. With these assumptions, the difference differential equations of the model are

$$\frac{d}{dt}P_{n,m}(t) = -(m+n)(b+\beta+d+\theta)P_{n,m}(t) + (m-1)(b+\beta)P_{n,m-1}(t)$$

$$+(\alpha+\beta)nP_{n,m-1}(t) + (b-\alpha)(n-1)P_{n-1,m}(t)$$

$$+(d+\theta)(n+1)P_{n+1,m}(t) + (d+\theta)(m+1)P_{n,m+1}(t);\ m \geq 1,\ n \geq 1 \qquad (2.4.1)$$

$$\frac{d}{dt}P_{1,0}(t) = -(b+\beta+d+\theta)P_{1,0}(t) + 2(d+\theta)P_{2,0}(t) + (d+\theta)P_{1,1}(t) \qquad (2.4.2)$$

$$\frac{d}{dt}P_{0,1}(t) = -(b+\beta+d+\theta)P_{0,1}(t) + 2(d+\theta)P_{1,1}(t) + 2(d+\theta)P_{0,2}(t) \qquad (2.4.3)$$

$$\frac{d}{dt}P_{0,0}(t) = (d+\theta)P_{1,0}(t) + (d+\theta)P_{0,1}(t) \qquad (2.4.4)$$

With the boundary condition $P_{N_0,M_0}(0) = 1$

Let $P(x,y;t)$ be the Joint probability generating function of $P_{n,m}(t)$,

$$P(x,y;t) = \sum_{m=0}\sum_{n=0} x^n y^m P_{n,m}(t) \qquad (2.4.5)$$

Multiplying the equations (2.4.1) to (2.4.4) by $x^n y^m$ and summing over all 'n' and 'm', we have

$$\frac{d}{dt}P(x,y;t) = -(b+\beta+d+\theta)\left[y\frac{\partial}{\partial y}P(x,y;t) + x\frac{\partial}{\partial x}P(x,y;t)\right]$$

$$+(d+\theta)\left[\frac{\partial}{\partial y}P(x,y;t)+\frac{\partial}{\partial x}P(x,y;t)\right]+(\alpha+\beta)\left[xy\frac{\partial}{\partial x}P(x,y;t)\right]$$

$$+(b-\alpha)\left[x^2\frac{\partial}{\partial x}P(x,y;t)\right]+(b+\beta)\left[y^2\frac{\partial}{\partial y}P(x,y;t)\right] \qquad (2.4.6)$$

Further simplification of the equation (2.4.6) gives

$$\frac{d}{dt}P(x,y;t) = \left[(b-\alpha)x^2+\{(\alpha+\beta)y-(b+\beta+d+\theta)\}x+(d+\theta)\right]\frac{\partial}{\partial x}P(x,y;t)$$

$$+\left[(b+\beta)y^2-(b+\beta+d+\theta)y+(d-\theta)\right]\frac{\partial}{\partial y}P(x,y;t) \qquad (2.4.7)$$

Solving the equation (2.4.3) as done in section (2.3) we get,

$$P(x,y;t) = \left[\frac{(d+\theta)+ze^{-\delta t}}{b+\beta+ze^{-\delta t}}\right]^{M_0}\left[\left(\frac{d+\theta+ze^{-\delta t}}{b+\beta+ze^{-\delta t}}\right)+\left\{\left(\frac{b+\beta+ze^{-\delta t}}{b+\beta+z}\right)\right.\right.$$

$$\left.\left.\phi(ze^{-\delta t})+\left(\frac{1}{x-y}-\phi(z)\right)\left(\frac{b+\beta+z}{b+\beta+ze^{-\delta t}}\right)^{\left(\frac{A}{b+\beta}+B\right)}e^{\left(\frac{A\delta t}{b+\beta}\right)}\right\}\right]$$

Where $\delta = b+\beta-d-\theta$ $\qquad A = \dfrac{(b+\beta)^2+(d+\theta)(\alpha-b)}{(b+\beta-d-\theta)}$

$$z = \frac{(b+\beta)y-(d+\theta)}{1-y} \qquad B = \frac{b-\alpha-d-\theta}{b+\beta-d-\theta}$$

$$\phi(z) = \frac{(b+\beta+z)(b-\alpha)}{(b+\beta-d-\theta)A}; \qquad F\left(1-B,1,\frac{A}{b+\beta}+1,\frac{-z}{b+\beta}\right)$$

and F is a hypergeometric function (2.4.8)

Using the equation (2.4.8), we can obtain the characteristics of the model.

The expected number of Normal cells in the tumor at time t is

$$m_{1,0}(t) = N_0 e^{(b-d-\theta)t} \qquad (2.4.9)$$

The expected number of mutant cells in the tumor at time 't' is

$$m_{0,1}(t) = e^{(b-d-\theta)t}\left[(N_0 + M_0)e^{\beta t} - N_0 e^{-\alpha t}\right] \quad (2.4.10)$$

The variability of the normal cells in the tumor at time t is

$$m_{2,0}(t) = A_1 e^{-(\alpha+d+\theta-b)t}\left(1 - e^{-(\alpha+d+\theta-b)t}\right);\ A_1 = \left(\frac{b-\alpha+d+\theta}{\alpha-b+d+\theta}\right)N_0 \quad (2.4.11)$$

The variability of the mutant cells in the tumor at time 't' is

$$m_{0,2}(t) = (E+H)e^{-(d+\theta)t}\left(e^{(b-\alpha)t} - e^{(b+\beta-d-\theta)t}\right)$$

$$+e^{(b+\beta-2(d+\theta))t}\left[F\left(e^{(b-2\alpha-\beta)t} - 1\right) + G\left(e^{(b-\alpha)t} - 1\right)\right]$$

$$+e^{(b+\beta-d-\theta)t}\left[I\left(1 - e^{-(d+\theta)t}\right)\right] - Je^{-(d+\theta)t}\left[e^{(\beta-\alpha)t} - e^{(-(d+\theta)+(b+\beta))t}\right]$$

Where

$$E = \frac{2(\alpha+\beta)A_1 D}{(b-\alpha)+(d+\theta)-(b+\beta)}; \qquad F = \frac{A_1}{(b-\alpha)-(\alpha+\beta)}$$

$$G = \frac{A_1 B_1}{b-\alpha}; \qquad H = \frac{(\alpha+\beta)N_0}{(d+\theta)-(b+\beta)+(b-\alpha)}$$

$$I = \left(\frac{b+\beta+d+\theta}{d+\theta}\right)(N_0 + M_0); \qquad J = \left(\frac{b+\beta+d+\theta}{-\beta-\alpha+d+\theta}\right)N_0$$

$$B_1 = \frac{\alpha-b+d+\theta}{b+\beta-d-\theta} \qquad D = \frac{\alpha+\beta}{d+\theta-b-\beta}$$

and A is as given in the equation (2.4.11) (2.4.12)

The covariance between the number of normal cells and mutant cell is

$$m_{1,1}(t) = A_1\left[De^{(b-\alpha-d-\theta)t} + e^{2(b-\alpha-d-\theta)t} + B_1 e^{(-\alpha+\beta+2(b-d-\theta))t}\right]$$

where A_1, B_1 and D are as given in the equation (2.4.12). (2.4.13)

Using equations (2.4.9) to (2.4.13) the values of $m_{10}(t)$, $m_{01}(t)$, $m_{20}(t)$, $m_{11}(t)$ and $m_{02}(t)$ are computed for given in values of the parameters and time t and are presented in table (2.3).

Table – 2.3: The values of $m_{10}(t)$, $m_{01}(t)$, $m_{20}(t)$, $m_{11}(t)$& $m_{02}(t)$ for various values of the parameters

α	b	β	θ	d	t	M_0	N_0	$m_{10(t)}$	$m_{01(t)}$	$m_{20(t)}$	$m_{11(t)}$	$m_{02(t)}$
0.123	0.435	0.321	0.945	0.89	2	3	3	0.1	3.821	0.13	0.04	0.089
0.521								0.04	3.873	0.04	0.02	0.362
0.684								0.03	3.885	0.02	0.02	0.438
0.897								0.2	3.895	0.01	0.01	0.497
0.123	0.286	0.921	0.245	0.55	2	3	3	0.84	20.353	0.19	1.59	168.713
0.521								0.38	20.816	0.18	0.48	23.474
0.684								0.28	20.921	0.08	0.26	14.623
0.897								0.18	21.017	0.02	0.08	11.415
0.987	0.98	0.921	0.457	1.55	2	3	3	0.05	19.68	0.05	0.14	7.69
	1.492							0.15	21.023	0.24	0.91	427.093
	1.682							0.22	21.991	0.41	1.84	1.119×10^{-3}
	1.983							0.4	24.521	1.02	5.61	4.547×10^{-3}
0.792	0.323	0.121	0.994	0.99	2	3	3	0.22	3.845	0.01	0.01	0.289
		0.269							5.177		0.01	0.358
		0.459							7.581		0.01	0.367
		0.62							10.169		0.02	0.056
0.123	0.286	0.921	0.245	0.55	2	3	3	0.84	20.353	0.92	1.59	168.713
		1.246							39.759		2.77	322.775
		1.682							96.264		5.58	1.198×10^{-3}
		1.993							180.03		9.11	3.405×10^{-3}
0.412	0.286	0.921	0.245	0.35	2	3	3	0.71	21.606	0.35	0.95	24.955
			0.386					0.53	20.948	0.31	0.77	33.056
			0.495					0.43	20.552	0.27	0.63	38.813
			0.894					0.19	19.659	0.15	0.27	173.624
0.172	0.286	0.092	0.189	0.35	2	3	3	1.27	3.053	1.12	0.3	2.348
			0.384					0.86	3.232	0.84	0.21	2.053
			0.694					0.47	3.405	0.49	0.11	1.1111
			0.941					0.28	3.484	0.31	0.06	0.666

α	b	β	θ	d	t	M_0	N_0	$m_{10(t)}$	$m_{01(t)}$	$m_{20(t)}$	$m_{11(t)}$	$m_{02(t)}$
0.743	0.856	0.216	0.994	0.15	2	3	3	0.38	5.104	0.4	0.49	34.939
				0.49				0.19	4.868	0.21	0.21	5.905
				0.78				0.11	4.758	0.12	0.1	2.328
				0.94				0.08	4.721	0.09	0.07	1.533
0.174	0.286	0.216	0.994	0.19	2	3	3	0.35	4.526	0.37	0.12	0.772
				0.27				0.3	4.539	0.32	0.1	0.663
				0.69				0.13	4.586	0.14	0.04	0.278
				0.97				0.07	4.601	0.08	0.02	0.158
0.123	0.435	0.321	0.945	0.89	1	2	2	0.44	5.418	0.48	0.09	1.419
					2			0.1	7.621	0.13	0.04	0.405
					3			0.02	10.497	0.21	0.01	0.083
					4			0.16	164.2	0.22	1.31	1.672×10^{3}
0.012	0.044	0.032	0.945	0.89	2	1	2	0.05	1.042	0.05	0	0.027
						2			2.108			0.057
						3			3.174			0.087
						4			4.241			0.117
0.123	0.285	0.921	0.245	0.55	2	1	2	0.56	8.013	0.61	1.06	107.867
						2			14.323			112.405
						3			20.632			116.943
						4			26.941			121.481
0.123	0.285	0.921	0.245	0.55	2	2	1	0.28	14.603	0.31	0.53	60.741
							2	0.56	14.323	0.61	1.06	112.405
							3	0.84	14.042	0.92	1.59	164.069
							4	1.12	13.761	1.22	2.11	215.734

From equations (2.4.9), (2.4.10) and table (2.3) we observe that the average number of mutant cells and normal cells at a given time 't' are decreasing functions of θ when other parameters remain fixed. The average number of mutant cells is an increasing function of M_0 at a given time when other parameters are fixed. Hence it is observed that, with the appropriate drug administration, the average number of mutant cells can reduced by increasing the rate of death of mutant cells.

From the equations (2.4.11); (2.4.12) and table (2.3) we observe that the variance of number of mutant cells is an increasing function of the parameters θ, when other parameters remain fixed. The variance of the number of normal and mutant cells are decreasing functions of time 't' when $(\alpha+b+\beta)<d+\theta$. The variance of number of mutant cells is an increasing function of M_0 and both the variance are also increasing functions of N_0.

From the equations (2.4.13) and table (2.3), we observe that the covariance between the number of mutant cells and normal cells is a decreasing function of θ when other parameters are fixed. It is also observed that the covariance is a decreasing function of 't' when other parameters are fixed. The covariance between the number of normal and mutant cells is independent of M_0 and it is an increasing function of N_0. This model also includes the model given in section 2.3 when $\theta\to 0$. Following heuristic arguments of Goldie and Coldman (1979, 1983), here also we assume that normal cells corresponding to drug sensitive cells and mutant cell to resistant cells to study the drug resistance in chemotherapy. When a tumor is treated with chemotherapy, the best that can be achieved is complete eradication of sensitive cells. The probability of cure is then equivalent to probability of eventual extinction of the remaining resistant cells under the stochastic process (Birkhead (1986)).

Suppose at time 't' during cancer development, a tumor has 'n' cells which are sensitive to drug of choice them the probability of cure is given by

$$C(n,t)=\sum_{m=0}^{\infty}P_{m/n}(t)\left(\frac{d+\theta}{b+\beta}\right)^{n} \qquad (2.4.14)$$

Where, the conditional probability $P_{m/n}(t)=\frac{P_{n,m}(t)}{P_n(t)}$; and $\left(\frac{d+\theta}{b+\beta}\right)^{n}$ is the probability of eventual extinction of 'm' resistant cell is a linear birth-death process. $P_n(t)$ is the probability that there being 'n' sensitive cells at time t. Therefore

$$C(n,t)=\frac{\text{Coefficient of } x^n \text{ in } P\left(x,\frac{d+\theta}{b+\beta},t\right)}{P_n(t)} \tag{2.4.15}$$

$$P\left(x,\frac{d+\theta}{b+\beta},t\right)=\left[\frac{\left(\frac{d+\theta}{b+\beta}\right)\left[(b-\alpha)x-(b+\beta)\right]-(b+\beta)\left(x-\frac{d+\theta}{b+\beta}\right)G(t)}{\left((b-\alpha)x-(b+\beta)-\left(x-\frac{d+\theta}{b+\beta}\right)(b-\alpha)G(t)\right.}\right]^{N_0}\left(\frac{d+\theta}{b+\beta}\right)^{M_0}$$

Where

$$G(t)=\exp\left\{\frac{\left[(d+\theta)(b+\beta)-(\alpha+\beta)(d+\theta)-(b+\beta)^2\right]t}{(b+\beta)}\right\} \tag{2.4.16}$$

If, for simplicity, we assume that the tumor has developed from a single sensitive cell $(N_0=1,\ M_0=0)$ then the recursive differentiation of (2.4.16) gives. Coefficient of

$$x^n \text{ in } P\left(x,\frac{d+\theta}{b+\beta},t\right)=G(t)\left[\frac{(b+\beta)-\left(\frac{d+\theta}{b+\beta}\right)(b-\alpha)}{(b+\beta)-\left(\frac{d+\theta}{b+\beta}\right)(b-\alpha)G(t)}\right]^2\left[\frac{1-G(t)}{\left(\frac{b+\beta}{b-\alpha}\right)-\left(\frac{d+\theta}{b+\beta}\right)G(t)}\right]^{n-1} \tag{2.4.17}$$

From (2.4.8), the marginal probability mass function of n is obtained as

$$P_n(t)=\left[\frac{\left(\tau e^{\pi}-(d+\theta)\tau\right)}{\left((d+\theta)-(b-\alpha)e^{\pi t}\right)^2}\right]\left[\frac{(b-\alpha)\left(1-e^{\pi t}\right)}{(d+\theta)-(b-\alpha)e^{\pi t}}\right]^{n-1} \tag{2.4.18}$$

Where $\tau=b-\alpha-d-\theta$, since the sensitive cell population itself proliferates under a linear birth-death process with parameters b-α and d+θ. Substituting the equations (2.4.17) and (2.4.18) in the equation (2.4.15), we have

$$C(n,t)=\frac{G(t)\left[\frac{(b+\beta)-\left(\frac{d+\theta}{b+\beta}\right)(b-\alpha)}{(b+\beta)-\left(\frac{d+\theta}{b+\beta}\right)(b-\alpha)G(t)}\right]^2\left[\frac{1-G(t)}{\left(\frac{b+\beta}{b-\alpha}\right)-\left(\frac{d+\theta}{b+\beta}\right)G(t)}\right]^{n-1}}{\left[\frac{\left(\tau e^{\pi t}-(d+\theta)\right)\tau}{\left((d+\theta)-(b-\alpha)e^{\pi t}\right)^2}\right]\left[\frac{(b-\alpha)\left(1-e^{\pi t}\right)}{(d+\theta)-(b-\alpha)e^{\pi t}}\right]^{n-1}} \tag{2.4.19}$$

From the equation (2.4.19) and for given values of the parameters b, d, θ, β, n and time 't' the values of c (n,t) are computed and presented in table (2.4). From the table it is observed that the probability of survival of cell is influenced by the parameters θand β.

For a range of different mutation rates θ and β the value of C (n, t) is a decreasing function of 't' and n. These results coincide with that of Goldie and Coldman (1983).

TABLE 2.4: VALUES OF C (n, t)

α	β	d	θ	b	t	c (n, t)
0.0194	0.0214	0.1294	0.0134	0.1562	1	0.04
					3	0.038
					5	0.037
					7	0.035
					9	0.034
0.0194	0.0214	0.1294	0.9741	0.9842	1	0.099
					3	0.079
					5	0.062
					7	0.05
					9	0.04
0.0194	0.9535	0.9932	0.0134	0.1562	1	0.233
					3	0.041
					5	0.006
					7	8.341×10^{-4}
					9	1.163×10^{-4}
0.9648	0.0214	0.1294	0.134	0.9842	1	0.127
					3	0.012
					5	0.001
					7	1.55×10^{-4}
					9	1.989×10^{-5}
0.9648	0.214	0.9932	0.0134	0.9842	1	0.268
					3	0.048
					5	0.007
					7	9.851×10^{-4}
					9	1.372×10^{-4}
0.9648	0.214	0.9932	0.0134	0.9842	1	0.268
					3	0.048
					5	0.007
					7	9.851×10^{-4}
					9	1.372×10^{-4}
0.9648	0.9535	0.1294	0.0134	0.1562	1	0.066
					3	0.001
					5	5.865×10^{-5}
					7	4.787×10^{-6}
					9	4.174×10^{-7}
0.9648	0.9535	0.1294	0.9741	0.9842	1	0.08
					3	0.002
					5	3.754×10^{-5}
					7	7.963×10^{-6}
					9	1.689×10^{-8}
0.9648	0.9535	0.9932	0.9741	0.9842	1	0.129
					3	0.003
					5	6.872×10^{-5}
					7	1.483×10^{-6}
					9	3.2×10^{-8}

CHAPTER 3
Two Stage Stochastic Model for Cancer Cell Growth

3.1 INTRODUCTION

In this chapter a two stage stochastic model is developed for cancer cell growth with an assumption that in any malignant tumor, there will be premalignant and malignant clones. In the beginning a normal clone become premalignant and later on it becomes malignant if it takes further proliferation. A premalignant cell either may extinct without becoming a malignant cell or it may take the mutation and become a malignant cell. Denote that the cell in the stage of premalignancy as in state 'A' and the premalignant cell which will become a malignant stage as in state B. after some period of time both the premalignant cells in state A and malignant cells in the state B will die and enter into to state 'C'.

For an effective administration of chemotherapy it is needed to estimate the number of cells in state A as well as in state B. for this sort of phenomenon a two stage model for cancer cell growth is useful. Here we assume that the growth process, the mutation process and the loss process in both states are random. Assuming poisson process for growth, mutation and loss process, the joint probability distribution of the number of cells in state A and state B at a given time, 't' is derived. The expected number of cells in both the states and their variability are analyzed. The cancer cell growth is also analysed by deriving the probability of cell survival time in the tumor. The expected survival time of the cell in the tumor and its variability are also derived. This model is very useful for effective administration of chemotherapy. The schematic diagram representing the two stage cell growth is shown in Figure-1.

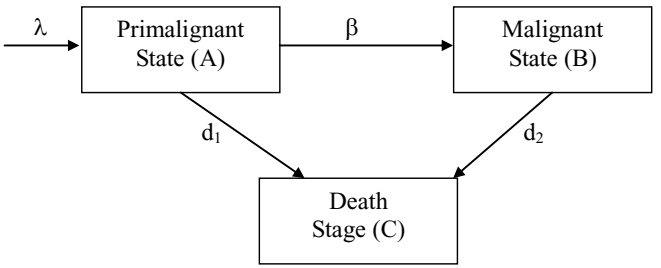

Fig.1 : Two Stage cell growth

3.2 JOINT DISTRIBUTION OF NUMBER OF CELLS IN BOTH STATES

In this section, the tumor size distribution is developed by deriving the joint probability distribution of number of cells in state A and state B. Let the growth process of the malignant cells in the tumor is poison with parameters λ in the state A. Let the transition of a malignant cells from state A to state B and from state 'A' to state C are also poison with parameters β and d_1 respectively. Further assume that the transition from state B to state C is also poison with parameter d_2. With this structure the postulates of the model are,

1) The probability that a cell moves from state A to state B, when there are 'n' cells in state 'A' during a small interval of time 'h' is $n\beta h + o(h)$.
2) The probability that a cell moves from state A to state C, when there are 'n' cells in state A during a small interval of time 'h' is $nd_1h + o(h)$.
3) The probability that a cell moves from state B to state C, when there are 'm' cells in the state B during a small interval of time 'h' is $md_2h + o(h)$.
4) The probability that there is a growth of premalignant cell in state A during the small interval of time h is $\lambda h + o(h)$
5) The probability that the occurrence of other than the above events during a small interval of time 'h' is o(h) and
6) The occurrence of events in non-overlapping intervals of time are stochastically independent.

Let $P_{n,\,m}(t)$ be the probability that there are 'n' cells in state A and 'm' cells in state B during time 't' then the difference equations of the mode are

$$\begin{aligned} P_{n,m}(t+h) = {} & P_{n,m}(t)\left[1-(md_2+nd_1+n\beta+\lambda)h+o(h)\right] \\ & +P_{n-1,m}(t)\left[\lambda h+o(h)\right]+P_{n-1,m}(t)\left[(n+1)d_1h+o(h)\right] \\ & +P_{n,m-1}(t)\left[(m+1)d_2+o(h)\right]+P_{n-1,m-1}(t)\left[(n+1)\beta h+o(h)\right] \\ & +\sum_{i\neq 0,1} P_{n+1,m+1}(t)\,o(h);\text{for } m,n\geq 1 \end{aligned} \tag{3.2.1}$$

$$P_{0,0}(t+h) = P_{0,0}(t)\left[1-\lambda h+o(h)\right]+P_{1,0}(t)\left[d_1h+o(h)\right]+P_{0,1}(t)\left[d_2h+o(h)\right] \tag{3.2.2}$$

$$P_{1,0}(t+h) = P_{1,0}(t)\left[1-\lambda h-d_1h-\beta h+o(h)\right]+P_{2,0}(t)\left[2d_1h+o(h)\right]$$

$$+P_{1,1}(t)\left[d_2h+o(h)\right]+P_{0,0}(t)\left[\lambda h+o(h)\right] \tag{3.2.3}$$

$$P_{0,1}(t+h)=P_{0,1}\left[1-\lambda h-d_2h+o(h)\right]+P_{1,1}(t)\left[d_2h+o(h)\right]$$

$$+P_{1,0}(t)\left[\beta h+o(h)\right]+P_{0,2}(t)\left[d_2h+o(h)\right] \tag{3.2.4}$$

The difference differential equations of the model are

$$\frac{d}{dt}P_{n,m}(t)=-(md_2+nd_1+n\beta+\lambda)P_{n,m}(t)+\lambda P_{n-1,m}(t)+(n+1)\beta P_{n+1,m-1}(t)$$

$$+(n+1)d_1P_{n+1,m}(t)+(m+1)d_2P_{n,m-1}(t);\qquad \text{for } n,m\geq 1 \tag{3.2.5}$$

$$\frac{d}{dt}P_{0,0}(t)=-\lambda P_{0,0}(t)+d_1P_{1,0}(t)+d_2P_{0,1}(t) \tag{3.2.6}$$

$$\frac{d}{dt}P_{1,0}(t)=-(\lambda+d_1+\beta)P_{1,0}(t)+2d_1P_{2,0}(t)+d_2P_{1,1}(t)+\lambda p_{0,0}(t) \tag{3.2.7}$$

$$\frac{d}{dt}p_{0,1}(t)=-(\lambda+d_2)p_{0,1}(t)+d_1p_{1,1}(t)+\beta p_{1,0}(t)+d_2p_{0,2}(t) \tag{3.2.8}$$

Let P (x, y;t) denotes the joint probability generating function of $p_{n,m}(t)$, then

$$P(x,y;t)=\sum_{n=0}\sum_{m=0}x^ny^np_{n,m}(t);\ |x|<1,|y|<1 \tag{3.2.9}$$

Multiplying the equation (3.2.5) to (3.2.8) with x^n and y^m and summing over all 'n' and 'm' and adding we get

$$\frac{d}{dt}P(x,y;t)=-\lambda\left[\sum_n\sum_m x^ny^np_{n,m}(t)-\sum_n\sum_m xx^{n-1}y^mp_{n-1,m}(t)\right]$$

$$+d_1\left[\sum_n\sum_m(n+1)x^ny^mp_{n-1,m}(t)-\sum_n\sum_m nxx^{n-1}y^mp_{n,m}(t)\right]$$

$$-\beta\left[\sum_n\sum_m nxx^{n-1}y^mp_{n,m}(t)-\sum_n\sum_m(n+1)x^nyy^{m-1}p_{n-1,m-1}(t)\right]$$

$$-d_2\left[\sum_n\sum_m mx^nyy^{m-1}p_{n,m}(t)-\sum_n\sum_m(m+1)x^ny^mp_{n,m-1}(t)\right] \tag{3.2.10}$$

After simplification, we get

$$\frac{d}{dt}P(x,y;t)=\left[-(d_1+\beta)x-\beta y+d_1\right]\frac{\partial p}{\partial x}+d_2(1-y)\frac{\partial p}{\partial y}-\lambda p(1-x)$$

Which can be rearranged as

$$\frac{dp}{dt}-\left[-(d_1+\beta)x-\beta y+d_1\right]\frac{\partial p}{\partial x}-d_2(1+y)\frac{\partial p}{\partial y}=p\lambda(x-1) \tag{3.2.11}$$

We can solve the equation (3.2.11) using the Lagrange's method, we have

$$\frac{dt}{1}=\frac{-dx}{-(d_1+\beta)x-\beta y+d_1}=\frac{-dy}{d_2(1-y)}=\frac{dp}{\lambda(x-1)p}$$

(i) (ii) (iii) (iv) (3.2.12)

Solving the system of equations (i), (ii), (iii) and (iv) in (3.2.12) we get the arbitrary constants a, b, c as below

$$a=e^{-d_2 t}(y-1) \tag{3.2.13}$$

$$b=\left[(1-x)-\frac{\beta}{d_1+\beta-d_2}(1-y)\right](1-y)^{-\left(\frac{d_1+\beta}{d_2}\right)} \tag{3.2.14}$$

and

$$c=\exp\left\{\frac{\lambda}{d_1+\beta}(1-x)+\frac{\beta}{d_1+\beta}(1-y)\right\} \tag{3.2.15}$$

Using the arbitrary constants given in equations (3.2.13), (3.2.14) and (3.3.15), the general solutions of (3.2.11) can be obtained as

$$P(x,y,t)=\exp\left\{\frac{-\lambda}{d_1+\beta}(1-x)+\frac{\beta}{d_1+\beta}(1-y)\right\}$$

$$\Phi\left[e^{-d_2 t}(1-y)\left\{(1-x)-\frac{\beta}{d_1+\beta-d_2}(1-y)\right\}(1-y)^{-\left(\frac{d_1+\beta}{d_2}\right)}\right] \tag{3.2.16}$$

Where Φ is an arbitrary function of two variables. Therefore substituting the initial condition $P_{N_0,M_0}(0)=1$, we get

$$P(x,y;t)=\exp\left\{\begin{array}{c}\frac{\lambda}{d_2}\left\{\frac{-d_2}{d_1+\beta}(1-x)\left(1-e^{-(d_1+\beta)t}\right)\right. \\ \left.-\left[\frac{\beta}{d_1+\beta}(1-y)\left(1-e^{-d_2 t}\right)\right]-\left[\frac{-d_2\beta(1-y)\left(e^{-d_2 t}-e^{-(d_1+\beta)t}\right)}{(d_1+\beta)(d_1+\beta+d_2)}\right]\right\}\end{array}\right\}$$

$$\left[1-(1-x)e^{-(d_1+\beta)t}-\frac{\beta}{d_1+\beta-d_2}(1-y)\left(e^{-d_2 t}-e^{-(d_1+\beta)t}\right)\right]^{N_0}$$

$$\left[1-(1-y)e^{-d_2 t}\right]^{M_0} \tag{3.2.17}$$

The average number of cells in state A at time 't' is $E[N(t)]=\frac{\partial}{\partial x}P(x,y;t)\Big|_{x=1}$

This implies $E\left[N(t)\right]=\frac{\lambda}{d_1+\beta}\left(1-e^{-(d_1+\beta)t}\right)+N_0e^{-(d_1+\beta)t}$ (3.2.18)

The average number of cells in state B at time 't' is

$$E\left[M(t)\right]=\frac{\partial}{\partial y}P(x,y;t)\Big|_{y=1}$$

This implies $E\left[M(t)\right]=\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2}-\frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]+\left(\frac{N_0\beta}{d_1+\beta-d_2}\right)$

$$\left(e^{-d_2t}-e^{-(d_1+\beta)t}\right)+M_0e^{-d_2t} \quad (3.2.19)$$

The second order raw factorial moment for both stages A and B are obtained as

$$E\left[N(t)^2-N(t)\right]=\left[\frac{\lambda}{d_1+\beta}\left(1-e^{-(d_1+\beta)t}\right)\right]^2+N_0\left(N_0-1\right)e^{-2(d_1+\beta)t}$$

$$\left(\frac{2\lambda N_0}{d_1+\beta}\right)\left(1-e^{-(d_1+\beta)t}\right)\left(e^{-(d_1+\beta)t}\right) \quad (3.2.20)$$

$$E\left[M(t)^2-M(t)\right]=\left[\frac{\lambda\beta}{d_1+\beta}\left(\frac{1-e^{-d_2t}}{d_2}-\frac{e^{-d_2t}-e^{-(d_1-\beta)t}}{d_1+\beta-d_2}\right)\right]^2$$

$$+N_0\left(N_0-1\right)\left[\frac{\beta}{d_1+\beta-d_2}\left(e^{-d_2t}-e^{-(d_1+\beta)t}\right)\right]^2$$

$$+M_0\left(M_0-1\right)e^{-2d_2t}+2\left[\frac{\beta N_0\left(e^{-d_2t}-e^{-(d_1+\beta)t}\right)}{d_1+\beta-d_2}+M_0e^{-d_2t}\right]$$

$$\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2}-\frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]$$

$$+2N_0M_0\beta e^{-d_2t}\left[\frac{\left(e^{-d_2t}-e^{-(d_1+\beta)t}\right)}{d_1+\beta-d_2}\right] \quad (3.2.21)$$

The Product raw moment of first order is

$$E\left[M(t)N(t)\right]=\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2}-\frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]\left[\frac{\lambda}{d_1+\beta}\left(1-e^{-(d_1+\beta)t}\right)+N_0e^{-(d_1+\beta)t}\right]$$

$$+\left(e^{-d_2t}-e^{-(d_1+\beta)t}\right)\frac{\beta N_0}{d_1+\beta-d_2}\left[\left(N_0-1\right)e^{-(d_1+\beta)t}+\frac{\lambda}{d_1+\beta}\left(1-e^{-(d_1+\beta)t}\right)\right]$$

$$+\left[\frac{\lambda M_0}{d_1+\beta}e^{-d_2 t}\left(1-e^{-(d_1+\beta)t}\right)+N_0 M_0 e^{-(d_1+\beta+d_2)t}\right] \tag{3.2.22}$$

The variance of the number of cells in state A is

$$V\left[N(t)\right]=E\left[N(t)^2-N(t)\right]+E\left[N(t)\right]-\left[E\left[N(t)\right]\right]^2 \tag{3.2.23}$$

Substituting the equations (3.2.18) and (3.2.20) in equation (3.2.23) we have,

$$V\left[N(t)\right]=\left[\frac{\lambda}{d_1+\beta}\left(1-e^{-(d_1+\beta)t}\right)\right]^2+N_0\left(N_0-1\right)e^{-2(d_1+\beta)t}+\left(\frac{2\lambda N_0}{d_1+\beta}\right)\left(1-e^{-(d_1+\beta)t}\right)\left(e^{-(d_1+\beta)t}\right)$$
$$+\left[\frac{\lambda}{d_1+\beta}\left(1-e^{-(d_1+\beta)t}\right)+N_0 e^{-(d_1+\beta)t}\right]\left[1-\left\{\frac{\lambda}{d_1+\beta}\left(1-e^{-(d_1+\beta)t}\right)+N_0 e^{-(d_1+\beta)t}\right\}\right] \tag{3.2.24}$$

Similarly from equations (3.2.19) and (3.2.21), the variance of the number of malignant cells in state B is obtained as

$$V\left[M(t)\right]=\left[\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2 t}}{d_2}-\frac{e^{-d_2 t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]^2\right.$$
$$+N_0\left(N_0-1\right)\left[\frac{\beta}{d_1+\beta-d_2}\left(e^{-d_2 t}-e^{-(d_1+\beta)t}\right)\right]^2$$
$$+M_0\left(M_0-1\right)e^{-2d_2 t}+2N_0 M_0\beta e^{-d_2 t}\left[\frac{\left(e^{-d_2 t}-e^{-(d_1+\beta)t}\right)}{d_1+\beta-d_2}\right]$$
$$+2\left[\frac{\beta N_0\left(e^{-d_2 t}-e^{-(d_1+\beta)t}\right)}{d_1+\beta-d_2}+M_0 e^{-d_2 t}\right]\left[\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2 t}}{d_2}-\frac{e^{-d_2 t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]\right]$$
$$+\left[\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2 t}}{d_2}-\frac{e^{-d_2 t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]+\left[\frac{\beta N_0\left(e^{-d_2 t}-e^{-(d_1+\beta)t}\right)}{d_1+\beta-d_2}+M_0 e^{-d_2 t}\right]\right]$$
$$\left.\left[1-\left[\frac{\lambda\beta}{d_1-\beta}\left\{\frac{1-e^{-d_2 t}}{d_2}-\frac{e^{-d_2 t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]+\left[\frac{\beta N_0\left(e^{-d_2 t}-e^{-(d_1+\beta)t}\right)}{d_1+\beta-d_2}+M_0 e^{-d_2 t}\right]\right]\right. \tag{3.2.25}$$

The covariance between the number of cells in state A and in State B is

$$Cov\left[M(t),N(t)\right]=E\left[M(t)N(t)\right]-E(M)(t).E\left(N(T)\right) \tag{3.2.26}$$

By substituting the equations (3.2.18), (3.2.19) and (3.2.22) in the equation (3.2.26) we have

$$\begin{aligned}
\mathrm{Cov}\left[M(t),N(t)\right] &= \left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2 t}}{d_2}-\frac{e^{-d_2 t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]\left[\frac{\lambda}{d_1+\beta}\left(1-e^{-(d_1+\beta)t}\right)+N_0 e^{-(d_1+\beta)t}\right] \\
&+\left(e^{-d_2 t}-e^{-(d_1+\beta)t}\right)\frac{\beta N_0}{d_1+\beta-d_2}\left[\left(N_0-1\right)e^{-(d_1+\beta)t}+\frac{\lambda}{d_1+\beta}\left(1-e^{-(d_1+\beta)t}\right)\right] \\
&+\left[\frac{\lambda M_0}{d_1+\beta}e^{-d_2 t}\left(1-e^{-(d_1+\beta)t}\right)+N_0 M_0 e^{-(d_1+\beta+d_2)t}\right] \\
&-\left[\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2 t}}{d_2}-\frac{e^{-d_2 t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]\right. \\
&\left.+\left[\frac{\beta N_0\left(e^{-d_2 t}-e^{-(d_1+\beta)t}\right)}{d_1+\beta-d_2}+M_0 e^{-d_2 t}\right]\right] \\
&\left[\frac{\lambda}{d_1+\beta}\left(1-e^{-(d_1+\beta)t}\right)+N_0 e^{-(d_1-\beta)t}\right] \qquad (3.2.27)
\end{aligned}$$

For various values of t, λ, d_1, β and d_2 the values of $E\left[M(t)\right]$, $E\left[N(t)\right]$, $V\left[M(t)\right]$, $V\left[N(t)\right]$ and $COV\left[M(t),\ N(t)\right]$ are computed and are given in the table (3.1).

Table – 3.1: Values of $E(N(t)), E(M(t)), V(M(t))$ and $Cov(M(t), N(t))$ for different values of the parameters

l	d_1	β	d_2	M_0	N_0	t	E[N(t)]	E[M(t)]	Var. [N(t)]	Var. [M(t)	COV (M(t), N(t)
0.13	0.188	0.193	0.01	10	10	5	6.769	15.396	2.478	2.878	-2.019
			0.42					3.344		2.757	-0.727
			0.83					1.209		1.098	-0.362
			1.24					0.679		0.636	-0.227
0.49	0.542	0.193	0.42	8	5	4	0.899	2.111	0.885	1.795	-0.022
		0.384					0.642	2.451	0.639	2.093	-0.015
		0.574					0.494	2.657	0.494	2.269	-0.008
		1.145					0.03	2.946	0.298	2.522	-0.0009
0.79	0.02	0.564	0.66	7	9	13	2.676	3.949	2.406	3.203	-0.408
	0.597						0.935	2.457	0.926	2.196	-0.033
	0.796						0.722	2.201	0.721	1.985	-0.015
	1.194						0.492	1.868	0.492	1.695	-0.003
0.13	0.995	0.783	0.94	6	4	10	0.008	0.006	0.008	0.006	-5.663×10^{12}
0.49							0.277	0.219	0.277	0.219	
0.79							0.444	0.35	0.444	0.35	
1.22							0.683	0.539	0.683	0.539	
0.66	1.342	0.213	0.86	5	1	2	1.002	0.199	0.841	0.449	-0.002
						6	0.134	0.09	0.134	0.426	-1.523×10^{7}
						10	0.106	0.058	0.106	0.426	-9.78×10^{12}
						14	0.105	0.043	0.105	0.426	0
0.66	0.342	1.213	0.06	5	1	2	5.78	0.289	1.413	0.449	-0.03
						6	6.356	0.104	3.666	0.426	-4.968×10^{56}
						10	6.789	0.064	5.151	0.426	-7.714×10^{8}
						14	7.127	0.046	6.13	0.426	1.19×10^{10}
0.82	1.032	0.432	0.58	5	1	2	1.709	0.029	1.206	0.104	-0.007
						6	0.207	0.012	0.202	0.056	-2.272×10^{6}
						10	0.508	0.007	0.058	0.056	-6.372×10^{10}
						14	0.043	0.005	0.043	0.056	-1.779×10^{13}
0.93	0.742	0.494	0.13	11	10	2	1.536	8.522	1.465	1.93	-0.26
					12		1.705	8.523	1.619	1.931	-0.312
					14		1.874	8.524	1.774	1.932	-0.363
					16		2.043	8.525	1.929	1.933	-0.415
0.93	0.442	0.294	0.13	5	5	4	1.465	3	4.52	1.205	-0.07
				10				5.997		1.205	
				15				8.993		3.606	

From equations (3.2.18), (3.2.19) and the table (3.1) we observe that the average number of mutant cells and normal cells at any given time 't' are increasing functions of 'λ' when other parameters are fixed. It is also observed that $E(N(t))$ and $E(M(t))$ are decreasing functions of d_1 when other parameters remain fixed. It is further observed that the mean number of mutant cells at any given time 't' is an increasing function of β and $E(N(t))$ is a decreasing function of β, when other parameters remain fixed. $E(M(t))$ is a decreasing function of d_2 and $E[N(t)]$ is not influenced by d_2. So by suitable administration of anticancer drug into the body one can increase the 'd_2' and hence can reduce the tumor size. The $E[N(t)]$ is an increasing function of N_0 for given values of the other parameters. The average number of normal cells is an increasing function of 't' when $(\lambda+\beta)>(d_1+d_2)$ and it is a decreasing function of t when $(\lambda+\beta)<(d_1+d_2)$ for given values of other parameters. The average number of mutant cells is a decreasing function of 't' when other parameters are fixed.

From equations (3.2.24), (3.2.25) and the table (3.1) we observe that the variances of number of normal and mutant cells for given value of time 't' are increasing functions of 'λ' when other parameters remain fixed. The values of $V[N(t)], V[M(t)]$ are decreasing functions of 'd_1' for fixed values of other parameters. It is also observed that the variance of $N(t)$ is a decreasing function of β and $V[M(t)]$ is an increasing function of d_2 when other parameters remain fixed. It is observed that variability of number of normal cells at a given time is an increasing function of N_0 for fixed values of the parameters and it is also noticed that $V[M(t)]$ is an increasing function of M_0, when other parameters are fixed. $V[N(t)]$ and $V[M(t)]$ are decreasing functions of 't' as $(\lambda+\beta)<(d_1+d_2)$. When other parameters are fixed $V[N(t)]$ is an increasing function of 't' and $V[M(t)]$ is decreasing function of 't'. The covariance between the number of normal and mutant cells is negative for given values of the parameters.

The average total number of pre malignant and malignant cells in the tumor in both states A and B is $E[L(t)]=E[M(t)]+E[N(t)]$ (3.2.28)

Substituting the values from equations (3.2.18) and (3.2.19) in the equation (3.2.28),

$$E\left[L(t)\right]=\left[\frac{\lambda}{d_1+\beta}\left(1-e^{-(d_1+\beta)t}\right)+N_0e^{-(d_1+\beta)t}\right]+\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2}-\frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]$$
$$+\left[\frac{\beta N_0\left(e^{-d_2t}-e^{-(d_1+\beta)t}\right)}{d_1+\beta-d_2}+M_0e^{-d_2t}\right] \quad (3.2.29)$$

The variability of total number of cells in both the states is obtained from

$$V\left[L(t)\right]=V\left[M(t)\right]+V\left[N(t)\right]+2Cov\left[M(t),N(t)\right] \quad (3.2.30)$$

By substituting the values from equations (3.2.24), (3.2.25) and (3.2.27) in the equation (3.2.30) we have

$$V\left[L(t)\right]=\left[\frac{\lambda}{d_1+\beta}\left(1-e^{-(d_1+\beta)t}\right)\right]^2+N_0\left(N_0-1\right)e^{-2(d_1-\beta)t}+\left(\frac{2\lambda N_0}{d_{1+}\beta}\right)\left(1-e^{-(d_1+\beta)t}\right)\left(e^{-(d_1+\beta)t}\right)$$
$$+\left[\frac{\lambda}{d_1+\beta}\left(1-e^{-(d_1+\beta)t}\right)+N_0e^{-(d_1+\beta)t}\right]\left[1-\left\{\frac{\lambda}{d_1+\beta}\left(1-e^{-(d_1+\beta)t}\right)+N_0e^{-(d_1+\beta)t}\right\}\right]$$
$$+\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2}-\frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]^2+N_0\left(N_0-1\right)\left[\frac{\beta}{d_1+\beta-d_2}\left(e^{-d_2t}-e^{-(d_1+\beta)t}\right)\right]^2$$
$$+M_0\left(M_0-1\right)e^{-2d_2t}+2\left[\frac{\beta N_0\left(e^{-d_2t}-e^{-(d_1+\beta)t}\right)}{d_1+\beta-d_2}+M_0e^{-d_2t}\right]$$
$$\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2}-\frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]\quad+2N_0M_0\beta e^{-d_2t}\left[\frac{\left(e^{-d_2t}-e^{-(d_1+\beta)t}\right)}{d_1+\beta-d_2}\right]$$
$$+\left[\left[\frac{\lambda B}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2}-\frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]+\left[\frac{\beta N_0\left(e^{-d_2t}-e^{-(d_1-\beta)t}\right)}{d_1+\beta-d_2}+M_0e^{-d_2t}\right]\right]$$
$$\left[1-\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2}-\frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]+\left[\frac{\beta N_0\left(e^{-d_2t}-e^{-(d_1+\beta)t}\right)}{d_1+\beta-d_2}+M_0e^{-d_2t}\right]\right.$$
$$+2\left[\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2}-\frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]\left[\frac{\lambda}{d_1+\beta}\left(1-e^{-(d_1-\beta)t}\right)+N_0e^{-(d_1-\beta)t}\right]\right.$$
$$+\left[\frac{\beta N_0\left(e^{-d_2t}-e^{-(d_1+\beta)t}\right)}{d_1+\beta-d_2}\right]\left[\frac{\lambda}{d_1+\beta}\left(1-e^{-(d_1+\beta)t}\right)+\left(N_0-1\right)e^{-(d_1-\beta)t}\right]$$
$$\left.\left.+\left[\frac{\lambda M_0}{d_1+\beta}e^{-d_2t}\left(1-e^{-(d_1+\beta)t}\right)+N_0M_0e^{-(d_1+\beta+d_2)t}\right]\right]$$
$$-2\left[\left[\frac{\lambda}{d_1+\beta}\left(1-e^{-(e_1+\beta)t}\right)+N_0e^{-(d_1+\beta)t}\right]\left[\left[1-\frac{\lambda\beta}{d_1\beta}\left\{\frac{1-e^{-d_2t}}{d_2}-\frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]\right]\right.$$

$$+\left[\frac{\beta N_0\left(e^{-d_2 t}-e^{-(d_1,\beta)t}\right)}{d_1+\beta-d_2}+M_0 e^{-d_2 t}\right]\Bigg] \qquad (3.2.31)$$

For various values of t, λ, d_1, β, M_0, N_0, d_2 the values of $E\left[L(t)\right]$ and $V\left[L(t)\right]$ are computed and given in Table (3.2).

TABLE 3.2: Values of E[L(t)], V[L(t)] for various values of the parameters

α	d_1	β	d_2	M_0	N_0	T	E[L(t)]	V[L(t)]
0.93	0.02	0.78	0.24	10	15	5	12.629	35.565
			0.35				8.985	33.92
			0.47				6.701	32.45
			0.54				5.636	31.653
1.43	0.87	0.08	0.76	10	15	5	22.434	176.47
		0.23					22.59	130.15
		0.39					22.691	112.01
		0.54					22.759	107.62
1.43	0.12	0.03	0.46	2	5	5	7.909	106.4
	0.28						5.232	82.234
	0.33						4.656	78.426
	0.4						3.987	75.205
0.49	0.02	0.01	0.46	20	5	5	8.845	77.285
0.68							9.762	112.82
0.95							11.036	167.64
1.43							13.32	299.22
0.68	0.02	0.01	0.46	10	5	5	17.801	111.93
						8	17.926	187.42
						10	18.313	241.8
						12	18.763	299.22
0.95	0.02	0.01	0.46	20	10	5	15.551	124.93
				40			17.536	126.72
				60			19.521	128.51
				80			21.507	130.29
0.99	0.78	0.01	0.86	40	20	5	2.195	42.186
						7	1.449	103.85
						9	1.306	402.96
						10	1.287	852.92
0.99	0.78	0.01	0.86	2	4	5	1.355	21.225
					6		1.396	23.782
					8		1.437	26.34
					9		1.458	27.618
0.99	0.78	0.01	0.86	5	4	5	1.395	21.265
				6			1.409	21.278
				7			1.422	21.292
				8			1.436	21.305

From the equation (3.2.29) and Table (3.2), we observe that the average total number of cells in the tumor at a given time 't' is a decreasing function of d_2 when

$(\lambda+\beta)>(d_1+d_2)$. It is also observed that $E[L(t)]$ is an increasing function of β as $(\lambda+\beta)>(d_1+d_2)$ and $M_0 < N_0$. The mean number of cells in the tumor at any given time 't' is a decreasing function of d_1 as $(\lambda+\beta)>(d_1+d_2)$. It is further observed that $E[L(t)]$ is an increasing function of 'λ' as $(\lambda+\beta)>(d_1+d_2)$ when other parameters remain fixed. $E[L(t)]$ is an increasing function of 't' as $(\lambda+\beta)>(d_1+d_2)$.

From the equation (3.2.31) and Table (3.2) It is observed that the variability of total number of cells in the tumor is an increasing function of λ. It is further observed that $V[L(t)]$ is an increasing function of both M_0 and N_0.

Taking $t\to\infty$ in the equation (3.2.17), we can obtain the equilibrium position of the tumor model. The probability generating function of premalignant and malignant cells in the tumor at any arbitrary time is

$$P(x,y;t)=\exp\left\{\frac{\lambda}{d_1+\beta}(x-1)+\frac{\lambda\beta}{(d_1+\beta)d_2}(y-1)\right\} \tag{3.2.32}$$

This implies that N(t) is asymptotically poison with Mean $\lambda/(d_1+\beta)$ and M(t) is also asymptotically poison with Mean $\lambda\beta/(d_1+\beta)d_2$, where N(t) and M(t) are the number of cells in state A and state B respectively at any time 't'. The total tumor size is therefore asymptotically poison with Mean $\lambda(d_2+\beta)/(d_1+\beta)d_2$.

3.3 TWO STAGE STOCHASTIC MODEL FOR CELL DURATION IN THE TUMOR

In this model it is assumed that every malignant cell in the tumor is in state A in the beginning. After a period of time in state A, the malignant cell will either dead (going to state C) or divides in to two mutant cells (going to state B).

Let f(x) be the probability density function of a cell that the time spent in state A until leaving to State 'C'. Let g(x) be the probability density function of the time that a cell will spent in state 'A' until leaving to state B and h(x) be the probability density function of a cell that the time spent in state B until leaving to state 'C'. Then the survival function of the cell in the states A, B and C respectively are

$$F(t)=1-\int_0^t f(x)dx \tag{3.3.1}$$

$$G(t) = 1 - \int_0^t g(x)\,dx \tag{3.3.2}$$

$$H(t) = 1 - \int_0^t h(x)\,dx \tag{3.3.3}$$

Therefore the force of transition from state A to state C, state A to state B and from state B to state C respectively are

$$\Phi_1(t) = \frac{f(t)}{F(t)} \tag{3.3.4}$$

$$\Phi_2(t) = \frac{g(t)}{G(t)} \tag{3.3.5}$$

$$\Phi_3(t) = \frac{h(t)}{H(t)} \tag{3.3.6}$$

The probability that a malignant cell generated initially at time t=0 is still in the tumor in state A at time 't' is

$$a(t) = \int_t^\infty \left[F(x)g(x) + G(x)f(x)\right]dx \tag{3.3.7}$$

The probability that a mutant malignant cell in a state 'B' at time t is

$$b(t) = \int_0^t \left[\int_0^\infty \left[F(y)g(y) + f(y)G(y)\right]dy\right] \frac{g(x)H(t-x)}{G(x)}\,dx \tag{3.3.8}$$

The probability that a malignant (either mutant or premutant) cell is in state 'C' at time 't' is $c(t) = 1 - a(t) - b(t)$ for all $t \geq 0$ (3.3.9)

In order to analyse transition probabilities, it is assumed that the duration of time a cell spent in state A before reaching to state B, the duration of time a cell in the state B before reaching to state C and the duration of time a cell in the state 'A' before reaching to state C are all exponential with parameters β, d_2 and d_1 respectively.

$$f(x) = d_1 e^{-d_1 x};\ g(x) = \beta e^{-\beta x};\ h(x) = d_2 e^{-d_2 x} \tag{3.3. 10}$$

Therefore the expected duration of a pre malignant cell is in state A before reaching state C is $(1/d_1)$ the expected duration of pre malignant cell in state A before reaching the state B is $(1/\beta)$ and the expected duration of a mutant malignant cell in state B before reaching state C is $(1/d_2)$.

Substituting (3.3.10) in the equations (3.3.7), (3.3.8) and in (3.3.9) we get

$$a(t) = e^{-(d_1+\beta)t} \tag{3.3.11}$$

$$b(t)=\frac{\beta}{d_1+\beta-d_2}\left[e^{-d_2 t}-e^{-(d_1+\beta)t}\right] \tag{3.3.12}$$

$$c(t)=1-\left(\frac{d_1-d_2}{d_1+\beta-d_2}\right)e^{-(d_1+\beta)t}-\left(\frac{\beta}{d_1+\beta-d_2}\right)e^{-d_2 t} \tag{3.3.13}$$

Let s(t) be the probability that a premalignant cell generated at time t=0 is still in the tumour at time t, then

$$s(t)=\left(\frac{d_1-d_2}{d_1+\beta-d_2}\right)e^{-(d_1+\beta)t}+\left(\frac{\beta}{d_1+\beta-d_2}\right)e^{-d_2 t} \tag{3.3.14}$$

Which can be rearranged as

$$s(t)=Pe^{-\lambda_1(t)}+(1-P)e^{-\lambda_2(t)}$$

Where $\lambda_1=d_1+\beta;\lambda_2=d_2$ and $p=\frac{d_1-d_2}{d_1-\beta-d_2}$ therefore s(t) is the probability density function of the mixture of exponential distribution with parameters p,λ_1,λ_2.

For different values of d_1, β, d_2 and t the values of s(t) are computed and given in table (3.3). From table (3.3) it is observed that s (t) is a decreasing function of t when other parameters remain fixed.

Let 'T' be the total duration of a cell in the tumour before reaching state C. Then its expected duration in the tumour is

$$E(T)=\int_0^\infty t\left[d_1 a(t)+d_2 b(t)\right]dt \tag{3.3.15}$$

By substituting the equations (3.3.7) and (3.3.8) in the equation (3.3.15), we get

$$E(T)=\frac{\beta+d_2}{(d_1+\beta)d_2}, \tag{3.3.16}$$

Similarly

$$E(T^2)=\frac{2d_1}{(d_1+\beta)^3}+\frac{2d_2\beta}{(d_1+\beta-d_2)}\left(\frac{1}{d_2^3}-\frac{1}{(d_1+\beta)^3}\right) \tag{3.3.17}$$

TABLE 3.3: The values of S (T) for different values of α, β, γ and t

d_1	β	d_2	t	S(t)
0.123	0.017	0.001	0	1
			2	0.785
			4	0.622
			6	0.5
			8	0.407
			10	0.337
0.567	0.017	0.456	0	1
			2	0.323
			4	0.105
			6	0.035
			8	0.012
			10	0.004
0.985	0.683	0.174	0	1
			2	0.421
			4	0.387
			6	0.373
			8	0.36
			10	0.348
0.123	0.985	0.453	0	1
			2	0.553
			4	0.239
			6	0.098
			8	0.04
			10	0.016
0.567	0.683	0.001	0	1
			2	0.582
			4	0.547
			6	0.543
			8	0.541
			10	0.54
0.985	0.99	0.974	0	1
			2	0.141
			4	0.02
			6	0.003
			8	4.076×10^{-4}
			10	5.805×10^{-5}

The variance of T is

$$V(T) = \frac{2d_1}{(d_1+\beta)^3} + \frac{2d_2\beta}{(d_1+\beta-d_2)}\left(\frac{1}{d_2^3} - \frac{1}{(d_1+\beta^3)}\right) - \left(\frac{\beta+d_2}{d_1+\beta-d_2}\right)^2 \qquad (3.3.18)$$

For different values of d_1, β, d_2 the expected duration of time a cell is in the time tumor and its variability are calculated and given in the table (3.4).

TABLE 3.4: The values of E(T) and V(T) for different values of d_1, β and d_2

d_1	β	d_2	E(T)	V(T)
0.0181	0.1934	0.213	9.0291	552.18
0.542	0.1934	0.213	1.74	47.877
0.903	0.1934	0.213	2.594	78.329
1.264	0.1934	0.213	1.309	34.417
0.542	0.1934	0.827	1.678	13.387
0.542	0.574	0.827	1.518	4.477
0.542	0.384	0.827	1.581	7.362
0.542	1.145	0.827	1.413	1.228
0.903	0.955	0.009	57.649	0.001
0.903	0.955	0.418	1.16	5.015
0.903	0.955	0.827	1.768	1.523
0.0903	0.955	1.235	0.954	0.857

From the equation (3.3.16) and Table (3.4), it is observed that expected total duration of a cell in the tumor before reaching state 'C' is a decreasing function of d_1 when $d_1 > (\beta + d_2)$. It is also observed that E(T) is a decreasing function of β, when $\beta < (d_1 + d_2)$. It is further observed that the expected total duration of the cell in the tumor is a decreasing function of $d_2$when $(d_1 + \beta) > d_2$.

From the equation (3.3.18) and table (3.4), it is observed that the variability of total duration of the cell in the tumour before reaching state 'C' is a decreasing function of d_1, β and d_2 as $d_1 > (\beta + d_2); \beta < (d_1 + d_2)$ and d_2 as $(d_1 + \beta) > d_2$ respectively.

CHAPTER 4

Stochastic Model for Mutant Cell Growth under Chemotherapy

4.1 INTRODUCTION

Chemotherapy is a medical treatment for the control of cancer cell growth through drugs. Malignant tumors (cancer) tends to grow rapidly and show differences in size and shape. in the earlier chapters 2 and 3, the author has consider the mutant cell growth with an assumption that the drugs are continued for a long period of time. However in some chemotherapy treatments, the chemotherapy is prescribed on cyclic basis. When an anticancer drug is induced to the body, both normal and cancer cells are killed. The white blood cells fall to the lower level and care is needed to evaluate the status of the patient. If the outcome is not favourable, life threatening hazards may develop so an interval of time is to be specified during which the chemotherapy may be discontinued to recover. But due to discontinuation of Chemotherapy, the tumour will also grow. At the end of this recovery period, the chemotherapy is to be started again. Due to the stochastic nature of the constituent process, the situation is to be well analyzed through stochastic modeling of cancer cells during the chemotherapy and its absence.

It is assumed that the loss process of the malignant cells follows the poisson process with different parameters, when the patient is under chemotherapy and when the patient is in recovery state. Similarly the growth process of the cancer cells is also poison with different parameters for two states of the patient. It is also assumed that the recovery periods are independently and identically distributed exponential varieties. With these considerations, in this chapter we develop a stochastic model for cancer cell growth, which is much useful for determining the optimal drug dose regimes.

4.2 STOCHASTIC MODEL FOR CANCER CELL GROWTH UNDER CHEMOTHERAPY

Let the growth of the cancer cells is poison with growth rates 'o' and $n\lambda$ during the presence of chemotherapy and in the absence of chemotherapy respectively. The time for which the patient is in recovery state is exponentially distributed with parameters η_{rc}, i.e the time in which the patient moves from the state of recovery to chemotherapy with mean duration η_{rc}. The time in which the patient is under the chemotherapy treatment is a random variable with probability density function f(x). If $\eta_{rc}(x)$ is the conditional

probability that the patient will move from chemotherapy state to recovery state given that the patient has been under treatment for a time 'x' then $f(x) = \eta_{cr}(x) e^{-\int_0^x \eta_{cr}(x)dx}$

Also assume that the loss process of cancer cells is poisson with death rates $n\mu^r$ and $n\mu^c$ when the patient is under recovery and under the chemotherapy states respectively. Let the maximum size of tumour (number of cells in the tumor) be N. Let $P_{r,n}(t)$ be the proability that the patient is under recovery state and there are 'n' cancer cells present in the tumor at time 't' and $P_{c,n}(t, x)$ be the probability that the patient is under the treatment of chemotherapy and 'n' cancer cells are present in the tumor at time 't' and has been the recovery state for the period of time, $(x, x+dx)$.

With the above assumptions, the difference equations of the model are

$$P_{r,n}(t+h) = (1-\lambda h - \eta_{r,c}h)p_{r,0}(t) + \mu^r h p_{r,1}(t) + \int_0^\infty \eta_{c,r}(x) h p_{c,0}(t, x)dx \quad (4.2.1)$$

$$P_{r,n}(t+h) = (1-n\lambda h - n\mu^r h - \eta_{r,c}h)p_{r,n}(t) + (n+1)\mu^r h p_{r,n-1}(t) + (n-1)\lambda h p_{r,n-1}(t) + \int_0^\infty \eta_{c,r}(x) h p_{r,n}(t,x)dx + o(h),\ O \le n \le N-1 \quad (4.2.2)$$

$$p_{r,N}(t+h) = (1-N\mu^r h - \eta_{r,c}h)p_{r,N}(t) + (N-1)\lambda h p_{r,N-1}(t) + \int_0^\infty \eta_{c,r}(x) h p_{r,N}(t,x)dx + o(h) \quad (4.2.3)$$

$$p_{c,0}(t+h, x+h)dx = (1-\eta_{cr}(x)h)p_{c,0}(t,x)dx + \mu^c h p_{c,1}(t,x)dx + 0(h) \quad (4.2.4)$$

$$p_{c,n}(t+h, x+h)dx = (1-n\mu^r h - \eta_{cr}(x)h)p_{c,n}(t,x)dx + (n+1)\mu^c h p_{c,n+1}(t,x)dx + o(h)\ 1 \le n \le N-1 \quad (4.2.5)$$

$$p_{c,N}(t+h, x+h)dx = 1(1-N\mu^c h - \eta_{cr}(x)h)p_{c,N}(t,x)dx + o(h), \quad n = N \quad (4.2.6)$$

With the boundary conditions,

$p_{c,N}(0) 1$ for $n = 0$

$= 0$ otherwise

$p_{c,n}(o, x) = 0$ for all $n \ge 0$; $\quad p_{c,n}(t,0) = \eta_{rc} p_{r,n}(t)$, for $n \le N$

The difference differential equations of the model are

$$\frac{d}{dt}p_{r,0}(t) = -(\lambda+\eta_{rc})p_{r,0}(t) + \mu^r p_{r,1}(t) + \int_0^\infty \eta_{cr}(x)p_{c,0}(t,x)dx \tag{4.2.7}$$

$$\frac{d}{dt}p_{r,n}(t) = -(n\lambda + n\mu^r + \eta_{rc})p_{r,n}(t) + (n+1)\mu^r p_{r(n-1)}(t)$$

$$+(n-1)\lambda p_{r,n-1}(t) + \int_0^\infty \eta_{cr}(x)p_{c,n}(t,x)dx, \text{ for } 1 \le n \le N-1 \tag{4.2.8}$$

$$\frac{d}{dt}p_{r,N}(t) = -(N\mu^r + \eta_{rc})P_{r,N}(t) + (N-1)\lambda p_{r,(N-1)}(t) + \int_0^\infty \eta_{cr}(x)p_{c,N}(t,x)dx \tag{4.2.9}$$

$$\frac{\partial}{\partial x}p_{c,0}(t,x) + \frac{\partial}{\partial t}p_{c,0}(t,x) + \eta_{cr}(x)p_{c,0}(t,x) - \mu^c p_{c,1}(t,x) = 0 \tag{4.2.10}$$

$$\frac{\partial}{\partial x}p_{c,n}(t,x) + \frac{\partial}{\partial t}p_{c,n}(t,x) + (n\mu^c + \eta_{cr}(x))p_{c,n}(t,x)$$

$$+(n+1)\mu^c p_{c,n+1}(t,x) = 0, \qquad \text{for} 1 \le n \le N-1 \tag{4.2.11}$$

$$\frac{\partial}{\partial x}p_{c,N}(t,x) + \frac{\partial}{\partial t}p_{c,N}(t,x) + (N\mu^c + \eta_{cr}(x))p_{c,N}(t,x) = 0 \tag{4.2.12}$$

For solving these difference differential equations, we use Laplace transformation. Multiplying the equation (4.2.7) with e^{-st} on both sides and integrating, we have

$$\frac{d}{dt}\int e^{-st}p_{r,0}(t)dt = -(\lambda+\eta_{rc})\int e^{-st}p_{r,0}(t)dt + \mu^r \int e^{-st}p_{r,1}(t)dt$$

$$\int_0^\infty (\eta_{cr}(x)P_{c,0}(t,x)e^{-st})dx \tag{4.2.13}$$

Denoting $\bar{P}_{r,0}(s) = \int e^{-st}p_{r,0}(t)dt$ and substituting in the equation (4.2.13) and after some simplifications we have

$$\frac{d}{dt}\bar{P}_{r,0}(s) = -(s+\lambda+\eta_{rc})\bar{P}_{r,0}(s) + \mu^r \bar{P}_{r,1}(s) + \int_0^\infty (\eta_{cr}(x)\bar{P}_{c,0}(s,x))dx \tag{4.2.14}$$

Using the boundry conditions and on simplification, we get

$$(s+\lambda+\eta_{rc})\bar{P}_{r,0}(s) = 1 + \mu^r \bar{P}_{r,1}(s) + \int_0^\infty (\eta_{rc}(x)\bar{P}_{c,0}(s,x))dx \tag{4.2.15}$$

Considering the equations (4.2.8) to (4.2.12) and taking the Laplace transformation and using the boundary conditions, we have

$$(s+n\lambda+\eta_{rc}+n\mu^r)\bar{p}_{r,n}(s) = (n+1)\mu^r \bar{p}_{r,n+1}(s) + (n-1)\lambda \bar{p}_{r,n-1}(s)$$

$$\int_0^{\infty}\left(\eta_{cr}(x)\bar{p}_{c,n}(s,x)\right)dx,\ 1\le n\le N-1 \tag{4.2.16}$$

$$\left(s+\eta_{rc}+N\mu^{r}\right)\bar{P}_{r,N}(s)=(N-1)\lambda\bar{P}_{r,N-1}(s)+\int_0^{\infty}\left(\eta_{cr}(x)\bar{P}_{c,N}(s,x)\right)dx \tag{4.2.17}$$

$$\left(s+\eta_{cr}(x)\right)\bar{p}_{c,0}(s,x)=\mu^{c}\bar{P}_{c,1}(s,x)-\frac{\partial}{\partial x}\bar{p}_{c,0}(s,x) \tag{4.2.18}$$

$$\left(s+n\mu^{c}+\eta_{cr}(x)\right)\bar{P}_{c,n}(s,x)=(n+1)\mu^{c}\bar{P}_{c,n+1}(s,x)-\frac{\partial}{\partial x}\bar{P}_{c,n}(s,x)$$

$$1\le n\le N-1 \tag{4.2.19}$$

$$-\left(s+N\mu^{c}+\eta_{cr}(x)\right)\bar{p}_{c,N}(s,x)=\frac{\partial}{\partial x}\bar{p}_{c,N}(s,x) \tag{4.2.20}$$

Solving the linear differential equation (4.2.20), we get

$$\bar{p}_{c,N}(s,x)=\bar{p}_{c,N}(s,0)e^{-\left(s+N\mu^{c}\right)x-\int_0^{x}\eta_{cr}(x)dx} \tag{4.2.21}$$

Taking n = N – 1 in the equation (4.2.19), we have

$$\frac{\partial}{\partial x}\bar{P}_{c,N-1}(s,x)+\left(s+(N-1)\mu^{c}+\eta_{cr}(x)\right)\bar{P}_{c,N-1}(s,x)-N\mu^{c}\bar{P}_{c,N}(s,x)=0 \tag{4.2.22}$$

using (4.2.21) and solving the equation (4.2.20) we get

$$\bar{P}_{c,N-1}(s,x)=N\mu^{c}\bar{A}_1,\bar{P}_{c,N}(s,0)+\bar{P}_{c,N-1}(s,0)e^{-\left(s+(N-1)\mu^{c}\right)x-\int_0^{x}\eta_{cr}(x)dx}$$

$$\text{Where }\ \bar{A}_1=\frac{1-e^{-(\mu^{c})x}}{\mu^{c}} \tag{4.2.23}$$

Taking n = N – 2 in the equation (4.2.19) and solving we get

$$\bar{P}_{c,N-2}(s,x)=\left[N(N-1)\mu^{c}\bar{A}_2,\bar{p}_{c,N}(s,0)+(N-1)\mu^{c}\bar{P}_{c,N-1}(s,0)\bar{A}_1\right.$$

$$\left.+\bar{P}_{c,N-2}(s,0)\right]e^{-\left(s-(N-2)\mu^{c}\right)x-\int_0^{x}\eta_{cr}(x)dx}$$

$$\text{Where }\ \bar{A}_2=\frac{\left(e^{-(\mu^{c})x}-1\right)^{2}}{2!\left(\mu^{c}\right)^{2}} \tag{4.2.24}$$

and for $1\le i\le N-1$

$$\bar{P}_{c,N-1}(s,x)=\left[\sum_{k=0}^{i}\binom{(N-k)}{P\ (i-k)}\left(\mu^{c}\right)^{i-k}\bar{A}_{i-k}\bar{P}_{cN-k}(s,0)\right]\left[e^{-\left(s+(N-i)\mu^{c}\right)x-\int_0^{x}\eta_{cr}(x)dx}\right]$$

where $\bar{A}_0 = 1$ and $\bar{A}_k = \dfrac{(-1)^k\left[e^{-(\mu^c)x}-1\right]^k}{k!(\mu^c)^k}$ (4.2.25)

taking i = N – 1 we have

$$\bar{P}_{c,1}(s,x) = \left[\sum_{k=0}^{N-1}\begin{pmatrix}(N-k)\\ P\\ (N-k-1)\end{pmatrix}(\mu^c)^{N-1-k}\,\bar{A}_{N-K-1}\bar{P}_{c,N-k}(s,0)\right]\left[e^{-(s-\mu^c)x-\int_0^x \eta_{cr}(x)dx}\right] \quad (4.2.26)$$

Substituting the value of $\bar{P}_{c,1}(s,x)$ from the equation (4.2.26) in the equation (4.2.18), we have

$$\bar{P}_{c,0}(s,x) = \left[\sum_{k=0}^{N-1}\begin{pmatrix}(N-k)\\ P\\ (N-k-1)\end{pmatrix}(\mu^c)^{N-k}\,\bar{A}_{N-k}\bar{P}_{c,N-k}(s,0)+\bar{P}_{c,0}(s,x)\right]\left[e^{-sx\int_0^x \eta_{cr}(x)dx}\right] \quad (4.2.27)$$

By taking (N – i) = n in equation (4.2.25) we have

$$\bar{P}_{c,n}(s,x) = \left[\sum_{k=0}^{N-n}\begin{pmatrix}(N-k)\\ P\\ (N-k-n)\end{pmatrix}(\mu^c)^{N-n-k}\,\bar{A}_{N-n-k}\bar{P}_{c,N-k}(s,0)\right]\left[e^{-(s+n\mu^c)x-\int_0^x \eta_{cr}(x)dx}\right]$$

for $1 \le n \le N-1$

where $\bar{A}_k$ is as given in the eqution (4.2.25) (4.2.28)

substituting the value of $\bar{p}_{c,0}(s,x)$ from the equation (4.2.27) in the equation (4.2.18) and using the boundary conditions, we get $\bar{p}_{r,0}(s)$

Therefore

$$\left(s+\lambda+\eta_{rc}-\eta_{rc}\bar{f}(s)\right)\bar{p}_{r,0}(s) = 1+\mu^c\bar{p}_{c,1}(s) + \left[\sum_{k=0}^{N-1}\begin{pmatrix}(N-k)\\ P\\ (N-k-1)\end{pmatrix}(\mu^c)^{N-k}\,\eta_{rc}\bar{P}_{r,N-k}(s)\,L\left(A_{N-k}(x)f(x)\right)\right]$$

Where $\bar{f}(s) = \int_0^\infty \eta_{rc}(x)e^{-\int_0^x (s+\eta_{cr}(x))dx}dx$ (4.2.29)

Where L is the Laplace transform operator. Substituting the value of $\bar{P}_{c,n}(s,x)$ from the equation (4.2.28) in the equation (4.2.16) and using the boundary conditions, we get

$$\left(s+n\lambda+n\mu^{r}+\eta_{rc}\right)\bar{p}_{r,n}(s)=(n+1)\mu^{c}\bar{p}_{r,n+1}(s)+(n-1)\lambda\bar{p}_{r,n-1}(s)+\int_{0}^{\infty}\eta_{cr}(x)$$

$$\left[\sum_{k=0}^{N-n}\begin{pmatrix}(N-k)\\P\\(N-n-k)\end{pmatrix}\left(\mu^{c}\right)^{N-n-k}\bar{P}_{c,N-k}(s,0)\bar{A}_{N-n-k}\right]$$

$$e^{-\left(s+\mu^{c}\right)x-\int_{0}^{x}\eta_{cr}(x)dx} \tag{4.2.30}$$

On simplification we have

$$\left(s+n\lambda+n\mu^{r}+\eta_{rc}\right)\bar{P}_{r,n}(s)=(n+1)\mu^{r}\bar{p}_{r,n+1}(s)+(n-1)\lambda\bar{p}_{r,n-1}(s)$$

$$+\left[\sum_{k=0}^{N-k}\begin{pmatrix}(N-k)\\p\\(N-n-k)\end{pmatrix}\eta_{rc}\bar{P}_{r,N-k}(s)\right]\frac{(-1)^{N-n-k}}{(N-n-k)!}$$

$$\int_{0}^{\infty}f(x)e^{-\left(s+n\mu^{c}\right)x}\left[e^{-\left(\mu^{c}\right)x}-1\right]^{N-n-k}dx$$

Where $f(x)=\eta_{cr}(x)e^{-\int_{0}^{x}\eta_{cr}(x)dx}$ (4.2.31)

This implies

$$\left(s+n\lambda+n\mu^{r}+\eta_{rc}\right)\bar{P}_{r,n}(s)=(n+1)\mu^{r}\bar{p}_{r,n+1}(s)+(n-1)\lambda\bar{p}_{r,n-1}(s)$$

$$+\left[\sum_{k=0}^{N-n}(-1)^{N-n-k}\begin{pmatrix}(N-k)\\P\\(N-n-k)\end{pmatrix}\eta_{rc}\bar{P}_{r,N-k}(s)\right]$$

$$\sum_{i=0}^{N-n-k}\begin{pmatrix}N-r-k\\c\\i\end{pmatrix}(-1)^{i}\bar{f}\left(s_{N-k-i}\right) \tag{4.2.32}$$

Substituting the value of $\bar{P}_{c,N}(s)$ in (4.2.17) and using the boundry conditions, we have

$$\left(s+N\mu^{r}+\eta_{rc}\right)\bar{P}_{r,N}(s)=(N-1)\lambda\bar{P}_{r,N-1}(s)+\bar{f}\left(s_{N}\right)\eta_{rc}\bar{p}_{r,N}(s) \tag{4.2.33}$$

This implies

$$\left[s+N\mu^{r}+\eta_{rc}-\eta_{rc}\bar{f}\left(s_{N}\right)\right]=(N-1)\lambda\bar{p}_{r,N}(s) \tag{4.2.34}$$

The equation (4.2.34) can also be written as

$$\bar{p}_{r,N-1}(s)=\left(A_{1}-1\right)\bar{p}_{r,N}(s)$$

Where $A_1 = \frac{1}{(N-1)\lambda}\left[s + N\mu^r(N-1)\lambda + \eta_{rc} - \eta_{rc}\bar{f}(s_N)\right]$ and

$$s_N = s + N(\mu^c) \tag{4.2.35}$$

Taking n = N – 1, N – 2, … in equation (4.2.32)

$\bar{P}_{r,N-2}(s) = \left[A_2(A_1 - 1) - B_2\right]\bar{p}_{r,N}(s)$

This implies

$\bar{P}_{r,N-2}(s) = K_2\bar{p}_{r,N}(s)$ and

$\bar{P}_{r,N-3}(s) = K_3\bar{p}_{r,N}(s)$

Where $K_3 = A_3\left[A_2(A_1 - 1) - B_2\right] - B_3(A_1 - 1) - D_3$ (4.2.36)

In general

$\bar{P}_{r,N-k}(s) = K_k\bar{P}_{r,N}(s)$ for $2 \le k \le N$

Where $K_k = \left[A_kK_{k-1} - B_kK_{k-2} - D_k\right]$

$$A_k = \frac{1}{(N-k)\lambda}\left[s + (N-k+1)\mu^r + (N-k+1)\lambda + \eta_{rc} - \eta_{rc}\bar{f}(s_{N-k+1})\right]; 2 \le k \le N$$

$$B_k = \frac{1}{(N-k)\lambda}\left[(N-k+2)\mu^r - \eta_{rc}(N-k+2)\bar{f}(s_{N-k+2}) - \bar{f}(s_{N-k+3})\right]$$

$$D_k = \left[\frac{1}{(N-k)\lambda}\sum_{j=0}^{k-3}(-1)^{k-(j+1)}\binom{(N-j)}{P}{(k-(j+1))}\eta_{rc}\right]\left[\sum_{i=0}^{k-(j+1)}\binom{k-j-1}{C}{i}(-1)^i\bar{f}(s_{N-j-i})\right] \tag{4.2.37}$$

The equation (4.2.37) gives the values of $\bar{P}_{r,N}(s)$ interms of $\bar{P}_{r,N}(s)$. We can obtain $\bar{P}_{r,N}(s)$ as

$$\left[\bar{P}_{r,N}(s)\right]^{-1} = \left[s + \lambda + \eta_{rc} - \eta_{rc}\bar{f}(s)\right]K_N - (\mu^r)K_{N-1}$$

$$-\eta_{rc}\left[\sum_{k=0}^{N-1}\binom{(N-k)}{P}{(N-k-1)}(\mu^c)^{N-k}\right]K_kL\left(\bar{A}_{N-k}(x)\bar{f}(x)\right)$$

Where $L\left(\bar{A}_N(x)f(x)\right) = \dfrac{\sum_{i=0}^{N}(-1)^{N+i}\binom{N}{C}{i}\bar{f}(s_{N-i})}{N!(\mu^c)^N}$ and

K_k as given in the equation (4.2.37) (4.2.38)

The laplace transformation of the probability that at time t there are (N-i) malignant cells in the tumor when the patient is under chemotherapy is obtained as

$$\bar{P}_{c,N-i}(s)=\sum_{k=0}^{i}\left[\frac{\binom{(N-k)}{P}_{(i-k)}}{(i-k)!}\right]\eta_{rc}\bar{p}_{r,N-k}(s)(-1)^{i=k}\sum_{l=0}^{i=k}\binom{i-k}{C}_{1}(-1)^{l}\left[\frac{1-\bar{f}(s_{N-k-l})}{s_{N-k-l}}\right]$$

Where, $1-F(x)=e^{-\int_0^x \eta_{rc}(\mu)du}$ (4.2.39)

On simplification, we have

$$\bar{p}_{c,N-i}(s)=\left[\frac{\binom{N}{p}_{i}}{i!}\eta_{rc}\sum_{l=0}^{i}\binom{i}{C}_{1}(-1)^{i+1}\left[\frac{1-\bar{f}(s_{N-1})}{s_{N-1}}\right]\right.$$

$$+(1-\delta_{i,0})\frac{\binom{N-1}{P}_{i-1}}{(i-1)!}\eta_{rc}K_1\sum_{l=0}^{i-l}\binom{i-1}{C}_{1}(-1)^{i+l-1}\left[\frac{1-\bar{f}(s_{N-l-1})}{s_{N-l-1}}\right]$$

$$\left.+\sum_{k=2}^{i}\left[\frac{\binom{(N-k)}{P}_{(i-k)}}{(i-k)!}\right]\eta_{rc}K_k\sum_{i=0}^{i-k}\binom{i-k}{C}_{1}(-1)^{i+1-k}\left[\frac{1-\bar{f}(s_{N-k-l})}{s_{N-k-l}}\right]\right]\bar{p}_{r,N}(s)$$

$$0\le i\le N-1$$

and $\delta_{ij}=0$ if i =j, $\delta_{ij}=1$ if $i\neq j$ and K_k is as given in the equation (4.2.37) (4.2.40)

$$\bar{P}_{c,0}(s)=\sum_{k=0}^{N-1}\left[\frac{\binom{(N-k)}{P}\binom{(N-k-1)}{}}{(N-k)!}\right]\eta_{rc}\bar{P}_{r,N-k}(s)\sum_{i=0}^{N-k}(-1)^{N-k+i}\left[\frac{1-\bar{f}(s_{N-k-i})}{s_{N-k-i}}\right]+\eta_{rc}\bar{P}_{r,0}(s)\left[\frac{1-\bar{f}(s)}{s}\right] \tag{4.2.41}$$

Using the boundary conditions, we have

$$\bar{P}_{c,0}(s)=\left\{\left[\sum_{k=0}^{N-1}\binom{(N-k)}{P}\binom{(N-k-1)}{}\eta_{rc}\right]K_k\sum_{i=0}^{N-k}(-1)^{N-k-i}\left[\frac{1-\bar{f}(s_{N-k-i})}{s_{N-k-i}}\right]+\eta_{rc}K_N\left[\frac{1-\bar{f}(s)}{s}\right]\right\}\bar{P}_{r,N}(s) \tag{4.2.42}$$

4.3 LIMITING BEHAVIOUR OF THE MODEL

Assuming that the tumor is in the equilibrium state we have $\lim_{s\to 0} sF(s)=\lim_{t\to\infty}F(t)$,

$\lim_{t\to 0}P_{r,n}(t)=p_{r,n}$ and $\lim_{t\to 0}P_{c,n}(t)=p_{c,n}$

The equilibrium probabilities of the tumor size when the patient is under chemotherapy is obtained as

$$P_{c,N-i}=\left\{\frac{\binom{N}{P}\binom{i}{}}{i!}\eta_{rc}\sum_{l=0}^{i}\binom{i}{C}\binom{}{1}(-1)^{i+1}\left[\frac{1-f_{(N-1)\mu^c}}{(N-1)\mu^c}\right]\right.$$

$$\left.+(1-\delta_{i,0})\frac{\binom{N-1}{P}\binom{i-1}{}}{(i-1)!}\eta_{rc}K_i\sum_{l=0}^{i-1}\binom{i-1}{C}\binom{}{1}(-1)^{i+1-l}\left[\frac{1-\bar{f}_{(N-1-l)\mu^c}}{(N-1-l)\mu^c}\right]\right.$$

$$+\sum_{k=2}^{i}\frac{\binom{N-k}{p}\binom{}{i-k}}{(i-k)!}\eta_{rc}K_k\sum_{l=0}^{i-k}\binom{i-k}{C}\binom{}{1}(-1)^{i+1-k}\left[\frac{1-\bar{f}_{(N-k-1)\mu^c}}{(N-k-1)\mu^c}\right]\Bigg\}P_{r,N}$$

where, $\lim_{s\to 0} f_{N-j}(s)=\int_0^{\infty}\eta_{cr}(x)\bar{A}_{N-j}e^{-\int_0^x\eta_{cr}(x)dx}dx$ (4.3.1)

$$P_{c,0}=\left[\sum_{k=0}^{N-1}\frac{\binom{N-k}{P}\binom{}{N-k-1}}{(N-k)!}\eta_{rc}K_k\sum_{i=0}^{N-k}(-1)^{N-k+i}\left[\frac{1-\bar{f}_{(N-k-i)\mu^c}}{(N-k-i)\mu^c}\right]+\eta_{rc}K_N m_f\right]P_{r,N} \quad (4.3.2)$$

Where $m_f=\lim_{s\to 0}\left[\frac{1-\bar{f}(s)}{s}\right]$ is the mean duration for which the patient is under chemotherapy.

Similarly the equilibrium probabilities of the tumor size when the patient is under recovery state are $P_{r,N-1}=(A_1-1)P_{r,N}$

and $P_{r,N-k}=K_kP_{r,N}$ where A_1 and K_k is as given in equations (4.2.35) and (4.2.37) respectively.

Using the boundary condition, $P_{r,N}+P_{r,N-1}+\sum_{k=2}^{N}P_{r,N-k}+\sum_{k=1}^{N-1}P_{c,N-k}+P_{c,0}=1$ (4.3.3)

We have

$$\left[p_{r,N}\right]^{-1}=1+\sum_{k=1}^{N}K_k+\sum_{i=1}^{N-1}\frac{\binom{N}{P}\binom{}{i}}{i!}\eta_{rc}\sum_{l=0}^{i}\binom{i}{C}\binom{}{1}(-1)^{i+1}\left[\frac{1-\bar{f}_{(N-1)\mu^c}}{(N-1)\mu^c}\right]$$

$$+\left(1-\delta_{i,0}\right)\frac{\begin{pmatrix} N-1 \\ P \\ i-1 \end{pmatrix}}{(i-1)!}\eta_{rc}K_1\sum_{l=0}^{i-1}\begin{pmatrix} i-1 \\ C \\ 1 \end{pmatrix}(-1)^{i+l-1}\left[\frac{1-\bar{f}_{(N-1-l)\mu^c}}{(N-1-l)\mu^c}\right]$$

$$+\sum_{k=2}^{i}\frac{\begin{pmatrix} N-k \\ P \\ i-k \end{pmatrix}}{(i-k)!}\eta_{rc}K_k\sum_{l=0}^{i-k}\begin{pmatrix} i-k \\ C \\ 1 \end{pmatrix}(-1)^{i+l-k}\left[\frac{1-\bar{f}_{(N-k-l)\mu^c}}{(N-k-l)\mu^c}\right]$$

$$+\sum_{k=0}^{N-1}\frac{\begin{pmatrix} N-k \\ P \\ N-k-1 \end{pmatrix}}{(N-k)!}\eta_{rc}K_k\sum_{i=0}^{N-k}(-1)^{N-k-i}\left[\frac{1-\bar{f}_{(N-k-i)\mu^c}}{(N-k-i)\mu^c}\right]+\eta_{rc}K_N m_f$$

Where

$$A_k=\frac{1}{(N-k)\lambda}\left\{(N-k+1)\mu^r+(N-k+1)\lambda+\eta_{rc}-\eta_{rc}\bar{f}_{(N-k+1)\mu^c}\right\}$$

$$B_k=\frac{1}{(N-k)\lambda}\left\{(N-k+2)\mu^r-\eta_{rc}(N-k+2)p_{(1)}\left(\bar{f}_{(N-k+2)\mu^c}-\bar{f}_{(N-k+3)\mu^c}\right)\right\}$$

$$D_k=\frac{1}{(N-k)\lambda}\left[\sum_{l=0}^{k-3}(-1)^{k-(l+1)}\begin{pmatrix} (N-1) \\ P \\ (k-(l+1)) \end{pmatrix}\eta_{rc}\right]\sum_{i=0}^{(k-l-1)}\begin{pmatrix} k-l-1 \\ C \\ i \end{pmatrix}(-1)^i f_{(N-l-i)\mu^c}$$

(4.3.4)

4.4 MODEL BEHAVIOUR WHEN THE CYCLE LENGTH IS EXPONENTIAL

Since the distribution of the tumor size depends on the random time X, during which the patient is under chemotherapy, let us assume that it follows an exponential distribution with parameter η_{cr}. Then the transition probability from presence of chemotherapy to the recovery state $\eta_{cr}(x)$ becomes η_{cr}

$$\bar{f}(s_l)=\int_0^\infty \eta_{cr}e^{-(s_l+\eta_{cr})}dx=\frac{\eta_{cr}}{\eta_{cr}+s_l} \tag{4.4.1}$$

We have

$$\bar{P}_{r,N-l}(s)=(A_l-1)\bar{p}_{r,N}(s) \tag{4.4.2}$$

$$\bar{P}_{r,N-k}(s)=K_k\bar{p}_{r,n}(s),\ 2\le k\le N \tag{4.4.3}$$

and

$$\left[p_{r,N}\right]^{-1}\left\{s+\lambda+\eta_{rc}-\eta_{rc}\bar{f}(s)\right\}K_N-\mu^r K_{N-1}$$

$$-\eta_{rc}\left[\sum_{k=0}^{N-1}\begin{pmatrix}(N-k)\\P\\(N-k-1)\end{pmatrix}\left(\mu^c\right)^{N-k}K_k L\left(\bar{A}_{N-k}(x)f(x)\right)\right] \tag{4.4.4}$$

Where K_k and $\bar{A}_{N-k}$ are as given in the equations (4.2.37) and (4.2.38). When the patient is under chemotherapy, we have

$$\frac{1-\bar{f}(s_1)}{s_1}=\frac{1}{\eta_{cr}+s_1} \tag{4.4.5}$$

This implies

$$\left[\bar{p}_{c,N-1}(s)\right]^{-1}\left[\frac{\begin{pmatrix}N\\p\\i\end{pmatrix}}{i!}\eta_{cr}\sum_{l=0}^{i}\begin{pmatrix}i\\c\\1\end{pmatrix}(-1)^{i+1}\left[\frac{1}{\eta_{cr}+s_{N-1}}\right]\right.$$

$$+\left(1-\delta_{1,0}\right)\frac{\begin{pmatrix}N-1\\P\\i-1\end{pmatrix}}{(i-1)!}\eta_{rc}K_1\sum_{l=0}^{i-1}\begin{pmatrix}i-1\\c\\1\end{pmatrix}(-1)^{i+1-1}\left[\frac{1}{\eta_{cr}+s_{N-1-1}}\right]$$

$$\left.+\sum_{k=2}^{i}\frac{\begin{pmatrix}N-k\\P\\i-k\end{pmatrix}}{(i-k)!}\eta_{rc}K_k\sum_{l=0}^{i-k}\begin{pmatrix}i-k\\c\\1\end{pmatrix}(-1)^{i+1-k}\left[\frac{1}{\eta_{cr}+s_{N-k-1}}\right]\right]\bar{P}_{r,N}(s)$$

Where $s_n=s+n\left(\mu^r\right)$ (4.4.6)

$$\bar{P}_{c,0}(s)=\left[\sum_{k=0}^{N-1}\frac{\begin{pmatrix}N\\p\\N-k-1\end{pmatrix}}{(N-k)!}\eta_{rc}K_k\sum_{i=0}^{N-k}(-1)^{N+i-k}\left[\frac{1}{\eta_{rc}+s_{N-k-i}}\right]\right.$$

$$+\left[\frac{1-\bar{f}(s)}{s}\right]\eta_{rc}K_N\Bigg]\bar{P}_{r,N}(s)$$

Where

$$A_1=\frac{1}{(N-1)\lambda}\left[s+N\mu^r+(N-1)\lambda+\eta_{rc}-\eta_{rc}\left(\frac{\eta_{cr}}{\eta_{cr}+s_{N-i}}\right)\right]$$

$$A_k=\frac{1}{(N-k)\lambda}\left[s+(N-k+1)\mu^r+(N-k+1)\lambda+\eta_{rc}-\eta_{rc}\left(\frac{\eta_{cr}}{\eta_{cr}+s_{N-k-1}}\right)\right]$$

$$2\le k\le N$$

$$B_k=\frac{1}{(N-k)\lambda}\Big[(N-k+2)\mu^r+\eta_{rc}(N-k+2)$$

$$\left(\frac{\eta_{cr}}{\eta_{cr}+s_{N-k+2}}-\frac{\eta_{cr}}{\eta_{cr}+s_{N-k+3}}\right)\Big]$$

$$D_k=\frac{1}{(N-k)\lambda}\left[\sum_{j=0}^{k-3}(-1)^{k-(j+1)}\binom{(N-j)}{p}\binom{}{(k-(j+1))}\eta_{rc}\right]\left[\sum_{i=0}^{(k-j-1)}\binom{k-j-1}{c}\binom{}{i}\left(\frac{\eta_{cr}}{\eta_{cr}+s_{N-j-i}}\right)\right] \qquad (4.4.7)$$

The probability that the patient is under chemotherapy and (N-i) cancer cells are in the tumor at any arbitrary time after reaching the equilibrium position is denoted as $p_{c,N-i}$ then

$$P_{c-N-i}=\Bigg[\frac{\binom{N}{p}\binom{}{i}}{i!}\eta_{rc}\sum_{l=0}^{i}\binom{i}{c}\binom{}{1}(-1)^{i+1}\left[\frac{1}{\eta_{cr}+(N-1)\mu^c}\right]$$

$$+(1-\delta_{i,0})\frac{\binom{N-1}{p}\binom{}{i-1}}{(i-1)!}\eta_{rc}K_1\sum_{l=0}^{i-1}\binom{i-1}{c}\binom{}{1}(-1)^{i+1-1}\left[\frac{1}{\eta_{cr}+(N-1-1)\mu^c}\right]$$

$$+\sum_{k=2}^{i}\frac{\binom{N-k}{p}}{(i-k)!}\eta_{rc}K_k\sum_{l=0}^{i-k}\binom{i-k}{c}{1}(-1)^{i+1-k}\left[\frac{1}{\eta_{cr}+(N-k-1)\mu^c}\right]\Bigg]P_{r,N} \qquad (4.4.8)$$

$$p_{c,0}=\left[\sum_{k=0}^{N-1}\frac{\binom{N}{p}}{(N-k)!}\eta_{rc}K_k\sum_{i=0}^{N-k}(-1)^{N-k+i}\left[\frac{1}{\eta_{cr}+(N-k-i)\mu^c}\right]+\eta_{rc}K_N m_f\right]P_{r,N} \qquad (4.4.9)$$

Where m_f is as given in the equation (4.3.2)

When the patient is in recovery state. We can obtain the probability that there are (N-r) cancer cells in the tumor as $P_{r,N-1}=(A_1-1)p_{r,N}$

$$P_{r,N-k}=K_k p_{r,N}$$

Where K_k is as given in the equation (4.2.37) and

$$\left[p_{r,N}\right]^{-1}=1+\sum_{k=1}^{N}K_k+\frac{\binom{N}{P}}{i!}\eta_{rc}\sum_{l=0}^{i}\binom{i}{c}{1}(-1)^{i+1}\left[\frac{1}{\eta_{cr}}+\frac{1}{(N-1)\mu^c}\right]$$

$$+(1-\delta_{i,0})\frac{\binom{N-1}{p}}{(i-1)!}\eta_{rc}K_1\sum_{l=0}^{i-1}\binom{i-1}{c}{1}(-1)^{i+1-1}\left[\frac{1}{\eta_{cr}+(N-1-1)\mu^c}\right]$$

$$+\sum_{k=2}^{i}\frac{\binom{N-k}{p}}{(i-k)!}\eta_{rc}K_k\sum_{l=0}^{i-k}\binom{i-k}{c}{1}(-1)^{i+1-k}\left[\frac{1}{\eta_{cr}(N-k-1)\mu^c}\right]$$

$$+\sum_{k=0}^{N}\frac{\binom{N}{p}}{(N-k)!}\eta_{rc}K_k\sum_{i=0}^{N-k}(-1)^{N-k+i}\left[\frac{1}{\eta_{cr}+(N-k-i)\mu^c}\right]+\eta_{rc}K_N m_f$$

Where

$$A_1 = \frac{1}{(N-1)\lambda}\left\{N\mu^r + (N-1)\lambda + \eta_{rc} - \eta_{rc}\left(\frac{1}{\eta_{cr} + N\mu^r}\right)\right\}$$

$$A_k = \frac{1}{(N-k)\lambda}\left\{(N-k+1)\mu^r + (N-k+1)\lambda + \eta_{rc} - \eta_{rc}\left[\frac{1}{\eta_{cr} + (N-k-1)\mu^c}\right]\right\} \qquad 2 \le r \le N$$

$$B_k = \frac{1}{(N-k)\lambda}\left\{(N-k+2)\mu^r + \eta_{rc}(N-k+2)\right.$$

$$\left.\left(\frac{\eta_{cr}}{\eta_{cr} + (N-k+2)\mu^c} - \frac{\eta_{cr}}{\eta_{cr} + (N-k+3)\mu^c}\right)\right\}$$

$$D_k = \frac{1}{(N-k)\lambda}\left[\left[\sum_{j=0}^{k-3}(-1)^{k-(j+1)}\begin{pmatrix}(N-j)\\ P\\ (k-(j+1))\end{pmatrix}\eta_{rc}\right]\right.$$

$$\left.\sum_{i=0}^{(k-j-1)}\begin{pmatrix}k-j-1\\ C\\ i\end{pmatrix}(-1)^i\left[\frac{\eta_{cr}}{\eta_{cr} + (N-j-i)\mu^c}\right]\right]$$

$$K_k = Ak.K_{k-1} - B_k K_{k-2}. - D_k \qquad (4.4.11)$$

With this probability distribution of the tumor size in both the states, we can analyse the tumour behaviour by obtaining the characteristics of the model.

The probability that there are no cancer cells in the tumor when the chemotherapy is under administration is

$$P_{c,0} = \left\{\sum_{k=0}^{N-1}\frac{\begin{pmatrix}N\\ p\\ N-k-1\end{pmatrix}}{(N-k)!}\eta_{rc}K_k\sum_{i=0}^{N-k}(-1)^{N-k+i}\left[\frac{1}{\eta_{cr} + (N-k-i)\mu^c}\right] + \eta_{rc}K_N m_f\right\}(p_{r,N})$$

(4.4.12)

Similarly the probability that there are no cancer cells in the tumor when the patient is in recovery state is

$$P_{r,0} = (A_N K_{N-1} - B_N K_{N-2} - D_N)P_{r,N} \qquad (4.4.13)$$

where $p_{r,N}$ and K_N are as given in the equations (4.4.11) and (4.2.37).

from the equations (4.4.12) and (4.4.13) we observe that $p_{c,0}$ and $p_{r,0}$ are increasing functions of μ^r and μ^c when other parameters are fixed. The values of $P_{c,0}$ and $P_{r,0}$ are decreasing when λ is increasing for fixed values of μ^r, μ^c and N. The probability of extinction of the malignant cells in the tumor can be increased by choosing optimal drug dose.

The average number of cancer cells in the tumor is

$$L = \sum_{n=0}^{N} np_{r,n} + \sum_{n=0}^{N} np_{c,n} \tag{4.4.14}$$

The variance of number of cancer cells in the tumor is

$$V = \sum_{n=0}^{N} n^2 p_{r,n} + \sum_{n=0}^{N} n^2 p_{c,n} - (L)^2$$

Where L is given in the equation (4.4.14). (4.4.15)

From the equations (4.4.14) and (4.4.15) it is observed that mean and variance of the number of malignant cells in the tumor is a decreasing function of μ^r and μ^c when other parameters are fixed. This model also gives the result of the model when the chemotherapy is continued for long time (not on cyclic basis) when $\eta_{cr} \to 0$.

CHAPTER – 5
Summary and Conclusion

This book has presented the descriptive modeling of malignant tumor growth based on cell kinetics. The tumor growth models gain a lot of importance in Biometrics and Medical Statistics due to their wide applicability in optimal design and analysis of therapy. A tumor is a mass of tissues formed as a result of abnormal, excessive and inappropriate proliferation of cells. Due to the complex nature of growth process of tumor, it is necessary to formulate and integrate models that attempt to describe the growth and development process of tumors at different levels. Tumor growth models describe the evolution of the size of a tumor which is assumed to be originate from an initial transformed (or) proginator cell. The size of cells in tumor is approximated by the number of cells in it. The number of cells in tumor can usually be estimated indirectly using the measurements of volume, weight or chemical markers of the tumor. The growth of tumors is heavily influenced by spontaneous mutation and proliferation and loss processes. The growth of the number of cells in the tumor is random and time dependent.

Stochastic models are much useful for understanding the cell kinetics of the tumors and in particularly malignant tumors. Tumor is said to be malignant tumor if it contains malignant cells. Malignant cells can also be referred as mutant cells. In this dissertation an attempt is made to develop some suitable stochastic models for cancer cell growth by assuming the mutation, proliferation and loss process are all poisson for both normal and mutant cells and analysed using the difference differential equations, generating functions and Laplace transformation techniques. The behaviour of tumour growth is analyzed in the light of mutant rates, loss rates and growth rates of cells by deriving the explicit expressions for the characteristics of the models.

The first chapter of this dissertation briefly introduces the motivation of present research work along with a review on some relevant contributions in tumour growth models. Swan (1990) categorized the cancer cell growth models into three categories namely, (i) Miscellaneous growth kinetic model, (ii) cell cycle model and (iii) other models, in which the study deals with the first category of models. Mayneord (1932) pioneered the systematic study of tumour growth. The works of Laird (1964), Burton (1966), Simpson – Hersen and Lioyed (1970), Sullivan and Solmon (1972) and Steel (1977) demonstrate the applicability of the Gompertz growth law to tumour growth. Their results are based upon curve fitting. The Gompertz model is deterministic. In real

situations tumor cells are subject to irregular growth due to various random factors. The irregular growth can result in tumor sizes that are different than those predicted by the deterministic models. To account for the irregular growth stochastic models of tumor growth have been introduced particularly in the model of cancer cells. Iverson and Arley (1950) described the growth of transformed cell, a progenitor of a tumor by a pure linear birth process. Kendall (1960), Neyman and Scott (1967) used a linear birth and death process to describe the tumor growth. Their model used constant birth and death rates and hence is also a density independent. Wette, katz and Rodin (1974) developed a stochastic model for growth of solid tumors based upon the physical characteristics of tumor. This leads to a density dependent stochastic process for the mean tumor sizes. Dubin (1976) formulated a density dependent, birth and death processes, to describe the tumor growth subject to immunological response. Swan (1977) described a method for obtaining the exact solution to Dubin's model. Hanson and Tier (1982) developed a stochastic model for tumor growth which is the diffusion limit of a continuous time density dependent branching processes. Jain et al. (1995) developed a stochastic model for multistage tumerogenesis and observed that the tumor latency was strongly influenced by number of stages and stem cell number at lower mutation rates than at higher rates. Zheng (1998) has discussed the role of Kolmogrov forward and backward equations in stochastic carcinogenesis models.

With the brief review, it is evident that very little work has been reported in literature regarding the tumor growth models with spontaneous mutation and proliferation process except the models of Birkhead (1986). The spontaneous mutation and proliferation of tumor cells can be described as a process of cell division with three major considerations namely, (i) a normal cell may be divided into two normal cells. (ii) a normal cell may be divided into one normal and one mutant cell and (iii) a mutant cell may be divided into two mutant cells. Due to the recessive oncogenesis hypothesis the malignant tumor growth can be attributable to the inactivation of both allele genes. Hence the growth rates and mutation rates of the normal and mutant cells are not homogeneous. It is also important that the chemotherapy can be administered on cyclical basis, which creates two heterogeneous environments for the tumor growth namely (i) when the patient is under chemotherapy and (ii) when the patient is under recovery (Temporary absence of chemotherapy). So to analyze the tumor growth, with all these considerations (which are very important for effective drug administration) suitable stochastic models are developed. The chapter outline of the study is also presented.

In chapter – II, a stochastic model for tumor growth with spontaneous mutation and proliferation is developed by assuming that the mutation process of normal and mutant cells are Poisson with different parameters. It is assumed that the loss process of the normal and mutant cells are poisson with parameters d_1, d_2 respectively. Using the Kolmogrov's equations, the Joint probability generating function of the normal and mutant cells at a given time 't' is obtained. The size of the tumor is the sum of the number of normal cells and the number of mutant cells in the tumor. So the expected number of normal cells at any given time 't', the expected number of mutant cells at any given time 't' the variances of normal and mutant cells at any given time 't' and the co-variance between the number of normal and mutant cells at time 't' are derived by using the relation between the cumulant generating function and probability generating function. Using PCAT computer and MATHCAD+, the sensitivity of the parameters is analyzed by computing the values of tumor characteristics for different values of the parameters. It is observed that when other parameters are fixed, the expected tumor size is an increasing function of growth and mutant rates. Similarly when the loss parameters d_1 and d_2 are decreasing, the growth of tumor is increasing. It is also observed that the tumor size and its variability are also influenced by the initial size of the tumor. The dependence between the normal and mutant cells is increasing as time 't' increases.

The heterogeneity of the growth rates of normal and mutant cells in the tumor may be attributable to inactivation of both allele genes which is known as recessive oncogenesis hypothesis. This is incorporated by assuming that the proliferation of mutant cells is due to sum of natural proliferation and due to inactivation of allele genes. By using the difference differential equations, the Joint probability generating function of the number of normal and mutant cells at a given time 't' is derived, when the tumor is subject to spontaneous mutation and proliferation. The expected number of normal cells, the expected number of mutant cells and their variances at given time 't' are derived by using the probability generating function. It is observed that, the inactivation of allele genes has a tremendous influence on the tumor size. The drug efficiency on the tumor is also investigated by developing and analyzing another stochastic model with the assumption that when the tumor is under drug administration the loss process of the cells is due to natural loss and loss due to drug administration. The joint probability generating function for the number of normal and mutant cells at given time 't' is derived. Using this probability generating function the expected number of normal cells and their variance are derived explicitly. The mean tumor size and its variability at given time 't' are analysed in

the light of the loss rate due to drug administration. The mean tumor size is reduced when θ, (the loss rate due to drug administration) increases at a given time 't'. The covariance between the number of normal and mutant cells at a given time 't' is a decreasing function of θ when other parameters are fixed. It is also observed that the variances of number of both normal and mutant cells are decreasing functions of time 't' when $(\alpha+b+\beta)< (d+\theta)$. Following the heuristic argument of Goldie and Coldman (1979, 85) the drug sensitivity of this model is investigated by obtaining the probability of cure, which is the probability of eventual extinction of remaining resistance cells after complete eradication of sensitive cells.

chapter III deals with a two stage stochastic model for a cancer cell growth with the assumption that in any malignant tumors there will be premalignant and malignant clones. In the beginning a normal clone becomes premalignant and later it becomes malignant if it takes further proliferation. A premalignant cell may extinct without becoming a malignant cell or it may take mutation and become a malignant cell. The size of the malignant tumor is heavily influenced by these growth kinetics of malignant cells, that make up the foci within the foci. This situation in the tumor growth can be suitably approximated by developing a two stage stochastic model with the assumption that the growth of premalignant cell, mutation and loss of premalignant and malignant cells are random and follows poisson process with different parameters. The joint probability generating function of the number of premalignant cells and malignant cells in the tumor at a given time is derived by using the difference differential equations. The expected number of premalignant and malignant cells at a given time 't' and their variances are obtained explicitly. The average tumor size and its variability are also obtained and analyzed in the light of the parameters. It is observed that the tumor size is an increasing function of growth rate. The average tumor size is a decreasing function of d_2, the loss rates at a given time 't'. this model is also further extended to analyse the cell duration in the tumor. The probability that a malignant cell (either premalignant or malignant) which is initial at t=0 is still in the tumor at time 't' is obtained. The expected duration of a malignant cell in the tumor and its variance are also obtained. If the mutation rate of premalignant cells is increasing the average duration of cell in the tumor is increasing when other parameters are fixed.

In Chapter IV of this study a stochastic model for the mutant cell growth under chemotherapy is developed and analyzed. In some chemotherapy treatments, the

chemotherapy is prescribed on cyclic basis. When an anti cancer drug is induced to the body both normal and cancer cells are killed. When the normal cells come to a lower level, care is needed to evaluate the status of the patient because life threatening hazards may be developed. So an interval of time is to be considered during which the drug may be discontinued and the patient is allowed to recover, but due to discontinuation of the drug the tumor will also grow. So at the end of the recovery period, the drug is to be administered again. This situation is modeled through assuming the growth process and loss process of the cancer cells are poisson with different parameters for two stages of the patient, namely (i) when the patient is in recovery state and (ii) when the patient is under chemotherapy. using the supplementary variable technique the difference differential equation governing the tumor size probabilities in both state are obtained. The Laplace transformation of the tumor size distribution under transient conditions is also derived. Assuming that the tumor is under equilibrium the tumor size distribution when the patient is under chemotherapy as well as under recovery period are also obtained. Assuming that the time in which the patient is under chemotherapy is also exponential. The probability of extinction of the tumor and expected number of cancer cells in the tumor and its variability are also obtained and analyzed. It is also observed that the efficiency of the drug is directly linked with the extinction of the malignant cells in the tumor. This model is very useful for administration of chemotherapy as one can have the prediction of the tumor size distribution in both states of the patient.

In this last chapter five the ideas and results derived in the earlier chapters are summarized. Some interesting topics for further research in this area are also pointed out.

SCOPE FOR FURTHER RESEARCH

This study is carried out on the descriptive modeling of the cancer cell growth. It is also possible to develop optimal control policies based on these models by considering various risk functions and optimization of the model parameters. The inferential aspects of these models can also be investigated by developing suitable estimators which require further investigations.

With the above discussions the stochastic models developed for the cancer cell growth are useful in approximating the malignant cell growth more accurately under different conditions. These models are much useful for understanding the cell kinetics and to administer optimal drug doses in chemotherapy. it is also highly probable to develop many more stochastic models for cancer cell growth with plausible assumptions in order to approximate the natural phenomenon more closely.

BIBLIOGRAPHY

1. **Abundo, M., and Rossi, C., (1989)** "Numerical simultations of a stochastic model for cancerous cells submitted to chemotherapy", J. Math. Biol., 27, 81-90.
2. **Adam. J.A., (1989)** "A simplified mathematical model of tumor growth", Math. Biosci., 81, 229-244.
3. **Adam, J.A., (1989)** "A mathematical model of tumor growth IV, effects of necrotic core", Math. Biosci., 97, 121-136.
4. **Alexander, D.T, Asselain, B. and Andrej. Y.Y., (1987)** "A distribution of tumor size at detection: an application to breast cancer data", Biometrics, 53, 1495-1502.
5. **Arley, N. and Iversen, S., (1952)** "On the mechanism of experimental carcinogenesis", Acta. Path. Microbiol Scan., 31, 164-171.
6. **Armitage, P. and Doll, R., (1957)** "A two stage theory of careinogenesis in relation to the age distribution of human cancer", British. J. Cancer, 11, 161-169.
7. **Armitage, P. and Doll, R., (1961)** "Stochastic models for carcinogenesis", Proc. 4th. Berkeley symposium on mathematical statistics and probability; 4, 19-38, University of California press. Berkeley, Losangles.
8. **Asselian, B., Fourquet, A., Hoang, Thu., Myasinkova, C. and Yakovlev, A. (1994)** "Testing the independence of competing risks: an application to the analysis of breast cancer recurrence", Biom. J., 36, 465-473.
9. **Atkinson, E.N., Bartozynski, R., Brown, B and Thompson, J., (1983)** "On estimating the growth function of tumors", 67, 145-166.
10. **Bahrami, K. and Kim, M., (1975)** "Optimal control of multiplicative control system arising from cancer therapy", IEEE. Trans. Auton., Control., 20, 534-542.
11. **Bartoszynski, R., Brown, B.W., Mc. Bride, C.M. and Thompson, J.R., (1981)** "Some one-parametric techniques for estimating the intensity function of cancer related non stationary passion process", Ann. Statist., 9, 1050-1060.
12. **Birkhead, B.G. and Gregory, W.M., (1984)** "A Mathematical model of the effect of drug resistance in cancer chemotherapy", Math. Biosci., 72, 59-69.
13. **Birkhead, B.G., (1986)** "The transient solution of the linear birth death process with random spontaneous mutation", Math. Biosci., 82, 193-200.
14. **Biswas, S., and Jha, S.K., (1994)** "On the estimation of relative risks and longevities of a class of cancer patients based on randomly censored data"., Biom. J., 36, 885-892.

15. **Burton, A.L., (1966)** "Rate growth of solid tumors as a problem of diffusion"., 30, 151-181.

16. **Byrne, H.M., and Chaplain, M.A.J., (1995)** "Growth of nonnecrotic tumors in the presence and absence of inhibitors"., Math. Biosci. 130, 151-181.

17. **Carriere, J.F., (1995)** "Removing cancer when it is correlated with other causes of death", Biom. J., 37, 339-350.

18. **Chen, H.H., Duffy, S.W., and Tabar, L. (1997)** "A mover-stayer mixture of markov chain models for the assessment of differentiation and tumor progression in breast cancer", J.Appl. Statist., 24, 265-278.

19. **Chen, T.T. Simon, R.M., Korn, E.L., Anderson, S.J., Linobland, A.S., Hamilton, J.M. and Friedman, M.A., (1998)** "Investigation of disease-free survival as a surrogate end point for survival in cancer clinical trials". Commun. Statist. Theory, Methods., 27, 1363-1378.

20. **Chiang, C.L., (1983)** "The thory of multistage carcinogenesis", Math. Biosci., 67, 33-40.

21. **Chiang, C.L. and Paul, M.C., (1989)** "A survival model and estimation of time to tumor", Math. Bosci. 94, 1-29.

22. **Coldman, A. J. and Goldie, J. H., (1983)** "A model for the resistance of tumor cells to cancer chemotherapeutic agents", Math. Biosci., 65, 291-307.

23. **Coldman, A. J. and Goldie, J. H., (1985)** "The effects of cellular differentiation on the development of permanent drug resistance", Math. Biosci., 74, 177-198.

24. **Coldman, A.J. and Goldie, J.H., (1985)** "Role of mathematical modeling in protocol formulation in cancer chemotherapy", cancer. Treat. Rep., 69, 1041-1048.

25. **Coldman, A.J. and Goldie, J.H., (1986)** "A stochastic model for the origin and treatment of tumors containing drug resistant cells", Bull. Math. Biol., 48, 279-292.

26. **Coldman, A.J., Coppin, C.M.L. and Goldie, J.H., (1988)** "Models for dose intensity", math. Biosci., 92, 97-113.

27. **Dewanji, A. Venzon, D.V., and Moolgavkar, S.H. (1989)** "A stochastic two stage model for cancer risk assessment-II, the number and size of premalignant clones", Risk. Anal., 9, 179-187.

28. **Dewanji, A., Moolgavkar, S.H., and Georg. E.L., (1991)** "Two mutation model for carcinogenesis" Joint analysis of premalignant and malignant lesions" Math. Biosci., 104, 97-109.

29. **Dewanji, A., Krewski, D., and Goddard, M.J., (1993)** "A weibull model for the estimation of tumorigenic poteney", Biometrics, 49, 367-377.

30. **Dibrov, B.F., Zhabotinsky, A.M. Neyfakh, Y.A., Oriova, M.P., and Churikova, L.I. (1984)** "Mathematical model of cancer chemotherapy, periodic schedules of phase-specific cytotoxic-agent administration increasing the selectivities of therapy" Math. Biosci, 73, 1-31.

31. **Dinse, G.E., (1988)** "A prevalence analysis that adjusts for survival and tumor lethality" Appl. Statist., 37, 435-445.

32. **Dinse, G.E., (1988)** "Estimating tumor incidence rates in animal carcinogenesis experiments" 44, 405-415.

33. **Dubin, N., (1976)** "A stochastic model for immunological feed back in carcinogenesis: analysis and approximations", Lect. Notes in Biomath., 9, Springer, New york.

34. **Duffy, S.W. Chen, H. H., Tabar, L. and Day, N (1995)** "Estimation of mean sojourn time in breast cancer

35. **Flehinger, B.J. and Kimmel, M., (1987)** "The natural history of lung cancer in a periodically screened population Biometrics, 43, 127-144.

36. **Forbes, W.F. and Gibberd, R.W., (1984)** "Mathematical model of carcinogenesis-A review", Math. Scientist., 9, 95-110.

37. **Goldie, J.H. and Coldman, A.J., (1979)** "A mathematical model for relating the drug sensitivity of tumors to their spontaneous mutation rate", Can. Treat. Rep., 63, 1727-1733.

38. **Hanson, F.B. and Tier, C., (1981)** "An asymptotic solution to the first passage time problem for singular diffusion arising in population biology" SLAM. J. Appl. Math., 53, 89-117.

39. **Hanson, F.B. and Tier, C., (1982)** "A stochastic model of tumor growth", Math. Biosci., 67, 73-100.

40. **Hanin, L.G., Rachev, S.T., Tsodikov, A.D. and Yakovlen, A.Y. (1997)** "A stochastic model for carcinogenesis and tumor size at detection", Adv. Appl. Prob., 29, 607-628.

41. **Hiep, N.D., (1985)** "A stochastic model of mutant growth due to mutation in tumors, based on stem cell consideration", Math. Biosci., 74, 23-35.

42. **Iversion, S., and Arley, N., (1950)** "On the mechanism of experimental carcinogenesis" Acta. Path. Micro. Biol. Scand., 27, 773-803.

43. **Jackson, R.C., (1986)** "Kinetic simulation of anti cancer drug effects on metabolic path way fluxes: Two case studies", Bull. Math. Biol., 48, 337-357.

44. **Jain, H.M. and Tom, E.W., (1995)** "A stochastic model for multistagae tumorgenesis in developing and adult mice" Math. Biosci., 129, 95-110.

45. **Jushua, C. and James, H.K., (1985)** "The early growth of cancer", J. Math. Biol., 21, 329-346.

46. **Kang, G.S. and Richard, P., (1982)** "Design of optimal cancer chemotherapy using a continuous – time state model of cell Kinetics", Math. Biosci., 59, 225-248.

47. **Kendall, D.G., (1952)** "Les. Processus stochastiques de", Ann. Inst. Pioncari., 13, 43-108.

48. **Kendall, D.G., (1960)** "Birth and death processes and the theory of carcinogenesis". Math. Biosci., 73, 103-107.

49. **Kendal, W.S., (1984)** "Gompertzian growth as a consequence of tumor heterogeneity", Math. Biosci., 73, 103-107.

50. **Kinsella, A. and Dunne, A., (1987)** "Quantitative assessment of a lung tumor treatment using a multiple regression spline model", J. Appl. Statist., 14, 269-273.

51. **Kranz, G.R., (1985)** "Growth models with stochastic differential equations, an example from tumor immunology, 75-175-186.

52. **Laird, A.K., (1964)** "The dynamics of tumor growth", Br. J. Cancer., 28, 490-502.

53. **Little, M.P., (1995)** "Are two mutations sufficient to cause cancer? Some generalizations of the two-mutation model of carcinogenesis of Moolgavkar, Venzon and Knudson and of the multistate model of Armitage and Doll", Biometrics, 51, 1278-1291.

54. **Little, M.P., Muirhead, C.R. and Stiller, C.A., (1996)** "Modelling lymphocytic leukaemia in England and Wales using generalizations of the two-mutation models of carcinogenesis of Moolgarkar, Venzon and Knudson", Statistic. Med., 15, 1003-1022.

55. **Mathisca, C.M.D. and Lerebeck, E.G., (1994)** "Quantitative analysis of two-dimensional observation of premalignant clones in the presence or absence of malignance tumors", Math. Biosci., 119. 5-34.

56. **Marco, L. B., Antino, C. C., and Pier, F. P., (1984)** "A mathematical model for the evolution of cell population under the action of mutogenic agents.", Math. Biosci., 71, 19-40.

57. **Martin, R.B., Fisher, M.E., Minchen, R.F. and Teo, K.L., (1990)** "A mathematical model of cancer chemotherapy with an optimal selection of parameters", Math, Biosci., 99, 205-230.

58. **Martin, R.B., Fisher, M.E., Minchen. R.F. and Teo, K.L., (1992)** "Low potency combination chemotherapy maximizes host survival time for tumors containing drug resistant cells", Math. Biosci., 100, 221-252.

59. **Marek, K. and Frank, T., (1986)** "Estimation and prediction of cell cycle specific effects of antic cancer drugs", Math. Biosci., 80, 187-208.

60. **Maynerod, W.V., (1932)** "On a law of growth of Jenson's rat sarcoma", Amer. J. Cancer., 16, 841-846.

61. **Michelson, S., Ito, H., Traw, H. and Leight, J.T., (1989)** "Stochastic models for sub populations emergence in heterogenous tumors", Bull. Math. Biol., 51, 731-747.

62. **Miklavcic, D., Jarm, T., Karba, R. and Sersa, G., (1995)** "Mathematical modeling of tumor growth in mice following electropathy and belomycin treatment", Maths. Computers. Simul., 39, 597-602.

63. **Moolgavkar, S.H., Dewanji, A. and Venzon, D. J., (1988)** "A stochastic two stage model for cancer risk assessment I the hazard function and the probability of tumor"; Risk. Anal., 8, 383-392.

64. **Morell, C.H., Pearson, J.D., Carter, H.B. and Brant, L.J. (1995)** "Estimating unknown transition times using a piece wise non-linear mixed – effects model in men with prostate cancer", J. Amer. Statist. Assoc., 90, 45-53.

65. **Murray, J.M., (1990)** "Optimal control for a cancer chemotherapy", Math. Biosci., 98, 273-287.

66. **Murray, J.M., (1990)** "Some optimal control problems in cancer chemotheraphy with toxicity limit", Math. Biosci., 100, 49-67.

67. **Neyman, J., (1958)** "A stochastic model of carcinogenesis", Seminar talks at National Institute of Health.

68. **Neyman, J., (1958)** "A two-step mutation theory of carcinogenesis", Mimeograph, US National Institute of Health.

69. **Neyman, J. and Scott, E., (1967)** "Statistical aspects of the problem of Carcinogenesis", Fifth Berkely Symposium on Mathematical Statistics and Probability", Uni. Of Calif. Press, Berkeley, 745-776.

70. **Piaggio, H. T.H., (1950)** "An elementary treatise on differential equations and their applications" Bell. London.

71. **Rashevsky, N., (1945)** "Out line of a mathematical approach to the cancer problem", Bull. Math. Biophys., 7, 69-81.

72. **Schwartz, M., (1978)** "A mathematical model used to analyse breast cancer screening strategies", Operat. Res., 26, 937-955.

73. **Serio, G., (1984)** "Two-stage stochastic model for carcinogenesis with time-dependent parameters" Statist. Prob. Letters, 2, 95-103.

74. **Simpson, L.H. and Lloyd, H. H., (1970)** "Kinetics parameters and growth curves for experimental tumor system", Cancer Chem. Reps., 54, 143-174.

75. **Steel, G.G., (1977)** "Growth kinetics of tumor's, Edn. Claredon, Oxford.

76. **Sullivan, P.W. and Salmon, S.E., (1972)** "Kinetics of tumor growth and regression in Ig. G Multiple myeloma", J. Clin. Invest., 51, 1697-1708.

77. **Steven, P.D., Hazelrig, J.B. and Malcolm, E.T., (1983)** "A model of tumor growth based on cell cycle kinetics", Math. Biosci., 66, 283-306.

78. **Swan, G.W., (1977)** "Some strategies for harvesting a single species', Bull. Math. Biol., 37, 659-673.

79. **Swan, G.W., (1977)** "Some current mathematical topics in cancer research", Edn. Univ. Microfilms. Inter, Ann Arbor.

80. **Swan, G.W. and Vincent, T.L. (1977)** "Optimal control analysis in the chemotherapy of Ig. G. Multiple myeloma", Bull. Math. Biol., 39, 317-337.

81. **Swan, G. W., (1990)** "Role of optimal control theory in cancer chemotherapy", Math. Biosci., 101, 237-284.

82. **Tan, W.Y. and Gastardo, M.T.C., (1985)** "On the assessment of effect of environmental agents on cancer tumor development by a two-stage model of carcinogenesis", Math. Biosci., 74, 143-155.

83. **Tan, W.Y. and Brown, C.C. (1989)** "Cancer chemotherapy with immunostimulation: A non-homogeneous stochastic model for drug resistance: One drug case", Math. Biosci., 97, 145-160.

84. **Tusnady, G., (1992)** "Mathematical methods of cancer research", Alk. Math. Lapok, 16, 115-130.

85. **Wette, R., Katz, I.N. and Rodin, E.Y., (1974)** "Stochastic processes for solid tumor kinetics", Math. Biosci., 19, 231-255.

86. **Xu, J.L. and Prorok, P.C. (1998)** "Estimating a distribution function of the tumor size at metastasis", Biometrics, 54, 859-864.

87. **Ying, L. and Malani, H.M., (1995)** "Analysis of animal carcinogenicity experiments with multiple tumor types", Biometrics, 51, 73-86.

88. **Zheng, Q., (1998)** "To use or not to use? Backward equations in stochastic carcinogenesis models", Biometrics, 54, 384-388.

89. **Zheng, Q., (1998)** "On a trinity role of the survival hazard function of the two-stage carcinogenesis models", Commun. Statist. – Simu. Comp., 27.