This book has discussed some stochastic models on cancer cell growth with Bi-variate stochastic processes. The pathophysiology of cancer growth was modeled with postulates of Poisson processes. In the first phase, the mathematical relations for various statistical measures like expected number, variances of both normal and mutant cells were derived for normal and mutant cells. The second phase deals with extension of proposed model to study the tumor behaviour during drug administration and during drug vacation as a part of cancer treatment with chemotherapy. Sensitivity analysis of the model is carried out with suitable simulated numerical data. Stochastic model for cancer growth as a result of spontaneous mutation and proliferation of cells during drug vacation and during chemotherapy were developed. The model is extended for two stage mutant cell growth. The third phase of the study has formulated two stochastic programming problems for optimal drug administration in drug presence and absence, for calculating the drug effectiveness during chemotherapy. Health care industry may make use of these studies for optimal management of disease

Kunchi Madhavi

Author: Dr Madhavi Kunchi,Lecturer, Mathematics, Govt.Degree College, Kuppam,Chittore,A.P., India. Research areas are Mathematical programming, Differential Equations Co-Author: Dr. Tirupathi Rao, Padi. Associate Professor, Dept. of Statistics, Pondicherry University, Puducherry, India; Research areas are Stochastic Modeling, Operations Research

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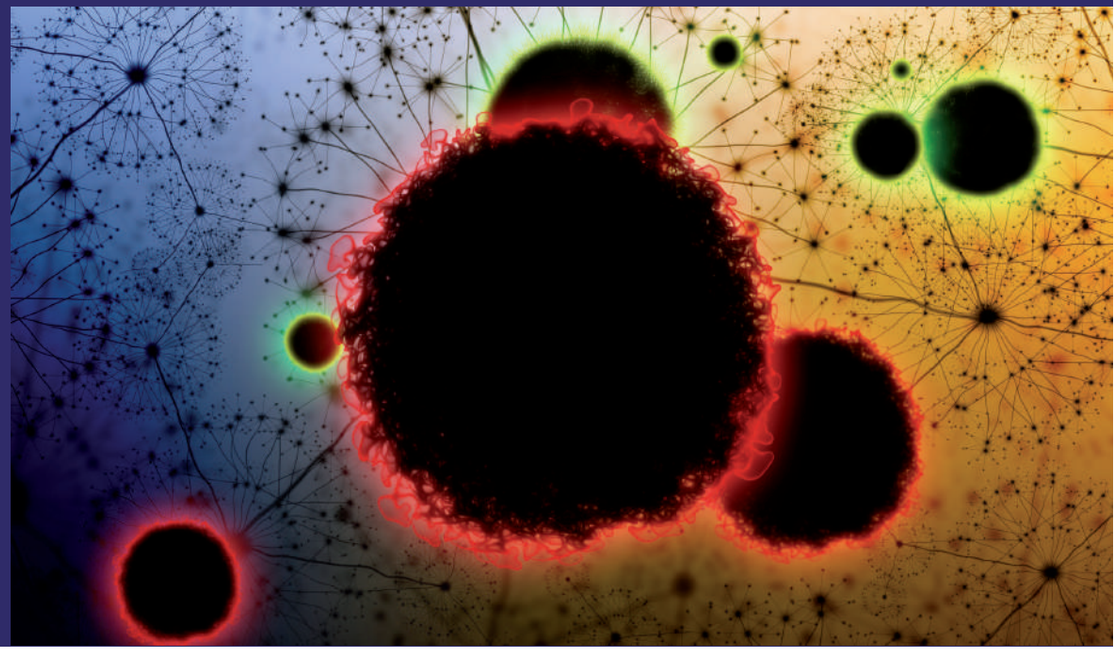

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Dedications

The Authors Have Dedicated This Book

in Loving Memory of The Father of First Author

(Late) ***K. Krishna Moorthy***

Preface

Studies on biological concepts with mathematical approaches are the current trend for proper understanding of various disease related problems. Formulation of mathematical relations with relevant assumptions on pathophysiological issues will provide sound theoretical support for measuring different parameters of health disorders. Quantification of qualitative characteristics of diseases with mathematical methods becomes a revolution in almost all disciplines. It leads to make mathematical biology become a frontline discipline. Assessment of the severity of disease through clinical methods is a nonparametric approach, which gives much ambiguity in measuring its intensity.

Mathematical study for measuring the tumor growth was pioneered by Mayneord (1932). It has initiated much attention to develop many models for cancer cell growth. Biological and mathematical assumptions have explained and analyzed the kinetics of tumor growth. Modeling of tumor growth has gained the importance due to the scope of its uses in optimal drug administration. This study has modeled the tumor growth with the notion of spontaneous mutation and proliferation of cells with heterogeneity and stochastic behaviour. The study has three domains namely (1) development of stochastic model under heterogeneous time dependent Poisson processes (2) Development of stochastic models for cancer related cell growth under the drug administration and drug recovery periods, (3) Development of stochastic optimization programming problem for effective and optimal drug administration by keeping the stable health of the patient.

This study is organized in five chapters. The overview and literature review on Mathematical, Stochastic and Optimization models was presented in the first chapter. Developed stochastic model includes differential equations, probability function, statistical measures with first and second order moments and sensitivity analysis for cancer growth with spontaneous mutation/proliferation; along with the extension model for cancer growth during drug administration/drug vacation periods are presented in the second chapter. A two stage stochastic model for mutant cell growth with an assumption of growth/loss processes of cancer cell is a combination of growth/loss of premalignant and malignant cells is presented in chapter three.

A similar model during chemotherapy is presented along with the sensitivity analysis is presented in the same chapter as an extension. Optimization problems for cancer chemotherapy are developed through stochastic programming in chapter four. The decision parameters like arrival/death rates of mutant/normal cells are estimated through the developed problem. The optimality of drug effectiveness is studied and analyzed through a suitable data. An objective function for maximizing the drug effectiveness is formulated by considering various inputs like intensity of drug dose, times of drug administration, times of drug vacation, cycle lengths of drug administration and drug vacation, loss of WBC and expected number of existing premalignant and malignant cells etc. Constraints are also formulated by considering upper and lower desired limits of premalignant cells, malignant cells, WBC etc. Chapter five is concluded with summary and research findings.

The study has concentrated mostly on stochastic modeling of cancer cell growth for normal and mutant cells, two stage mutant cell growth in general environment as well as chemotherapy environments. While developing stochastic programming problem for optional drug administration, the expected number of normal and mutant cells, expected number of premalignant and malignant cells are estimated through the method of moments.

This work is categorized as theoretical development through which the cancer cell growth can be understood on mathematical lines. These models will be more useful for applied scientists working in health care industry. As the complexity of the model and its relevance to the real life data, cumbersome and heavy calculations require the attention of computer technologists to prepare suitable software. User friendly computer automation can also be developed by combining the developed mathematical models and suitable computer programs.

The authors are very much delighted to acknowledge the needful support and motivation of Prof. S. Ramakrishna, Department of Mathematics, Prof. P. Rajasekhara Reddy, Dept. of Statistics of SV University, Tirupati, A.P., India (both are the research supervisors) during the doctoral program of the first author. They are further indebted to Prof. K. Srinivasa Rao, Dept. of Statistics, Andhra University, Vishakhapatnam, A.P., India for his scholarly assistance and guidance to bring out this book.

Madhavi Kunchi
Tirupathi Rao Padi

CONTENTS

Chapter –1

Stochastic Modeling, Optimization Programming of Cancer Growth and it Treatment with Chemotherapy

1.1. Introduction:

Mathematical Biology becomes the buzzword to study the biological issues with mathematical approach. It is also useful for making the mathematical endeavors in understanding the disease patterns. Assessment of the disease severity through clinical methods is a nonparametric approach, which has a scope for much ambiguity in assessment of disease behaviour. Researchers are making many efforts 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 att5racted 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. The study has divided in to three phases. In the first phase, the stochastic models for growth of cancer are developed. 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. In the second phase, the cancer growth model during the chemotherapy is derived. The statistical measures as mentioned in the first phase were derived. In third phase, an optimization programming problem was developed with the derived relations in the first and second phases. Simulated data sets were considered to make the sensitivity analysis for all the three developed models.

1.2: Pathophysiology of Cancer

Cancer is described as group of diseases in which the process of uncontrolled growth and spread of cells. It is not a specific disease; it is a combination of several tissue and muscle responses that result in uncontrolled cell growth. Healthy tissues are composed of cells having the specific structure and behave with genetical instructions. Whereas cancer cells differ from normal cells in size, structure,

function, and growth rate as result of mutant behaviour of genetical instructions. They lack the normal controls of growth seen in healthy cells, and grow uncontrollably. The continuous and uninterrupted cell division leads to invading of cancer cells to adjacent structures and makes disordered cell growth in the surrounding tissues and organs. Malignant cells may also metastasize to other areas of the body through the lymphatic systems. The spread and invasion of cancer causing cells eventually effects the normal functions of some vital organs leads to nonfunctioning of the effected organ.

Malignant cells will lose their ability to differentiate from normal and healthy cells. Dysplasia is a general category that indicates a disorganization of cells. The cells vary from its normal parent cell in size and shape. Metaplasia is the first level of dysplasia (early dysplasia) which is a reversible, benign, but abnormal change seen when a cell changes from one type to another. Anaplasia is the loss of cellular differentiation. It is the most advanced form of metaplasia and is a defining characteristic of malignant cells. Hyperplasia refers to an increase in the number of cells in a tissue or in a part of a tissue results in increased cell mass. It can be a normal consequence of certain physiologic alterations or it can be a sign of malignancy. A Neoplastic Hyperplasia is responsible for an abnormal increase in cell mass due to tumor formation.

There are also considerable differences in the growth rates of malignant tumors. Some tumors are very slow-growing, even in a malignant state; some may grow slowly at initial stage and they grow at a rapid pace later; some may grow very rapidly throughout their entire existence. Understanding the causes of cancer is a complex as it is due to many factors, such as environmental exposures, lifestyle practices, medical interventions, genetic traits, viruses, familial susceptibility, etc. It may be the result of interactions between repeated carcinogenic exposures and an individual's susceptibility to the disease. There are several factors that influence tumor growth may attributed to type of the organ on which the cancer is formed, gender of the patient, individual immunity capabilities, growth and loss rates of cancer cells, rate of tumor formation, number of active tumor cells, rate of normal cell growth, etc. Cancer used suppresses the immune system during in early and later stages of the disease. Oncogenes are categorized as mutated genes and they are

responsible for uncontrolled growth in cells. More often, cellular growth rates are regulated by proteins produced by the genetic material and it can be altered or mutated by environmental factors, errors in genetic replication, repair processes, tumor viruses, etc.

An irregular and continuous cell division beyond the control of regulating mechanism of body system may be referred as cancer. Usually the growth of cell population is controlled and regulated by allele of a gene. The human body system used to repair or construct the cells as per the requirement and alternative compensation of lost cells. Continuous proliferation of a cell in a tissue leads to formulation of tumors and the metastasis which leads to formulation of secondary liasons and may spread through blood circulation via lymphatic system. It is a result of uncontrolled cell growth.

It is customary to assess the severity of the cancer problem through conventional procedures like measuring the volume of tumor through scanning, Bio markers, analyzing biopsy etc. There are many models through which the cancer growth can be studied such as mathematical, statistical, computational, deterministic and stochastic models. Mathematical models may accommodate the hypothetical assumption where the growth and loss rates are deterministic and certain. In fact the cause of cancer growth cannot be attributed to a single reason. There may be million and odd reasons and factors that influence the growth of cancer and hence the cancer cell growth is considered to be influenced by several random and chance causes.

Stochastic models used to provide the basic frame work for understanding and analyzing the natural phenomena behind the cancer growth. A tumor is defined as a mass of tissues formed as a result of inappropriate and excessive proliferation of cells. The complexity in understanding and measuring the tumor growth made it necessary to formulate and integrate the classical mathematical and the real life statistical models. Describing the growth of tumor at different levels is possible only when the construction of the model is rational. In practice uncertainty prevails everywhere in various aspects of tumor growth. Hence stochastic modeling will be the suitable option for formulating the cancer growth.

1.3. Mathematical Biology for Cancer Studies:

Cancer is a disease to be handled with mathematical modeling rather than clinical trials for assessing the severity of the disease. The phenomena of frequent clinical screening become tedious and impossible due to the complexity involved in the study. This research is a combination of mathematical modeling, mechanics and scientific computing applied to the domain areas of disease based on the assumptions of Pathophysiology. It is the exercise of making use of Mathematics, Computing techniques, Optimization methods to resolve the nonmathematical problem at hand. Stochasticity principles to biological problems play an important role in biological processes. Cancer studies with mathematical modeling deals with formulation of relational functions of cellular division, the movement and growth of single cells and soft tissues. These models are meant for understanding the growth and movement based on principles of deformable body mechanics.

Traditionally, biology has been considered to be an experimental science in which mainly qualitative observations are important. Over the last one to two decades, the need for quantitative analysis in biological fields has significantly increased. There are two major reasons for the said. The former is, a biological experiment can address one small aspect of a much larger and more complex process and the later require manipulation of mechanical properties on a cellular level, are extremely difficult to perform. Simulations based on mathematical models can provide insight as to what might happen in a biological system on which an experiment cannot be done. Mathematical models aimed to understand the interplay between the biochemistry and mechanics involved. These models can describe the effect of mechanical stresses on growing tumor.

With Mayneord's (1932) pioneering work on mathematical study for measuring the tumor growth, several authors have developed various cancer cell growth models with different assumptions. Those works have explained and analyzed the kinetics of tumor growth. Modeling of tumor growth has gained the importance due to the scope of its uses in optimal drug administration. The growth and loss rates of both normal and mutant cells are considered to be random variables due to the influence of innumerable reasons. Conventional method of modeling the tumor growth through mathematical means in the assumption of deterministic situation has shifted its

paradigm to stochastic modeling. Time dependency is an essential consideration while observing the dynamics of tumor growth. The vital factors of tumor growth process are spontaneous mutation, proliferation, growth and loss of the cells etc. Modeling cancer growth in a single environment has lost its significance and hence there is a need of constructing it with heterogeneous environments. The behaviour of growth and loss patterns of both normal and mutant cells has to be modeled with stochasticity.

In this chapter a detailed review is presented on various mathematical models, stochastic models and also on computational models. The literature review is also extended on modeling aspects of stochastic optimization problem formulation used in cancer chemotherapy.

1.4. Models on Cancer Growth and Treatment:

In this section, a brief review was carried for cancer growth & loss processes along with its treatment using chemotherapy. The focus is made on three broad categories of literature namely mathematical models, stochastic models and optimization models of cancer growth as well as its treatment.

1.4.1 Mathematical Models:

Mayneord (1932) pioneered the study on growth of the tumor in volume through the application of a differential equations 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. Arley et al. (1952) developed a model based on 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 phenotypical delayed mutation. Armitage et al. (1957) developed a model for two stage theory of carcinogenesis in relation to the age distribution of human cancer. This model is characterized by a deterministic assumption that the clone of first order mutants grow in exponential form.

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.

Laird (1964) discussed the dynamics 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 that 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 the initial size referred as the first passage-time formula.

Sullivan et.al (1972) described the kinetics of tumor growth and regression relation in Ig. G multiple myolema through Gompertz law. Steel (1977) studied various growth kinetics of tumor through the logistic model and demonstrated 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 Dubins'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. 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. 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 it is optimal where it 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.

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. Forbes et al. (1984) reviewed various mathematical models of carcinogenesis with certain biological assumptions. Kendall (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 states and is inversely proportional to the total number of inter cellular interactions when tumor's growth is Gomperzian.

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. Adam. J.A. (1986) developed a one-dimensional model of tumor tissue growth in which the source of mitotic inhibitor is non-uniformly distributed within the tissue. Jackson (1986) reviewed some applications of kinetic simulation of multi enzyme networks to the study of anti metabolic drugs used as anticancer agents; Kinetic models consist 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. 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.

Kinsella, A. (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. 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.

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 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. 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 descended from a single type-I premalignant cell, not counting the dead or differentiated cells. 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.

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 ontogenesis hypothesis. As per this model, inactivation of homogeneous tumor suppresser genes leads to cancer. This model has been used for the analysis of altered hepatic foci in rodents. Martin (1992) investigated three types of tumor growth models namely Gompertz, Logistic and Exponential. They observed that the tumor burden therapy have a little impact on survival time for exponential and logistic growth tumors. Tusnady (1992) discussed various mathematical methods of cancer research as (i) understanding the description of processes leading to cancer such as investigation of non- ergodic sequence of stochastic automate (ii) diagnostic methods for steaming the growth factors by algorithms and (iii) follow up studies using the Kelpan-Meier estimator and Cox regression for one dimensional and multi-dimensional survival distributions.

Dewanji et al (1993) developed a new method of estimating tumorigenic 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 cause other than tumor occurrence (Z) through the Weibull distribution. 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.

Carriere (1995) studied an identifiability theorem in the theory of dependent competing risks. He has discussed the modeling of dependence with copila function

and he has also calculated the survival probabilities after cancer is removed by solving a system of non linear differential equations. Miklavcic 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. Morell et al. (1995) used a nonlinear mixed effects model to describe longitudinal changes in prostate specific antigen (PSA) in men before their prostate cancer were detected clinically through a piece wise model. The time at which the PSA levels change from non-linear to exponential could be estimated including random terms that allow each subject to have his own transition time.

Little et al. (1996) fitted a two mutation carcinogenesis model of Moolgavkar, Venzon & Knudson and generalized to lymphatic leukemia incidence data. Both Acute and Lymphatic Leukemia 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. 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 metastases, 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.

De Pillis, L.G. and Radunskaya, A. (2000) presented a competition model of cancer tumor growth that includes both the immune system response and drug therapy. It is a four-population model that includes tumor cells, host cells, immune cells and drug interaction. Using optimal control therapy with constraints and numerical simulations they obtained new therapy protocols and then they compared with traditional pulsed periodic treatment. Roberto Serra and Marco Villani (2001) discussed differential equations and cellular automata models of the growth of cell cultures and transformation foci.

Bao-Quan ai et al. (2003) studied tumor cell growth model in the presence of correlated additive and multiplicative noise, and showed that the noise correlation

can dynamically cause the tumor cell extension. Francis D. Alfano (2006) model gave a quantitative assessment of the amount of cellular death or growth inhibition that result from the ablation of an Oncogene's protein product. Mikhail Blogosklonny et al. (2006) reviewed a complete parametric analysis of dynamic regimes of a conceptual model of anti-tumor virus therapy. The role and limitations of mass action kinetics are discussed. They showed that in a certain area of parameter values, the trajectories of the model form a family of homo clinics to the origin.

Anderson A.R.A. et al. (2007) have presented three different multi scale individual - cell-based models, each motivated by cancer-related problems emerging from each of the spatial scales, extracellular, cellular or sub cellular, but also incorporating relevant information from other levels. Tinna Roose et al. (2007) have given a brief review on mathematical models describing the growth of avascular tumors. Monika Joanna Piotrowska et al. (2008) discussed an overview of different mathematical and numerical approaches to describe stem cell proliferation, differentiation and the development of small cancer stem cell populations that are origins of neoplasm disease.

Christophe Deroulers et al. (2009) reviewed the modeling of tumor cell migration from microscopic to macroscopic models. They showed that a diffusion equation arises, as is often postulated in the field of glioma modeling, but it is nonlinear because of the interaction. They gave the explicit dependence of diffusivity on the cell density and on a parameter governing cell to cell interactions. They noticed that the families of microscopic models were started from some kinetically constrained models that were introduced for the study of the physics of gases super cooled liquids and jamming systems.

1.4.2 Stochastic Models:

Iverson et al. (1950) studied the mechanism of experimental carcinogenesis. The probability distribution of latent period, the lethality of allied carcinogenesis etc. were estimated through the stochastic theory. Neyman (1958) discussed the biological situations of cell growth as a stochastic model and phonotypical delayed mutation process for a quantitative theory of carcinogenesis. Armitage et al. (1961) developed a stochastic model for carcinogenesis and reviewed various mathematical

models, which discussed the induction period of carcinogenesis and transition probability density per unit time for each tissue.

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. 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.

Bartoszynski (1981) developed a model on the appearance times of metastases as a non-stationary Poisson process and developed algorithm using probability density estimation, mortality measurements and discrete maximum penalized likelihood approach. Hanson et al. (1982) derived a stochastic model for tumor growth based on diffusion approximation of continuous time and density dependent branching process with a Gompertz law as the deterministic part.

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-stage stochastic model for carcinogenesis with time-dependent parameters. This model is viewed also as a generalization of the model of Moolgavkar and Venzon (1979) for the adult tumors.

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. 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 cell during growth is explored. This model relates the mutant stem cells and overall tumor mutant cell population sizes.

Jushua, C. et al. (1985) compared two types of stochastic models for the initial growth of cancerous 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, whereas in second type tumor differ from one another essentially via these growth rates. Kranz (1985) studied the effects of demographic and environmental stochasticity on the qualitative behaviour of mathematical model from tumor immunology. A stochastic differential equation whose solution is a limiting diffusion process to a branching process with random environment is used. Tan et al. (1985) derived the probability distribution for the number of tumors and the incidence rates the experiments using two-stage model, when an individual is continuously exposed to environmental agents of cancer.

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. 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 how the model can be used to make deduction regarding the optimum scheduling of therapy.

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. 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 ignores birth and death of malignant cells.

Abundo, M. et al. (1989) developed a stochastic model to study the problem of inherent resistance by cell population. They have introduced stochastic differential and numerically integrated methods to simulate expected response to the chemotherapeutic strategies as a function of different parameters. Chaing et al.

(1989) studied a stochastic model of survival distribution, where the mortality intensity is a function of the accumulated affect of an individual's continuous exposure to toxin absorbed. They have given the formulae for the density function, the distribution function and expectation of life time.

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 Flokker-plank or forward kolmogorov equation. The results of the simulation supported the stochastic model, as the basic dynamic of its deterministic counterpart. Tan et al. (1989) developed a non-homogeneous stochastic model for drug resistant cells with immune stimulation. The probability of distribution of the number of resistant tumor cells, the probability of nonresistant cells, the expected value and cumulates of the number of resistant tumor cells are derived.

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 markov process. Jain et al. (1995) developed a stochastic model for one, two and three stage malignant transformation 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.

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. 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.

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 ration of survival for the same two treatments. Zheng (1998a, 1998b) suggested a method to compute the hazard function for the multistage carcinogenesis model based on the Kolmogorov forward equation: It highlights the interplay of the forward equation and the backward characteristic methods. He also discussed the advantages and disadvantages of the forward and backward equations. He also reports that as far as the survival and hazard functions are concerned, all three models given by detectable when its size attain some threshold level which treated as a random variable. The model yields a parametric family of joint distribution of tumor size and age at detection.

Andrew J. Coldman and J. M. Murray (2000) extended a stochastic model of chemotherapy for cancer to incorporate its concomitant effect on the normal system and derived overall measures of outcome. The model includes the development of drug resistance and is sufficiently flexible to include a variety of tumor and normal system growth functions. The model is able to mimic the data and provides a description of the optimal regimen. Marek Kimmel and Olga Y. Gorlova (2003) proposed a stochastic model of lung cancer risk and progression. The genetic and behavioural determinants of susceptibility are the essential elements of the model. The mortality reduction caused by early-detection and intervention programs can be predicted under different scenarios through the model estimates as a foundation.

L. Ferrante et al. (2004) considered Gompertz Model with a stochastic version in vivo tumor growth and its sensitivity to treatment with antiangiogenic drugs. An explicit likelihood function is defined. Some properties of the maximum likelihood estimator for the intrinsic growth of the stochastic Gompertzian model are discussed. Rao, P.T and Rao K.S. (2004a, 2004b, 2004c) studied a stochastic model for cancer cell growth under chemotherapy, with spontaneous mutation and proliferation, mutant cell growth with inactivation of allele genes etc.

Anna Ochab-Marcinek (2005) investigated noise-induced pattern formation in a model of cancer growth based on Michaelis Menten Kinetics, subject to additive and multiplicative noises. Artam et al. (2006) reviewed applications of the birth and death process theory in biological and evolutionary genomics. N. Komarova (2006) formulated and analysed a stochastic model for multi-drug resistance and investigated the treatment outcomes on initial tumor load, mutation rates and the turnover rates of cancer cells.

R. Horhat et al. (2006) developed a simulation of a stochastic model for tumor immunization using wiener process. Artem S. Novozhilov et al. (2006) discussed the applications of the theory of birth and death processes to problems in biology, primarily those of evolutionary genomics. Rinaldo B. Schinazi (2006) proposed a simple stochastic model based on the two successive mutations hypothesis to compute cancer risks. Rao, P.T and Rao K.S. (2006) studied a two stage stochastic model for cancer cell growth.

Chignola et al. (2008) have considered a stochastic model on proliferation and death of cell as eco system in a binary environment. Christine et al. (2008) reported a stochastic model for cancer stem cell origin in metastatic colon cancer. R. Chignola et.al (2008) considered a general stochastic model of the interplay between cells and environmental cellular niches. The model reduces to a set of four non-linear differential equations. The analysis of a stochastic model of its deterministic limit and a normal fluctuations is provided. C.F.Lo (2009) developed a stochastic nonlinear Gompertz model of tumor growth for size dependent therapy strategy of tumors. He proposed a stochastic non-linear model of tumor growth based upon the deterministic Gompertz growth law, and also considered the conventional size-dependent therapy strategy of tumors. Wen Juan Mo etal. (2009) studied a gene pair co-expression change by using stochastic process model for approximating the underlying dynamic procedure of the co-expression change during cancer progression.

Craig J. Thalhauser et al. (2010) studied the selection dynamics in a heterogeneous spatial colony of cells. They used two spatial generalizations of the Moran process, which include cell divisions, death and migration were discussed. In the first model, migration is included explicitly as a movement to a proximal location. In the second, it is implicit through the varied ability of cell types to place their offspring a distance away, in response to another cell's death. These models explained, whether the genes involved in cells migratory and invasive machiney or not.

1.4.3 Optimization models:

Bahrmi et al. (1975) dealt with the applications of engineering optimal control theory to investigate the drug regimen for reducing an exponential tumor cell

population. Swan et al. (1977) has utilized engineering optimal control theory for chemotherapy problems involving a human tumor. 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-Harvster Overy (CHO) cell population is simulated and an optimal strategy for cancer treatment is derived to balance the effects on cancerous as normal tissues.

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 regimen that minimize the tumor population by satisfying the constraints of the drug toxicity and intermediate tumor size. Swan (1990) reviewed various ways in which optimal control theory interacts with cancer chemotherapy. He suggested the models on designs of chemotherapy strategies.

Matveev A.S. and Savkin A.V. (2000) studied cancer chemotherapy in the case of one drug. The negative and inhibiting effect of the tumor on normal cells is taken into account. They determined optimal regimen that minimizes the tumor burden at the end of a fixed period of therapy, while maintaining certain normal cell populations above the prescribed levels. Lim C.C. and Teo K.L. (2002) derived a mathematical model for an optimal control problem involving drug administration policy. The problem is stochastic in nature, as there are uncertainties in both the drug effectiveness and initial physiological state of the patient.

Marek Kimmel and Andrez Swierniak (2003) applied optimal control theory to mathematical models of cell dynamics. They are (1) the cell-cycle phase dependence of treatment and (2) the emergence of resistance of cancer cells to cytotoxic agents. They have also reviewed results in mathematical modeling and control of the cell cycle and of the mechanisms of gene amplification (related to drug resistance), and estimation of parameters of the constructed models. Jasmine Foo, Franziska Michor (2005) investigated optimal drug dosing schedules to prevent, or atleast delay, the emergence of resistance they designed and analyzed a stochastic mathematical model describing the evolutionary dynamics of a tumor cell population during therapy treatment optimization on risk of resistance is minimal while considering drug toxicity and side effects as constraints, to identify optimum drug administration.

Eyupcetin (2007) derived a mathematical anticancer tool selection model, which minimizes (or maximizes) the overall survival (or damage) probability of tumor while keeping the total side effect and the cost of the tool at acceptable levels, for immuno, chemo radiotherapy planning. The developed model is an integer non-linear programming problem essentially a therapy portfolio selection problem. It is assumed that cancer-anticancer interaction may be modeled as customer-server paradigm of queueing theory. This theoretical study contributes the applications of operations research in medicine.

Jean clairambault (2009) determined optimal control of drug delivery with constraints according to the main pharmacological issues encountered in the clinic unwanted toxic side-effects, occurrence of drug resistance. Omid Nohadani et al. (2009) introduced a robust optimization method which handles dosimetric errors and warrants for high-quality IMRT plans. Dongning Li et al. (2010) addressed the problem of optimal administration of chemotherapeutic agents for the treatment of brain tumors by convection-enhanced drug delivery. The optimal catheter position is located by a novel optimization technique, which simultaneously maximizes drugs concentration in the desired brain region. A modified finite volume discretization method is used inside a nonlinear hybrid optimization algorithm. Rao, P.T et al. (2010) studied a stochastic model for optimal drug administration in cancer chemotherapy.

1.5 MOTIVATION OF THE STUDY:

Understanding about a disease like cancer requires much attention on conventional means. Regarding the reasons for getting cancer, there are innumerable causes either by physiological or by other external factors of the patient. Modeling cancer cell growth using mathematical aspects is considered to be a conventional approach. Measuring severity of a cancer through estimation is possible when structural mathematical model behind it is suitable due to physiological and environmental factors. The problem of cancer cell growth has to be considered as stochastic rather than deterministic. There is much literature evidence on modeling of cancer cell growth using stochastic models.

With reference to the pioneering work of Mayneord (1932), much work has been reported on tumor growth. Research Conversions have established that the growth of tumor is random and not a constant. Iverson and Arley (1950) have described the growth of tumor as pure linear birth process by assuming the probability of a birth is a constant and it is analogous to a constant specific growth rate. Kendal (1960), Neyman and Scott (1967) have used a linear birth and death process to describe a growth of tumor by assuming the probabilities of birth and death are constant and density independent. Witte et al. (1974) have developed a stochastic model for growth of solid tumors by considering the physical characteristics of a tumor growth are dependent and stochastic. It leads to development of density dependent birth and death process by Dubin (1976). Hanson and Charles Tier (1982) have developed stochastic model for tumor growth as the diffusion limit of a continuous time density dependent branching process. John et al. (1984) have developed a stochastic numerical model of breast cancer node using Gompertzian Kinetics. Serio (1984) developed a two stage stochastic model with time dependent parameters for carcinogensis. Gerd Rosenkarinz (1985) used stochastic differential equation for tumor immunology growth model. Stochastic model using birth and death processes with spontaneous mutation is developed by Birkhead (1986). Stochastic Modeling on cancer research assessment using the size of malignant clones is developed by Dewanji (1989, 1991). Rao, P.T. and Rao, K. S. (2004, 2006) have developed different types of stochastic models under spontaneous mutation and proliferation; cancer cell growth under chemotherapy; Proliferation with inactivation of allele genes and also in two stage of pre-malignancy and malignancy. Marcinek, A.O. (2005) investigated noise induced pattern formation in a model of cancer growth based on additive and multiplicative noises. Alphano, F.D. (2006) developed a stochastic model on one Gene Expression Relevant to cancer therapy. Rinaldo (2006) considered two successive mutation hypothesis to develop a stochastic model for cancer cells. Lo, C.F. (2009) developed a stochastic non-linear model of tumor growth for size dependent tumors. Mo, W.I. (2009) has identified differential gene pair co-expression patterns in prostate cancer by developing a stochastic model.

Contribution on formulation of optimization modeling on drug administration is reported in the literature. Baianu, I.C. (1986) developed cancer chemotherapy

optimization computing models using branching processes and tree-like morphology which is similar to human bronchial tree. Matreer, A.S. and Savkin, A.V. (2000) studied the cancer chemotherapy optimal control drug administration applied to single drug by considering negative and inhibiting effects of the tumor on normal cell. Coldman, A.J. and Murray, J.M. (2000) developed a stochastic model of Chemotherapy for cancer which includes the development of drug resistance, the concomitant effect on normal system and derived overall measures of outcome. Stochastic model of drug resistance in cancer was formulated and analyzed by komarova, N. (2006). Cetin, E. (2007) developed an integer non-linear programming problem by assuming cancer and anti-cancer interaction is modeled as customer and server paradigm of Queueing theory. Nohadani, O. et al. (2009) introduced a robust optimization method to handle dosimetric errors and warrants for high quality IMRT plans. Rao, P.T. et al. (2010) developed stochastic models for optimal drug administration in cancer chemotherapy.

They have considered the growth of cancer in a homogeneous environment whereas the health status of the patient under drug administration has to be considered as heterogeneous. The factors like individual physiological, environmental and other extraneous condition leads to the growth of cancer as not only heterogeneous but also time dependent. A Very few work on development of stochastic models, optimal drug design and administration is reported in the literature. In this thesis an attempt is made to fill the gap of developing stochastic models as well as stochastic program optimization under heterogeneity and time dependence in cancer growth. Our work is dedicated in three domains namely (1) development of stochastic model under heterogeneous time dependent poisson process (2) Developing stochastic models for cancer related cell (mutant, premalignant, malignant) growth under the drug administration and drug recovery periods, (3) Developing stochastic optimization programming problem for effective and optimal drug administration subject to monitoring the safe health norms of the patient. This study is useful in developing suitable decision support systems for optimal drug administration as well as optimal drug vacation during chemotherapy treatment.

1.6 FOCUS AND ORGANIZATION OF STUDY:

Observing the cell Kinetics in tumor it is understand that spontaneous mutation, proliferation of mutant cells, transformation of cells from one stage to other stages like from normal to mutancy, from mutancy to pre-malignancy and from pre-malignancy to malignancy and the loss processes of cell at every stage are playing very important role in studying the growth behaviour, mostly regulated by alleles of gene. Usually the cell growth is categorized as 1. A normal cell can be divided in to two normal cells; 2. A normal cell can be divided in to one normal and one mutant cell (a cell with abnormal behaviour); 3. A mutant cell shall be divided in to two mutant cells; 4. Mutant cells transformed to premalignant cell; 5. Premalignant cell will be transformed to malignant cell and 6. A malignant cell (a full fledged transformed mutant cell as cancer cell) will be further proliferated with faster growth. It is also evident that there is a loss of normal and mutant cells due to the immune system of the body. The growth and development of both normal and mutant cells are non-homogeneous due to several physiological and environmental factors. Similarly in the case of death or loss of normal and mutant cells are also non-homogeneous. So, in order to analyze and to develop the tumor growth more close to reality it is essential to develop density dependent stochastic models with heterogeneous growth and loss rates for normal and cancer cells.

Chemotherapy is one of the treatments in cancer control with a combination of drugs administered in cycles with different intensified spells within the cycle. The very objective of drug administration is to kill the cancer causing cells but it may harm some of the healthy and normal cells also. Continuous drug administration may leads to health hazards due to unwanted loss of white blood cells as well as normal and healthy cells. Hence the patient under the treatment of chemotherapy needs periodic check of health status and he may be allowed to drug vacation to get recovery. Contrary, drug vacation leads to reaggravate the growth of mutant cell population and hence long term drug vacation also is unwanted. Regarding the dosage levels, drug administration above the required quantity may harm both normal cells and white blood cells significantly. Contrary the drug quantity less than the required level prepare the body drug resistance. And hence there is a need of optimal drug dosage levels that are to be administrated. As the behaviour of growth, loss of both normal and mutant cells influenced by drug administration and drug vacation

conditions, the number of cells within the tumor are to be considered as random. Both internal and external conditions of the patient are also considered to be purely random and highly volatile. Considering all the above there is an absolute need of developing an optimization problem with an objective of maximizing the drug efficacy subject to minimum risk or loss of WBC. Stochastic optimization modeling is a suitable device in exploring the required decision parameters.

In this thesis an attempt is made to develop stochastic optimization problem for optimal drug administration. In the first part, a bi-variate stochastic model is developed for cancer cell growth with an assumption that the growth and loss processes of normal and mutant cells follows poisson process. In order to observe the behaviour of the model during chemotherapy, the model is extended for studying cancer cell growth in the presence and absence of the drug. As chemotherapy is executed in cycles with different intensified spells, the growth and loss rates of both normal and mutant cells are considered as heterogeneous and follow Poisson process. The statistical measures in terms of model parameters are derived such as means, covariances and variances of both normal and mutant cells. In order to estimate the parameters of the model a stochastic program problem is formulated. The objective function for maximizing the drug efficacy was formulated with decision parameters such as rates of arrivals of normal cells, mutant cells, rate of transformation of normal cells to mutant cells and the rates of deaths of normal and mutant cells. The objective function has accommodated the above mentioned decision parameters in both drug administration and drug vacation periods. The constraints were formulated by considering the optimal loss of WBC, optimal minimum size of healthy and normal cells, optimal targeted size of mutant cells during the period of chemotherapy. Sensitivity of the model was analyzed through numerical data sets using MATHCAD. Decision parameters are explored using LINGO software. All the numerical values are thoroughly analyzed and the stochastic optimization model is interpreted.

This work is very useful for extracting the crucial decision parameters like rates of arrivals and rates of deaths of normal cells, mutant cells, premalignant cells, malignant cells at desired levels of WBC count and other health standards. Development of suitable software and desktop automation to this work will give a remarkable usage to derive efficient decision support systems.

This study is organized in 5 chapters, chapter-1 deals with overview on cancer problem, models importance in studying the cancer growth by reviewing the literature from 1932 to 2010. A brief summary on stochastic models, mathematical models and optimization models on cancer growth is made. Focus of thesis, motivation of study is given by highlighting the current developed work and existing gap in the thrust area of stochastic modeling of cancer cell growth. Chapter-2 deals with development of stochastic model for cancer growth with spontaneous mutation and proliferation on normal and mutant cells. As an extension of this section, a stochastic model for cancer growth during drug administration and drug vacation periods is developed. In both the sections difference-differential equation are developed by assuming Linear Bivariate Poisson process in cancer cell growth. Statistical constants were derived by using probability generating function. Sensitivity analysis of the model for both the sections is carried out.

Chapter-3 consists of a two stage stochastic model for mutant cell growth assuming the growth and loss processes of cancer cell growth are combination of growth of premalignant and malignant cells. A Bivariate Poisson process is considered to develop this model under the assumption that the cancer growth is in the environment of an individual self immunity. A similar model is developed in the extension section when the patient is under chemotherapy, exposed to drug administration and drug vacation. Statistical measures are derived from joint probability function of premalignant and malignant cells using cumulant generating function. While developing a two-stage model, it is assumed that the growth and loss of premalignant and malignant cell population is a linear combination of drug administration and drug vacation periods. Sensitivity analysis for stochastic models is carried out.

Chapter-4 contains optimization problems for cancer chemotherapy is developed through stochastic programming. The arrival and death rates of mutant and normal cells are assumed as stochastic parameters and estimated them through the developed stochastic optimization programming problem. The optimality of drug effectiveness is studied and analyzed through a suitable data. An objective function for maximizing the drug effectiveness is formulated by considering various inputs like intensity of drug dose, times of drug administration, times of drug vacation,

cycle lengths of drug administration and drug vacation, loss of WBC and expected number of existing premalignant and malignant cells etc. Constraints are also formulated by considering upper and lower desired limits of premalignant cells, malignant cells, WBC etc. Stochastic parameters namely arrival and death rates of premalignant and malignant cells during drug vacation and drug administration are assumed as non-negative. Optimal drug administration policy is analyzed, through suitable numerical data sets. Chapter-5 includes the summary research findings and conclusion. The scope of future research work is focused. Computer automation of this thesis work will give a remarkable advantage to develop decision support system for health care management people. A detailed bibliography is also presented for effective reference.

Chapter-2

STOCHASTIC MODEL FOR CANCER GROWTH FOR SPONTANEOUS MUTATION AND PROLIFERATION OF CELLS DURING CHEMOTHERAPY

2.1 INTRODUCTION

Abnormal, excessive and uninterrupted proliferation of a cell is referred as cancer. The multiplication of cells in a faster growth is referred as malignancy, it is observed in the cells differed with normal growth. Human system has a mechanism of cell growth and its regulation with alleles of a gene. The failure of growth control or regulation mechanism due to inactivation of alleles is one of the innumerable number of reasons for getting cancer. The body system has a cell growth process as a measure of compensation to wear & tear and the death of a cell after a specified period of time. Usually a normal cell which is under regulation of control mechanism deviates due to unspecified reasons may be named as mutancy. A cell will get a different behaviour from the usual growth procedure and it further transforms in the process of cell division. When a normal cell change into a mutant cell then it may be further transformed into a malignant cell. Once malignancy is formulated to the cell then the cell growth will be at faster rate and it behaves beyond the control of natural regulating mechanism.

There is much literature evidence on the formulation of malignancy to a normal cell attributed to the number of reasons; one among them is spontaneous mutation and proliferation. In the process of cell division an accumulation of normal and mutant cells within a tissue may cause a tumor and the tumor will grow further upto the permissible levels of tissue structure and its mechanism. When the accumulated cancerous cells are above the unwanted limits within the tumor then the mutant cells may invade from the origin to various parts of the body through blood flow. Due to the structure of blood vessels, the mutant cells in the blood flow may be stopped at the lymph nodes and further it may start in growing of new colonies at the lymphatic systems. This sort of phenomena can be referred as formulation of secondaries and invasion of the cancer cells to different parts of the body so that the stomatasis is formulated.

In order to understand the behaviour pattern from initial formation of mutancy to final stage of cancer cell growth, a well defined model structure is required. Conventional researchers have suggested number of mathematical / deterministic models to assess the situation. The assumption considering the deterministic situations in modeling makes the mathematical models confine to very limited applications. The behaviour of cell division and tumor growth reveals that cell division from initial growth to accumulation of such cells in a tumor is purely random and it will have complete stochastic behaviour. Hence model development with stochasticity is more appropriate for understanding the behaviour of tumor growth due to spontaneous mutation and proliferation.

In this chapter, we develop a bi-varaite stochastic model for normal and mutant cell growth. The growth and loss rates processes of both mutant and normal cells are assumed as Poisson parameters. Difference differential equations and cumulant generating function are used for finding the statistical measures like expected number of normal cells and mutant cells at time t. The variance number of normal and mutant cells and also the covariance number of normal cells and mutant cells are derived. The model behaviour is observed further by applying a secondary data obtained from various types of cancer patients with the source of TIFR (Tata Institute of Fundamental Research), collected through Internet. The sensitivity analysis is carried out with the available data sets.

In section-II, A bi-varaite stochastic model for normal and mutant cell growths for the environment of cancer chemotherapy is developed. Drug administration and drug vacation periods are considered separately in the assumptions and the model is developed with an intension of exploring more suitable model to the cancer patients under chemotherapy. The difference differential equations and cumulant generating function are used in deriving the statistical measures of the model. The source data is also applied to the model and sensitivity analysis is carried out. These models are very much useful for health care administration to cancer patients during chemotherapy.

2.2 STOCHASTIC MODEL FOR CANCER GROWTH:

In this section a stochastic model using bivariate Poisson process is developed. Usually cell division behaviour of normal and mutant cells have the mechanism of a normal cell may be divided into two normal cells; a normal cell may contribute in

generating a normal cell and a mutant cell; a mutant cell once formulated may generate two mutant cells. Regarding the loss process, a normal cell may get death either after transforming to mutant cell or without transforming to mutant cell. The following schematic diagram will explain the mechanics of the process.

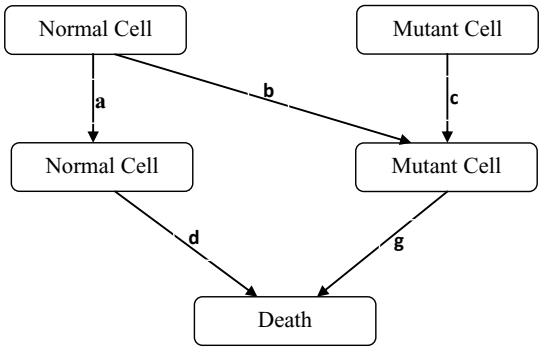

Figure 2.2.1: Schematic Diagram of the model

2.2.1 Assumptions and Postulates of the Model:

Let the events occurred in non-overlapping intervals of time are statistically independent. Let Δt be an infinitesimal interval of time. Let there be 'n' normal cells and 'm' mutant cells initially at time 't'. Let 'a', 'b', 'c', be the rates of generation of normal cell from normal cell, mutant cell from normal cell, mutant cell from mutant cell and 'd', 'g' rates of death of normal cell, and death of mutant cell respectively. Also it is assumed that all the events are Poisson parameters. With these assumptions, the postulates of the model are:

1. The probability of generation of one normal cell during Δt, provided there exists 'n' normal cells at 't' is $na\ \Delta t + 0(\Delta t)$
2. The probability of generation of one mutant cell from a normal cell during Δt provided there exists 'n' normal cells at 't' is $nb\ \Delta t + 0(\Delta t)$
3. The probability of generation of one mutant cell from a mutant cell during Δt provided there exists 'm' mutant cells at 't' is $mc\ \Delta t + 0(\Delta t)$
4. The probability of death of one normal cell during Δt provided there exists 'n' normal cells at 't' is $nd\ \Delta t + 0(\Delta t)$

5. The probability of death of one mutant cell during Δt provided there exists 'm' mutant cells at time 't' is $mg\ \Delta t + 0(\Delta t)$
6. The probability of generating no normal cell from a normal cell, no mutant cell from a normal cell, no mutant cell from mutant cell, no death of normal cell, no death of mutant cell during an infinitesimal interval of time Δt is
$$1 - [n(a + b + d) + m(c + g)]\ \Delta t + 0(\Delta t)$$
7. The probability of occurrence of other than the above events during an infinitesimal interval of time Δt is $0(\Delta t)^2$

2.2.2 The Difference-Differential Equations of the Model:

Let $p_{n,m}(t)$ be the joint probability of existing of 'n' normal cells and 'm' mutant cells in a tumor per unit time't'. Then the difference-differential equations of the model are:

$$p'_{n,m}(t) = [n(a + b + d) + m(c + g)](-1)\ p_{n,m}(t) + [nb + (m - 1)c]p_{n,m-1}(t)$$
$$+[(m + 1)g]p_{n,m+1}(t) + [(n - 1)a]\ p_{n-1,m}(t) + (n + 1)d\ p_{n+1,m}(t)$$
for n,m≥1 ... (2.2.2.1)

$$p'_{1,0}(t) = [a + b + d]\ (-1)p_{1,0}(t) + g\ p_{1,1}(t) + 2d\ p_{2,0}(t) \quad \text{... (2.2.2.2)}$$

$$p'_{0,1}(t) = (c + g)(-1)\ p_{0,1}(t) + 2g\ p_{0,2}(t) + d\ p_{1,1}(t) \quad \text{... (2.2.2.3)}$$

$$p'_{0,0}(t) = g\ p_{0,1}(t) + d\ p_{1,0}(t) \quad \text{... (2.2.2.4)}$$

With the initial conditions $p_{N_0,M_0}(0) = 1,\ p_{N_0,M_0}(t) = 0,$ where N_0, M_0 are the initial sizes of normal and mutant cells in the tumor.

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

Where $$p(x, y; t) = \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} x^n y^m\ p_{n,m}(t) \quad \text{... (2.2.2.5)}$$

Multiplying the equations (2.2.2.1) to (2.2.2.4) with $x^n y^m$ and summing overall m and n, we obtain

$$\sum_{m=0}^{\infty}\sum_{n=0}^{\infty} x^n y^m \; p'_{n,m}(t) = \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} [n(a+b+d)+m(c+g)]x^n y^m \,(-1)p_{n,m}(t)$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (n-1)a\, x^n y^m \, p_{n-1,m}(t)$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (n+1)d\, x^n y^m \, p_{n+1,m}(t)$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} nb\, x^n y^m \, p_{n,m-1}(t)$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (m-1)c\, x^n y^m \, p_{n,m-1}(t)$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (m+1)g\, x^n y^m \, p_{n,m+1}(t) \qquad \ldots (2.2.2.6)$$

Simplifying the equation (2.2.2.6) and reorganizing the terms we get,

$$\frac{\partial}{\partial t}p(x,y;t) = (a+b+d)x \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} - n\, x^{n-1} y^m \, p_{n,m}(t)$$
$$-(c+g)y \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} m\, x^n y^{m-1} p_{n,m}(t)$$
$$+ ax^2 \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (n-1)\, x^{n-2} y^m \, p_{n-1,m}(t)$$
$$+ d \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (n+1)\, x^n y^m \, p_{n+1,m}(t)$$
$$+ b\, xy \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} n\; x^{n-1} y^m \, p_{n,m-1}(t)$$
$$+ c\, y^2 \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (m-1)\, x^n y^{m-2} \, p_{n,m-1}(t)$$
$$+ g \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (m+1) x^n y^m \, p_{n,m-1}(t) \qquad \ldots (2.2.2.7)$$

Further simplification of the equation (2.2.2.7) gives

$$\frac{\partial}{\partial t}p(x,y;t) = [ax^2 + bxy + d - (a+b+d)x]\frac{\partial}{\partial x}p(x,y;t)$$

$$+[cy^2 + g - (c+g)y]\frac{\partial}{\partial y}p(x,y;t) \quad \text{... (2.2.2.8)}$$

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 cummulant generating function of $p_{n,m}$(t), eq. (2.2.2.8) becomes

$$\frac{\partial}{\partial t}k(u,v;t) = [a\,e^u + b\,e^v + d\,e^{-u} - (a+b+d)]\frac{\partial k}{\partial u}$$

$$+[c\,e^v + g\,e^{-v} - (c+g)]\frac{\partial k}{\partial v} \quad \text{... (2.2.2.9)}$$

2.2.3 Differential Equations and Statistical Measures of the Model:

Let $m_{i,j}$(t) denotes 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:

$$\frac{\partial}{\partial t}m_{1,0}(t) = (a-d)\,m_{1,0}(t) \quad \text{... (2.2.3.1)}$$

$$\frac{\partial}{\partial t}m_{0,1}(t) = b\,m_{1,0}(t) + (c-g)m_{0,1}(t) \quad \text{... (2.2.3.2)}$$

$$\frac{\partial}{\partial t}m_{2,0}(t) = (a+d)m_{1,0}(t) + 2(a-d)m_{2,0}(t) \quad \text{... (2.2.3.3)}$$

$$\frac{\partial}{\partial t}m_{1,1}(t) = (a-d+c-g)m_{1,1}(t) + b\,m_{2,0}(t) \quad \text{... (2.2.3.4)}$$

$$\frac{\partial}{\partial t}m_{0,2}(t) = 2\,b\,m_{1,1}(t) + b\,m_{1,0}(t) + (c+g)m_{0,1}(t) + 2(c-g)m_{0,2}(t)$$

... (2.2.3.5)

Solving (2.2.3.1) we obtain

Expected number of normal cells at time't' is

$$m_{1,0}(t) = N_0 e^{(a-d)t} \quad \text{... (2.2.3.6)}$$

Substituting the equation (2.2.3.6) in the equation (2.2.3.2) we get,

$$\frac{\partial}{\partial t}m_{0,1}(t) + (g-c)m_{0,1}(t) = b\,N_0 e^{(a-d)t} \quad \text{... (2.2.3.7)}$$

Solving the equation (2.2.3.7) we get,

Expected number of mutant cells at time't' is

$$m_{0,1}(t) = A[e^{(a-d)t} - e^{(c-g)t}] + M_0\,e^{(c-g)t}$$

$$where \quad A = \frac{b\,N_0}{a-d+g-c} \qquad \ldots (2.2.3.8)$$

Substituting the equation (2.2.3.6) in the equation (2.2.3.3) we get,

$$\frac{\partial}{\partial t} m_{2,0}(t) + 2(d-a)m_{2,0}(t) = (a+d)N_0 \mathrm{e}^{(\mathrm{a-d})\mathrm{t}} \qquad \ldots (2.2.3.9)$$

Solving the equation (2.2.3.9) we get

$$m_{2,0}(t) = \frac{a+d}{d-a} N_0\, \mathrm{e}^{(\mathrm{a-d})\mathrm{t}} + \frac{a+d}{d-a} N_0\, \mathrm{e}^{2(\mathrm{a-d})\mathrm{t}} \qquad \ldots (2.2.3.10)$$

On simplifying the equation (2.2.3.10) we get,

Variance of normal cells at time‘t’ is

$$m_{2,0}(t) = B\, \mathrm{e}^{(\mathrm{a-d})\mathrm{t}}[\mathrm{e}^{(\mathrm{a-d})\mathrm{t}} - 1]$$

$$\text{Where} \qquad B = \frac{a+d}{a-d} N_0 \qquad \ldots (2.2.3.11)$$

Substituting the equation (2.2.3.11) in the equation (2.2.3.4) we get,

$$\frac{\partial}{\partial t} m_{1,1}(t) + (d+g-a-c)m_{1,1}(t) = b\left[B\, \mathrm{e}^{(\mathrm{a-d})\mathrm{t}}\left[\mathrm{e}^{(\mathrm{a-d})\mathrm{t}} - 1\right]\right] \qquad \ldots (2.2.3.12)$$

On solving the equation (2.2.3.12) we get,

$$m_{1,1}(t) = b\,B\left[\frac{\mathrm{e}^{2(\mathrm{a-d})\mathrm{t}}}{\mathrm{a+g-d-c}} - \frac{\mathrm{e}^{(\mathrm{a-d})\mathrm{t}}}{g-c}\right] + b\,B\left[\frac{1}{g-c} - \frac{1}{\mathrm{a+g-d-c}}\right] \ldots (2.2.3.13)$$

On simplifying the equation (2.2.3.13) we get,

Covariance between normal cells and mutant cells at time ‘t’ is

$$m_{1,1}(t) = D\mathrm{e}^{(\mathrm{a-d})\mathrm{t}}\left[\frac{(g-c)\mathrm{e}^{(\mathrm{a-d})\mathrm{t}} - (\mathrm{a+g-d-c})}{a-d} + \mathrm{e}^{(\mathrm{c-g})\mathrm{t}}\right]$$

$$\text{Where} \quad D = \frac{b(a+d)}{(a+g-d-c)(g-c)} N_0 \qquad \ldots (2.2.3.14)$$

Substituting the equations (2.2.3.6),(2.2.3.8) and (2.2.3.14) in the equation (2.2.3.5) we get,

$$\frac{\partial}{\partial t}m_{0,2}(t) + 2(g-c)m_{0,2}(t)$$

$$= 2bD\mathrm{e}^{(\mathrm{a}-\mathrm{d})\mathrm{t}}\left[\frac{(g-c)\mathrm{e}^{(\mathrm{a}-\mathrm{d})\mathrm{t}} - (\mathrm{a}+\mathrm{g}-\mathrm{d}-\mathrm{c})}{a-d} + \mathrm{e}^{(\mathrm{c}-\mathrm{g})\mathrm{t}}\right]$$

$$+(c+g)\left[A\left[\mathrm{e}^{(\mathrm{a}-\mathrm{d})\mathrm{t}} - \mathrm{e}^{(\mathrm{c}-\mathrm{g})\mathrm{t}}\right] + M_0\mathrm{e}^{(\mathrm{g}-\mathrm{c})\mathrm{t}}\right]$$

$$+\mathrm{b}\,N_0\,\mathrm{e}^{(\mathrm{a}-\mathrm{d})\mathrm{t}} \qquad \ldots(2.2.3.15)$$

Solving the equation (2.2.3.15) we get,

$$m_{0,2}(t) = E\mathrm{e}^{2(\mathrm{a}-\mathrm{d})\mathrm{t}} + F\mathrm{e}^{(\mathrm{a}-\mathrm{d})\mathrm{t}} + G\mathrm{e}^{(\mathrm{a}-\mathrm{d}-\mathrm{g}+\mathrm{c})\mathrm{t}} + H\mathrm{e}^{(\mathrm{a}-\mathrm{d})\mathrm{t}} + I\mathrm{e}^{(\mathrm{a}-\mathrm{d})\mathrm{t}}$$

$$+J\mathrm{e}^{(\mathrm{c}-\mathrm{g})\mathrm{t}} + K\mathrm{e}^{(\mathrm{c}-\mathrm{g})\mathrm{t}} + const\ \mathrm{e}^{2(\mathrm{c}-\mathrm{g})\mathrm{t}} \qquad \ldots(2.2.3.16)$$

Simplifying the equation (2.2.3.16) we get,

Variance of mutant cells at time‘t’ is

$$m_{0,2}(t) = E\left[\mathrm{e}^{2(\mathrm{a}-\mathrm{d})\mathrm{t}} - \mathrm{e}^{2(\mathrm{c}-\mathrm{g})\mathrm{t}}\right] + (F+I+H)\left[\mathrm{e}^{(\mathrm{a}-\mathrm{d})\mathrm{t}} - \mathrm{e}^{2(\mathrm{c}-\mathrm{g})\mathrm{t}}\right.$$

$$+ G\left[\mathrm{e}^{(\mathrm{a}-\mathrm{d}-\mathrm{g}+\mathrm{c})\mathrm{t}} - \mathrm{e}^{2(\mathrm{c}-\mathrm{g})\mathrm{t}}\right] + (J+K)\left[\mathrm{e}^{(\mathrm{c}-\mathrm{g})\mathrm{t}} - \mathrm{e}^{2(\mathrm{c}-\mathrm{g})\mathrm{t}}\right]$$

Where

$$E = \frac{bD(g-c)}{(a-d)(a-d+g-c)} \qquad F = \frac{2bD(a+g-d-c)}{(d-a)(a-d+2(g-c))}$$

$$G = \frac{2bD}{a-d+g-c)} \qquad H = \frac{b}{a-d+2(g-c)}N_0$$

$$I = \frac{(c+g)A}{a-d+2(g-c)} \qquad J = \frac{(c+g)A}{(c-g)}$$

$$K = \frac{(g+c)}{(g-c)}M_0 \qquad A = \frac{b}{(a-d+g-c)}N_0$$

$$B = \frac{(a+d)}{(a-d)}N_0 \qquad D = \frac{b(a+d)}{(a+g-d-c)(g-c)}N_0$$

…(2.2.3.17)

2.2.4 Numerical Illustration and Sensitivity Analysis:

In order to verify the model behaviour a simulated data set based on the assumptions were generated and presented from table number 2.2.4.1 to 2.2.4.8. From equations (2.2.3.6), (2.2.3.8), (2.2.3.11), (2.2.3.14) and (2.2.3.17) the values

of $m_{1,0}(t)$, $m_{0,1}(t), m_{2,0}(t), m_{1,1}(t)$ and $m_{0,2}(t)$are computed for various values of the parameters and presented in the tables.

Table 2.2.4.1

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of N_0 at the fixed values of other parameters with values M_0=80; a=0.8; b=0.1; c=1; d=0.5; g=0.9; t=2

N_0	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
102	185.86	128.35	662.12	63.59	952.53
104	189.50	128.95	675.10	64.84	963.15
106	193.15	129.55	688.08	66.08	973.77
108	196.79	130.15	701.06	67.33	984.38
110	200.43	130.75	714.05	68.58	995.00

From table 2.2.4.1 it is observed that expected number of normal cells, expected number of mutant cells, variance of normal cells, variance of mutant cells, covariance between normal cells and mutant cells are increasing functions of the initial number of normal cells (N_0) when all the other parameters are constants.

Table 2.2.4.2

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of M_0 at the fixed values of other parameters with values N0=100; a=0.8; b=0.1; c=1; d=0.5; g=0.9; t=2

M_0	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
85	182.21	133.86	649.13	62.34	967.60
90	182.21	139.96	649.13	62.34	993.29
95	182.21	146.07	649.13	62.34	1019.00
100	182.21	152.18	649.13	62.34	1045.00
105	182.21	158.28	649.13	62.34	1070.00

From table 2.2.4.2, it is observed that expected number of mutant cells and variance of mutant cells are increasing functions of initial number of mutant cells (M_0) when all the other parameters are constants. It is also observed that expected number of normal cells, variance of normal cells and covariance between normal cells and

mutant cells are invariant of change of initial size of the mutant cells (M_0) when all the other parameters are constants.

Table 2.2.4.3

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of 'a' at the fixed values of other parameters with values N_0=100; M_0=80; b=0.1; c=1; d=0.5; g=0.9; t=2

a	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.82	189.65	128.40	701.32	66.85	915.47
0.84	197.39	129.07	757.62	71.67	894.09
0.86	205.44	129.75	818.37	76.83	876.63
0.88	213.83	130.46	883.91	82.35	862.28
0.9	222.55	131.183	954.62	88.26	850.44

From table 2.2.4.3 it is observed that expected number of normal cells, expected number of mutant cells, variance of normal cells, covariance between normal and mutant cells are increasing functions of rate of generation of normal cells from normal cells (a) when all the other parameters are constant. And it is also observed that variance of mutant cells is a decreasing function of rate of generation of normal cell from normal cells (a) when all the parameters are constants.

Table 2.2.4.4

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of 'b' at the fixed values of other parameters with values N_0=100; M_0=80; a=0.8; c=1; d=0.5; g=0.9;t=2

b	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.2	182.212	157.784	649.13	124.684	2355.00
0.3	182.212	187.82	649.13	187.026	4649.00
0.4	182.212	217.855	649.13	249.368	7826.00
0.5	182.212	247.891	649.13	311.709	11880.00
0.6	182.212	277.927	649.13	374.051	16830.00

From table 2.2.4.4 it is observed that expected number of mutant cells, covariance between normal cells and mutant cells, Variance of mutant cells are increasing functions of the rate of generation of mutant cell from normal cell (b) when all the other parameters are constant. And it is also observed that expected number of normal cells, variance of normal cells are invariant of rate of generation of mutant cell from normal cell (b) when all the other parameters are constant.

Table 2.2.4.5

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of 'c' at the fixed values of other parameters with values N_0=100; M_0=80; a=0.8; b=0.1; d=0.5; g=0.9; t=2

c	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
1.1	182.212	152.375	649.13	66.627	1322.00
1.4	182.212	262.271	649.13	82.453	1631.00
1.6	182.212	380.243	649.13	96.182	3727.00
1.8	182.212	554.431	649.13	113.318	7829.00
2	182.212	812.037	649.13	134.873	16300.00

From table 2.2.4.5 it is observed that expected number of mutant cells, covariance between normal and mutant cells and variance of mutant cells are increasing functions of rate of generation of mutant cells from mutant cells (c) when all the other parameters are constants. Also it is observed that expected number of normal cells and variance of normal cells are invariant with respect to rate of generation of mutant cells from mutant cells (c) when all the other parameters are constant.

Table 2.2.4.6

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of 'd' at the fixed values of other parameters with values N_0=100; M_0=80; a=0.8; b=0.1; c=1; g=0.9; t=2

d	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.53	171.601	126.807	605.24	58.782	1018.00
0.56	161.607	125.903	564.19	55.41	1129.00
0.59	152.196	125.036	525.82	52.216	1301.00
0.62	143.333	124.203	489.98	49.193	1603.00
0.65	134.986	123.403	456.52	46.335	2272.00

From table2.2.4.6, it is observed that expected number of normal cells, expected number of mutant cells, variance of normal cells and covariance between normal and mutant cells are decreasing functions of rate of death of normal cells (d) when all other parameters are constant. Also it is observed that the variance of mutant cells is an increasing function of rate of death of normal cells.

Table 2.2.4.7

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of 'g' at the fixed values of other parameters with values N_0=100; M_0=80; a=0.8; b=0.1; c=1; d=0.5; t=2

g	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.92	182.212	123.363	649.13	61.535	945.65
0.94	182.212	119.142	649.13	60.744	989.23
0.96	182.212	115.08	649.13	59.968	1123.00
0.98	182.212	111.169	649.13	59.207	1605.00
0.99	182.212	109.268	649.13	58.832	2622.00

From table 2.2.4.7 it is observed that expected number of normal cells, variance of normal cells are invariant of rate of death of mutant cells (g) when all other parameters are constant. It is also observed that expected number of mutant cells and

covariance between normal and mutant cells are decreasing functions of death of mutant cells (g) when all the other parameters are constant. It is also observed that variance of mutant cells is increasing function of rate of death of mutant cells (g) when all the other parameters are constant.

Table 2.2.4.8

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of 't' at the fixed values of other parameters with values N_0=100; M_0=80; a=0.8; b=0.1; c=1; d=0.5; g=0.9

t	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
3	245.96	163.476	1556.00	218.51	1860.00
4	332.012	210.761	3338.00	607.60	3308.00
5	448.169	273.546	6762.00	1491.00	5595.00
6	604.965	357.146	13240.00	3386.00	9235.00
7	816.617	468.721	25360.00	7298.00	15100.00

From table 2.2.4.8, it is observed that expected number of normal cells, expected number of mutant cells, variance of normal cells, covariance between normal and mutant cells and variance of mutant cells are increasing functions of time (t) when all the other parameters are constant.

2.3 STOCHASTIC MODEL FOR CANCER GROWTH DURING CHEMOTHERAPY:

With a similar argument of the previous section 2.2, in this section a bivariate stochastic model for cell division of normal and mutant cells growth and losses during drug administration and drug vacation periods are presented. The following schematic diagram will explain the model in more detailed way.

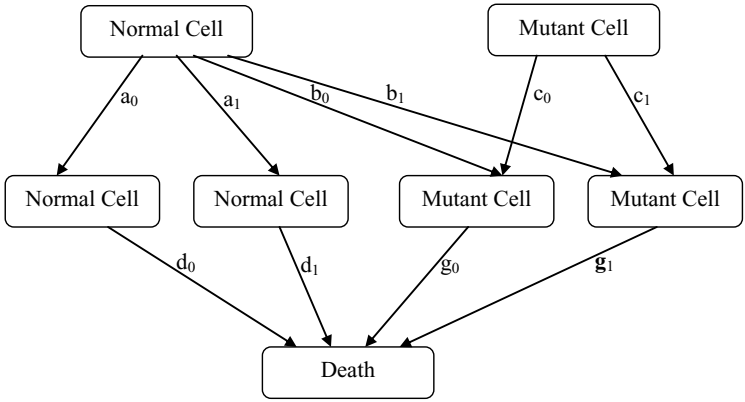

Figure 2.3.1: Schematic Diagram of the model

2.3.1 Assumptions and Postulates of the model:

Let the events occurred in non-overlapping intervals of time are statistically independent. Let Δt be an infinitesimal interval of time. Let there be 'n' normal cells and 'm' mutant cells initially at time 't'. Let 'a_0', 'b_0', 'c_0', 'd_0', 'g_0' respectively be the rate of generation of normal cell from normal cell, rate of generation of mutant cell from normal cell, rate of generation of mutant cell from mutant cell, rate of death of normal cell, rate of death of mutant cell under the absence of chemotherapy. Let 'a_1', 'b_1', 'c_1', 'd_1', 'g_1' respectively be the rate of generation of normal cell from normal cell, rate of generation of mutant cell from normal cell, rate of generation of mutant cell from mutant cell, rate of death of normal cell, rate of death of mutant cell under the presence of chemotherapy. Also it is assumed that all the events are Poisson parameters. With the above assumptions, the postulates of the model are

1. The probability of generation of one normal cell during Δt, provided there exists 'n' normal cells during 't' is $n(a_0 + a_1)\,\Delta t + 0(\Delta t)$
2. The probability of generation of one mutant cell from a normal cell during Δt provided there exists 'n' normal cells during 't' is $n(b_0+b_1)\;\;\Delta t + 0(\Delta t)$
3. The probability of generation of one mutant cell from a mutant cell during Δt provided there exists 'm' mutant cells during 't' is $m(c_0 + c_1)\,\Delta t + 0(\Delta t)$
4. The probability of death of one normal cell during Δt provided ∃ 'n' normal cells at time 't' is $n(d_0 + d_1)\,\Delta t + 0(\Delta t)$

5. The probability of death of one mutant cell during Δt provided there exists 'm' mutant cells at time 't' is $m(g_0 + g_1)\,\Delta t + 0(\Delta t)$
6. The probability of no generation of normal cell from a normal cell, mutant cell from normal cell, mutant cell from mutant cell and no death of normal cell, no death of mutant cell during an infinitesimal interval of time Δt is $1 - [n(a_0 + a_1 + b_0 + b_1 + d_0 + d_1) + \mathrm{m}(c_0 + c_1 + g_0 + g_1)]\Delta\mathrm{t} + 0(\Delta\mathrm{t})$
7. The probability of occurrence of other than the above events during an infinitesimal interval of time Δt is $0(\Delta\mathrm{t})^2$

2.3.2 The Difference-Differential Equations of the Model:

Let $p_{n,m}(\mathrm{t})$ be the joint probability of existing of 'n' normal cells and 'm' mutant cells in a tumor during chemotherapy per unit time't'. Then the difference differential equations of the model are:

$$\begin{aligned} p'_{n,m}(t) = {} & [\, n(a_0 + a_1 + b_0 + b_1 + d_0 + d_1) + m(c_0 + c_1 + g_0 + g_1)](-1)p_{n,m}(t) \\ & + (n-1)(a_0 + a_1)p_{n-1,m}(t) + [(n+1)(d_0 + d_1)]\, p_{n+1,m}(t) \\ & + [(n(b_0 + b_1) + (m-1)(c_0 + c_1)]p_{n,m-1}(t) \\ & + (m+1)(g_0 + g_1)\, p_{n,m+1}(t) \qquad \text{for n,m} \geq 1 \qquad \ldots(2.3.2.1) \end{aligned}$$

$$\begin{aligned} p'_{1,0}(t) = {} & (a_0 + a_1 + b_0 + b_1 + d_0 + d_1)(-1)p_{1,0}(t) + 2(d_0 + d_1)p_{2,0}(t) \\ & + (g_0 + g_1)\, p_{1,1}(t) \qquad \ldots(2.3.2.2) \end{aligned}$$

$$\begin{aligned} p'_{0,1}(t) = {} & (c_0 + c_1 + g_0 + g_1)(-1)\, p_{0,1}(t) + (d_0 + d_1)\, p_{1,1}(t) 2(g_0 + g_1)\, p_{0,2}(t) \\ & \qquad \ldots(2.3.2.3) \end{aligned}$$

$$p'_{0,0}(t) = (d_0 + d_1)\, p_{1,0}(t) + (g_0 + g_1)\, p_{0,1}(t) \qquad \ldots(2.3.2.4)$$

With the initial conditions

$$p_{N_0,M_0}(0) = 1,\ p_{N_0,M_0}(t) = 0$$

Where N_0, M_0 are the initial sizes of normal and mutant cells in the tumor during chemotherapy.

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

$$\text{Where} \quad p(x, y; t) = \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} x^n y^m\, p_{n,m}(t) \qquad \ldots (2.3.2.5)$$

Multiplying the equations (2.3.2.1) to (2.3.2.4) with $x^n y^m$ and summing overall m

and n we get,

$$\frac{\partial}{\partial t}p(x,y;t) = (a_0 + a_1 + b_0 + b_1 + d_0 + d_1)x \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} - n\,x^{n-1}y^m\,p_{n,m}(t)$$

$$+(c_0 + c_1 + g_0 + g_1)y \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} - m\,x^n y^{m-1} p_{n,m}(t)$$

$$+(a_0 + a_1)x^2 \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (n-1)x^{n-2}y^m\,p_{n-1,m}(t)$$

$$+(d_0 + d_1) \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (n+1)x^n y^m\,p_{n+1,m}(t)$$

$$+(b_0 + b_1)xy \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} n\,x^{n-1}y^{m-1} p_{n,m-1}(t)$$

$$+(c_0 + c_1)y^2 \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (m-1)x^n y^{m-2} p_{n,m-1}(t)$$

$$+(g_0 + g_1) \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (m+1)x^n y^m\,p_{n,m+1}(t) \qquad \ldots (2.3.2.6)$$

Rearranging the terms in the equation (2.3.2.6) we get

$$\frac{\partial}{\partial t}p(x,y;t) = (a_0 + a_1 + b_0 + b_1 + d_0 + d_1)x(-1)\frac{\partial}{\partial x}p(x,y;t)$$

$$-(c_0 + c_1 + g_{0+}g_1)y\frac{\partial}{\partial y}p(x,y;t) + (a_0 + a_1)x^2\frac{\partial}{\partial x}p(x,y;t)$$

$$+(d_0 + d_1)\frac{\partial}{\partial x}p(x,y;t) + (b_0 + b_1)xy\frac{\partial}{\partial x}p(x,y;t)$$

$$+(c_0 + c_1)y^2\frac{\partial}{\partial y}p(x,y;t) + (g_0 + g_1)\frac{\partial}{\partial y}p(x,y;t) \qquad \ldots (2.3.2.7)$$

Further simplification of equation (2.3.2.7) gives

$$\frac{\partial}{\partial t}p(x,y;t) = [-(a_0 + a_1 + b_0 + b_1 + d_{0+}d_1)x + (a_0 + a_1)x^2$$

$$+(d_0 + d_1) + (b_0 + b_1)xy]\frac{\partial}{\partial x}p(x,y;t)$$

$$+[-(c_0 + c_1 + g_0 + g_1)\,y + (c_0 + c_1)y^2$$

$$+(g_0 + g_1)\frac{\partial}{\partial y}p(x, y; t) \quad \text{... (2.3.2.8)}$$

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 cummulant generating function of $p_{n,m}$(t), the equation (2.3.2.8) becomes

$$\frac{\partial}{\partial t}k(u, v; t) = [-(a_0 + a_1 + b_0 + b_1 + d_0 + d_1) + (a_{0+}a_1)e^u + (b_{0+}b_1)\, e^v$$
$$+ (d_0 + d_1)\, e^{-u}\,]\,\frac{\partial k}{\partial u} + [-(c_0 + c_1 + g_0 + g_1) + (c_0 + c_1)\, e^v$$
$$+(g_0 + g_1)\, e^{-v}\,]\frac{\partial k}{\partial v} \quad \text{.... (2.3.2.9)}$$

2.3.3 Differential Equations and Statistical Measures:

Let $m_{i,j}$(t) denotes the moments of order (i, j) of normal and mutant cells at time 't'. Then the differential equations of the model are:

$$\frac{\partial}{\partial t}m_{1,0}(t) = (a_0 + a_1 - d_0 - d_1)m_{1,0}(t) \quad \text{... (2.3.3.1)}$$

$$\frac{\partial}{\partial t}m_{0,1}(t) = (b_0{+}b_1)m_{1,0}(t) + (c_0 + c_1 - g_0 - g_1)\, m_{0,1}(t) \quad \text{... (2.3.3.2)}$$

$$\frac{\partial}{\partial t}m_{2,0}(t) = (a_0 + a_1 + d_0 + d_1)m_{1,0}(t) + 2(a_0 + a_1 - d_0 - d_1)m_{2,0}(t)$$

... (2.3.3.3)

$$\frac{\partial}{\partial t}m_{1,1}(t) = (a_0 + a_1 - d_0 - d_1 + c_0 + c_1 - g_0 - g_1)m_{1,1}(t) + (b_0{+}b_1)m_{2,0}(t)$$

... (2.3.3.4)

$$\frac{\partial}{\partial t}m_{0,2}(t) = 2(b_0{+}b_1)m_{1,1}(t) + (b_0{+}b_1)m_{1,0}(t) + (c_0 + c_1 + g_{0+}g_1)m_{0,1}(t)$$
$$+2(c_0 + c_1 - g_0 - g_1)m_{0,2}(t) \quad \text{... (2.3.3.5)}$$

We can obtain the characteristics of the model by solving the equations from 2.3.3.1 to 2.3.3.5

Solving the equation 2.3.3.1 we get,

Expected number of normal cells during chemotherapy at time 't' is

$$m_{1,0}(\text{t}) = N_0\, \text{e}^{(a_0+a_1-d_0-d_1)\text{t}} \quad \text{... (2.3.3.6)}$$

where N_0 is the initial size of the normal cells.

Substituting the equation (2.3.3.6) in the equation (2.3.3.2), we get

$$\frac{\partial}{\partial t}m_{0,1}(t) + (g_0 + g_1 - c_0 - c_1)m_{0,1}(t) = (b_0+b_1)N_0\, e^{(a_0+a_1-d_0-d_1)t} \quad \ldots (2.3.3.7)$$

Solving the equation 2.3.3.7 we get

Expected number of mutant cells during chemotherapy at time't' is

$$m_{0,1}(t) = A[e^{(a_0+a_1-d_0-d_1)t} - e^{(c_0+c_1-g_0-g_1)t}] + M_0\, e^{(c_0+c_1-g_0-g_1)t}$$

$$\text{Where } A = \frac{(b_0+b_1)\, N_0}{a_0 + a_1 - d_0 - d_1+g_0 + g_1 - c_0 - c_1} \quad \ldots (2.3.3.8)$$

and M_0 is the initial size of the mutant cells.

Substituting the equation (2.3.3.6) in the equation (2.3.3.3) we get,

$$\frac{d}{dt}m_{2,0}(t) + 2(d_0 + d_1 - a_0 - a_1)m_{2,0}(t) = (a_0 + a_1 + d_0 + d_1).N_0\, e^{(a_0+a_1-d_0-d_1)t} \quad \ldots (2.3.3.9)$$

Solving the equation (2.3.3.9) we get

Variance of normal cells during chemotherapy at time't' is

$$m_{2,0}(t) = B\, e^{(a_0+a_1-d_0-d_1)t} - [e^{(a_0+a_1-d_0-d_1)t} - 1]$$

$$\text{Where} \quad B = \frac{a_0 + a_1 + d_0 + d_1}{a_0 + a_1 - d_0 - d_1}N_0 \quad \ldots (2.3.3.10)$$

Substituting the equation (2.3.3.10) in (2.3.3.4) we get,

$$\frac{d}{dt}m_{1,1}(t) + (d_0 + d_1 - a_0 - a_1 - c_0 - c_1 + g_0 + g_1)m_{1,1}(t) = (b_0+b_1)\, B\, e^{(a_0+a_1-d_0-d_1)t}\, [e^{(a_0+a_1-d_0-d_1)t} - 1] \quad \ldots (2.3.3.11)$$

Solving the equation (2.3.3.11) we get,

Covariance between normal cells and mutant cells during chemotherapy at time't' is

$$m_{1,1}(t) = D\, e^{(a_0+a_1-d_0-d_1)t} \times [\frac{(g_0 + g_1 - c_0 - c_1)\, e^{(a_0+a_1-d_0-d_1)t}}{a_0 + a_1 - d_0 - d_1} - \frac{(a_0 + a_1 - d_0 - d_1 - c_0 - c_1 + g_0 + g_1)}{a_0 + a_1 - d_0 - d_1} + e^{(c_0+c_1-g_0-g_1)t}]$$

Where $D = \dfrac{(b_0+b_1)(a_0+a_1+d_0+d_1)}{(a_0+a_1-d_0-d_1-c_0-c_1+g_0+g_1)(g_0+g_1-c_0-c_1)} N_0$

... (2.3.3.12)

Substituting the equations (2.3.3.6), (2.3.3.8) and (2.3.3.12) in the equation (2.3.3.5) we get,

$$\frac{d}{dt} m_{0,2}(t) + 2(g_0+g_1-c_0-c_1) m_{0,2}(t) = 2(b_0+b_1)[D\ e^{(a_0+a_1-d_0-d_1)t} \times$$

$$\frac{(g_0+g_1-c_0-c_1)\ e^{(a_0+a_1-d_0-d_1)t} - (a_0+a_1-d_0-d_1-c_0-c_1+g_0+g_1)}{a_0+a_1-d_0-d_1}$$

$$+\ e^{(c_0+c_1-g_0-g_1)t}] + (b_0+b_1).N_0\ e^{(a_0+a_1-d_0-d_1)t}$$

$$+ (c_0+c_1+g_{0+}g_1)\ A[e^{(a_0+a_1-d_0-d_1)t} -\ e^{(c_0+c_1-g_0-g_1)t}]$$

$$+ M_0\ e^{(c_0+c_1-g_0-g_1)t}] \quad \text{... (2.3.3.13)}$$

Solving the equation (2.3.3.13) we get,

Variance of mutant cells during chemotherapy at time 't' is

$$m_{0,2}(t) = E\ [e^{2(g_0+g_1-c_0-c_1)t} - e^{2(c_0+c_1-g_0-g_1)t}]$$
$$+ (F+I+H)\big[\ e^{(a_0+a_1-d_0-d_1)t} - e^{2(c_0+c_1-g_0-g_1)t}\big]$$
$$+ G\big[\ e^{(a_0+a_1-d_0-d_1-g_0-g_1+c_0+c_1)t} - e^{2(c_0+c_1-g_0-g_1)t}\big]$$
$$+ (J+K)\ [e^{(c_0+c_1-g_0-g_1)t} - e^{2(c_0+c_1-g_0-g_1)t}]$$

Where

$$E = \frac{(b_0+b_1)\ D[g_0+g_1-c_0-c_1]}{(a_0+a_1-d_0-d_1)(a_0+a_1-d_0-d_1+g_0+g_1-c_0-c_1)}$$

$$F = \frac{2(b_0+b_1)\ D\ (a_0+a_1+g_0+g_1-d_0-d_1-c_0-c_1)}{(d_0+d_1-a_0-a_1)[(a_0+a_1-d_0-d_1+2(g_0+g_1-c_0-c_1)]}$$

$$G = \frac{2(b_0+b_1)\ D}{(a_0+a_1-d_0-d_1+g_0+g_1-c_0-c_1)}$$

$$H = \frac{(b_0+b_1)\ N_0}{2(g_0+g_1-c_0-c_1)(a_0+a_1-d_0-d_1)}$$

$$I = \frac{(c_0+c_1+g_0+g_1)A}{2(g_0+g_1-c_0-c_1)+(a_0+a_1-d_0-d_1)}$$

$$J = \frac{(c_0+c_1+g_0+g_1)A}{(c_0+c_1-g_0-g_1)}$$

$$K = \frac{(g_0 + g_1 + c_0 + c_1)M_0}{(g_0 + g_1 - c_0 - c_1)}$$

$$A = \frac{(b_0+b_1)\ N_0}{(a_0 + a_1 - d_0 - d_1 + g_0 + g_1 - c_0 - c_1)}$$

$$B = \frac{(a_0 + a_1 + d_0 + d_1)N_0}{(a_0 + a_1 - d_0 - d_1)}$$

$$D = \frac{(b_0+b_1)\ (a_0 + a_1 + d_0 + d_1)N_0}{(a_0 + a_1 + g_0 + g_1 - d_0 - d_1 - c_0 - c_1)(g_0 + g_1 - c_0 - c_1)} \quad \ldots (2.3.3.14)$$

2.3.4 Numerical Illustration and Sensitivity Analysis:

From equations (2.3.3.6), (2.3.3.8), (2.3.3.10), (2.3.2.12) and (2.3.3.14) the values of $m_{1,0}(t), m_{0,1}(t), m_{2,0}(t), m_{1,1}(t)$ and $m_{0,2}(t)$are computed for various values of the parameters and presented in the tables from Table (2.3.4.1) to (2.3.4.13)

Table 2.3.4.1

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of N_0 at the fixed values of other parameters with values M_0=50; t=7; a_0=0.3; a_1=0.2; b_0=0.5; b_1=0.3; c_0=0.4; c_1=0.3; d_0=0.4; d_1=0.5; g_0=0.9; g_1=2

N_0	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
102	45.832	20.427	88.333	44.096	36.818
104	46.73	20.815	90.065	44.961	37.520
106	47.629	21.204	91.797	45.826	38.223
108	48.528	21.592	93.529	46.690	38.925
110	49.426	21.981	95.261	47.555	39.628

From table 2.3.4.1 it is observed that expected number of normal cells, expected number of mutant cells, variance of normal cells, variance of mutant cells and covariance between normal and mutant cells are increasing functions of the initial number of normal cells (N_0) when all the other parameters are constants.

Table 2.3.4.2

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of M_0 at the fixed values of other parameters with values N_0=100; t=7; a_0=0.3; a_1=0.2; b_0=0.5; b_1=0.3; c_0=0.4; c_1=0.3; d_0=0.4; d_1=0.5; g_0=0.9; g_1=2

$\mathbf{M_0}$	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
55	44.933	20.1	86.601	43.232	36.214
60	44.933	20.161	86.601	43.232	36.314
65	44.933	20.223	86.601	43.232	36.413
70	44.933	20.284	86.601	43.232	36.512
75	44.933	20.345	86.601	43.232	36.611

From table 2.3.4.2, it is observed that expected number of normal cells, variance of normal cells and covariance between normal and mutant cells are invariant of change of initial number of mutant cells (M_0) when all the other parameters are constants. It is also observed that the expected number of mutant cells variance of mutant cells, are increasing functions of initial number of mutant cells (M_0) when all the other parameters are constants.

Table 2.3.4.3

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of a0 at the fixed values of other parameters with values N_0=100; M_0=50; t=7; a_1=0.2; b_0=0.5; b_1=0.3; c_0=0.4; c_1=0.3; d_0=0.4; d_1=0.5; g_0=0.9; g_1=2

a_0	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.35	49.659	21.557	103.567	55.134	39.622
0.4	54.881	23.205	123.809	71.486	43.55
0.45	60.653	24.993	147.964	94.915	47.955
0.5	67.032	26.936	176.793	130.635	52.904
0.55	74.082	29.045	211.207	190.737	58.472

From table 2.3.4.3 it is observed that expected number of normal cells, expected number of mutant cells, Variance of normal cells, variance of mutant cells and covariance between normal cells and mutant cells are increasing functions of the rate of generation of normal cell from normal cell during the absence of drug (a_0) when all the other parameters are constant.

Table 2.3.4.4

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of a_1 at the fixed values of other parameters with values N_0=100; M_0=50;t=7;a_0=0.3;b_0=0.5;b_1=0.3;c_0=0.4; c_1=0.3; d_0=0.4; d_1=0.5; g_0=0.9; g_1=2

a_1	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.22	46.767	20.631	93.03	48.811	37.471
0.24	48.675	21.243	99.93	55.193	38.889
0.26	50.662	21.876	107.334	62.531	40.372
0.28	52.729	22.529	115.28	71.012	41.925
0.3	54.881	23.205	123.809	80.879	43.55

From table 2.3.4.4, it is observed that the expected number of normal cells, expected number of mutant cells, variance of normal cells, variance of mutant cells and covariance between normal cells and mutant cells are increasing functions of rate of generation of normal cell from normal cell (a_1) during the presence of drug when all the other parameters are constant.

Table 2.3.4.5

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of b_0 at the fixed values of other parameters with values N_0=100; M_0=50; t=7; a_0=0.3; a_1=0.2; b_1=0.3; c_0=0.4; c_1=0.3; d_0=0.4; d_1=0.5; g_0=0.9; g_1=2

b_0	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.55	44.933	21.252	86.601	45.934	38.912
0.6	44.933	22.466	86.601	48.636	41.779
0.65	44.933	23.68	86.601	51.338	44.717
0.7	44.933	24.895	86.601	54.04	47.725
0.75	44.933	26.109	86.601	56.742	50.805

From table number 2.3.4.5, it is observed that expected number of normal cells and variance of normal cells are invariant of rate of generation of mutant cell from normal cell during absence of drug (b_0) when all the other parameters are constant. It is also observed that expected number of mutant cells, covariance between normal and mutant cells and variance of mutant cells are increasing function of rate of generation of mutant cell from normal cell during absence of drug (b_0) when all the other parameters are constant.

Table 2.3.4.6

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of b1 at the fixed values of other parameters with values N_0=100; M_0=50; t=7; a_0=0.3; a_1=0.2; b_0=0.5; c_0=0.4; c_1=0.3; d_0=0.4; d_1=0.5; g_0=0.9; g_1=2

b_1	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.33	44.933	20.767	86.601	44.853	37.785
0.36	44.933	21.495	86.601	46.474	39.479
0.39	44.933	22.224	86.601	48.095	41.2
0.42	44.933	22.952	86.601	49.716	42.946
0.45	44.933	23.68	86.601	51.338	44.717

From table 2.3.4.6 it is observed that expected number of normal cells and variance of normal cells are invariant of rate of generation of mutant cell from normal cell during the presence of drug (b_1) when all the parameters are constant. It is also observed that expected number of mutant cells, covariance between normal cells and mutant cells and variance of mutant cells are increasing functions of rate of generation of mutant cell from normal cell during the presence of drug (b_1) when all the parameters are constant.

Table 2.3.4.7

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of c_0 at the fixed values of other parameters with values N_0=100; M_0=50; t=7; a_0=0.3; a_1=0.2; b_0=0.5; b_1=0.3; c_1=0.3; d_0=0.4; d_1=0.5; g_0=0.9; g_1=2

c_0	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.5	44.933	21.189	86.601	45.18	39.883
0.6	44.933	22.466	86.601	47.318	44.252
0.7	44.933	23.89	86.601	49.678	49.345
0.8	44.933	25.481	86.601	52.298	55.321
0.9	44.933	27.266	86.601	55.228	62.377

From table 2.3.4.7 it is observed that expected number of normal cells and variance of normal cells are invariant of rate of generation of mutant cell from mutant cell during the absence of drug (c_0) when all the other parameters are constant. It is also observed that expected number of mutant cells, covariance between normal and mutant cells and variance of mutant cells are increasing functions of rate of generation of mutant cell from mutant cell during the absence of drug (c_0) when all the other parameters are constant.

Table 2.3.4.8

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of c_1 at the fixed values of other parameters with values N_0=100; M_0=50; t=7; a_0=0.3; a_1=0.2; b_0=0.5; b_1=0.3; c_0=0.4; d_0=0.4; d_1=0.5; g_0=0.9; g_1=2

c_1	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.32	44.933	20.259	86.601	43.607	36.826
0.34	44.933	20.484	86.601	43.99	37.557
0.36	44.933	20.714	86.601	44.379	38.31
0.38	44.933	20.949	86.601	44.776	39.085
0.4	44.933	21.189	86.601	45.18	39.883

From table 2.3.4.8 it is observed that expected number of normal cells and variance of normal cells are invariant of rate of generation of mutant cell from mutant cell during the presence of drug (c_1) when all the other parameters are constant. It is also observed from this table that expected number of mutant cells, covariance between normal and mutant cells and variance of mutant cells are increasing functions of rate of generation of mutant cells from mutant cells during the presence of drug (c_1) when all the other parameters are constant.

Table 2.3.4.9

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of d_0 at the fixed values of other parameters with values N_0=100; M_0=50; t=7; a_0=0.3; a_1=0.2; b_0=0.5; b_1=0.3; c_0=0.4; c_1=0.3; d_1=0.5; g_0=0.9; g_1=2

d_0	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.42	43.171	19.465	82.947	40.505	35.065
0.44	41.478	18.91	79.442	38.014	34.048
0.46	39.852	18.372	76.079	35.731	33.063
0.48	38.289	17.852	72.855	33.63	32.108
0.5	36.788	17.348	69.763	31.692	31.184

Table 2.3.4.10

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of d1 at the fixed values of other parameters with values N_0=100; M_0=50; t=7; a_0=0.3; a_1=0.2; b_0=0.5; b_1=0.3; c_0=0.4; c_1=0.3; d_0=0.4; g_0=0.9; g_1=2

d_1	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.55	40.657	18.639	77.743	36.848	33.551
0.6	36.788	17.348	69.763	31.692	31.184
0.65	33.287	16.158	62.583	27.449	28.998
0.7	30.119	15.06	56.127	23.906	26.98
0.75	27.253	14.046	50.327	20.914	25.118

From tables 2.3.4.9 and 2.3.4.10, it is observed that expected number cells from normal cells, expected number of mutant cells, covariance between normal cells and mutant cells, variance of normal cells and variance of mutant cells are decreasing functions of rate of death of normal cell during the absence of drug (d_0) and also the rate of death of normal cell during the presence of drug (d_1) when all the other parameters are constant.

Table 2.3.4.11

Values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of g0 at the fixed values of other parameters with values N_0=100; M_0=50; t=7; a_0=0.3; a_1=0.2; b_0=0.5; b_1=0.3; c_0=0.4; c_1=0.3; d_0=0.4; d_1=0.5; g_1=2

g_0	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.95	44.933	19.506	86.601	42.321	34.901
1	44.933	18.998	86.601	41.448	33.754
1.05	44.933	18.516	86.601	40.611	32.669
1.1	44.933	18.055	86.601	39.807	31.642
1.15	44.933	17.617	86.601	39.036	30.67

Table 2.3.4.12

Values of m_{10}, m_{01}, m_{20}, m_{11}, m_{02} for varying values of g1 at the fixed values of other parameters with values N_0=100; M_0=50; t=7; a_0=0.3; a_1=0.2; b_0=0.5; b_1=0.3; c_0=0.4; c_1=0.3; d_0=0.4; d_1=0.5; g_0=0.9;

g_1	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
2.2	44.933	18.055	86.601	39.807	31.642
2.4	44.933	16.414	86.601	36.892	28.039
2.6	44.933	15.039	86.601	34.377	25.094
2.8	44.933	13.873	86.601	32.184	22.653
3	44.933	12.874	86.601	30.254	20.606

From tables 2.3.4.11 and 2.3.4.12 it is observed that expected number of normal cells and variance of normal cells are invariant of change of rate death of mutant cell during the absence (g_0) and presence of drug (g_1) when all the other parameters are constant. It is also observed that expected number of mutant cells, covariance between normal cells and mutant cells and variance of mutant cells are decreasing functions of rate of death of mutant cells during the absence (g_0) and presence of drug(g_1) when all the other parameters are constant.

Table 2.3.4.13

Values of m_{10}, m_{01}, m_{20}, m_{11}, m_{02} for varying values of t at the fixed values of other parameters with values N_0=100; M_0=50; a_0=0.3; a_1=0.2; b_0=0.5; b_1=0.3; c_0=0.4; c_1=0.3; d_0=0.4; d_1=0.5; g_0=0.9; g_1=2

t	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
3	30.119	13.394	73.667	34.095	27.156
4	20.19	8.974	56.397	24.417	19.576
5	13.534	6.015	40.957	16.839	13.744
6	9.072	4.032	28.871	11.43	9.492
7	6.081	2.703	19.989	7.704	6.489

It is observed from table 2.3.4.13 that expected number of normal cells, expected number of mutant cells, covariance between normal and mutant cells, variance of normal cells and variance of mutant cells are decreasing functions of time (t) when all the other parameters are constant.

Chapter-3

MUTANT CELL GROWTH THROUGH TWO STAGE STOCHASTIC MODELS DURING CHEMOTHERAPY

3.1 INTRODUCTION:

In this chapter we propose a two stage stochastic model for cancer cell growth. A mutant cell, after required stages of transformation will be converted into a malignant, from then the cell division is at faster growth. In this model we consider that mutant cell is transformed into premalignant cell and then it will be converted into malignant cell as a full-fledged cancerous cell. The rates of arrivals to the premalignant and malignant stages from mutant stage and the death rates of premalignant and malignant cells are assumed as bivariate Poisson parameters. The rate of conversion of premalignant cell to malignant cell is also a bivariate Poisson parameter. A bivariate time dependent Poisson process is developed from which the necessary differential equations and statistical measures are derived.

In order to observe the model behaviour during chemotherapy, a state dependent bivariate Poisson process along with time dependency is developed by incorporating the drug absence as state zero and presence as state one. Difference differential equations and differential equations of the model are derived from the developed bivariate Poisson process with the help of probability and cumulant generating functions. Statistical measures are also derived in both the states. The states are combined by assuming the relationship between them is a linear combination.

3.2 STOCHASTIC MODEL:

In this section a mutant cell growth is studied as a two stage stochastic model. A specified behaviour from normal cell division is observed with mutant cell. This cell always has a different mechanism in division. A mutant cell once transformed from the normal cell it may take further conversion towards a full pledged cancer cell in two steps namely premalignant and malignant. The rates of growth of premalignant and malignant cells are varying. Similarly the death rates of cells in both the stages are different. The following schematic diagram will be helpful in understanding the dynamics of cell growth.

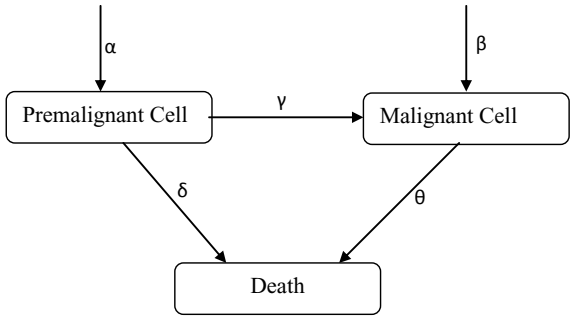

Figure: 3.2.1: Schematic diagram of the model

3.2.1 Assumptions and Postulates of the Model:

Let the events occurred in non-overlapping intervals of time are statistically independent. Let Δt be an infinitesimal interval of time. Let there be 'n' premalignant cells and 'm' malignant cells initially at time't'. Let α, β, γ, δ, θ be the rate of arrival to premalignancy, rate of arrival to malignancy, rate of transformation from premalignancy to malignancy, rate of death of premalignant cell without transforming to malignancy, rate of death of malignant cell respectively. Also it is assumed that all the events are Poisson parameters. The postulates of the model with the above assumption are:

1. The probability of arrival of one premalignant cell during Δt is $\alpha\,\Delta t + 0(\Delta t)$
2. The probability of arrival of one malignant cell during Δt is $\beta\,\Delta t + 0(\Delta t)$
3. The probability of transformation of premalignant cell to malignant cell provided there are 'n' premalignant cells already at time 't' is $n\gamma\,\Delta t + 0(\Delta t)$
4. The probability of death of one premalignant cell provided there are 'n' premalignant cells already at time't' is $n\delta\Delta t + 0(\Delta t)$
5. The probability of death of one malignant cell provided there are 'm' malignant cells at time't' is $m\theta\Delta t + 0(\Delta t)$
6. The probability of no arrival of premalignant cell, no arrival of malignant cell no transformation from premalignancy to malignancy, no death of premalignant cell no death of malignant cell during an infinitesimal interval of time Δt is $1 - [\alpha + \beta + n(\gamma + \delta) + m\theta]\Delta t + 0(\Delta t)$

7. The probability of occurrence of other than the above events during an infinitesimal interval of time Δt is $0(\Delta t)^2$

3.2.2 The Difference-Differential Equations of the Model:

Let $p_{n,m}(t)$ be the joint probability of existence of 'n' premalignant cells and 'm' malignant cells in a tumor per unit time't', Then the difference differential equations of the model are:

$$p'_{n,m}(t) = [\alpha + \beta + n(\gamma + \delta) + m\theta](-1)p_{n,m}(t) + (\alpha)p_{n-1,m}(t) + (n+1)\delta p_{n+1,m}(t) + (n+1)\gamma\, p_{n+1,m-1}(t) + (\beta)p_{n,m-1}(t) + (m+1)\theta\, p_{n,m+1}(t) \quad \text{for n,m} \geq 1 \quad \ldots(3.2.2.1)$$

$$p'_{1,0}(t) = [\alpha + \beta + \gamma + \delta](-1)p_{1,0}(t) + \alpha\, p_{0,0}(t) + 2\delta\, p_{2,0}(t) + \theta\, p_{1,1}(t) \quad \ldots(3.2.2.2)$$

$$p'_{0,1}(t) = -(\alpha + \beta + \theta)p_{0,1}(t) + \delta\, p_{1,1}(t) + \gamma\, p_{1,0}(t) + \beta\, p_{0,0}(t) + 2\theta\, p_{0,2}(t) \quad \ldots(3.2.2.3)$$

$$p'_{0,0}(t) = -(\alpha + \beta)p_{0,0}(t) + \delta\, p_{1,0}(t) + \theta\, p_{0,1}(t) \quad \ldots(3.2.2.4)$$

With the initial conditions

$$p_{N_0,M_0}(0) = 1,\ p_{N_0,M_0}(t) = 0$$

Where N_0, M_0 are the initial sizes of the premalignant and the malignant cells in the tumor.

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

Multiplying the equation (3.2.2.1) to (3.3.2.4) with $x^n y^m$ and summing overall m and n, we obtain

$$p(x, y; t) = \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} x^n y^m\, p_{n,m}(t) \quad \ldots(3.2.2.5)$$

This implies

$$\sum_{m=0}^{\infty}\sum_{n=0}^{\infty} x^n y^m\, p'_{n,m}(t) = \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} \left[-[\alpha+\beta+\mathrm{n}(\gamma+\delta)+\mathrm{m}\theta]x^n y^m\, p_{n,m}(t)\right]$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} \alpha\, x^n y^m\, p_{n-1,m}(t)$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (n+1)\delta\, x^n y^m\, p_{n+1,m}(t)$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (n+1)\gamma\, x^n y^m\, p_{n+1,m-1}(t)$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} \beta\, x^n y^m\, p_{n,m-1}(t)$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (m+1)\theta\, x^n y^m\, p_{n,m+1}(\mathrm{t}) \qquad \ldots (3.2.2.6)$$

On simplifying the equation (3.2.2.6) we get,

$$\frac{\partial}{\partial t}p(x,y;t) = [\alpha(x-1)+\beta(y-1)]p(x,y;t)$$
$$+[-(\gamma+\delta)\,x+\delta+\gamma y\,]\frac{\partial}{\partial x}\,p(x,y;t)$$
$$+[\theta(1-y)]\frac{\partial}{\partial y}p(x,y;t) \qquad \ldots (3.2.2.7)$$

We can obtain the characteristics of the model by using the joint cummulant generating function of $p_{n,m}(\mathrm{t})$. Taking $x = e^u$ and $y = e^v$ and denoting $k(u,v;t)$ as the joint cummulant generating function of $p_{n,m}(\mathrm{t})$, we obtain the following:

$$\frac{\partial}{\partial t}k(u,v;t) = [-(\gamma+\delta)+\gamma\, e^{-u+v}+\delta\, e^{-u}\,]\frac{\partial k}{\partial u}+\theta(\,e^{-v}-1)\frac{\partial k}{\partial v}$$
$$+[\alpha(\,e^u-1)\,e^v+\beta(\,e^v-1)]k(u,v;t) \qquad \ldots (3.2.2.8)$$

3.2.3 Differential Equations and Statistical Measures of the Model:

Let $m_{i,j}(\mathrm{t})$ denotes the moments of order (i,j) of premalignant and malignant cells at time 't'. Then the differential equations governing $m_{i,j}(\mathrm{t})$ are obtained as:

$$\frac{\partial}{\partial t} m_{1,0}(t) = -(\gamma + \delta) m_{1,0}(t) + \alpha \quad \ldots (3.2.3.1)$$

$$\frac{\partial}{\partial t} m_{0,1}(t) = \gamma\, m_{1,0}(t) - \theta\, m_{0,1}(t) + \beta \quad \ldots (3.2.3.2)$$

$$\frac{\partial}{\partial t} m_{2,0}(t) = (\delta + \gamma) m_{1,0}(t) - 2(\delta + \gamma) m_{2,0}(t) + \alpha \quad \ldots (3.2.3.3)$$

$$\frac{\partial}{\partial t} m_{1,1}(t) = -\gamma\, m_{1,0}(t) + \gamma\, m_{2,0}(t) - (\delta + \gamma + \theta) m_{1,1}(t) \quad \ldots (3.2.3.4)$$

$$\frac{\partial}{\partial t} m_{0,2}(t) = \gamma\, m_{1,0}(t) + 2\gamma\, m_{1,1}(t) + \theta\, m_{0,1}(t) - 2\theta\, m_{0,2}(t) + \beta \quad \ldots (3.2.3.5)$$

Solving the equation 3.2.3.1 we get,

$$m_{1,0}(t) = \frac{\alpha}{\gamma + \delta} + \left[N_0 - \frac{\alpha}{\gamma + \delta}\right] \mathrm{e}^{-(\gamma+\delta)\mathrm{t}} \quad \ldots (3.2.3.6)$$

On simplifying the equation 3.2.3.6 we get,

Expected number of premalignant cells at time't' is

$$m_{1,0}(t) = \frac{\alpha}{\gamma + \delta}\left[1 - \mathrm{e}^{-(\gamma+\delta)\mathrm{t}}\right] + N_0 \mathrm{e}^{-(\gamma+\delta)\mathrm{t}} \quad \ldots (3.2.3.7)$$

Substituting the equation 3.2.3.7 in the equation 3.2.3.2 and on solving the resultant equation we get,

$$m_{0,1}(t) = \frac{\alpha\,\gamma}{\gamma + \delta}\frac{1}{\theta} + \frac{\alpha\,\gamma}{\gamma + \delta}\frac{\mathrm{e}^{-(\gamma+\delta)\mathrm{t}}}{(\gamma + \delta) - \theta} - N_0\gamma\frac{\mathrm{e}^{-(\gamma+\delta)\mathrm{t}}}{(\gamma + \delta) - \theta} + \frac{\beta}{\theta} + \left[M_0 - \frac{\alpha\,\gamma}{\gamma + \delta}\frac{1}{\theta} - \frac{\alpha\,\gamma}{\gamma + \delta}\frac{1}{(\gamma + \delta) - \theta} + N_0\gamma\frac{1}{(\gamma + \delta) - \theta} - \frac{\beta}{\theta}\right] \mathrm{e}^{-\theta\mathrm{t}} \quad \ldots (3.2.3.8)$$

On simplifying the equation 3.2.3.8 we get,

Expected number of malignant cells at time't' is

$$m_{0,1}(t) = \frac{\alpha\,\gamma}{\gamma + \delta}\left[\frac{1 - \mathrm{e}^{-\theta\mathrm{t}}}{\theta} + \frac{\mathrm{e}^{-(\gamma+\delta)\mathrm{t}} - \mathrm{e}^{-\theta\mathrm{t}}}{(\gamma + \delta) - \theta}\right] - \frac{N_0\gamma}{(\gamma + \delta) - \theta}\left[\mathrm{e}^{-(\gamma+\delta)\mathrm{t}} - \mathrm{e}^{-\theta\mathrm{t}}\right] + \frac{\beta}{\theta}\left(1 - \mathrm{e}^{-\theta\mathrm{t}}\right) + M_0\mathrm{e}^{-\theta\mathrm{t}} \quad \ldots (3.2.3.9)$$

Substituting the equation 3.2.3.7 in the equation 3.2.3.3 we get,

$$\frac{\partial}{\partial t}m_{2,0}(t) + 2(\delta+\gamma)m_{2,0}(t) = (\delta+\gamma)\left[\frac{\alpha}{\gamma+\delta} + \left[1 - \mathrm{e}^{-(\gamma+\delta)t} + N_0\mathrm{e}^{-(\gamma+\delta)t}\right]\right] + \alpha \quad \ldots (3.2.3.10)$$

Solving the equation 3.2.3.10 we get,

Variance of premalignant cells at time‘t’ is

$$m_{2,0}(t) = \frac{\alpha}{\gamma+\delta}\left[1 - \mathrm{e}^{-(\gamma+\delta)t}\right] + N_0\mathrm{e}^{-(\gamma+\delta)t}\left[1 - \mathrm{e}^{-(\gamma+\delta)t}\right] \quad \ldots (3.2.3.11)$$

Substituting the equations 3.2.3.6 and 3.2.3.11 and solving the equation we get,

Covariance between premalignant and malignant cells at time‘t’ is

$$m_{1,1}(t) = \frac{N_0\gamma}{(\gamma+\delta)-\theta}\left[\mathrm{e}^{-2(\gamma+\delta)t} - \mathrm{e}^{-(\theta+\gamma+\delta)t}\right] \quad \ldots (3.2.3.12)$$

Substituting the equations (3.2.3.7), (3.2.3.9) and (3.2.3.12) in the equation (3.2.3.5) and solving we get

$$\begin{aligned} m_{0,2}(t) = {} & \frac{\alpha\gamma}{\gamma+\delta}\left[\frac{1}{\theta} + \frac{\mathrm{e}^{-(\gamma+\delta)t}}{(\gamma+\delta)-\theta} - \frac{\gamma+\delta}{\theta(\gamma+\delta-\theta)}\mathrm{e}^{-\theta t}\right] \\ & + \frac{N_0\gamma}{(\gamma+\delta)-\theta}\left[\mathrm{e}^{-\theta t} - \mathrm{e}^{-(\gamma+\delta)t}\right] \\ & + \frac{\gamma^2 N_0}{(\gamma+\delta-\theta)^2}\left[\left(2\mathrm{e}^{-\theta t} - \mathrm{e}^{-(\gamma+\delta)t}\right)\mathrm{e}^{-(\gamma+\delta)t}\right] \\ & + \frac{\beta}{\theta}\left(1 - \mathrm{e}^{-\theta t}\right) + M_0\mathrm{e}^{-\theta t} + const\ \mathrm{e}^{-2\theta t} \end{aligned} \quad \ldots (3.2.3.13)$$

On simplifying the equation 3.2.3.13 we get,

Variance of malignant cells at time ‘t’ is

$$\begin{aligned} m_{0,2}(t) = {} & \frac{\alpha\gamma}{\theta(\gamma+\delta-\theta)}\left(1 - \mathrm{e}^{-\theta t}\right) + \frac{\alpha\gamma}{\gamma+\delta}\cdot\frac{\mathrm{e}^{-(\gamma+\delta)t} - 1}{(\gamma+\delta)-\theta} \\ & + \frac{N_0\gamma}{(\gamma+\delta)-\theta}\left[\mathrm{e}^{-\theta t} - \mathrm{e}^{-(\gamma+\delta)t}\right] \\ & + \frac{\gamma^2 N_0}{(\gamma+\delta-\theta)^2}\left[\left(2\mathrm{e}^{-(\theta+\gamma+\delta)t} - \mathrm{e}^{-2(\gamma+\delta)t} - \mathrm{e}^{-2\theta t}\right]\right. \\ & + \frac{\beta}{\theta}\left(1 - \mathrm{e}^{-\theta t}\right) + M_0\mathrm{e}^{-\theta t}\left(1 - \mathrm{e}^{-\theta t}\right) \end{aligned} \quad \ldots (3.2.3.14)$$

3.2.4 Numerical Illustration and Sensitivity Analysis:

In order to verify the model behaviour, a simulated data set based on the mentioned assumptions are generated and presented from tables 3.2.4.1 to 3.2.4.8. From

equations (3.2.3.7), (3.2.3.9), (3.2.3.11), (3.2.3.12) and (3.2.3.14) the values of $m_{1,0}(t), m_{0,1}(t), m_{2,0}(t), m_{1,1}(t)$ and $m_{0,2}(t)$are computed for various values of the parameters and presented in the tables.

Table 3.2.4.1

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of N_0 at the fixed values of other parameters with values M_0=50; α=0.9; β=0.5; γ=0.4; δ=1; t=2; θ=5;

N_0	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
102	6.806	0.838	6.429	-0.042	0.833
104	6.928	0.852	6.543	-0.043	0.847
106	7.05	0.865	6.658	-0.044	0.86
108	7.171	0.879	6.772	-0.044	0.874
110	7.293	0.892	6.886	-0.045	0.887

It is observed from table 3.2.4.1 that expected number of premalignant cells, expected number of malignant cells, variance of premalignant cells and malignant cells are increasing functions of initial number of premalignant cells (N_0) when all other parameters are constant. Also it is observed that covariance between premalignant and malignant cells is negative and decreasing with respect to increase in the initial number of premalignant cells.

Table 3.2.4.2

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of M_0 at the fixed values of other parameters with values N_0=100; α=0.9; β=0.5; γ=0.4; δ=1; t=2; θ=5;

M_0	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
100	6.685	0.827	6.315	-0.041	0.822
150	6.685	0.829	6.315	-0.041	0.824
200	6.685	0.831	6.315	-0.041	0.827
250	6.685	0.834	6.315	-0.041	0.829
300	6.685	0.836	6.315	-0.041	0.831

It is observed from the table 3.2.4.2 that expected number of premalignant cells and variance of number of premalignant cells are invariant of change of initial number of

malignant cells(M_0) when all other parameters are constant. And it is also observed that expected number of malignant cells and variance of malignant cells are increasing functions of initial number of malignant cells (M_0) when all other parameters are constant.

Table 3.2.4.3

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of alpha at the fixed values of other parameters with values N_0=100; M_0=50; β=0.5; γ=0.4; δ=1; t=2; θ=5;

alpha	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
1	6.752	0.83	6.382	-0.041	0.825
1.5	7.087	0.856	6.717	-0.041	0.851
2	7.423	0.882	7.053	-0.041	0.878
2.5	7.758	0.908	7.388	-0.041	0.904
3	8.094	0.934	7.724	-0.041	0.93

From table 3.2.4.3 it is observed that expected number of premalignant cells, expected number of malignant cells variance of premalignant cells and variance of malignant cells are increasing functions of rate of generation of premalignant cells and covariance between premalignant and malignant cells is negative and invariant of rate of generation of premalignant cells (α) when all the other parameters are constant.

Table 3.2.4.4

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of beta at the fixed values of other parameters with values N_0=100; M_0=50; α=0.9; γ=0.4; δ=1; t=2; θ=5;

beta	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.55	6.685	0.835	6.315	-0.041	0.83
0.6	6.685	0.845	6.315	-0.041	0.84
0.65	6.685	0.855	6.315	-0.041	0.85
0.7	6.685	0.865	6.315	-0.041	0.86
0.75	6.685	0.875	6.315	-0.041	0.87

From table 3.2.4.4 it is observed that expected number of premalignant cells and variance of premalignant cells are invariant of rate of generation of malignant cells (β) when all other parameters are constant. It is also observed that expected number of malignant cells and variances of malignant cells are increasing functions of rate of generation of malignant cells (β) when all the other parameters are constant. Further it is observed that covariance between premalignant and malignant cells are negative and invariant of rate of generation of malignant cells.

Table 3.2.4.5

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of gamma at the fixed values of other parameters with values N_0=100; M_0=50; α=0.9; β=0.5; δ=1; t=2; θ=5;

gamma	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.44	6.203	0.846	5.888	-0.039	0.841
0.48	5.758	0.862	5.49	-0.037	0.857
0.52	5.347	0.874	5.118	-0.034	0.869
0.56	4.967	0.881	4.772	-0.032	0.876
0.6	4.616	0.884	4.45	-0.029	0.879

From table 3.2.4.5 it is observed that expected number of premalignant cells and variance of premalignant cells are decreasing functions of rate of transformation to malignant cells from premalignant cells (γ) when all other parameters are constant. It is also observed from table 3.2.4.5 that variance of malignant cells is an increasing function of rate of transformation of malignant cell from premalignant cell (γ) when all other parameters are constant. Further it is observed that covariance between premalignant and malignant cells are negative and increasing with respect to rate of transformation from premalignant cell to malignant cell.

Table 3.2.4.6

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of delta at the fixed values of other parameters with values N_0=100; M_0=50; α=0.9; β=0.5; γ=0.4; t=2; θ=5;

delta	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
1.2	4.616	0.624	4.45	-0.02	0.621
1.3	3.849	0.546	3.738	-0.013	0.545
1.4	3.219	0.482	3.144	-0.01	0.48
1.5	2.7	0.427	2.65	-0.01	0.426
1.6	2.273	0.381	2.24	-0.004	0.38

From table 3.2.4.6 it is observed that the expected numbers of premalignant cells, expected number of malignant cells, variance of premalignant cells and variance of malignant cells are decreasing functions of rate of death of premalignant cells. Also it is observed that covariance between premalignant and malignant cells is negative and increasing with respect to rate of death of premalignant cells.

Table 3.2.4.7

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of teta at the fixed values of other parameters with values N_0=100; M_0=50; α=0.9; β=0.5; γ=0.4; δ=1; t=2;

theta	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
6	6.685	0.652	6.315	-0.032	0.649
7	6.685	0.54	6.315	-0.026	0.538
8	6.685	0.461	6.315	-0.022	0.459
9	6.685	0.402	6.315	-0.019	0.401
10	6.685	0.357	6.315	-0.017	0.356

From table 3.2.4.7 it is observed that expected number of premalignant cells and variance of premalignant cells are invariant of rate of death of malignant cells (θ) when all other parameters are constant. It is also observed that expected number of malignant cells variance of malignant cells are decreasing functions of rate of death

of malignant cells (θ) when all other parameters are constant. Further it is observed that covariance between premalignant and malignant cells are negative and increasing with respect to rate of death of malignant cells when all other parameters are constant.

Table 3.2.4.8

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of 't' at the fixed values of other parameters with values N_0=100; M_0=50; α=0.9; β=0.5; γ=0.4; δ=1; θ=5;

t	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
3	2.133	0.317	2.11	-0.00250	0.317
4	1.01	0.192	1.009	-0.00015	0.192
5	0.733	0.161	0.733	-0.00001	0.161
6	0.665	0.154	0.665	0.00000	0.154
7	0.648	0.152	0.648	0.00000	0.152

From table 3.2.4.8 it is observed that expected number of premalignant cells, expected number of malignant cells and variance of premalignant cells and variance of malignant cells are decreasing functions of time (t) when all other parameters are constant. It is also observed that covariance between premalignant and malignant cells is negative and increasing with respect to change of time 't'.

3.3 STOCHASTIC MODEL DURING CHEMOTHERAPY:

With a similar view of mechanism of previous section 3.2, in this section a two stage stochastic model for cell division in premalignant and malignant cells during the chemotherapy is explained. The following schematic diagram will explain the model behaviour in more detailed lines.

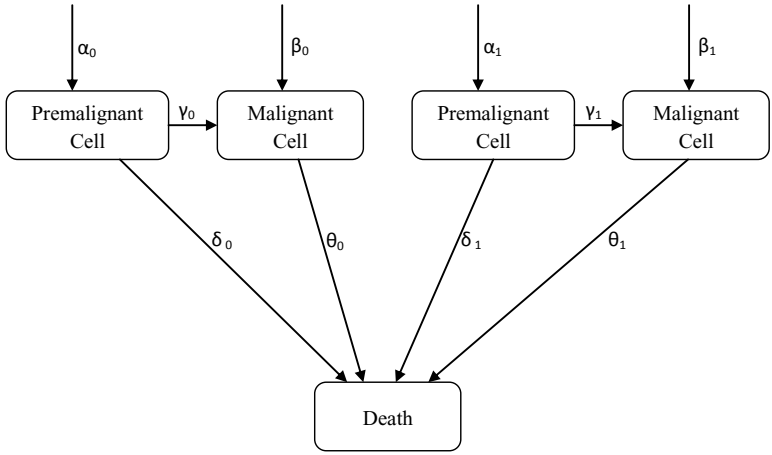

Figure 3.3.1: Schematic diagram of the model

3.3.1 Assumptions and Postulates of the Model:

Let the events occurred in non-overlapping intervals of time are statistically independent. Let Δt be an infinitesimal interval of time. Let there be 'n' premalignant cells and 'm' malignant cells initially at time't'. Let α_0, β_0, γ_0, δ_0, θ_0 respectively be the rate of arrival to pre-malignancy, rate of arrival to malignancy, rate of transformation from pre-malignancy to malignancy, rate of death of premalignant cell without transforming to malignancy, rate of death of malignant cell during the absence of chemotherapy.

Let α_1, β_1, γ_1, δ_1, θ_1 respectively be the rate of arrival to pre-malignancy, rate of arrival to malignancy, rate of transformation from pre-malignancy to malignancy, rate of death of premalignant cell without transforming to malignancy, rate of death of malignant cell during the presence of chemotherapy. Also it is assumed that all the events are Poisson parameters. Further in the previous model we assume that the cell growth of normal and mutant cells are additive in nature irrespective of drug absence or presence. In this section we consider the mutant cell growth during the presence and absence of chemotherapy, in which the growth/loss of rates of mutant cells are a linear/convex combination of its growth/loss rates.

Since α_0, α_1 are the rates of arrival of premalignant cells during the absence and presence of chemotherapy the arrival rate of premalignant cells at time 't' is,

$a\,\alpha_0 + (1-a)\,\alpha_1; 0 \le a \le 1$; Similarly the rate of arrival of malignant cells at time't' is $b\,\beta_0 + (1-b)\,\beta_1;\ 0 \le b \le 1$;The rate of transformation of premalignant cells to malignant cells at time 't' is, $c\,\gamma_0 + (1-c)\gamma_1;\ 0 \le c \le 1$; The rate of death of premalignant cell at time 't' is $d\,\delta_0 + (1-d)\,\delta_1;\ 0 \le d \le 1$; The rate of death of malignant cells at time 't' is, $g\,\theta_0 + (1-g)\,\theta_1;\ 0 \le g \le 1$;

With the above assumptions, the postulates of the model are:

1. The probability of arrival of one premalignant cell during Δt is$(a\,\alpha_0 + (1-a)\,\alpha_1)\Delta t + 0(\Delta t)$
2. The probability of arrival of one malignant cell during Δt is $(b\,\beta_0 + (1-b)\,\beta_1)\,\Delta t + 0(\Delta t)$
3. The probability of transformation of premalignant cell to malignant cell provided there exists 'n' premalignant cells at time't' is $n(c\,\gamma_0 + (1-c)\,\gamma_1)\,\Delta t + 0(\Delta t)$
4. The probability of death of one premalignant cell provided there exists 'n' premalignant cells at time't' is $n(d\,\delta_0 + (1-d)\,\delta_1)\,\Delta t + 0(\Delta t)$
5. The probability of death of one malignant cell provided there exists 'n' malignant cell at time 't' is $m(g\,\theta_0 + (1-g)\,\theta_1)\,\Delta t + 0(\Delta t)$
6. The probability of no arrival of premalignant cell, no arrival of malignant cell, no transformation from pre-malignancy to malignancy, no death of premalignant cell, and no death of malignant cell during an infinitesimal interval of time Δt is

$$1 - [(a\,\alpha_0 + (1-a)\alpha_1 + b\,\beta_0 + (1-b)\beta_1) + n[c\,\gamma_0 + (1-c)\gamma_1 + d\,\delta_0 + (1-d)\delta_1] + m(g\,\theta_0 + (1-g)\,\theta_1)]\Delta t + 0(\Delta t)$$

7. The probability of occurrence of other than the above events during an infinitesimal interval of time Δt is $0(\Delta t)^2$

3.3.2 The Difference-Differential Equations of the Model:

Let $p_{n,m}(t)$ be the joint probability of existing of 'n' premalignant cells and 'm' malignant cells in a tumor during chemotherapy per unit time't'. Then the difference-differential equations of the model are:

$$p'_{n,m}(t) = [(a\,\alpha_0 + (1-a)\alpha_1 + b\,\beta_0 + (1-b)\beta_1) + n(c\,\gamma_0 + (1-c)\gamma_1 + d\,\delta_0 + (1-d)\delta_1) + m(g\,\theta_0 + (1-g)\theta_1)](-1)p_{n,m}(t) + [a\,\alpha_0 + (1-a)\alpha_1]p_{n-1,m}(t) + (n+1)[d\,\delta_0 + (1-d)\delta_1]p_{n+1,m}(t) + (n+1)[c\,\gamma_0 + (1-c)\gamma_1]p_{n+1,m-1}(t) + [b\,\beta_0 + (1-b)\beta_1]p_{n,m-1}(t) + (m+1)[g\,\theta_0 + (1-g)\theta_1]p_{n,m+1}(t)$$ for n,m≥1 … (3.3.2.1)

$$p'_{1,0}(t) = [(a\,\alpha_0 + (1-a)\alpha_1 + b\,\beta_0 + (1-b)\beta_1 + c\,\gamma_0 + (1-c)\gamma_1 + d\,\delta_0 + (1-d)\delta_1)](-1)p_{1,0}(t) + [a\,\alpha_0 + (1-a)\alpha_1]p_{0,0}(t) + 2[d\,\delta_0 + (1-d)\delta_1]p_{2,0}(t) + [g\,\theta_0 + (1-g)\theta_1]p_{1,1}(t)$$ …(3.3.2.2)

$$p'_{0,1}(t) = [a\,\alpha_0 + (1-a)\alpha_1 + b\,\beta_0 + (1-b)\beta_1 + g\,\theta_0 + (1-g)\theta\delta_1](-1)p_{0,1}(t) + [d\,\delta_0 + (1-d)\delta_1]p_{1,1}(t) + [c\,\gamma_0 + (1-c)\gamma_1]p_{1,0}(t) + (b\,\beta_0 + (1-b)\beta_1)p_{0,0}(t) + 2[g\,\theta_0 + (1-g)\theta_1]p_{0,2}(t)$$ ... (3.3.2.3)

$$p'_{0,0}(t) = [a\,\alpha_0 + (1-a)\alpha_1 + b\,\beta_0 + (1-b)\beta_1](-1)p_{0,0}(t) + [d\,\delta_0 + (1-d)\delta_1]p_{1,0}(t) + [g\,\theta_0 + (1-g)\theta_1]p_{0,1}(t)$$ ... (3.3.2.4)

With the initial conditions

$p_{N_0,M_0}(0) = 1, \qquad p_{N_0,M_0}(t) = 0$

Where N_0, M_0 are the initial sizes of premalignant and malignant cells in the tumor during chemotherapy.

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

Where $$p(x,y;t) = \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} x^n y^m\, p_{n,m}(t)$$ ... (3.3.2.5)

Multiplying the equations (3.3.3.1) to (3.3.3.4) with $x^n y^m$ and summing overall m and n we have

$$\sum_{m=0}^{\infty}\sum_{n=0}^{\infty} x^n y^m \, p'_{n,m}(t)$$

$$= \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} [(\, a\, \alpha_0 + (1-a)\alpha_1 + b\, \beta_0 + (1-b)\beta_1) + \, n[c\, \gamma_0$$
$$+ (1-c)\gamma_1 + d\, \delta_0 + (1-d)\delta_1] + m[g\, \theta_0$$
$$+ (1-g)\theta_1]](-1)x^n y^m \, p_{n,m}(t)$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} [a\, \alpha_0 + (1-a)\alpha_1]x^n y^m \, p_{n-1,m}(t)$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (n+1)[d\, \delta_0 + (1-d)\delta_1]x^n y^m \, p_{n+1,m}(t)$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (n+1)[c\, \gamma_0 + (1-c)\gamma_1]x^n y^m \, p_{n+1,m-1}(t)$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} [b\, \beta_0 + (1-b)\beta_1]x^n y^m \, p_{n,m-1}(t)$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (m+1)[g\, \theta_0 + (1-g)\theta_1]x^n y^m \, p_{n,m+1}(t) \quad \ldots (3.3.2.6)$$

Simplifying and rearranging the terms in the equation 3.3.2.6, we get

$$\frac{\partial}{\partial t}p(x,y;t) = [(a\, \alpha_0 + (1-a)\alpha_1)(x-1)$$
$$+ (b\, \beta_0 + (1-b)\beta_1)(y-1)]\, p(x,y;t)$$
$$+ [-(c\, \gamma_0 + (1-c)\gamma_1 + d\, \delta_0 + (1-d)\delta_1)x$$
$$+ (\, c\, \gamma_0 + (1-c)\gamma_1)y + (d\, \delta_0 + (1-d)\delta_1)]\frac{\partial p}{\partial x}$$
$$+ [(\, g\, \theta_0 + (1-g)\theta_1)(1-y)]\frac{\partial}{\partial y}p(x,y;t) \quad \ldots (3.3.2.7)$$

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), we obtain the following:

$$\frac{\partial}{\partial t}k(u,v;t) = [-(c\,\gamma_0 + (1-c)\gamma_1 + d\,\delta_0 + (1-d)\delta_1)$$
$$+ (\,c\,\gamma_0 + (1-c)\gamma_1) + e^{-u+v} + (d\,\delta_0 + (1-d)\delta_1)e^{-u}\,]\frac{\partial k}{\partial u}$$
$$+ [(\,g\,\theta_0 + (1-g)\theta_1)\,(e^{-v} - 1)]\frac{\partial k}{\partial v}$$
$$+[(a\,\alpha_0 + (1-a)\alpha_1)\,(e^{u} - 1)$$
$$+ (b\,\beta_0 + (1-b)\beta_1)\;(e^{v} - 1)\,]k(u,v;t) \qquad \ldots (3.3.2.8)$$

3.3.3 Differential Equations and Statistical Measures of the Model:

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

$$\frac{\partial}{\partial t}m_{1,0}(t) = (c\,\gamma_0 + (1-c)\gamma_1 + d\,\delta_0 + (1-d)\delta_1)(-1)m_{1,0}(t)$$
$$+ a\,\alpha_0 + (1-a)\alpha_1 \qquad \ldots (3.3.3.1)$$
$$\frac{\partial}{\partial t}m_{0,1}(t) = (\,c\,\gamma_0 + (1-c)\gamma_1)m_{1,0}(t) - (\,g\,\theta_0 + (1-g)\theta_1)\,m_{0,1}(t)$$
$$+b\,\beta_0 + (1-b)\beta_1 \qquad \ldots (3.3.3.2)$$
$$\frac{\partial}{\partial t}m_{2,0}(t) = (d\,\delta_0 + (1-d)\delta_1 + c\,\gamma_0 + (1-c)\gamma_1)m_{1,0}$$
$$-2(d\,\delta_0 + (1-d)\delta_1 + c\,\gamma_0 + (1-c)\gamma_1)m_{2,0}(t)$$
$$+a\,\alpha_0 + (1-a)\alpha_1 \qquad \ldots (3.3.3.3)$$
$$\frac{\partial}{\partial t}m_{1,1}(t) = (c\,\gamma_0 + (1-c)\gamma_1)(-1)m_{1,0}(t) + (c\,\gamma_0 + (1-c)\gamma_1)m_{2,0}(t)$$
$$-[\,d\,\delta_0 + (1-d)\delta_1 + c\,\gamma_0 + (1-c)\gamma_1 + g\,\theta_0 +$$
$$(1-g)\theta_1]m_{1,1}(t) \qquad \ldots (3.3.3.4)$$
$$\frac{\partial}{\partial t}m_{0,2}(t) = (c\,\gamma_0 + (1-c)\gamma_1)m_{1,0}(t) + 2(c\,\gamma_0 + (1-c)\gamma_1)m_{1,1}(t)$$
$$+(g\,\theta_0 + (1-g)\theta_1)m_{0,1}(t) - 2(g\,\theta_0 + (1-g)\theta_1)m_{0,2}(t)$$
$$+b\,\beta_0 + (1-b)\beta_1 \qquad \ldots (3.3.3.5)$$

Solving the differential equations from 3.3.3.1 to 3.3.3.5 we get

Expected number of premalignant cells during chemotherapy at time‘t’ is

$$m_{1,0}(t) = \frac{a\,\alpha_0 + (1-a)\alpha_1}{c\,\gamma_0 + (1-c)\gamma_1 + d\,\delta_0 + (1-d)\delta_1} \times \left[1 - e^{-(c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1)t}\right] + N_0\, e^{-(c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1)t} \quad \ldots (3.3.3.6)$$

Expected number of malignant cells during chemotherapy at time‘t’ is

$$m_{0,1}(t) = \frac{[a\,\alpha_0 + (1-a)\alpha_1][c\,\gamma_0 + (1-c)\gamma_1]}{c\,\gamma_0 + (1-c)\gamma_1 + d\,\delta_0 + (1-d)\delta_1} \times \left[\frac{1 - e^{-(g\,\theta_0+(1-g)\theta_1)t}}{g\,\theta_0 + (1-g)\theta_1} + \frac{e^{-(c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1)t} - e^{-(g\,\theta_0+(1-g)\theta_1)t}}{c\,\gamma_0 + (1-c)\gamma_1 + d\,\delta_0 + (1-d)\delta_1 - g\,\theta_0 - (1-g)\theta_1}\right] - \frac{N_0[c\,\gamma_0 + (1-c)\gamma_1]}{c\,\gamma_0 + (1-c)\gamma_1 + d\,\delta_0 + (1-d)\delta_1 - g\,\theta_0 - (1-g)\theta_1}$$

$$\times \left[e^{-(c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1)t} - e^{-(g\,\theta_0+(1-g)\theta_1)t}\right] + \frac{b\,\beta_0 + (1-b)\beta_1}{g\,\theta_0 + (1-g)\theta_1}\left[1 - e^{-(g\,\theta_0+(1-g)\theta_1)t}\right] + M_0\, e^{-(g\,\theta_0+(1-g)\theta_1)t} \quad \ldots (3.3.3.7)$$

Variance of premalignant cells during chemotherapy at time‘t’ is

$$m_{2,0}(t) = \frac{a\,\alpha_0 + (1-a)\alpha_1}{d\,\delta_0 + (1-d)\delta_1 + c\,\gamma_0 + (1-c)\gamma_1} \times \left[1 - e^{-(c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1)t}\right] + N_0\, e^{-(c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1)t} \times \left[1 - e^{-(c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1)t}\right] \quad \ldots (3.3.3.8)$$

Covariance between premalignant and malignant cells during chemotherapy at time‘t’ is

$$m_{1,1}(t) = \frac{[c\,\gamma_0 + (1-c)\gamma_1]N_0}{c\,\gamma_0 + (1-c)\gamma_1 + d\,\delta_0 + (1-d)\delta_1 - g\,\theta_0 - (1-g)\theta_1} \times$$

$$\left[e^{-2[c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1]t} - e^{-[g\,\theta_0+(1-g)\theta_1+c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1]t} \right] \quad \ldots (3.3.3.9)$$

Variance of malignant cells during chemotherapy at time‘t’ is

$$m_{0,2}(t)$$

$$= \frac{(a\,\alpha_0 + (1-a)\alpha_1)(c\,\gamma_0 + (1-c)\gamma_1)}{[g\,\theta_0 + (1-g)\theta_1][c\,\gamma_0 + (1-c)\gamma_1 + d\,\delta_0 + (1-d)\delta_1 - g\,\theta_0 - (1-g)\theta_1]}$$

$$\times \left[1 - e^{-(g\,\theta_0+(1-g)\theta_1)t}\right] + \frac{(a\,\alpha_0 + (1-a)\alpha_1)(c\,\gamma_0 + (1-c)\gamma_1)}{c\,\gamma_0 + (1-c)\gamma_1 + d\,\delta_0 + (1-d)\delta_1}$$

$$\times \frac{e^{-(c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1)t} - 1}{c\,\gamma_0 + (1-c)\gamma_1 + d\,\delta_0 + (1-d)\delta_1 - g\,\theta_0 - (1-g)\theta_1}$$

$$+ \frac{(c\,\gamma_0 + (1-c)\gamma_1)N_0}{c\,\gamma_0 + (1-c)\gamma_1 + d\,\delta_0 + (1-d)\delta_1 - g\,\theta_0 - (1-g)\theta_1}$$

$$\times \left[e^{-(g\,\theta_0+(1-g)\theta_1)t} - e^{-(c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1)t} \right]$$

$$+ \frac{(c\,\gamma_0+(1-c)\gamma_1)^2 N_0}{(c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1-g\,\theta_0-(1-g)\theta_1)^2}$$

$$\times \left[2e^{-(g\,\theta_0+(1-g)\theta_1+c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1)t} - e^{-2(c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1)t} - e^{-2(g\,\theta_0+(1-g)\theta_1)t} \right]$$

$$+ \frac{b\,\beta_0 + (1-b)\beta_1}{g\,\theta_0 + (1-g)\theta_1}\left[1 - e^{-(g\,\theta_0+(1-g)\theta_1)t}\right]$$

$$+ M_0\, e^{-(g\,\theta_0+(1-g)\theta_1)t}\left[1 - e^{-(g\,\theta_0+(1-g)\theta_1)t}\right] \quad \ldots(3.3.3.10)$$

3.3.4 Numerical Illustration and Sensitivity Analysis:

From equations (3.3.3.6), (3.3.3.7), (3.3.3.8), (3.3.3.9) and (3.3.3.10) the values of $m_{1,0}(t), m_{0,1}(t), m_{2,0}(t), m_{1,1}(t)$ and $m_{0,2}(t)$are computed for various values of the parameters and presented in the tables from (3.3.4.1) to (3.3.4.13)

Table 3.3.4.1

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of $\alpha 0$ at the fixed values of other parameters with values N_0 =100; M_0= 50; β_0 = 0.6; γ_0= 0.9; δ_0= 0.3; θ_0= 0.8; α_1 = 0.4; β_1 = 0.4; γ_1= 0.1; δ_1= 0.7; θ_1= 0.9; t=5

α_0	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
1	1.811	2.969	1.796	-0.02	79.218
1.5	1.924	3	1.909	-0.02	82.204
2	2.036	3.032	2.021	-0.02	85.19
2.5	2.148	3.064	2.133	-0.02	88.177
3	2.26	3.095	2.245	-0.02	91.163

Table 3.3.4.2

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of $\alpha 1$ at the fixed values of other parameters with values N_0 =100; M_0= 50; α_0 = 0.9; β_0 = 0.6 ; γ_0= 0.9 ; δ_0= 0.3; θ_0= 0.8 ; β_1 = 0.4 ; γ_1= 0.1 ; δ_1= 0.7; θ_1= 0.9; t=5

α_1	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.45	1.834	2.975	1.819	-0.02	79.815
0.5	1.879	2.988	1.864	-0.02	81.01
0.55	1.924	3	1.909	-0.02	82.204
0.6	1.969	3.013	1.953	-0.02	83.399
0.65	2.013	3.026	1.998	-0.02	84.593

From table 3.3.4.1 and 3.3.4.2 it is observed that expected number of premalignant cells and malignant cells; variance of premalignant cells and variance of malignant cells are increasing functions of arrival rate of premalignant cells under the absence of drug (α_0) and the presence of drug (α_1) when all other parameter are constant. Further it is observed that covariance between premalignant and malignant cells is invariant of arrival rate of premalignant cells under the absence of drug (α_0) and under the presence of drug (α_1) when all other parameters are constant.

Table 3.3.4.3

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of β_0 at the fixed values of other parameters with values N_0 =100; M_0= 50; α_0 = 0.9; γ_0= 0.9; δ_0= 0.3; θ_0= 0.8; α_1 = 0.4; β_1 = 0.4; γ_1= 0.1; δ_1= 0.7; θ_1= 0.9; t=5

β_0	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.7	1.789	2.996	1.774	-0.02	78.655
0.8	1.789	3.03	1.774	-0.02	78.689
0.9	1.789	3.064	1.774	-0.02	78.723
1	1.789	3.098	1.774	-0.02	78.757
2	1.789	3.439	1.774	-0.02	79.097

Table 3.3.4.4

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of β_1 at the fixed values of other parameters with values N_0 =100; M_0= 50; α_0 = 0.9; β_0=0.6; γ_0=0.9; δ_0=0.3; θ_0= 0.8; α_1=0.4; γ_1=0.1; δ_1=0.7; θ_1=0.9; t=5

β_1	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.6	1.789	3.121	1.774	-0.02	78.78
0.8	1.789	3.28	1.774	-0.02	78.938
1	1.789	3.439	1.774	-0.02	79.097
1.2	1.789	3.598	1.774	-0.02	79.256
1.4	1.789	3.756	1.774	-0.02	79.415

From table 3.3.4.3 and 3.3.4.4 it is observed that expected number of premalignant cells, variance of premalignant cells and covariance between premalignant and malignant cells are invariant of arrival rate of malignant cells under the presence of drug (β_1) and the absence of drug (β_0) when all other parameters are constant. It is also observed that expected number of malignant cells and variance of malignant cells are increasing functions of arrival rate of malignant cells under absence of drug (β_0) and presence of drug(β_1) when all other parameters are constants.

Table 3.3.4.5

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of γ_0 at the fixed values of other parameters with values N_0 =100; M_0= 50; α_0 = 0.9; β_0 = 0.6; δ_0= 0.3; θ_0= 0.8; α_1 = 0.4; β_1 = 0.4; γ_1= 0.1; δ_1= 0.7; θ_1= 0.9; t=5

γ_0	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
1	1.66	3.012	1.648	-0.019	69.963
1.5	1.17	3.177	1.166	-0.012	65.511
2	0.861	3.247	0.86	-0.01	64.047
2.5	0.664	3.267	0.663	-0.005	63.076
3	0.534	3.26	0.534	-0.003	62.402

Table 3.3.4.6

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of γ_1 at the fixed values of other parameters with values N_0=100; M_0=50; α_0=0.9; β_0=0.6; γ_0=0.9; δ_0=0.3; θ_0=0.8; α_1= 0.4; β_1= 0.4; δ_1=0.7; θ_1=0.9; t=5

γ_1	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.4	0.815	3.254	0.813	-0.007	63.823
0.45	0.732	3.263	0.732	-0.006	63.422
0.5	0.664	3.267	0.663	-0.005	63.076
0.55	0.605	3.266	0.605	-0.004	62.776
0.6	0.556	3.263	0.556	-0.003	62.518

From tables 3.3.4.5 and 3.3.4.6 it is observed that expected number of premalignant cells, variance of pre malignant cells; variance of malignant cells are decreasing functions of rate of transformation of premalignant cells to malignant cells during the drug absence (γ_0) and the presence of the drug (γ_1) when all the other parameters are constant. Also it is observed that covariance between premalignant cells and malignant cells & expected number of malignant cells are increasing functions of rate of transformation of malignant cells from premalignant cells during the absence of drug(γ_0) and also during the presence of drug (γ_1) when all the other parameters are constants.

Table 3.3.4.7

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of δ_0 at the fixed values of other parameters with values N_0 =100; M_0= 50; α_0 = 0.9; β_0 = 0.6; γ_0= 0.9 ; θ_0= 0.8; α_1 = 0.4; β_1 = 0.4; γ_1= 0.1; δ_1= 0.7; θ_1= 0.9; t=5

δ_0	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.32	1.762	2.945	1.748	-0.02	72.25
0.36	1.71	2.913	1.697	-0.018	66.498
0.4	1.66	2.881	1.648	-0.017	63.85
0.44	1.612	2.849	1.601	-0.016	62.344
0.48	1.566	2.819	1.555	-0.015	61.384

Table 3.3.4.8

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of δ_1 at the fixed values of other parameters with values N_0 =100; M_0= 50; α_0 = 0.9; β_0 = 0.6; γ_0= 0.9; δ_0= 0.3; θ_0= 0.8; α_1 = 0.4; β_1 = 0.4; δ_1= 0.7; θ_1= 0.9; t=5

δ_1	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.75	1.543	2.804	1.533	-0.015	61.027
0.8	1.34	2.665	1.333	-0.011	59.335
0.85	1.17	2.542	1.166	-0.008	58.832
0.9	1.03	2.434	1.027	-0.006	58.657
0.95	0.913	2.338	0.91	-0.005	58.607

From tables 3.3.4.7 and 3.3.4.8 it is observed that expected number of premalignant cells and expected number of malignant cells, variance of premalignant and malignant cells are decreasing functions and covariance between premalignant and malignant cells is negative and decreasing function of rate of death of premalignant cells under absence of drug (δ_0) and presence of drug (δ_1) when all other parameters are constants.

Table 3.3.4.9

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of θ_0 at the fixed values of other parameters with values N_0 =100; M_0= 50; α_0 = 0.9; β_0 = 0.6; γ_0= 0.9 ; δ_0= 0.3; α_1 = 0.4; β_1 = 0.4; γ_1= 0.1; δ_1= 0.7; θ_1= 0.9; t=5

θ_0	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.82	1.789	2.914	1.774	-0.02	94.639
0.84	1.789	2.867	1.774	-0.019	3.507
0.86	1.789	2.822	1.774	-0.019	46.432
0.88	1.789	2.777	1.774	-0.019	51.12
0.9	1.789	2.733	1.774	-0.019	52.028

Table 3.3.4.10

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of θ_1 at the fixed values of other parameters with values N_0 =100; M_0= 50; α_0 = 0.9; β_0 = 0.6; γ_0= 0.9; δ_0= 0.3; θ_0= 0.8; α_1 = 0.4; β_1 = 0.4; γ_1= 0.1; δ_1= 0.7; t=5

θ_1	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
0.93	1.789	2.799	1.774	-0.02	27.326
0.94	1.789	2.748	1.774	-0.019	33.701
0.95	1.789	2.698	1.774	-0.018	35.469
0.96	1.789	2.649	1.774	-0.018	35.689
0.97	1.789	2.602	1.774	-0.018	35.225

From tables 3.3.4.9 and 3.3.4.10 it is observed that expected number and variance of premalignant cells are invariant. Expected number of malignant cells is decreasing function and variance of malignant cells is increasing function of rate of death of malignant cells under absence of drug (θ_0) and presence of drug (θ_1) when all other parameters are constants.

Table 3.3.4.11

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of N_0 at the fixed values of other parameters with values M_0= 50; α_0 = 0.9; β_0 = 0.6; γ_0= 0.9; δ_0= 0.3; θ_0= 0.8; α_1 = 0.4; β_1 = 0.4; γ_1= 0.1; δ_1= 0.7; θ_1= 0.9; t=5

N_0	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
102	1.813	2.995	1.798	-0.02	80.983
103	1.826	3.011	1.81	-0.021	82.163
104	1.838	3.028	1.822	-0.021	83.344
105	1.85	3.044	1.834	-0.021	84.525
106	1.863	3.06	1.847	-0.021	85.706

It is observed from table 3.3.4.11 that expected number of premalignant cells and expected number of malignant cells , variance of premalignant cells and malignant cells are increasing functions and covariance between premalignant and malignant cells is invariant of change of initial number of pre malignant cells (N_0) when all other parameters are constants.

Table 3.3.4.12

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of M_0 at the fixed values of other parameters with values N_0 =100; α_0 = 0.9; β_0 = 0.6; γ_0= 0.9; δ_0= 0.3; θ_0= 0.8; α_1 = 0.4; β_1 = 0.4; γ_1= 0.1; δ_1= 0.7; θ_1= 0.9; t=5

M_0	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
55	1.789	3.027	1.774	-0.02	84.493
60	1.789	3.091	1.774	-0.02	90.366
65	1.789	3.156	1.774	-0.02	96.239
70	1.789	3.22	1.774	-0.02	102.111
75	1.789	3.285	1.774	-0.02	107.984

From table 3.3.4.12 it is observed that expected number of premalignant cells; variance of premalignant cells and covariance between premalignant and malignant cells are invariant of change of initial number of malignant cells (M_0) when all other parameters are constant. Further it is observed that expected number of and variance of malignant cells are increasing functions of initial number of malignant cells (M_0) when all other parameters are constants.

Table 3.3.4.13

Values of $m_{1,0}$, $m_{1,0}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varying values of 't' at the fixed values of other parameters with values N_0 =100; M_0= 50; α_0 = 0.9; β_0 = 0.6; γ_0= 0.9; δ_0= 0.3; θ_0= 0.8; α_1 = 0.4; β_1 = 0.4; γ_1= 0.1; δ_1= 0.7; θ_1= 0.9; t=5

t	$m_{1,0}$	$m_{0,1}$	$m_{2,0}$	$m_{1,1}$	$m_{0,2}$
4.3	2.828	4.451	2.777	-0.059	176.026
4	3.511	5.34	3.424	-0.093	234.286
3.3	6.017	8.245	5.717	-0.262	428.378
3	7.664	9.942	7.155	-0.403	545.672
2.3	13.706	15.311	11.96	-1.056	938.608

From table 3.3.4.13 it is observed that expected number of premalignant cells, expected number of malignant cells, variance of premalignant cells and variance of malignant cells are increasing functions of time't' when all the other parameters are constants and covariance between of premalignant cells and malignant cells is decreasing function of time't' when all the other parameters are constants.

Chapter – 4

STOCHASTIC PROGRAMMING PROBLEM FOR OPTIMAL DRUG ADMINISTRATION DURING CHEMOTHERAPY

4.1: INTRODUCTION:

Stochastic models for cancer cell growth with spontaneous mutation and proliferation are developed in chapter 2. The model also considered the behaviour of cancer cell growth under chemotherapy environment for drug administration and drug vacation periods. A two stage stochastic model for cancer cell growth when a mutant cell has transformation of premalignant and malignant cells is developed in chapter 3. An extension model is developed for two stage cancer growth when the patient is under chemotherapy. The statistical measures like average number and variance number of different kinds of cells are derived in both the models.

Usually the drug administration for cancer treatment can be done with the chemotherapy, in which the treatment consisting of induced chemicals to kill cancer cells. In practice the drug may target the normal cells and leads to loss of white blood cells. Hence continuous drug administration to a cancer patient may give adverse effects by developing health hazards due to heavy loss of white blood cells. Therefore the patient may be allowed to drug vacation. During this period he will get recovery from health hazards due to the toxicity of the chemicals. But there is a problem of re-aggravating the cancer causing cells.

Both continuous drug administration and continuous drug vacation for long time are unwanted and hence threshold limits for minimum and maximum times for drug administration and drug vacation are very essential. Similarly the drug dosage levels less than the minimum required quantity and above the maximum required quantity are also harmful as the first case leads to drug resistance and the second case leads to loss of WBC. And hence threshold limits for minimum and maximum quantity of the drug has to be administered. The conventional method of chemotherapy consists of drug is administered in spells and different units of drug dosage is administered within each spell. For example there may be two to three times of drug administration per day and at each time there may be two to three tablets (units of

drug) are consumed. This sort of drug usage may be continued for successive days as per the baring abilities of the patient. And hence it is observed that two to three tablets per time; two to three times per day and consecutive days per spell of drug administration in the procedure of chemotherapy. Similarly the drug vacation also includes one to two units of vacation times per day; number of drug vacation days per spell and number of spells of drug vacation per cycle during the total period of chemotherapy.

The very important aspect of the treatment with chemotherapy is to evaluate the health status of the patient during the period of the treatment. Most often the count of white blood cells, the desired upper and lower limits of it have to be assessed thoroughly. Similarly it is always a good practice to estimate the number of normal cells, the number of mutant cells, the number of premalignant cells and also the number of malignant cells per unit time 't' in a tumor. The developed models mentioned in the previous chapters will help in understanding the above mentioned. Using all these, a stochastic programming problem for optimal designing of drug administration is formulated. An objective function is formulated to maximize the drug efficacy. The constraints with desired levels of upper and lower limits of normal cells, mutant cells, limits of WBC etc, are developed.

The decision variables like the rates of arrivals of normal and mutant cells, death rates from the normal and mutant cells etc. can be obtained with developed stochastic programming problem. In this chapter an optimization stochastic programming problem is developed to explore the parameters / decision variables like growth rates, death rates and the rate of transformation from one stage to another stage. The aspects like number of units of drug per spell, number of spells of drug administration per cycle, number of cycles for drug administration in a chemotherapy, number of time units per unit of vacation, number of days in a drug vacation, number of drug vacations during the total chemotherapy period are considered in developing the objective function as well as constraints. Further the statistical measures obtained through the developed stochastic models such as average number of normal and mutant cells in drug absence and drug presence are considered. These models will be helpful in development of optimal decision support systems, for health care industry.

4.2: PROGRAMMING PROBLEM FOR OPTIMAL DRUG ADMINISTRATION FOR NORMAL AND MUTANT CELLS:

4.2.1: Formulation of objective function:

Let 'c_{ij}'be the positive effectiveness of one unit of drug on one normal cell during i^{th}cycle and j^{th}spell of drug administration, where i = 1, 2,…l, the number of cycles; and j = 1, 2,..., k, the number of spells. Let a_{ij} be the number of units of drug doses given in i^{th} cycle and j^{th} spell on one normal cell. Which implies the impact of a_{ij} units of drug on one normal cell is $a_{ij} \cdot c_{ij}$. Therefore the total positive impact of drug during 'l' cycles and 'k' spells on one normal cell is

$$TPAN = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \cdot c_{ij} \quad \ldots (4.2.1.1)$$

Hence total positive impact of drug during 'l' cycles and 'k' spells on average number of normal cells at time 't' is

$$E(TPAN) = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \cdot c_{ij} \, \mathrm{E}(N_A) \quad \ldots (4.2.1.2)$$

Where E (N_A) is the average number of normal cells during drug administration at time't', obtained from the equation (2.3.3.6) assuming $a_0 = d_0 = 0$.

Let d_{ij} be the negative effectiveness of one unit of drug on one normal cell during i^{th} cycle and j^{th} spell of its administration. Then negative impact of a_{ij} units of drug on one normal cell is $a_{ij} \cdot d_{ij}$. Therefore the total negative impact of drug during 'l' cycles and 'k' spells on one normal cell is

$$TNAN = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \cdot d_{ij} \quad \ldots (4.2.1.3)$$

Hence total negative impact of drug during 'l' cycles and 'k' spells on average number of normal cells at time't' is

$$E(TNAN) = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \cdot d_{ij} \cdot \mathrm{E}(N_A) \quad \ldots (4.2.1.4)$$

Let Z_1 denotes the net effect of drug administration on average number of normal cells at time 't', then

$$Z_1 = \left(\sum_{i=1}^{l} \sum_{j=1}^{k} a_{ij} \, . c_{ij} - \sum_{i=1}^{l} \sum_{j=1}^{k} a_{ij} \, . d_{ij} \right) \mathrm{E}(N_A)$$

which implies

$$Z_1 = \sum_{i=1}^{l} \sum_{j=1}^{k} a_{ij} \left(c_{ij} - d_{ij} \right) . \mathrm{E}\,(N_A) \qquad \ldots (4.2.1.5)$$

Therefore $Z_1 = \mathrm{P} . \mathrm{E}\,(N_A)$; $\mathrm{P} \geq 0$; where

$$\mathrm{P} = \sum_{i=1}^{l} \sum_{j=1}^{k} a_{ij} \left(c_{ij} - d_{ij} \right) \qquad \ldots (4.2.1.6)$$

Let $'b_{ij}'$ be the positive effectiveness of one unit of drug on one mutant cell (i.e., killing of mutant cell) during i^{th} cycle and j^{th}spell of its administration. Then positive impact of a_{ij} units of drug on one mutant cell is $a_{ij} \, . \, b_{ij}$. Therefore total positive impact of drug during 'l' cycles and 'k' spells on one mutant cell is

$$TPAM = \sum_{i=1}^{l} \sum_{j=1}^{k} a_{ij} \, . b_{ij} \qquad \ldots (4.2.1.7)$$

Hence positive impact of drug during 'l' cycles and 'k' spells on average number of mutant cells at a time't' is

$$E(TPAM) = \sum_{i=1}^{l} \sum_{j=1}^{k} a_{ij} \, . b_{ij} \, . \mathrm{E}(M_A) \qquad \ldots (4.2.1.8)$$

where $E(M_A)$ is the average number of mutant cells during drug administration at time't', obtained from the equation (2.3.3.8), assuming $b_0=a_0=d_0=g_0=c_0=0$

Let f_{ij} be the negative impact of one unit of drug administration on one mutant cell during i^{th} cycle and j^{th} spell of its administration. Then negative impact of a_{ij} units of drug on one mutant cell is $a_{ij} \, . \, f_{ij}$. Therefore the total negative impact of drug during 'l' cycles and 'k' spells on one mutant cell is

$$TNAM = \sum_{i=1}^{l} \sum_{j=1}^{k} a_{ij} \, . f_{ij} \qquad \ldots (4.2.1.9)$$

Hence total negative impact of drug during 'l' cycles and 'k' spells on average number of mutant cells at a time't' is

$$E(TNAM) = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \ . f_{ij} \ \mathrm{E}\ (M_A) \qquad \ldots (4.2.1.10)$$

Let Z_2 denotes the net effect of drug administration on average number of mutant cells at time't' then

$$Z_2 = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \ . (b_{ij} - f_{ij})\mathrm{E}\ (M_A) \qquad \ldots (4.2.1.11)$$

Hence $Z_2 = \mathrm{Q}.\ \mathrm{E}\ (M_A)$, $\mathrm{Q} \geq 0$;

where $$\mathrm{Q} = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \ . (b_{ij} - f_{ij}) \qquad \ldots (4.2.1.12)$$

Let $'x_{rs}'$ be the positive impact of drug vacation per unit time on s^{th} day of r^{th} cycle on one normal cell where r= 1, 2,…l-1, the number of drug vacation cycles, s= 1, 2,…, n, the number of days in a vacation cycle. Let m_{rs} be the number of time units of drug vacation in s^{th} day of r^{th} cycle. Then positive impact of m_{rs} time units of drug vacation on one normal cell is $x_{rs}.m_{rs}$. The total positive impact of drug vacation on one normal cell during m_{rs} time units in s^{th} day of r^{th} cycle is

$$TPVN = \sum_{r=1}^{l-1}\sum_{s=1}^{n} x_{rs}\,.m_{rs} \qquad \ldots (4.2.1.13)$$

Which implies total positive impact of drug vacation on average number of normal cells during m_{rs} time units in r cycles and s number of days at time't' is

$$E(TPVN) = \sum_{r=1}^{l-1}\sum_{s=1}^{n} x_{rs}\,.m_{rs}\,.\mathrm{E}\ (N_V) \qquad \ldots (4.2.1.14)$$

Where E (N_V) denote the average number of normal cells during the drug vacation, obtained from the equation (2.3.3.6), by assuming a_1=d_1=0

Let 'y_{rs}' be the negative impact of drug vacation on one normal cell during s^{th} day of r^{th} cycle. Which implies negative impact of drug vacation on one normal cell is $y_{rs}.m_{rs}$. Then total negative impact of drug vacation on one normal cell during m_{rs} time units of r cycles and s number of days is

$$TNVN = \sum_{r=1}^{l-1}\sum_{s=1}^{n} y_{rs} \,.\, m_{rs} \qquad \ldots (4.2.1.15)$$

Therefore total negative impact of drug vacation on average number of normal cells during m_{rs} time units of r cycles and s number of days is

$$E(TNVN) = \sum_{r=1}^{l-1}\sum_{s=1}^{n} y_{rs} \,.\, m_{rs} \,..\, \mathrm{E}\,(N_V) \qquad \ldots (4.2.1.16)$$

Let Z_3 denote the net impact factor of drug vacation on average number of normal cell during m_{rs} time units of r cycles and s number of days, then

$$Z_3 = \left(\sum_{r=1}^{l-1}\sum_{s=1}^{n} (x_{rs} - y_{rs}) \,.\, m_{rs}\right) \mathrm{E}\,(N_V) \qquad \ldots (4.2.1.17)$$

Which implies Z_3= R. E (N_V); R≥0

Where $$\mathrm{R} = \sum_{r=1}^{l-1}\sum_{s=1}^{n} (x_{rs} - y_{rs}) \,.\, m_{rs} \qquad \ldots (4.2.1.18)$$

Let p_{rs} be the positive impact of drug vacation on one mutant cell during s^{th} day of r^{th} cycle. Then positive impact of m_{rs} time units of drug vacation on one mutant cell is $p_{rs} . m_{rs}$ Hence total positive impact of drug vacation on one mutant cell during m_{rs} time units in s^{th} day of r^{th} cycle is

$$TPVM = \sum_{r=1}^{l-1}\sum_{s=1}^{n} p_{rs} \,.\, m_{rs} \qquad \ldots (4.2.1.19)$$

The total positive impact of drug vacation on one mutant cell during m_{rs} time units of r cycles and s number of days is

$$E(TPVM) = \sum_{r=1}^{l-1}\sum_{s=1}^{n} p_{rs} \,.\, m_{rs}.\ \mathrm{E}(M_V) \qquad \ldots (4.2.1.20)$$

Where E(M_v) denote the average number of mutant cells during drug vacation, obtained from the equation (2.3.3.8), by assuming $a_1=b_1=d_1=g_1=c_1=0$

Let 'q_{rs}' be the negative impact of drug vacation on one mutant cell during s^{th} day of r^{th} cycle. Then the total negative impact factor of drug vacation on average number of mutant cells during m_{rs} time units of r cycles and s number of days is

$$E(TNVM) = \sum_{r=1}^{l-1}\sum_{s=1}^{n} q_{rs} \,.\, m_{rs} \;.\, \mathrm{E}(M_V) \qquad \ldots (4.2.1.21)$$

Let Z_4 denotes the net impact factor of drug vacation on average number of mutant cells during m_{rs} time units of r cycles and s number of days then

$$Z_4 = \sum_{r=1}^{l-1}\sum_{s=1}^{n} (p_{rs} - q_{rs}).\, m_{rs} \,.\, \mathrm{E}(M_V)$$

$$\text{Which implies } Z_4 = \mathrm{S}.\mathrm{E}(M_v), \text{Where } \mathrm{S} = \sum_{r=1}^{l-1}\sum_{s=1}^{n} (p_{rs} - q_{rs}).\, m_{rs} \ldots (4.2.1.22)$$

Now let Z be the overall positive impact of drug during chemotherapy on both normal and mutant cells due to drug administration and drug vacation. Then from equations 4.2.1.6, 4.2.1.12, 4.2.1.18 and 4.2.1.22, Z can be expressed as

$$Z = Z_1 + Z_2 + Z_3 + Z_4 \qquad \ldots (4.2.1.23)$$

Where $Z_1,\ Z_2,\ Z_3,\ Z_4$ are as given in the equations 4.2.1.6, 4.2.1.12, 4.2.1.18 and 4.2.1.22

4.2.2: Formulation of constraints:

Let w_{ij} denote the loss of WBC of one unit of drug administration for loss of one normal cell during i^{th}cycle and j^{th}spell. Then loss of WBC by a_{ij} units of drug administration for loss of one normal cell is $a_{ij} \,.\, w_{ij}$. The total loss of WBC during 'l' cycles and 'k' spells is

$$TLWA = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \;.\, w_{ij} \qquad \ldots (4.2.2.1)$$

Total loss of WBC due to drug administration during 'l' cycles and 'k' spells for expected number of normal cells is

$$E(TLWL) = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \;.\, w_{ij} \;.\, \mathrm{E}\,(N_A) \qquad \ldots (4.2.2.2)$$

Let WU, WL be the desired and optimal upper limit, lower healthy sizes of WBC respectively during which the drug administration will be suggested. Then the

constraint of drug administration with respect to WBC loss count on average number of normal cells is

$$\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \,.\, w_{ij} \,.\, \mathrm{E}\,(N_A) \leq (\mathrm{WU} - \mathrm{WL}) \qquad \ldots (4.2.2.3)$$

Let 'v_{rs}' be the loss of WBC per unit time during s^{th} day of r^{th} cycle of drug vacation due to growth of one mutant cell. Since m_{rs} is the number of unit times in s^{th} day of r^{th} cycle of drug vacation, the total loss of WBC per unit time in s^{th} day of r^{th} cycle is $v_{rs} \,.\, m_{rs}$. Then total loss of WBC in r cycles and s number of days on one mutant cell is

$$TLWV = \sum_{r=1}^{l-1}\sum_{s=1}^{n} v_{rs} \,.\, m_{rs} \qquad \ldots (4.2.2.4)$$

The total loss of WBC in r cycles and s number of days on average number of mutant cells is

$$E(TLWV) = \sum_{r=1}^{l-1}\sum_{s=1}^{n} v_{rs} \,.\, m_{rs} \,.\, \mathrm{E}(M_V) \qquad \ldots (4.2.2.5)$$

Therefore the constraint of drug vacation with respect to WBC loss count on mutant cells is

$$\sum_{r=1}^{l-1}\sum_{s=1}^{n} v_{rs} \,.\, m_{rs} \,.\, \mathrm{E}(M_V) \leq (\mathrm{WU} - \mathrm{WL}) \qquad \ldots (4.2.2.6)$$

During the treatment with chemotherapy the drug has to be administrated in cycles. When the drug is administered though the objective of the chemicals is to kill the cancer causing cells, they may kill some normal and healthy cells also. Due to this problem, there is a remarkable loss of WBC as well as normal cells. Hence there is a need of maintaining some minimum average number of normal cells during drug administration. When drug administration is stopped there is a possibility of growing normal cells, at the same time there is an equal chance of aggravating the growth of mutant cells. The growth of mutant cells will be either from existing mutant cells or from the existing normal cells. Let NL be the lower required limit of average number of normal cells in tumor and NU be the upper required limit in maintainance of

average number of normal cells. Then the constraint of drug administration and drug vacation regarding expected number of normal cells are

$$\mathrm{E}(N_A) + \mathrm{E}(N_V) \leq NU \quad \ldots (4.2.2.7)$$

$$\mathrm{E}(N_A) + \mathrm{E}(N_V) \geq NL \quad \ldots (4.2.2.8)$$

Let ML and MU respectively be the lower feasible limit and upper target limits of expected number of mutant cells during drug administration. Then the constraint with respect to drug administration on mutant cells is:

$$\mathrm{E}(M_A) \geq ML \quad \ldots (4.2.2.9)$$

$$\mathrm{E}(M_A) \leq MU \quad \ldots (4.2.2.10)$$

4.2.3: Optimization problem:

From equations 4.2.1.23, 4.2.2.3, 4.2.2.6, 4.2.2.7, 4.2.2.8, 4.2.2.9, 4.2.2.10, the optimization problem of chemotherapy is $Max\ Z = Z_1 + Z_2 + Z_3 + Z_4$

Which implies that $Max\ Z$ = P. $\mathrm{E}(N_A)$ + Q .$\mathrm{E}(M_A)$ + R. $\mathrm{E}(N_V)$ + S .$\mathrm{E}(M_V)$

$$Max\ Z = \mathrm{P}.\left[N_0\, e^{(a_1 - d_1)}\right] + \mathrm{Q}\left[A_1\left(e^{(a_1 - d_1)t} - e^{(c_1 - g_1)t}\right) + M_0\, e^{(c_1 - g_1)t}\right]$$

$$+\mathrm{R}\left[N_0\, e^{(a_0 - d_0)t}\right] + \mathrm{S}\left[A_0\left(e^{(a_0 - d_0)t} - e^{(c_0 - g_0)t}\right) + M_0\, e^{(c_0 - g_0)t}\right];$$

$$\mathrm{P}, \mathrm{Q}, \mathrm{R}, \mathrm{S} \geq 0$$

Where

$$\mathrm{P} = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\left(c_{ij} - d_{ij}\right) \qquad \mathrm{Q} = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\,.(b_{ij} - f_{ij})$$

$$\mathrm{R} = \sum_{r=1}^{l-1}\sum_{s=1}^{n}(x_{rs} - y_{rs})\,.m_{rs} \qquad S = \sum_{r=1}^{l-1}\sum_{s=1}^{n}(p_{rs} - q_{rs})\,.m_{rs}$$

$$A_0 = \frac{b_0 N_0}{a_0 - d_0 + g_0 - c_0} \qquad A_1 = \frac{b_1 N_0}{a_1 - d_1 + g_1 - c_1}$$

... (4.2.3.1)

Subject to the constraints

$$\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\,.w_{ij}\,.N_0\, e^{(a_1 - d_1)t} \leq (\mathrm{WU} - \mathrm{WL}) \quad \ldots (4.2.3.2)$$

$$\sum_{r=1}^{l-1}\sum_{s=1}^{n} v_{rs}\,.\,m_{rs}.\left[A_0\left(e^{(a_0-d_0)t}-e^{(c_0-g_0)t}\right)+M_0\,e^{(c_0-g_0)t}\right]\leq (\mathrm{WU}-\mathrm{WL})$$

... (4.2.3.3)

$$N_0\left[e^{(a_1-d_1)t}+e^{(a_0-d_0)t}\right]\leq \mathrm{NU} \qquad \text{... (4.2.3.4)}$$

$$N_0\left[e^{(a_1-d_1)t}+e^{(a_0-d_0)t}\right]\geq \mathrm{NL} \qquad \text{... (4.2.3.5)}$$

$$\left[A_1\left(e^{(a_1-d_1)t}-e^{(c_1-g_1)t}\right)+M_0\,e^{(c_1-g_1)t}\right]\geq \mathrm{ML} \qquad \text{... (4.2.3.6)}$$

$$\left[A_1\left(e^{(a_1-d_1)t}-e^{(c_1-g_1)t}\right)+M_0\,e^{(c_1-g_1)t}\right]\leq \mathrm{MU} \qquad \text{... (4.2.3.7)}$$

and the decision variables/parameters $a_0, b_0, c_0, d_0, g_0, a_1, b_1, c_1, d_1, g_1 \geq 0$

... (4.2.3.8)

4.2.4: Numerical Illustration and Analysis:

The above non-linear programming problem is solved with LINGO 8.0 and results are presented in the tables from 4.2.3.1 to 4.2.3.8

Table 4.2.3.1:

Values of a_1,b_1,c_1,d_1,g_1,a_0,b_0,c_0,d_0,g_0 for varying values of 'i' at fixed values of other parameters. t=2; j=5; r=4; s =5; N_0=5500000; M_0=970000; MU=58000; ML=47000; NU=10000000;WU=12000000;WL=10000000 N_0=7500000

i	Z	a_0	b_0	d_0	g_0	c_0	a_1	b_1	d_1	g_1	c_1
1	72135960	0.00	0.0000	0.08	1000	117064	274357	9999.63	1000.00	0.19	0.9216
2	72176790	2.11	0.0000	1.06	12.33	1.1105	0.0000	0.00	51.78	6.72	1.7844
3	72205210	225.29	0.0006	224.02	15.26	1.1117	0.0000	0.00	56.65	7.74	1.7831
6	72334750	900.16	0.0041	899.87	24.75	0.0867	0.0000	0.00	9.21	3.12	1.7500

From table 4.2.3.1, it is observed that the objective function Z (drug efficacy) is an increasing function of 'i' (number of drug administrations). When all the other parameters are constant. It implies that increasing number of drug cycles increase the drug efficiency. From the same table it is observed that the parameters in drug absence namely a_0, b_0, c_0, d_0, g_0 and the parameters in drug presence a_1, b_1, c_1, d_1 and g_1 behaves erratically and exhibiting the stochastic nature.

Table 4.2.3.2:

Values of a_1, b_1, c_1, d_1, g_1, a_0, b_0, c_0, d_0, g_0 for varying values of 'j' at fixed values of other parameters. t=2; i=4; r=4; s =5; N_0=5500000; M_0=970000; MU=58000; ML=47000; NU=10000000; WU=12000000; WL=10000000

j	Z	a_0	b_0	d_0	g_0	c_0	a_1	b_1	d_1	g_1	c_1
5	72015790.00	874.3295	0.00241	873.4491	18.9463	4.6886	0	0	42.1913	5.9534	1.8053
6	67735500.00	599.1285	0.00094	598.7046	10.4214	2.2090	0	0	20.8232	2.0178	0.0201
7	67711140.00	599.1285	0.0009	598.7046	10.4214	2.2090	0	0	20.8231	2.0177	0.0201
8	67708820.00	599.1285	0.0009	598.7046	10.4214	2.2090	0	0	20.8234	2.0177	0.0201

From table 4.2.3.2, it is observed that drug efficacy Z is decreasing function of number of drug administration spells per cycle (j) when other parameters are constant. Hence it may be inferred that more number of drug administration spells per cycle has adverse effect on drug efficacy. Further it is observed that all the parameters i.e., arrival and departure rates during absence and presence of drug exhibits pure stochasticity.

Table 4.2.3.3:

Values of a_1, b_1, c_1, d_1, g_1, a_0, b_0, c_0, d_0, g_0 for varying values of 'r' at fixed values of other parameters. t=2; i=4; j=5; s=5; N_0=5500000; M_0=970000; MU=58000; ML=47000; NU=10000000; WU=12000000; WL=10000000

r	Z	a_0	b_0	d_0	g_0	c_0	a	b	d_1	g_1	c_1
3	49012610.00	4.790342	0.00003	1.8062	31.2994	0.0000	0	0	132.4549	15.8680	1.8075
4	72615210.00	802.9884	0.00220	802.0177	18.9199	4.8127	0	0	41.9601	6.3769	1.8031
5	90514930.00	130.5484	0.00039	129.2273	18.3636	3.2590	0	0	50.1612	8.2105	1.9856
6	94513250.00	1.783129	0.00001	0.0000	23.3705	3.1537	0	0	51.2729	9.1166	0.7149

Table 4.2.3.4:

Values of a_1, b_1, c_1, d_1, g_1, a_0, b_0, c_0, d_0, g_0 for varying values of 's' at fixed values of other parameters. t=2; i=4; j=5; r=4; N_0=5500000; M_0=970000; MU=58000; ML=47000; NU=10000000; WU=12000000; WL=10000000

s	Z	a_0	b_0	d_0	g_0	c_0	a	b_1	d_1	g_1	c_1
3	37119530.00	3.234889	0.00002	0.0000	33.4144	1.5185	0	0	106.0550	15.2742	0.0322
4	50115480.00	1104.418	0.00629	1104.372	32.6589	1.4031	0	0	3395.912	1.5232	1.3067
5	72615210.00	802.9884	0.00220	802.0177	18.9199	4.8127	0	0	41.9601	6.3769	1.8031
6	94913940.00	2.594364	0.00001	1.3813	14.4652	1.0711	0	0	54.3983	7.7278	2.0122

From tables 4.2.3.3 and 4.2.3.4, it is observed that Z is increasing function of r and s respectively, when all the other parameters are constant. Hence it may be interpreted as the increasing effectiveness of the drug is influenced by increase in number of during vacations and also increasing number of time units with the drug vacation. Further it is observed that varying values of drug vacation number exhibits the stochasticity of all the other parameters during the absence and presence of drug.

Table 4.2.3.5:

Values of a_1, b_1, c_1, d_1, g_1, a_0, b_0, c_0, d_0, g_0 for varying values of 'r' at fixed values of other parameters. t=2; i=4; j=5; r=4; s=5; M_0=970000; MU=58000; ML=47000; NU=10000000; NL=9000000; WU=12000000; WL=10000000; (N_0=2500000; NU=9900000)

N_0	Z	a_0	b_0	d_0	g_0	c_0	a_1	b_1	d_1	g_1	c_1
250000	71281920	0.0000	0.000	0.1036	0.0000	27100000	651.642	0.168	3.5719	0.158	0.3
350000	72000920	0.0000	0.000	0.2251	0.0005	3238650	3.8209	0.000	0.0000	0.000	0.6
550500	72015790	562.314	0.001	561.372	16.479	4.9029	0.0000	0.000	42.127	6.248	1.8
650000	72924070	1072.60	0.009	1071.52	60.127	3.9794	0.0000	0.000	33.931	1.360	0.0

Form table 4.2.3.5 it is observed that drug efficacy Z is increasing function of initial number of normal cells when all the other parameters are constant. It implies that increasing number initial number of normal cells increase drug efficacy. It is also observe that from table 4.2.3.5 that the parameters during absence of drug a_0, b_0, c_0, d_0, g_0 and the parameters during presence of drug a_1, b_1, c_1, d_1, g_1 are exhibited pure stochasticity.

Table 4.2.3.6:

Values of a_1, b_1, c_1, d_1, g_1, a_0, b_0, c_0, d_0, g_0 for varying values of 'NU' at fixed values of other parameters. t=2; i=4; j=5; r=4; s=5; N_0=5500000; M_0=970000; MU=58000; ML=47000; NL=9000000; WU=12000000; WL=10000000

NU	Z	a_0	b_0	d_0	g_0	c_0	a	b	d_1	g_1	c_1
1000100	72022980.00	548.1147	0.00096	547.3820	13.8231	4.8745	0	0	42.1981	5.2577	1.8052
1000200	72030170.00	907.4093	0.00379	906.4628	26.0427	4.0064	0	0	42.2050	6.2630	1.8051
1000300	72037360.00	605.5618	0.00140	604.6169	16.7226	4.9114	0	0	42.2119	6.2548	1.8049
1000400	72044550.00	0.733399	0.00000	0.0000	13.1667	5.3487	0	0	42.2187	5.2581	1.8048
1000500	72051740.00	0.9453435	0.00000	0.0000	15.0404	4.9643	0	0	42.2256	6.2552	1.8047

From table 4.2.3.6 it is observed that drug efficacy Z and the parameter d_1 i.e., rate of death of normal cell during presence of drug are increasing function of normal cells upper limit when all the other parameters are constant. It implies that increasing number of normal cells upper limit increase drug efficacy and rate of death of normal cells during presence of chemotherapy. Also it is observed that the parameters during absence of drug a_0, b_0, c_0, d_0, g_0 and the parameters during presence of drug a_1, b_1, c_1, d_1, g_1 behaves erratically and exhibit stochastically.

Table 4.2.3.7

Values of a_1, b_1, c_1, d_1, g_1, a_0, b_0, c_0, d_0, g_0 for varying values of 'NL' at fixed values of other parameters. t=2; i=4; j=5; r=4; s=5; N_0=5500000; M_0=970000; MU=58000; ML=47000; WU=12000000; WL=10000000

NL	NU	Z	a_0	b_0	d_0	g_0	c_0	a	b	d_1	g_1	c_1
900000	1000000	7201579	907.5908	0.005	907.328	34.950	0.093	0	0	13.080	2.909	1.673
900100	1000100	7202298	907.5000	0.005	907.237	34.951	0.093	0	0	13.068	2.909	1.673
900200	1000200	7203017	907.4093	0.005	907.146	34.951	0.093	0	0	13.056	2.909	1.673
900030	1000300	7203736	907.3186	0.005	907.056	34.952	0.093	0	0	13.044	2.909	1.673

From table 4.2.3.7 it is observe that drug efficacy Z, rate of death of mutant cells during absence of drug g_0 are increasing function of normal cells lower limit when all the other parameters are constant. Hence it may be inferred that increasing number of lower limit of normal cells increase the drug efficacy and rate of death of mutant cells in the absence of drug. It is also observed from table 4.2.3.7 that parameters during absence of drug a_0, d_0 and parameters during presence of drug d_1,

c_1 are decreasing function of increase in number of normal cells lower limit when all the other parameters are constant.

Table 4.2.3.8

Values of a_1, b_1, c_1, d_1, g_1, a_0, b_0, c_0, d_0, g_0 for varying values of 'WU' at fixed values of other parameters. t=2; i=4; j=5; r=4; s=5; N_0=5500000; M_0=970000; MU=58000; ML=47000; NU=10000000; NL=9000000; WL=10000000

WU	Z	a_0	b_0	d_0	g_0	c_0	a	b	d_1	g_1	c_1
1200100	72015800.00	908.0446	0.00379	907.0987	26.0779	4.0915	0	0	42.1999	6.2622	1.8054
1200200	72015800.00	0.8876919	0.00000	0.1548	12.7701	4.9529	0	0	42.2086	5.2588	1.8055
1200300	72015810.00	908.9521	0.00294	908.2184	20.8765	3.8475	0	0	42.2173	5.2628	1.8055
1200400	72015820.00	909.4059	0.00261	908.7549	20.4395	5.3225	0	0	42.2260	4.8733	1.8056
1200500	72015830.00	882.9604	0.00266	882.0153	20.4852	4.8433	0	0	42.2346	6.2589	1.8057

From table 4.2.3.8 it is observed that drug efficacy Z and the parameter d_1 i.e., rate of death of normal cells during presence of drug are increasing functions of white blood cells upper limit when all other parameters are constant. It implies that increasing lower limit of white blood cells increases the efficacy and the parameter d_1, rate of normal cells during presence of drug. Further it is observed that parameters during absence of drug a_0, b_0, c_0, d_0, g_0 and parameters during presence of drug g_1, c_1 are exhibiting pure stochasticity.

4.3 PROGRAMMING PROBLEM FOR OPTIMAL DRUG ADMINISTRATION FOR TWO STAGE MUTANT CELL GROWTH:

4.3.1: Formulation of objective function:

Let $'p_{ij}'$ be the effectiveness of killing of one premalignant cell by one unit drug administration during i^{th} cycle and j^{th} spell Where i = 1,2…,l, the number of cycles and j = 1, 2,..., k, the number of spells. Let a_{ij} be the number of units of drug doses given in i^{th} cycle and j^{th} spell on one premalignant cell. Impact of a_{ij} units of drug in killing of one premalignant cell during ith cycle and jth spell is $a_{ij}.p_{ij}$. Therefore total impact of a_{ij} units of drug in killing of one premalignant cell during l cycles and k spells is

$$TPPA = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .p_{ij} \qquad \ldots (4.3.1.1)$$

Then total impact of drug during $'l'$ cycles and $'k'$ spells on average number of premalignant cells at time‘t’ is

$$E(TPPA) = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .p_{ij}\,\mathrm{E}\,(N_A) \qquad \ldots(4.3.1.2)$$

where E (N_A) is the average number of premalignant cells at a time‘t’ during drug administration, obtained from the equation 3.3.3.6, by assuming $\alpha_0=\gamma_0=\delta_0=0$

Let $'q_{ij}'$ be the negative effectiveness of one unit of drug administration on one premalignant cell during i^{th} cycle and j^{th} spell.Then negative impact of a_{ij} units of drug on one premalignant cell is $a_{ij}.q_{ij}$ which implies total negative impact of a_{ij} units for drug on one premalignant cell is

$$TNPA = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .q_{ij} \qquad \ldots(4.3.1.3)$$

Therefore total negative impact of drug during l cycles and k spells on average number of premalignant cells at a time ‘t’ is

$$E(TNPA) = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .q_{ij}.\,\mathrm{E}\,(N_A) \qquad \ldots(4.3.1.4)$$

Let Z_1denote the net effect of drug administration on average number of premalignant cells during l cycles and k spells then

$$Z_1 = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ (p_{ij} - q_{ij})\,.\,\mathrm{E}\,(N_A)$$

Which implies $Z_1 = \mathrm{A}.\,\mathrm{E}\,(N_A)$; A≥0

Where $\mathrm{A} = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ (p_{ij} - q_{ij})$ ...(4.3.1.5)

Let u_{ij} be the effectiveness of killing of one malignant cell during i^{th}cycle and j^{th}spell of drug administration. Then effectiveness of a_{ij} units of drug on one malignant cell is $a_{ij}.u_{ij}$. Which implies total effect of drug administration during $'l'$ cycles and $'k'$ spells on one malignant cell is

$$TPMA = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \,.\, u_{ij} \qquad \ldots (4.3.1.6)$$

The total impact of drug administration during l cycles and k spells on average number of malignant cells at a time 't' is,

$$\mathrm{E(TPMA)} = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \,.\, u_{ij} \,.\, \mathrm{E}(M_A) \qquad \ldots (4.3.1.7)$$

Where $\mathrm{E}(M_A)$ is the average number of malignant cells at time't', during drug administration, obtained from the equation 3.3.3.7, by assuming $\alpha_0=\beta_0=\gamma_0=\delta_0=\theta_0=0$

Let v_{ij} be the negative impact factor of one unit of drug administration on one malignant cell during i^{th} cycle and j^{th} spell. Then negative impact of a_{ij} units of drug administration on one malignant cell is $a_{ij} \,.\, v_{ij}$ Therefore total negative impact of drug administration during l cycles and k spells on one malignant cell is

$$TNMA = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \,.\, v_{ij} \qquad \ldots (4.3.1.8)$$

Hence total negative impact of drug administration during $'l'$ cycles and $'k'$ spells on average number of malignant cells at a time 't' is

$$E(TNMA) = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \,.\, v_{ij} \,.\, \mathrm{E}\,(M_A) \qquad \ldots (4.3.1.9)$$

Let Z_2 denotes the net effect of drug administration on average number of malignant cells then

$$Z_2 = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \,.\, (u_{ij} - v_{ij}) \,.\, \mathrm{E}\,(M_A)$$

Which implies that $Z_2 = \mathrm{B}.\ \mathrm{E}\,(M_A)$, $\mathrm{B} \geq 0$

Where $$\mathrm{B} = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \,.\, (u_{ij} - v_{ij}) \qquad \ldots (4.3.1.10)$$

Let b_{rs} be the positive impact of drug vacation on s^{th} day of r^{th} cycle on one premalignant cell. Where r= 1, 2,…, l-1, the number of cycles of drug vacation, s= 1, 2,…, n, the number of days of drug vacation. Let m_{rs} be the number of time units

of drug vacation. Then total positive impact of drug vacation on one premalignant cell during m_{rs} number of time units of drug vacation is

$$TPPV = \sum_{r=1}^{l-1}\sum_{s=1}^{n} b_{rs} \,.\, m_{rs} \qquad \ldots (4.3.1.11)$$

Hence total positive impact of drug vacation on average number of premalignant cells during m_{rs} number of time units in r cycles and s number of days at time 't' is

$$E(TPPV) = \sum_{r=1}^{l-1}\sum_{s=1}^{n} b_{rs} \,.\, m_{rs} \,.\, \mathrm{E}\,(N_V) \qquad \ldots (4.3.1.12)$$

Where E (N_V) denote the average number of premalignant cells at time 't' during drug vacation, obtained from the equation 3.3.3.6, by assuming $\alpha_1 = \gamma_1 = \delta_1 = 0$

Let d_{rs} be the negative impact of drug vacation on one premalignant cell during s^{th} day of r^{th} cycle. Then total negative impact of drug vacation on one premalignant cell during m_{rs} time units of drug in r cycles and s number of days is

$$TNPV = \sum_{r=1}^{l-1}\sum_{s=1}^{n} d_{rs} \,.\, m_{rs} \qquad \ldots (4.3.1.13)$$

Therefore the total negative impact of drug vacation on average number of premalignant cells during m_{rs} time units of drug vacation in $'r'$ cycles and $'s'$ number of days is,

$$E(TNPV) = \sum_{r=1}^{l-1}\sum_{s=1}^{n} d_{rs} \,.\, m_{rs} \,.\, \mathrm{E}\,(N_V) \qquad \ldots (4.3.1.14)$$

Let Z_3denotes the net impact of drug vacation on average number of premalignant cells during m_{rs} time units of drug in r cycles and s number of days then

$$Z_3 = \sum_{r=1}^{l-1}\sum_{s=1}^{n} (b_{rs} - d_{rs}) \,.\, m_{rs} \,.\, \mathrm{E}\,(N_V)$$

Which implies that $Z_3 = C.E(N_V)$; $\quad C \geq 0$

Where $$C = \sum_{r=1}^{l-1}\sum_{s=1}^{n} (b_{rs} - d_{rs}) \,.\, m_{rs} \qquad \ldots (4.3.1.15)$$

Let $'x_{rs}'$ be the positive impact of one unit time of drug vacation on one malignant cell during s^{th} day of r^{th} cycle. Then total positive impact of drug vacation on one malignant cell during m_{rs} time units of drug vacation in r cycles and s number of days is

$$TPMV = \sum_{r=1}^{l-1}\sum_{s=1}^{n} x_{rs}\,.\,m_{rs} \qquad \ldots (4.3.1.16)$$

Hence total positive impact of drug vacation on average number of malignant cells during m_{rs} time units of drug vacation in r cycles and s number of days is

$$E(TPMV) = \sum_{r=1}^{l-1}\sum_{s=1}^{n} x_{rs}\,.\,m_{rs}.\ \mathrm{E}(M_V) \qquad \ldots (4.3.1.17)$$

Where $\mathrm{E}(M_v)$ is the average number of mutant cells at time't' during the drug vacation, obtained form the equation 3.3.3.7, by assuming $\alpha_1=\beta_1=\gamma_1=\delta_1=\theta_1=0$

Similarly let $'y_{rs}'$ be the negative impact of drug vacation on one malignant cell, then the negative impact of drug vacation on average number of malignant cells during m_{rs} time units of drug vacation in r cycles and s number of days is

$$E(TNMV) = \sum_{r=1}^{l-1}\sum_{s=1}^{n} y_{rs}\,.\,m_{rs}\ .\mathrm{E}(M_V) \qquad \ldots (4.3.1.18)$$

Let Z_4 denote the net impact of drug vacation on average number of malignant cells during m_{rs} time units of drug vacation in r cycles and s number of days is

$$Z_4 = \sum_{r=1}^{l-1}\sum_{s=1}^{n}(x_{rs}-y_{rs}).m_{rs}\,.\mathrm{E}(M_V)$$

Which implies that $Z_4 = \mathrm{D}.\ \mathrm{E}(M_v),\ \mathrm{D}\geq 0$

Where $$\mathrm{D} = \sum_{r=1}^{l-1}\sum_{s=1}^{n}(x_{rs}-y_{rs}).m_{rs} \qquad \ldots (4.3.1.19)$$

If Z denote the objective function then the objective is to

$$maximise \qquad Z = Z_1 + Z_2 + Z_3 + Z_4 \qquad \ldots (4.3.1.20)$$

Where $Z_1\ Z_2\ Z_3\ and\ Z_4$ are as given in the equations (4.3.1.5),(4.3.1.10),(4.3.1.15) and(4.3.1.19)

4.3.2: Formulation of Constraints:

Let 'w_{ij}' denote the loss of WBC for one unit of drug administration while targeting one premalignant cell in i^{th}cycle and j^{th}spell. Since a_{ij} is the number of units of drug doses administrated in i^{th}cycle and j^{th} spell, the total loss of WBC during i^{th}cycle and j^{th}spell is $a_{ij}\,.w_{ij}$. Therefore total loss of WBC during l cycles and k spells of drug administration for targeting of killing one premalignant cell is

$$LWPA = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .w_{ij} \qquad \ldots(4.3.2.1)$$

Then the total loss of WBC due to drug administration during l cycles and k spells for targeting expected number of premalignant cells is

$$E(LWPA) = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .w_{ij}\ .\mathrm{E}\,(N_A) \qquad \ldots(4.3.2.2)$$

Let WU, WL be the desired optimal upper limit and lower healthy sizes of WBC during which the drug administration will be suggested. Then the constraint of drug administration with respect to WBC loss count on premalignant cells is,

$$\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .w_{ij}\ .\mathrm{E}\,(N_A) \leq (\mathrm{WU} - \mathrm{WL}) \qquad \ldots(4.3.2.3)$$

Let $'z_{ij}'$ be the loss of WBC for one unit of drug administration while targeting a malignant cell in i^{th}cycle and j^{th}spell. Then total loss of WBC for a_{ij} units of drug doses administered in i^{th}cycle and j^{th}spell is $a_{ij}\,.z_{ij}$. Therefore total loss of WBC during l cycles and k spells while targeting in killing of one malignant cell is

$$LWMA = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .z_{ij} \qquad \ldots(4.3.2.4)$$

Then the total loss of WBC due to drug administration during l cycles and k spells for targeting expected number of premalignant cells is

$$E(LWMA) = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .z_{ij}\ .\mathrm{E}\,(M_A) \qquad \ldots(4.3.2.5)$$

Hence the constraint of drug administration with respect to WBC loss count on malignant cells is,

$$\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \,.\, z_{ij} \,.\, \mathrm{E}\,(M_A) \leq (\mathrm{WU} - \mathrm{WL}) \qquad \ldots (4.3.2.6)$$

Therefore from the equations (4.3.2.3) and (4.3.2.6), the constraint of drug administration with respect to WBC loss count on expected number of premalignant cells and malignant cells is,

$$\left(\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \,.\, w_{ij} \,.\, \mathrm{E}\,(N_A) + \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij} \,.\, z_{ij} \,.\, \mathrm{E}\,(M_A)\right) \leq (\mathrm{WU} - \mathrm{WL}) \qquad \ldots (4.3.2.7)$$

Let $'\alpha_{rs}\,'$ be the loss of WBC per unit time during s^{th} day of r^{th} cycle of drug vacation due to growth of one premalignant cell Where r= 1, 2,…, l-1, the number of cycles, s= 1, 2,…, n, the number of days. Let $'m_{rs}\,'$ be the number of time units in s^{th} day of r^{th} cycle of drug vacation. Then total loss of WBC per unit time in s^{th} day of r^{th} cycle is $\alpha_{rs} \,.\, m_{rs}$. Hence total loss of WBC in r cycles and s number of days on one premalignant cell is

$$LWPV = \sum_{r=1}^{l-1}\sum_{s=1}^{n} \alpha_{rs} \,.\, m_{rs} \qquad \ldots (4.3.2.8)$$

The total loss of WBC during r cycles and s number of days on average number of premalignant cells is

$$E(LWPV) = \sum_{r=1}^{l-1}\sum_{s=1}^{n} \alpha_{rs} \,.\, m_{rs} \,.\, \mathrm{E}(N_V) \qquad \ldots (4.3.2.9)$$

Where $\mathrm{E}(N_V)$ is the average number of premalignant cells during drug vacation at time 't'

Therefore the constraint of drug vacation with respect to WBC loss count is

$$\sum_{r=1}^{l-1}\sum_{s=1}^{n} \alpha_{rs} \,.\, m_{rs} \,.\, \mathrm{E}(N_V) \leq (\,\mathrm{WU} - \mathrm{WL}\,) \qquad \ldots (4.3.2.10)$$

Let $'\beta_{rs}\,'$ be the loss of WBC per unit time during s^{th} day of r^{th} cycle's drug vacation due to growth of one malignant cell. Then total loss of WBC per unit time

in s^{th} day of r^{th} cycle is $\beta_{rs} . m_{rs}$. Hence total loss of WBC by r cycles and s number of days of drug vacation on one malignant cell is

$$LWMV = \sum_{r=1}^{l-1} \sum_{s=1}^{n} \beta_{rs} . m_{rs} \quad \ldots (4.3.2.11)$$

Therefore total loss of WBC in r cycles and s number of days of drug vacation on average number of malignant cells is

$$E(LWMV) = \sum_{r=1}^{l-1} \sum_{s=1}^{n} \beta_{rs} . m_{rs} . \mathrm{E}(M_V) \quad \ldots (4.3.2.12)$$

Therefore the constraint of drug vacation with respect to WBC loss count on average number of malignant cells is,

$$\sum_{r=1}^{l-1} \sum_{s=1}^{n} \beta_{rs} . m_{rs} . \mathrm{E}(M_V) \leq (\mathrm{WU} - \mathrm{WL}) \quad \ldots (4.3.2.13)$$

From equations (4.3.2.10) & (4.3.2.13) the constraint of drug vacation with respect to WBC loss count is

$$\left(\sum_{r=1}^{l-1} \sum_{s=1}^{n} \alpha_{rs} . m_{rs} . \mathrm{E}(N_V) + \sum_{r=1}^{l-1} \sum_{s=1}^{n} \beta_{rs} . m_{rs} . \mathrm{E}(M_V) \right) \leq (\mathrm{WU} - \mathrm{WL}) \ldots (4.3.2.14)$$

Let NCL be the critical target limit on size of the premalignant cells when the expected size of the premalignant cells at time 't' is less than or equal to NCL.

Which implies that $\mathrm{E(N)} \leq \mathrm{NCL}$ ... (4.3.2.15)

Let MCL be the critical target limit on size of the malignant cells when the expected size of the malignant cells at time t$\leq$ MCL

Which implies that $\mathrm{E(M)} \leq \mathrm{MCL}$ ... (4.3.2.16)

4.3.3 Optimization problem of two stage mutant cell growth:

From equations 4.3.1.20, 4.3.2.7, 4.3.2.14

$$
\begin{aligned}
Max\ Z \;=\;& A.\left[\frac{(1-a)\alpha_1}{(1-c)\gamma_1+(1-d)\delta_1}\times\left[1-\mathrm{e}^{-\left((1-c)\gamma_1+(1-d)\delta_1\right)\mathrm{t}}\right]\right.\\
&\left.+N_0\,\mathrm{e}^{-\left((1-c)\gamma_1+(1-d)\delta_1\right)\mathrm{t}}\right]\\
&+B.\left[\frac{\left((1-a)\alpha_1\right)\left((1-c)\gamma_1\right)}{(1-c)\gamma_1+(1-d)\delta_1}\right.\\
&\times\left[\frac{1-\mathrm{e}^{-((1-g)\theta_1)\mathrm{t}}}{(1-g)\theta_1}+\frac{\mathrm{e}^{-\left((1-c)\gamma_1+(1-d)\delta_1\right)\mathrm{t}}-\mathrm{e}^{-((1-g)\theta_1)\mathrm{t}}}{(1-c)\gamma_1+(1-d)\delta_1-(1-g)\theta_1}\right]\\
&-\frac{N_0\left((1-c)\gamma_1\right)}{(1-c)\gamma_1+(1-d)\delta_1-(1-g)\theta_1}\\
&\times\left[\mathrm{e}^{-\left((1-c)\gamma_1+(1-d)\delta_1\right)\mathrm{t}}-\mathrm{e}^{-((1-g)\theta_1)\mathrm{t}}\right]+\frac{(1-b)\beta_1}{(1-g)\theta_1}\left[1-\mathrm{e}^{-((1-g)\theta_1)\mathrm{t}}\right]\\
&\left.+M_0\,\mathrm{e}^{-((1-g)\theta_1)\mathrm{t}}\right]\\
&+\mathrm{C}.\left[\frac{a\,\alpha_0}{d\,\delta_0+c\,\gamma_0}\left[1-\mathrm{e}^{-(c\,\gamma_0+d\,\delta_0)\mathrm{t}}\right]+N_0\,\mathrm{e}^{-(c\,\gamma_0+d\,\delta_0)\mathrm{t}}\right]\\
&+\mathrm{D}.\left[\frac{a\,\alpha_0\,.\,c\,\gamma_0}{c\,\gamma_0+d\,\delta_0}\times\left[\frac{1-\mathrm{e}^{-(g\,\theta_0)\mathrm{t}}}{g\,\theta_0}+\frac{\mathrm{e}^{-(c\,\gamma_0+d\,\delta_0)\mathrm{t}}-\mathrm{e}^{-(g\,\theta_0)\mathrm{t}}}{c\,\gamma_0+d\,\delta_0-g\,\theta_0}\right]\right.\\
&-\frac{N_0\,.\,c\,\gamma_0}{c\,\gamma_0+d\,\delta_0-g\,\theta_0-}\left[\mathrm{e}^{-(c\,\gamma_0+d\,\delta_0)\mathrm{t}}-\mathrm{e}^{-(g\,\theta_0)\mathrm{t}}\right]+\frac{b\,\beta_0}{g\,\theta_0}\left[1-\mathrm{e}^{-(g\,\theta_0)\mathrm{t}}\right]\\
&\left.+M_0\,\mathrm{e}^{-(g\,\theta_0)\mathrm{t}}\right]
\end{aligned}
$$

Where

$$A = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ (p_{ij} - q_{ij}) \qquad B = \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .(u_{ij} - v_{ij})$$

$$C = \sum_{r=1}^{l-1}\sum_{s=1}^{n} (b_{rs} - d_{rs}).m_{rs} \qquad D = \sum_{r=1}^{l-1}\sum_{s=1}^{n} (x_{rs} - y_{rs}).m_{rs}$$

…(4.3.3.1)

Subject to the constraints

$$\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .w_{ij}\ \left[\frac{(1-a)\alpha_1}{(1-c)\gamma_1 + (1-d)\delta_1} \times \left[1 - e^{-\left((1-c)\gamma_1 + (1-d)\delta_1\right)t}\right]\right.$$

$$\left. + N_0\, e^{-\left((1-c)\gamma_1 + (1-d)\delta_1\right)t}\right]$$

$$+ \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .z_{ij}\ \left[\frac{\left((1-a)\alpha_1\right)\left((1-c)\gamma_1\right)}{(1-c)\gamma_1 + (1-d)\delta_1}\right.$$

$$\times \left[\frac{1 - e^{-((1-g)\theta_1)t}}{(1-g)\theta_1} + \frac{e^{-\left((1-c)\gamma_1 + (1-d)\delta_1\right)t} - e^{-((1-g)\theta_1)t}}{(1-c)\gamma_1 + (1-d)\delta_1 - (1-g)\theta_1}\right]$$

$$- \frac{N_0\left((1-c)\gamma_1\right)}{(1-c)\gamma_1 + (1-d)\delta_1 - (1-g)\theta_1}\left[e^{-\left((1-c)\gamma_1 + (1-d)\delta_1\right)t} - e^{-((1-g)\theta_1)t}\right]$$

$$\left. + \frac{(1-b)\beta_1}{(1-g)\theta_1}\left[1 - e^{-((1-g)\theta_1)t}\right] + M_0\, e^{-((1-g)\theta_1)t}\right]$$

$$\leq (WU - WL) \qquad \ldots (4.3.3.2)$$

$$\sum_{r=1}^{l-1}\sum_{s=1}^{n}\alpha_{rs}\,.\,m_{rs}.\left[\frac{a\,\alpha_0}{d\,\delta_0+c\,\gamma_0}\left[1-\ \mathrm{e}^{-\left(c\,\gamma_0+d\,\delta_0\right)\mathrm{t}}\right]+N_0\,\mathrm{e}^{-\left(c\,\gamma_0+d\,\delta_0\right)\mathrm{t}}\right]$$

$$+\sum_{r=1}^{l-1}\sum_{s=1}^{n}\beta_{rs}\,.\,m_{rs}\left[\frac{a\,\alpha_0.\ c\,\gamma_0}{c\,\gamma_0+d\,\delta_0}\right.$$

$$\times\left[\frac{1-\mathrm{e}^{-(g\,\theta_0)\mathrm{t}}}{g\,\theta_0}+\frac{\mathrm{e}^{-\left(c\,\gamma_0+d\,\delta_0\right)\mathrm{t}}-\ \mathrm{e}^{-(g\,\theta_0)\mathrm{t}}}{c\,\gamma_0+d\,\delta_0-g\,\theta_0}\right]$$

$$-\frac{N_0\,.\,c\,\gamma_0}{c\,\gamma_0+d\,\delta_0-g\,\theta_0}-\left[\mathrm{e}^{-\left(c\,\gamma_0+d\,\delta_0\right)\mathrm{t}}-\ \mathrm{e}^{-(g\,\theta_0)\mathrm{t}}\right]+\frac{b\,\beta_0}{g\,\theta_0}\left[1-\ \mathrm{e}^{-(g\,\theta_0)\mathrm{t}}\right]$$

$$\left.+M_0\,\mathrm{e}^{-(g\,\theta_0)\mathrm{t}}\right]\leq(\mathrm{WU}-\mathrm{WL})\qquad\ldots(4.3.3.3)$$

$$\left[\frac{a\,\alpha_0+(1-a)\alpha_1}{c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1}\times\left[1-\ \mathrm{e}^{-\left(c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1\right)\mathrm{t}}\right]\right.$$

$$\left.+N_0\,\mathrm{e}^{-\left(c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1\right)\mathrm{t}}\right]\leq\mathrm{NU}\qquad\ldots(4.3.3.4)$$

$$\left[\frac{(a\,\alpha_0+(1-a)\alpha_1)\left(c\,\gamma_0+(1-c)\gamma_1\right)}{c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1}\right.$$

$$\times\left[\frac{1-\mathrm{e}^{-(g\,\theta_0+(1-g)\theta_1)\mathrm{t}}}{g\,\theta_0+(1-g)\theta_1}\right.$$

$$\left.+\frac{\mathrm{e}^{-\left(c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1\right)\mathrm{t}}-\ \mathrm{e}^{-(g\,\theta_0+(1-g)\theta_1)\mathrm{t}}}{c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1-g\,\theta_0-(1-g)\theta_1}\right]$$

$$-\frac{N_0\left(c\,\gamma_0+(1-c)\gamma_1\right)}{c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1-g\,\theta_0-(1-g)\theta_1}$$

$$\times\left[\mathrm{e}^{-\left(c\,\gamma_0+(1-c)\gamma_1+d\,\delta_0+(1-d)\delta_1\right)\mathrm{t}}-\ \mathrm{e}^{-(g\,\theta_0+(1-g)\theta_1)\mathrm{t}}\right]+\frac{b\,\beta_0+(1-b)\beta_1}{g\,\theta_0+(1-g)\theta_1}$$

$$\left.\times\left[1-\ \mathrm{e}^{-(g\,\theta_0+(1-g)\theta_1)\mathrm{t}}\right]+M_0\,\mathrm{e}^{-(g\,\theta_0+(1-g)\theta_1)\mathrm{t}}\right]$$

$$\leq\ \mathrm{MU}\qquad\ldots(4.3.3.5)$$

and the decision parameters/variables $\alpha_0,\beta_0,\gamma_0,\delta_0,\theta_0,\alpha_1,\beta_1,\gamma_1,\delta_1,\theta_1\geq 0$... (4.3.3.6)

4.2.4: Numerical Illustration and Analysis:

The above non linear programming problem is solved with LINGO 8.0 and the following results are obtained.

Table 4.3.3.1

Values of $\alpha_0, \beta_0, \gamma_0, \delta_0, \theta_0, \alpha_1, \beta_1, \gamma_1, \delta_1, \theta_1$ for varying values of i at fixed values of other parameters. t=2; j=5; r=3; s=5; N_0=7600000; M_0=970000; WU=20100000; WL=1010000; NU=100000; NL=41000; MU=620000; ML=470000

i	Z	α_0	δ_0	γ_0	θ_0	β_0	α_1	δ_1	γ_1	θ_1	β_1
1	1417783	0	3.75	0	0.1731	30	6.25	0	6.666667	14.30776	0
4	1417787	0	3.75	0	0.1582	30	6.25	0	6.666667	14.36709	0
5	1417790	0	3.75	0	0.1576	30	6.25	0	6.666667	14.3696	0
6	1417791	0	3.75	0	0.1734	30	6.25	0	6.666667	14.30625	0

From table 4.3.3.1, it is observed that the objective function Z (drug efficacy) is an increasing function of 'i' when all the other parameters are constant (number of cycles of drug administration). It implies that the increasing number of drug cycles increase the drug efficacy. From the same table it is observed that the parameters in drug absence namely α_0, β_0, γ_0, δ_0, θ_0 and the parameters during drug presence α_1, β_1, γ_1, δ_1 and $\theta_1$behaves erratically and exhibiting the stochastic nature.

Table 4.3.3.2

Values of $\alpha_0, \beta_0, \gamma_0, \delta_0, \theta_0, \alpha_1, \beta_1, \gamma_1, \delta_1, \theta_1$ for varying values of j at fixed values of other parameters. t=2; i=4; r=3; s=5; N_0=7600000; M_0=970000; WU=20100000; WL=1010000; NU=100000; NL=41000; MU=620000; ML=470000

j	Z	α_0	δ_0	γ_0	θ_0	β_0	α_1	δ_1	γ_1	θ_1	β_1
3	1417775	0	3.75	0	0.1660	30	6.25	0	30	14.33595	0
4	1417776	0	3.75	0	0.1769	30	6.25	0	30	14.29233	0
5	1417787	0	3.75	0	0.1582	30	6.25	0	30	14.36709	0
6	1417788	0	3.75	0	0.1778	30	6.25	0	30	14.28881	0

From table 4.3.3.2, it is observe that drug efficacy Z is in stochastic nature of the function of number of drug administration spells per cycle (j) when all other

parameters are constant. Hence it may be inferred that more number of drug administration spells per cycle have adverse effect on drug efficacy. Further it is observed that all the parameters i.e., arrival and departure rates to and from premalignant and malignant cells are exhibiting pure stochasticity.

Table 4.3.3.3

Values of $\alpha_0, \beta_0, \gamma_0, \delta_0, \theta_0, \alpha_1, \beta_1, \gamma_1, \delta_1, \theta_1$ for varying values of r at fixed values of other parameters. t=2; i=4; J=5; s=5; N_0=7600000; M_0=970000; WU=20100000; WL=1010000; NU=100000; NL=41000; MU=620000; ML=470000

r	Z	α_0	δ_0	γ_0	θ_0	β_0	α_1	δ_1	γ_1	θ_1	β_1
3	1417787	0	3.75	0	0.1194	30	6.25	0	30	14.52251	0
4	1347102	0	3.75	0	0.2080	30	6.25	0	30	14.16813	0
5	1260834	0	2.352119	0	0.0881	30	6.25	5.591523	30	14.64764	0
7	1109939	0	3.75	0	0.2731	30	6.25	0	30	13.90772	0

Table 4.3.3.4

Values of $\alpha_0, \beta_0, \gamma_0, \delta_0, \theta_0, \alpha_1, \beta_1, \gamma_1, \delta_1, \theta_1$ for varying values of s at fixed values of other parameters. t=2; i=4; J=5; r=3; N_0=7600000; M_0=970000; WU=20100000; WL=1010000; NU=100000; NL=41000; MU=620000; ML=470000

s	Z	α_0	δ_0	γ_0	θ_0	β_0	α_1	δ_1	γ_1	θ_1	β_1
2	1692356	0	3.00141	0	0.1636	30	6.25	3.770851	30	14.32244	0
3	1682972	0	3.08169	10	2.2163	6636789	6.25	2.673241	0	19.27589	0
4	1681144	0	3.579964	10	2.2605	5311113	6.25	0.680144	0	5.958031	0
5	1417787	0	3.75	0	0.1194	30	6.25	0	6.666667	14.52251	0

From tables 4.3.3.3 and 4.3.3.4 it is observed that drug efficacy Z is decreasing function of r and s respectively, when all the other parameters are constant. Hence it may be interpreted as the decreasing effectiveness of the drug is influenced by increase in number of during vacations and also increasing number of time units within the drug vacation. Further it is observed that varying values of drug vacation number exhibits the stochasticity of all the other parameters during the drug presence and absence.

Table 4.3.3.5

Values of $\alpha_0, \beta_0, \gamma_0, \delta_0, \theta_0, \alpha_1, \beta_1, \gamma_1, \delta_1, \theta_1$ for varying values of N_0 at fixed values of other parameters. t=2; i=4; J=5; r=3; s=5; M_0=970000; WU=20100000; WL=1010000; NU=100000; NL=41000; MU=620000; ML=470000

N0	Z	α_0	δ_0	γ_0	θ_0	β_0	α_1	δ_1	γ_1	θ_1	β_1
5500000	1417787	0	0.60195	0	0.0355	30	6.25	12.5922	6.666667	14.85787	0
5511000	1004353	25	0	0.329759	0.0688	30	0	15	6.446828	14.72466	0
5515000	1004316	25	0	0.328526	0.0686	30	0	15	6.44765	14.72568	0
5520000	1004269	25	0	0.329883	0.0689	30	0	15	6.446745	14.72454	0
5525000	1004219	25	0	0.334818	0.0699	30	0	15	6.443455	14.72041	0

Form table 4.2.3.5 it is observed that drug efficacy Z is decreasing function of initial number of premalignant cells when all the other parameters are constant. It implies that increasing number initial number of premalignant cells decrease drug efficacy. Further it is also observed that from same table that the parameters during absence of drug α_0, β_0, γ_0, δ_0, θ_0 and the parameters during presence of drug are decreasing in nature.

Table 4.3.3.6

Values of $\alpha_0, \beta_0, \gamma_0, \delta_0, \theta_0, \alpha_1, \beta_1, \gamma_1, \delta_1, \theta_1$ for varying values of WU at fixed values of other parameters. t=2; i=4; J=5; r=3; s=5; N_0=7600000; WU=20100000; WL=1010000; NU=100000; NL=41000; MU=620000; ML=470000

WU	Z	α_0	δ_0	γ_0	θ_0	β_0	α_1	δ_1	γ_1	θ_1	β_1
20101000	1417861	0	3.75	0	0.1194	30	6.25	0	6.666667	14.52249	0
20102000	1417935	0	3.75	0	0.1194	30	6.25	0	6.666667	14.5225	0
20103000	1418009	0	3.75	0	0.1194	30	6.25	0	6.666667	14.5225	0
20104000	1418084	0	3.75	0	0.1193	30	6.25	0	6.666667	14.52262	0
20105000	1418158	0	3.75	0	0.1760	30	6.25	0	6.666667	14.29604	0

From table 4.3.3.6 it is observed that drug efficacy Z is decreasing function of initial number of malignancy cells when all the other parameters are constant. It implies that increasing number of initial number of malignancy cells decrease the drug efficacy. It is also observed that time unit during absence of drug are increasing function and presence of drug is in decreasing function.

Table 4.3.3.7

Values of $\alpha_0, \beta_0, \gamma_0, \delta_0, \theta_0, \alpha_1, \beta_1, \gamma_1, \delta_1, \theta_1$ for varying values of M_0 at fixed values of other parameters. t=2; i=4; J=5; r=3; s= 5; N_0=7600000; M_0=970000; WL=1010000; NU=100000; NL=41000; MU=620000; ML=470000

M0	Z	α_0	δ_0	γ_0	θ_0	β_0	α_1	δ_1	γ_1	θ_1	β_1
951000	1417787	0	3.75	0	0.1390	30	6.25	0	6.666667	14.4438	0
962000	1417777	0	3.75	0	0.1749	30	6.25	0	6.666667	14.30021	0
965000	1417776	0	3.75	0	0.1774	30	6.25	0	6.666667	14.2906	0
974000	1417773	0	3.75	0	0.1810	30	6.25	0	6.666667	14.27603	0

From table 4.3.3.7 it is observe that drug efficacy Z is increasing function of white blood cells upper limit when all the other parameters are constant. And the rate of θ_0 during the absence of drug is increasing and the rate of presence of drug θ_0 is decreasing in nature. Further it is also observe that all the parameters during absence and presence of drug are invariant of change when the number of white blood cells upper limit are increasing.

Table 4.3.3.8

Values of $\alpha_0, \beta_0, \gamma_0, \delta_0, \theta_0, \alpha_1, \beta_1, \gamma_1, \delta_1, \theta_1$ for varying values of WL at fixed values of other parameters. t=2; i=4; J=5; r=3; s= 5; N_0=7600000; M_0=970000; WU=20100000; NU=100000; NL=41000; MU=620000; ML=470000

WL	Z	α_0	δ_0	γ_0	θ_0	β_0	α_1	δ_1	γ_1	θ_1	β_1
1011000	1417712	0	3.75	0	0.1194	30	6.25	0	6.666667	14.52244	0
1012000	1417638	0	3.75	0	0.1760	30	6.25	0	6.666667	14.29594	0
1013000	1417564	0	3.75	0	0.1194	30	6.25	0	6.666667	14.5225	0
1014000	1417490	0	3.75	0	0.1194	30	6.25	0	6.666667	14.52242	0
1015000	1417406	0	3.75	0	0.1762	30	6.25	0	6.666667	14.2954	0

From table 4.3.3.8 it is observed that drug efficacy Z is decreasing function of white blood cells lower limit when all the other parameters are constant. Hence it may be interpreted that more number of white blood cells is influenced the decrease the drug efficacy. Further it is observed that all other parameters to and from the premalignancy and malignancy cells are pure stochastic nature.

Table 4.3.3.9

Values of $\alpha_0, \beta_0, \gamma_0, \delta_0, \theta_0, \alpha_1, \beta_1, \gamma_1, \delta_1, \theta_1$ for varying values of WL &NU at fixed values of other parameters. t=2; i=4; J=5; r=3; s=5; N_0=7600000; M_0=970000; WU=20100000; NL=41000; MU=620000; ML=470000

WL	NU	Z	α_0	δ_0	γ_0	θ_0	β_0	α_1	δ_1	γ_1	θ_1	β_1
1010000	101000	1417787	0	3.75	0.0000	0.119373	30	6.25	0	6.66667	14.52251	0
1011000	102000	1417712	0	3.75	0.0000	0.119391	30	6.25	0	6.66667	14.52244	0
1012000	103000	1417638	0	3.75	0.0000	0.176016	30	6.25	0	6.66667	14.29594	0
1013000	104000	1417564	0	3.75	0.0000	0.119376	30	6.25	0	6.66667	14.5225	0
1014000	105000	1417490	0	3.75	0.0000	0.119394	30	6.25	0	6.66667	14.52242	0

From table 4.3.3.9 it is observed that the drug efficacy is a decreasing function of upper limit number of premalignant cells when all other parameters are constant. It implies that increasing the number of premalignant cells will decrease the drug efficacy. Further it is observed that all parameters when the upper limit of number of premalignant cells are increasing.

Table 4.3.3.10

Values of $\alpha_0, \beta_0, \gamma_0, \delta_0, \theta_0, \alpha_1, \beta_1, \gamma_1, \delta_1, \theta_1$ for varying values of WU & NL at fixed values of other parameters. t=2; i=4; J=5; r=3; s=5; N_0=7600000; M_0=970000; WL=1010000; NU=100000; MU=620000; ML=470000

WU	NL	Z	α_0	δ_0	γ_0	θ_0	β_0	α_1	δ_1	γ_1	θ_1	β_1
20100000	42000	1417787	0	3.75	0.0000	0.11937	30	6.25	0	6.66667	14.52251	0
20101000	43000	1417861	0	3.75	0.0000	0.11937	30	6.25	0	6.66667	14.52249	0
20102000	44000	1417935	0	3.75	0.0000	0.11937	30	6.25	0	6.66667	14.5225	0
20103000	45000	1418009	0	3.75	0.0000	0.11937	30	6.25	0	6.66667	14.5225	0

From table 4.3.3.10 it is observed that the drug efficacy Z is increasing function of lower limit of premalignant cells when all other parameters are constant. It implies that increasing the number of premalignant cells will decrease the drug efficacy. Further it is observed that all parameters when the lower limit of number of premalignant cells are increasing.

Table 4.3.3.11

Values of $\alpha_0, \beta_0, \gamma_0, \delta_0, \theta_0, \alpha_1, \beta_1, \gamma_1, \delta_1, \theta_1$ for varying values of WL & MU at fixed values of other parameters. t=2; i=4; J=5; r=3; s=5; N_0=7600000; M_0=970000; WU=20100000; NU=100000; NL=41000; ML=470000

WL	MU	Z	α_0	δ_0	γ_0	θ_0	β_0	α_1	δ_1	γ_1	θ_1	β_1
1010100	621000	1417779	0	3.75	0.0000	0.119382	30	6.25	0	6.66667	14.52247	0
1010200	622000	1417772	0	3.75	0.0000	0.119374	30	6.25	0	6.66667	14.52251	0
1010300	623000	1417755	0	3.75	0.0000	0.176104	30	6.25	0	6.66667	14.29558	0
1010400	624000	1417757	0	3.75	0.0000	0.176028	30	6.25	0	6.66667	14.29589	0

Table 4.3.3.12

Values of $\alpha_0, \beta_0, \gamma_0, \delta_0, \theta_0, \alpha_1, \beta_1, \gamma_1, \delta_1, \theta_1$ for varying values of WU & ML at fixed values of other parameters. t=2; i=4; J=5; r=3; s= 5; N0=7600000; M0=970000; WL=1010000; NU=100000; NL=41000; MU=620000;

WU	ML	Z	α_0	δ_0	γ_0	θ_0	β_0	α_1	δ_1	γ_1	θ_1	β_1
20101000	471000	1417861	0	3.75	0.0000	0.181481	30	6.25	0	6.66667	14.27408	0
20102000	472000	1417935	0	3.75	0.0000	0.119376	30	6.25	0	6.66667	14.5225	0
20103000	473000	1418009	0	3.75	0.0000	0.119374	30	6.25	0	6.66667	14.5225	0
20104000	474000	1418084	0	3.75	0.0000	0.119345	30	6.25	0	6.66667	14.52262	0
20105000	475000	1418158	0	3.75	0.0000	0.175991	30	6.25	0	6.66667	14.29604	0

From table s 4.3.3.11 and 4.3.3.12 it is observed that the drug efficacy Z is increasing function of lower limit of malignancy cells when all other parameters are constant. It implies that increasing the number of malignancy cells will decrease the drug efficacy. Further it is observed that all parameters when the lower limit of number of malignancy cells are increasing.

Chapter - 5

SUMMARY AND CONCLUSIONS

This study has developed stochastic optimization problems for optimal drug administration after a thorough modeling of the tumor growth on stochasticity assumptions. In the first part, a bi-variate stochastic model was developed for cancer cell growth with an assumption that the growth and loss processes of normal and mutant cells follows Poisson process. In order to observe the behaviour of the model during chemotherapy, the model is extended for studying cancer cell growth in the presence and absence of the drug. As chemotherapy is executed in cycles with different intensified spells, the growth and loss rates of both normal and mutant cells are considered as heterogeneous and follows Poisson process. The statistical measures in terms of model parameters are derived such as means, covariances and variances of both normal and mutant cells. In order to estimate the parameters of the model a stochastic programming problem is formulated. The objective function for maximizing the drug efficacy was formulated with decision parameters such as rates of arrivals of normal cells, mutant cells, rate of transformation of normal cells to mutant cells and the rates of deaths of normal and mutant cells. The objective function has accommodated the above mentioned decision parameters in both drug administration and drug vacation periods. The constraints were formulated by considering the optimal loss of WBC, optimal minimum size of healthy and normal cells, optimal targeted size of mutant cells during the period of chemotherapy. Sensitivity of the model was analyzed through numerical data sets using MATHCAD. Decision parameters are explored using LINGO software. All the numerical values are thoroughly analyzed and the stochastic optimization model is interpreted.

The book is organized in 5 chapters, chapter-1 deals with overview on cancer problem, models importance in studying the cancer growth by reviewing the literature from 1932 to 2010. A brief summary on stochastic models, mathematical models and optimization models on cancer growth is made. Focus of thesis, motivation of study is given by highlighting the current developed work and existing gap in the thrust area of stochastic modeling of cancer cell growth.

Understanding about a disease like cancer requires much attention on conventional means. Regarding the reasons for getting cancer, there are innumerable causes either by physiological or by other external factors of the patient. Modeling cancer cell growth using mathematical aspects is considered to be a conventional approach. Measuring severity of a cancer through estimation is possible when structural mathematical model behind it is suitable due to physiological and environmental factors. The problem of cancer cell growth has to be considered as stochastic rather than deterministic. There is much literature evidence on modeling of cancer cell growth using stochastic models. Stochastic models used to provide the basic frame work for understanding and analyzing the natural phenomena behind the cancer growth. A tumor is defined as mass of tissues formed as a result of inappropriate and excessive proliferation of cells. The complexity in understanding and measuring the tumor growth made it necessary to formulate and integrate the classical, mathematical and the real life statistical models. Describing the growth of tumor at different levels is possible only when the construction of the model is rational. In practice uncertainty prevails everywhere in various aspects of tumor growth. Hence stochastic modeling will be the suitable option for formulating the cancer growth.

With Mayneord 1932 pioneering work on mathematical study for measuring the tumor growth, several authors have developed different cancer cell growth models with different assumptions. Those works have explained and analyzed the kinetics of tumor growth. Modeling of tumor growth has gained the importance due to the scope of its uses in optimal drug administration. The growth and loss rates of both normal and mutant cells are considered to be random variables due to the influence of innumerable reasons. Conventional method of modeling the tumor growth through mathematical means in the assumption of deterministic situation has shifted its paradigm to stochastic modeling. Time dependency is an essential consideration while observing the dynamics of tumor growth. The vital factors of tumor growth process are spontaneous mutation, proliferation, growth and loss of the cell etc. Modeling cancer growth in a single environment has lost its significance and hence there is a need of constructing it with heterogeneous environment. The behaviour of growth and loss patterns of both normal and mutant cells have to be modeled with stochasticity.

Observing the literature, in most of the works they have considered the growth of cancer in a homogeneous environment whereas the health status of the patient under drug administration has to be considered as heterogeneous. The factors like individual physiological, environmental and other extraneous condition lead to the growth of cancer as not only heterogeneous but also time dependent. A Very few work on development of stochastic models, optimal drug design and administration is reported in the literature. In this thesis an attempt is made to fill the gap of developing stochastic models as well as stochastic program optimization under heterogeneity and time dependence in cancer growth. Our work is dedicated in three domains namely (1) development of stochastic model under heterogeneous time dependent Poisson process (2) Developing stochastic models for cancer related cell (mutant, premalignant, malignant) growth under the drug administration and drug recovery periods, (3) Developing stochastic optimization programming problem for effective and optimal drug administration subject to monitoring the safe health norms of the patient. Observing the cell Kinetics in tumor it is understand that spontaneous mutation, proliferation of mutant cells, transformation of cells from one stage to other stages like from normal to mutancy, from mutancy to pre-malignancy and from pre-malignancy to malignancy and the loss processes of cell at every stage are playing very important role in studying the growth behaviour, mostly regulated by alleles of gene.

In Chapter-2 we develop stochastic models for cancer growth with spontaneous mutation and proliferation on normal and mutant cell. As an extension of this section, a stochastic model for cancer growth during drug administration and drug vacation periods is developed, in both the sections difference-differential equation were developed by assuming linear bivariate Poisson process in cancer cell growth. Statistical constants were derived by using probability generating function. Sensitivity analysis of the model for both the sections is carried out.

In section-I, we develop a bi-varaite stochastic model for normal and mutant cell growth. The growth and loss rates processes of both mutant and normal cells are assumed as Poisson parameters. Difference differential equations and cumulant generating function are used for finding the statistical measures like expected number of normal cells and mutant cells at time ‘t’. The variance number of normal and mutant cells and also the covariance between normal cells and mutant cells are

derived. The model behaviour is observed further by applying a secondary data obtained from various types of cancer patients with the source of TIFR (Tata Institute of Fundamental Research), collected through Internet. The sensitivity analysis is carried out with the available data sets. In section-II, A bi-varaite stochastic model for normal and mutant cell growths for the environment of cancer chemotherapy is developed. Drug administration and drug vacation periods are considered separately in the assumptions and the model is developed with an intension of exploring more suitable model to the cancer patients under chemotherapy. The difference differential equations and cumulant generating function are used in deriving the statistical measures of the model. The source data is also applied to the model and sensitivity analysis is carried out and placed in tables 2.2.4.1 to 2.2.4.8 and also in tables 2.3.4.1 to 2.3.4.13.

From tables 2.2.4.1 to 2.2.4.8 it is observed that expected number of normal cells, expected number of mutant cells, variance of normal cells, variance of mutant cells, covariance between normal cells and mutant cells are increasing functions of the initial number of normal cells (N_0); The expected number of mutant cells and variance of mutant cells are increasing functions and expected number of normal cells, variance of normal cells and covariance between normal cells and mutant cells are invariant of change of initial size of the mutant cells (M_0); The expected number of normal cells, expected number of mutant cells, variance of normal cells, covariance between normal and mutant cells are increasing functions and variance of mutant cells is a decreasing function of rate of generation of normal cell from normal cells (a); Expected number of mutant cells, covariance between normal cells and mutant cells, Variance of mutant cells are increasing functions and expected number of normal cells, variance of normal cells are invariant of rate of generation of mutant cell from normal cells (b); Expected number of mutant cells, covariance between normal and mutant cells and variance of mutant cells are increasing functions and expected number of normal cells and variance of normal cells are invariant with respect to rate of generation of mutant cells from mutant cells (c); Expected number of normal cells, expected number of mutant cells, variance of normal cells and covariance between normal and mutant cells are decreasing functions and the variance of mutant cells is an increasing function of rate of death of normal cells (d); Expected number of normal cells, variance of normal cells are invariant and

expected number of mutant cells, covariance between normal and mutant cells are decreasing functions, variance of mutant cells is increasing function of rate of death of mutant cells (g); Expected number of normal cells, expected number of mutant cells, variance of normal cells, covariance between normal and mutant cells and variance of mutant cells are increasing functions of time (t) when all the other parameters are constant.

Further from tables 2.3.4.1 to 2.3.4.13 it is observed that expected number of normal cells, expected number of mutant cells, variance of normal cells, variance of mutant cells and covariance between normal and mutant cells are increasing functions of the initial number of normal cells (N_0); Expected number of normal cells, variance of normal cells and covariance between normal and mutant cells are invariant, expected number of mutant cells, variance of mutant cells are increasing functions of initial number of mutant cells (M_0); Expected number of normal cells, expected number of mutant cells, Variance of normal cells, variance of mutant cells and covariance between normal cells and mutant cells are increasing functions of the rate of generation of normal cell from normal cell during the absence of drug (a_0); Expected number of normal cells, expected number of mutant cells, variance of normal cells, variance of mutant cells and covariance between normal cells and mutant cells are increasing functions of rate of generation of normal cell from normal cells during the presence of drug (a_1); Expected number of normal cells and variance of normal cells are invariant, expected number of mutant cells, covariance between normal and mutant cells, variance of mutant cells are increasing function of rate of generation of mutant cell from normal cell during absence of drug (b_0); Expected number of normal cells and variance of normal cells are invariant, expected number of mutant cells, covariance between normal cells and mutant cells, variance of mutant cells are increasing functions of rate of generation of mutant cell from normal cell during the presence of drug (b_1); Expected number of normal cells, variance of normal cells are invariant, expected number of mutant cells, covariance between normal and mutant cells, variance of mutant cells are increasing functions of rate of generation of mutant cell from mutant cell during the absence of drug (c_0); Expected number of normal cells and variance of number of normal cells are invariant, expected number of mutant cells, covariance between normal and mutant cells, variance of mutant cells are increasing functions of rate of generation of

mutant cells from mutant cells during the presence of drug (c_1). Expected number cells from normal cells, expected number of mutant cells, covariance between normal cells and mutant cells, variance of normal cells, variance of mutant cells are decreasing functions of rate of death of normal cell during the absence of drug (d_0) and during the presence of drug (d_1); Expected number of normal cells, variance of normal cells are invariant, expected number of mutant cells, covariance between normal cells and mutant cells, variance of mutant cells are decreasing functions of rate of death of mutant cells during the absence (g_0) and presence of drug(g_1). Expected number of normal cells, expected number of mutant cells, covariance between normal and mutant cells, variance of normal cells and variance of mutant cells are decreasing functions of time (t) when all the other parameters are constant.

In chapter-3 we develop a two stage stochastic model for mutant cell growth assuming the growth and loss processes of cancer cell growth are combination of growth of premalignant and malignant cells. In this model we consider that mutant cell is transformed into premalignant cell and then it will be converted into malignant cell as a full-fledged cancerous cell. The rates of arrivals to the premalignant and malignant stages from mutant stage and the death rates of premalignant and malignant cells are assumed as bivaraite Poisson parameters. The rate of conversion of premalignant cell to malignant cell is also a bivaraite Poisson parameter. A bivariate time dependent Poisson process is developed from which the necessary differential equations and statistical measures are derived. A similar model is developed in the extension section when the patient is under chemotherapy, exposed to drug administration and drug vacation. Statistical measures are derived from joint probability function of premalignant and malignant cells using cummulant generating function. While developing a two-stage model, it is assumed that the growth and loss of premalignant and malignant cell population is a linear combination of drug administration and drug vacation periods.

The sensitivity analysis is carried out based on the results obtained as per tables 3.2.4.1 to 3.2.4.8 and also from the tables 3.3.4.1 to. 3.3.4.14. From the tables it is observed that expected number of premalignant cells, expected number of malignant cells, variances of premalignant cells and malignant cells are increasing functions, covariance between premalignant and malignant cells are negative and decreasing with respect to increase in the initial number of premalignant cells (N_0); Expected

number of premalignant cells, variance of premalignant cells are invariant, expected number of malignant cells, variance of malignant cells are increasing functions of initial number of malignant cells (M_0); Expected number of premalignant cells, expected number of malignant cells, variance of premalignant cells, variance of malignant cells are increasing functions, covariance between premalignant and malignant cells is negative and invariant of rate of generation of premalignant cells (α); Expected number of premalignant cells, variance of pre malignant cells are invariant, expected number of malignant cells and variance of malignant cells are increasing functions, covariance of premalignant and malignant cells are negative and invariant of rate of generation of malignant cells (β_1); Expected number of premalignant cells, variance of premalignant cells are decreasing functions, variance of malignant cells is an increasing function, covariance between premalignant and malignant cells is negative and increasing with respect to rate of transformation from premalignant cell to malignant cell (γ); Expected numbers of premalignant cells, expected number of malignant cells, variance of premalignant cells, variance of malignant cells are decreasing functions, covariance between premalignant and malignant cells is negative and increasing with respect to rate of death of premalignant cells (δ); Expected number of premalignant cells, variance of premalignant cells are invariant, expected number of malignant cells, variance of malignant cells are decreasing functions, covariance between premalignant and malignant cells are negative and increasing with respect to rate of death of malignant cells (θ); Expected number of premalignant cells, expected number of malignant cells, variance of premalignant cells, variance of malignant cells are decreasing functions, covariance between premalignant and malignant cells is negative and increasing with respect to change of time't', when all other parameters are constant.

From tables 3.3.4.1 to 3.3.4.13 it is observed that expected number of premalignant cells and malignant cells; variances of premalignant cells and malignant cells are increasing functions, covariance between premalignant and malignant cells is invariant of arrival rate of premalignant cells under the absence of drug (α_0) and presence of drug (α_1); Expected number of premalignant cells, variance of premalignant cells, covariance between premalignant and malignant cells are invariant, expected number of malignant cells, variance of malignant cells are increasing functions of arrival rate of malignant cells under absence of drug (β_0)

and presence of drug(β_1); Expected number of premalignant cells, variance of premalignant cells, variance of malignant cells are decreasing functions, covariance between premalignant and malignant cells & expected number of malignant cells are increasing functions of rate of transformation of malignant cells from premalignant cells during the absence of drug(γ_0) and presence of drug (γ_1); Expected number of premalignant cells, expected number of malignant cells, variances of premalignant and malignant cells are decreasing functions, covariance between premalignant and malignant cells is negative and decreasing function of rate of death of premalignant cells under absence of drug (δ_0) and presence of drug (δ_1); Expected number of premalignant cells, variance of premalignant cells are invariant, expected number of malignant cells are decreasing functions of death of malignant cells under absence of drug (θ_0) and presence of drug (θ_1); Expected number of premalignant cells, expected number of malignant cells, variances of premalignant cells and malignant cells are increasing functions, covariance between premalignant and malignant cells is invariant of change of initial number of pre malignant cells (N_0); Expected number of premalignant cells; variance of premalignant cells, covariance between premalignant and malignant cells are invariant, expected number and variance of malignant cells are increasing functions of initial number of malignant cells (M_0); Expected number of premalignant cells, expected number of malignant cells, variances of premalignant cells, malignant cells are increasing functions, covariance between premalignant and malignant cells is decreasing function of time't' when all the other parameters are constants.

Continuous drug administration may lead to health hazards due to unwanted loss of white blood cells as well as normal and healthy cells. Hence the patient under the treatment of chemotherapy needs periodic check of health status and he may be allowed to drug vacation to get recovery. Contrary, drug vacation for long time leads to re-aggravate the growth of mutant cell population and hence long term drug vacation also is unwanted. Regarding the dosage levels, drug administration above the required quantity may harm both normal cells and white blood cells significantly. Contrary the drug quantity less than the required level prepare the body drug resistance. And hence there is a need of optimal drug dosage levels that are to be administrated. By considering all the above, we develop a nonlinear programming

problem with an objective of maximizing the drug efficacy subject to minimum risk or loss of WBC.

In chapter-4 optimization problems for cancer chemotherapy are developed through stochastic programming. The arrival and death rates of mutant and normal cells are assumed as stochastic parameters and estimated them through the developed stochastic optimization programming problem. The optimality of drug effectiveness is studied and analyzed through a suitable data. An objective function for maximizing the drug effectiveness is formulated by considering various inputs like intensity of drug dose, times of drug administration, times of drug vacation, cycle lengths of drug administration and drug vacation, loss of WBC and expected number of existing premalignant and malignant cells etc. Constraints are also formulated by considering upper and lower desired limits of premalignant cells, malignant cells, WBC etc. Stochastic parameters namely arrival and death rates of premalignant and malignant cells during drug vacation and drug administration are assumed as non-negative.

Stochastic models for cancer cell growth with spontaneous mutation and proliferation are developed in Chapter-2. The model also considered the behaviour of cancer cell growth under chemotherapy environment for drug administration and drug vacation periods. A two stage stochastic model for cancer cell growth is developed when a mutant cell has transformation of premalignant and malignant cells is developed in Chapter-3. An extension model is developed for two stage cancer growth when the patient is under chemotherapy. The statistical measures like average number and variance number of different kinds of cells are derived in both the models.

This programming problem is developed to explore the parameters/decision variables like growth rates, death rates and the rate of transformation from one stage to another stage. The aspects like number of units of drug per spell, number of spells of drug administration per cycle, number of cycles for drug administration in a chemotherapy, number of time units per unit of vacation, number of days in a drug vacation, number of drug vacations during the total chemotherapy period are considered in developing the objective function as well as constraints.

Programming problem is analysed with numerical data sets obtained in tables from 4.2.3.1 to 4.2.3.8 and also from the tables 4.3.3.1 to 4.3.3.12. From the numerical illustrations, 4.2.3.1 to 4.2.3.8, it is observed that the objective function Z (drug efficacy) is an increasing function of 'i' (number of drug administrations.) is decreasing function of number of drug administration spells per cycle (j); is an increasing function of r and s respectively; is an increasing function of initial number of normal cells; increasing function of normal cells upper limit; increasing function of normal cells lower limit; increasing function of white blood cells upper limit. From tables 4.3.3.1 to 4.3.3.12, it is observed that the drug efficacy is an increasing function of 'i'; The parameters in drug absence namely $\alpha_0, \beta_0, \gamma_0, \delta_0, \theta_0$ and the parameters during drug presence $\alpha_1, \beta_1, \gamma_1, \delta_1$ and θ_1 and T_1 behaves erratically and exhibiting the stochastic nature. Stochastic in nature of the function of number of drug administration spells per cycle (j); the parameters i.e., arrival and departure rates to and from premalignant and malignant cells are exhibiting pure stochasticity; decreasing function of r and s respectively; varying values of drug vacation number exhibits the stochasticity of all the other parameters during the drug presence and absence. Drug efficacy is decreasing function of initial number of premalignant cells, the parameters during absence of drug $\alpha_0, \beta_0, \gamma_0, \delta_0, \theta_0$ and the parameters during presence of drug are decreasing in nature. Drug efficacy is decreasing function of initial number of malignant cells; time unit during absence of drug are increasing function and presence of drug is in decreasing function. Drug efficacy is increasing function of white blood cells upper limit the rate of death of malignant cell during the absence of drug is increasing and the rate of death malignant cell presence of drug is decreasing in nature; the parameters during absence and presence of drug are invariant of change when the number of white blood cells upper limit are increasing. Drug efficacy is decreasing function of white blood cells lower limit; all other parameters to and from the premalignant and malignant cells are stochastic in nature. The drug efficacy is a decreasing function of upper limit number of premalignant cells; is an increasing function of lower limit of premalignant cells; is an increasing function of lower limit of malignant cells;

In chapter-5 the summary of research findings and conclusion are presented. The scope of future research work is mentioned. Bibliography is also presented for effective reference.

SCOPE FOR FURTHER RESEARCH:

In this thesis we have concentrated mostly on stochastic modeling of cancer cell growth for normal and mutant cells, two stage mutant cell growth in general environment as well as chemotherapy environments. While developing stochastic programming problem for optional drug administration, the expected number of normal and mutant cells, expected number of premalignant and malignant cells are estimated through the method of moments. As there are limitations on method of moments, the robustness of programming problem has to be verified with suitable techniques. While estimating the parameters like the rates of growth, the rates of transformations, the rates of deaths of different category of cells have to be estimated with valid estimation techniques like method of maximum likelihood estimation. Our work is mostly categorized under the theoretical development through which the cancer cell growth can be understood on mathematical lines. Whereas these models have to be made more accessible to the applied scientists working in health care industry. As the complexity of the model and its relevance to the real life data, cumbersome and heavy calculations require the attention of computer science technologists to prepare suitable softwares. User friendly computer automation can also be developed by embiding the developed mathematical models and suitable computer programs.

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