MODELLING AND SOLVING CANCER EQUATION

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

in

Physics

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I affectionately dedicate this thesis to my dear niece 'Mausmi'.

CERTIFICATE

I hereby declare that the report entitled **"MODELLING AND SOLVING CANCER EQUATION"** is an authentic record of my own work carried out for the partial fulfilment of the requirement for the award of the degree of M.Sc. (Masters of Science) at Thapar University, Patiala (Punjab), under the guidance of ***Dr. Soumendu Jana*** (School of Physics and Materials Science). The matter presented in the dissertation has not been submitted in part or full for the award of any other degree.

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CONTENTS

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ABSTRACT

The population dynamics of tumor cells in Breast Cancer, present in different stages of cell cycle has been studied for different drug delivery regimens and for different delay times. A modification in drug delivery function is introduced which results in decrease in tumor cell population. MATLAB solver `dde23` ***is used for the numerical runs. Stability analysis has been done to study the change in behavior of parameter space. Finally, the concept of DDEs is extended to another type of cancer i.e. Colon Cancer.***

CHAPTER 1

1.1 INTRODUCTION:

The uncontrolled growth and spread of the mutated cells in the body indicate cancer [1].The accumulation of cells in a specific part of the body forms tumor, thereby referred to as tumor cells. The part of the body where the growth and accumulation of the tumor cells take place decides the name/type of the cancer. Also the type of cancer is named after the starting place, no matter where it spreads in the body. For example, breast cancer that has spread to the liver is called metastatic breast cancer, not liver cancer. Likewise, metastatic prostate cancer is basically prostate cancer that has spread to the bone [4]. This is not actually bone cancer [8].

The uncontrolled spreading of these cells may lead to death [2]. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Cancer is basically the malfunctioning of genes which supervise the growth and division of body cells [3].

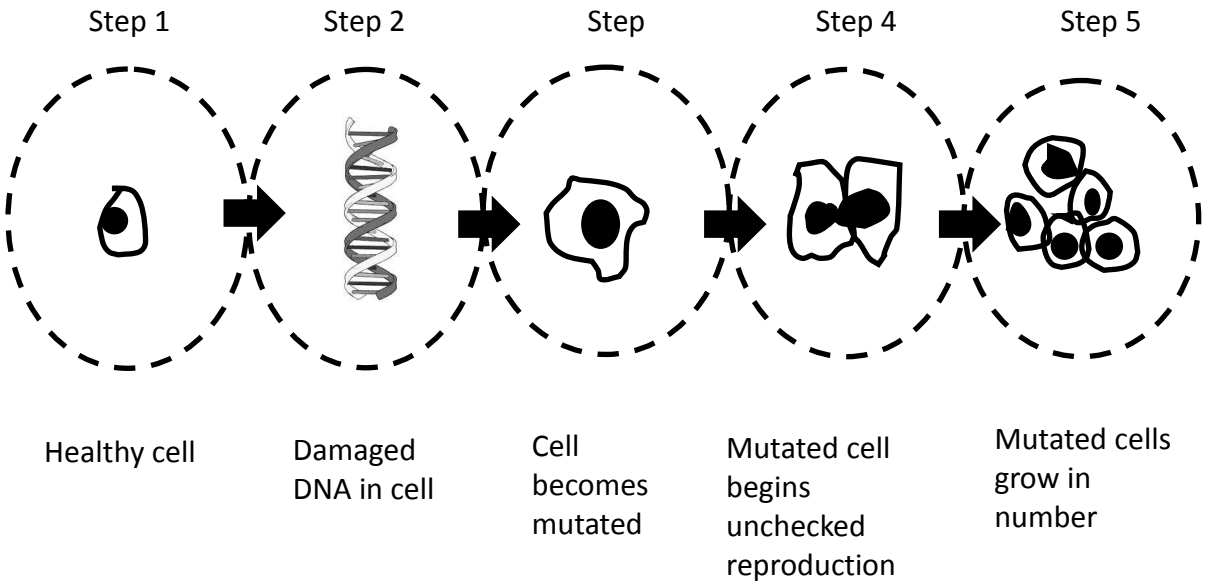

Fig. 1.1 *Reproduction of cancer cell*

Fig. 1.1 depicts the reproduction mechanism of a cancer cell. The DNA may get damaged due to a number of factors such as exposure to harmful rays, excess alcohol

intake, genetic factors, medical factors etc. The damaged DNA leads to the mutation of cells. Once the cells become mutated, there is non-cooperation among the cell functions, responsible for their untimely division or death [4]. As a result of which the cells begin unchecked reproduction in the body and may lead to death.

1.2 CAUSES OF CANCER:

There are various factors that are responsible for cancer development. These include many internal, external, chemical, medical and environmental factors [5-7].
Few of them are listed below:

- Excess intake of tobacco, alcohol; smoking.
- Exposure to radioactive chemicals, radiations and ultraviolet solar radiations.
- Unhealthy lifestyle, lack of physical activity, wrong dietary and food habits.
- Infection due to viruses like hepatitis B, hepatitis C etc.
- Inherited mutated hormones; immune conditions and mutations that occur from metabolism; poor immune system.
- Urban air pollution; household smoke; use of solid fuels etc.

1.3 BEHAVIOUR OF NORMAL CELLS IN BODY:

A number of trillion of living cells in our body are responsible for the development and healthy living of a human being [4**]**. There is a continuous and speedy reproduction of cells in the initial period of a person's life for the growth of the person. As the age increases, the cell division process is meant only for the replacement or repair of worn out cells [8].

1.4 INITIATION AND SPREAD OF CANCER:

Amongst the trillion of cells in our body, various processes are carried out with the help of the cooperation within these cells. As soon as this cooperation collapses, there is uncontrolled growth of cells in the body leading to eventual death of the organism [4]. Cancer cell growth is different from normal cell growth. Instead of dying, cancer cells continue to grow and form new, abnormal cells. Cancer cells have the ability to invade (grow into) other tissues, something that normal cells cannot do. Uncontrolled growth and

other tissue invasion are what make a cell cancerous [9]. This process is referred to as *metastasis* and most of the time the reason for death of organism is metastatic growth.

Cells become cancer cells because of DNA (deoxyribonucleic acid) damage. DNA is in every cell and it directs all the cell's actions. In a normal cell, when DNA gets damaged the cell either repairs the damage or the cell dies. In cancer cells, the damaged DNA is not repaired, and the cell doesn't die like it should. Instead, the cell goes on making new cells that the body doesn't need. These new cells all have the same abnormal DNA as the first cell does [4].

1.5 HOW CANCER DIFFERS:

As far as nomenclature is concerned the host organ and the source organ is important. Some cancer cells grow in a particular organ and the name of the cancer usually suggested after the organ's name. Some cancer cells have the ability to pass through the blood stream and travel to the other parts of the body and start its growth there. Still such type of cancer is named after the originating body part.

1.6 CELL CYCLE:

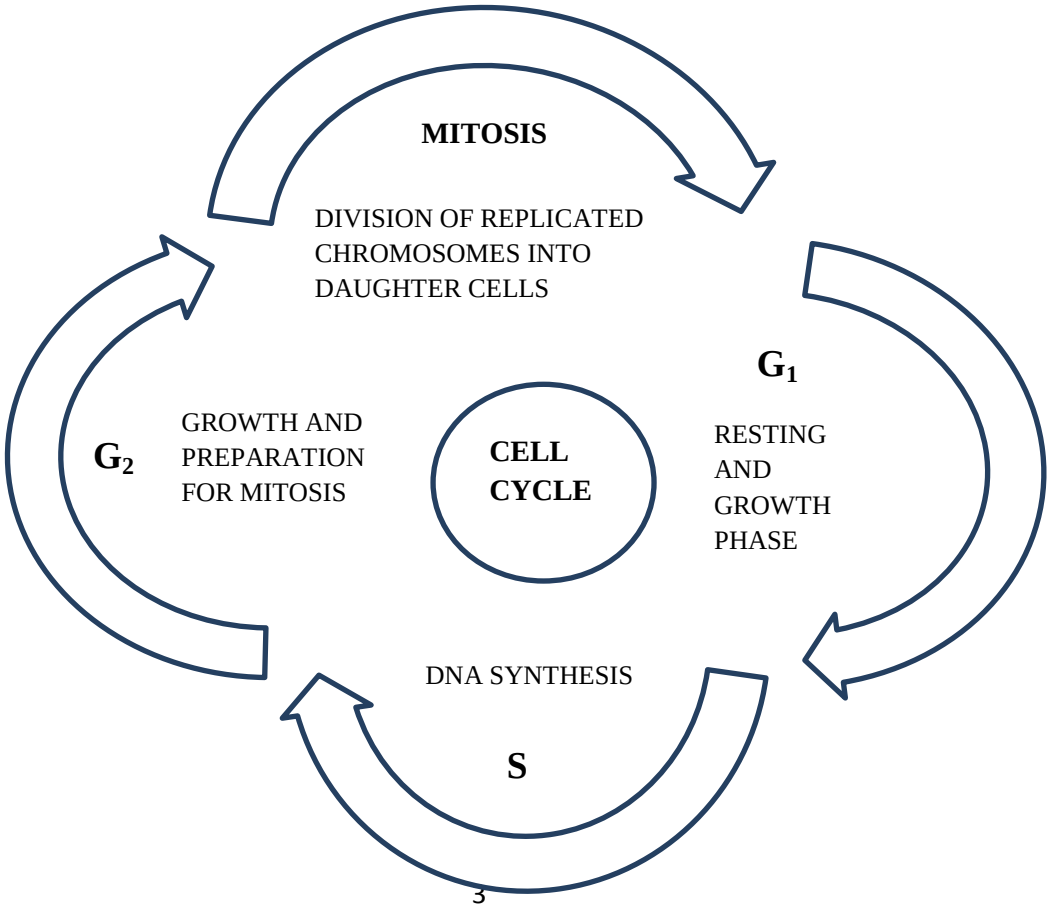

Fig. 1.2 *Cell cycle of normal cell*

Fig.1.2 represents the cell cycle of a normal cell. Cancer cells reproduce through a life cycle consisting of five phases of development: G_1 (pre-synthetic phase), S (synthetic phase), G_2 (post synthetic phase), and M (mitosis), as in fig 1.2. Between G_2 and M phases, an intermediate phase G_0 lies, often called as quiescent phase, in which the cells do not prefer to divide. In the G_1 phase the cell grows completely with addition of cytoplasm to it, the size of the cell keeps on increasing. This is the longest phase of all, may take up to forty eight hours [10]. During the S phase, replication of DNA takes place. This phase may last up to eight to twenty hours. The final preparations for the cell division are being made in phase G_2. The duration for this phase is too short, typically can be around four hours [13]. Finally, during Mitosis, there is an equal distribution of cell components and the DNA among the replicated chromosomes and division takes place. The duration of mitosis can be as short as half an hour. Moreover, the cells can go through the G_0 phase also but for this, it may require some external stimuli to enter in it [12].

1.7 QUIESCENT PHASE:

As discussed in previous subsection, the quiescent phase is the phase in which, if a cell enters, may not prefer to divide i.e. a quiescent cell needs some stimuli to enter the cell cycle. It is also noteworthy that some cells may never enter the quiescent phase, whereas others like many nerve cells may stay in it for their entire life cycle. These cells may be sometimes responsible for resistive behavior during chemotherapy and reoccurrence in post-therapy cancer patients [12, 22].

Amongst a number of different types of prevailing cancers, BREAST CANCER is one of the most frequent varieties. The non-skin cancer that is common among the women is the Breast Cancer and in men is Prostate Cancer [1]. Breast cancer starts in the cells of the breast as a group of cancer cells that can then invade surrounding tissues or spread (metastasize) to other areas of the body by flowing through the blood stream in the body.

1.8 FACTS AND FIGURES RELATED TO BREAST CANCER:

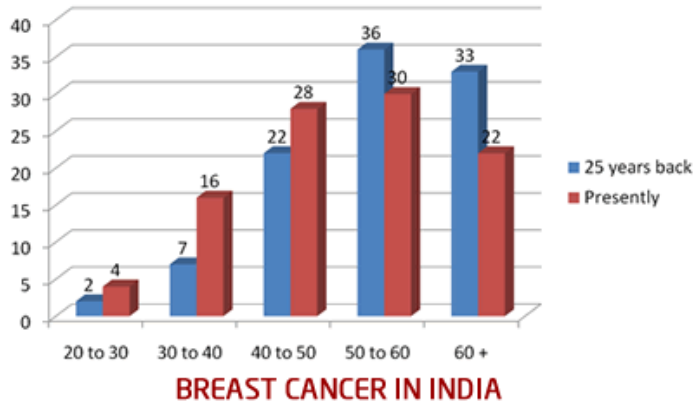

Fig. 1.3 *Breast cancer scenarios in India* [14].

Breast cancer is most common cancer in women in all urban areas in India. The phenomenon of AGE SHIFT is being witnessed in India with the age of developing breast cancer being sifted from **50-70** years to **30-50** years in women.

In above figure, the horizontal line lowers down represents the age groups: 20 to 30 years, 30 to 40 years and so on. And the vertical line represents the percentage of cases. The blue color represents the incidence 25 years back, and maroon color represents the situation today. 25 years back, out of every 100 breast cancer patients, 2% were in 20 to 30 years age group, 7% were in 30 to 40 and so on. 69% of the patients were above 50 years of age. Presently, 4% are in 20 to 30 years age group, 16% are in 30 to 40, 28% are in 40- 50 age group. So, almost 48% patients are below 50. An increasing numbers of patients are in the 25 to 40 years of age, and this definitely is a very disturbing trend [14].

Above figure depicts that:

- The number of breast cancer cases is increasing in younger age group.
- There is a gradual decrease in the breast cancer cases in older aged groups.

Chemotherapy is one of the several ways to battle cancer. There are two types of chemotherapy drugs. The first type interferes with the cellular activity of the tumor cells and the second type attacks the tumor cells during a specific cell cycle. Paclitaxel is one of the examples of cycle specific chemotherapy drug [15]. Paclitaxel is a drug used to treat breast, ovarian, head and neck cancer. It is a naturally occurring substance that is derived from the tree Pacific Yew. Together with the chemically closely related semi-

synthetic substance docetaxel it makes up the taxane group of anticancer drugs. Paclitaxel inhibit cell division by stiffening parts of the cell skeleton, and is used in cancer treatment (chemotherapy) primarily against ovarian, breast and non-small cell lung cancer. Like other chemotherapeutic drugs, paclitaxel has an overall effect on tumor cells as well as healthy cells but it has an effect against cancer because tumor cells divide more rapidly than normal cells [16]. Other anti-estrogen drugs like Tamoxifen, Raloxifene etc., have shown reduced risk of breast cancer in older women.

1.9 MOTIVATION BEHIND THE THESIS:

Various medical procedures such as chemotherapy, radiation therapy, surgery, hormone therapy, biological therapy and targeted therapy are available for the patients. There has been intensive research on cancer and its related factors viz. medicine, curing techniques, drug delivery and instrumentation. These methods, being pretty much costlier, no doubt provide significant benefits in curing cancer. But being a Physicist, we can also play a small role in supporting this fight against cancer. Mathematical models provide most promising approaches to be tested in labs, which are otherwise very expensive and time consuming. To help this reason, mathematical modelling is a valuable technique that has been developing since last decades. Mathematical modelling provides an interdisciplinary tool to bring together clinicians, biologists and mathematical and computational modelers [17]. People worldwide are working with mathematical models in various fields to bring out the best possible results so as to get a better approximation to the validity of their experimental results. The pace of the research can be accelerated by the use of mathematical models as these models may predict the action of the drug on the cancer cells as well as on the healthy cells. With the help of these models, a better understanding of the interaction of the drug and cells can be achieved which may provide better future strategies for the treatment and the quality and duration of patient's life can be improved. Mathematical modelling of cancer may help to understand the dynamics of cancer progression, its cure and is economic way to deal with such a disease. Not only for cancer but for various biological processes, mathematical modelling plays an important role. Different types of models focusing on different types of prevailing cancers have been put forward by numerous people working in this noble cause [3, 13, 18, 19, 20-26]. *Mamat et al., Rachel roe-dale et al., Kirschner-Penetta* etc in their papers have studied cancer treatment with a mathematical approach. People at international level have

contributed much more in this field. However, Indians being really efficient at theoretical mathematics, the status of mathematical handling of cancer in India is at a preliminary level. The level of theoretical research is not at par with the severity of disease in India. Henceforth, there lies a wide scope of research in this area.

1.10 OBJECTIVE BEHIND THE THESIS:

I. To solve Breast Cancer Equation.
II. To apply the concept of Delay Differential Equation on Another type of Cancer i.e. Colon Cancer.

1.11 DELAY DIFFERENTIAL EQUATIONS: AN INTRODUCTION

A diffusion reaction equations consists of a reaction term and a diffusion term, shown below

$$u_t = D\Delta u + f(u)$$

where $u = u(x, t)$ is a state variable and interprets density/concentration of a substance, a population .. etc. at any position x at any given time t. Δ represents the Laplace operator. The first term on the right side represents the diffusion term along with the diffusion coefficient *D*. The second term i.e. the reaction term $f(u)$ signifies the processes that change with any variation in u. This term may also depend on first derivative of *u* and/or explicitly on *x*. If the diffusion term in above equation is set to zero, the diffusion-reaction equation gets converted into an ODE. The DDE are also basically a type of diffusion reaction equations; the diffusion term taking care of the delay dynamics. For example the classic prey-predator model and population dynamics which are based on diffusion reaction equations have been well explained in [27].

"EVERY PROCESS TAKES TIME TO GET COMPLETED."

Except some physical phenomenon like velocity, acceleration take little amount of time as compared to biological processes such as gestation and maturation. Thus it becomes necessary to incorporate the study of these time taken, technically termed as 'delay times' and the models that incorporate such delay times are called as Delay Differential Equation Models.

"DELAY REFERS TO THE TIME LAG BETWEEN THE CAUSE AND EFFECT."

The simplest constant delay equation has the form [28, 29]:

$$y'(t) = f(t, y(t), y(t-\tau_1), y(t-\tau_2).....y(t-\tau_k)) \quad (1.1)$$

Where τ_i is the time delays (lags) and are positive constants. These delays may be time varying or their value may depend on the solution i.e. $\tau_i = \tau_i$ (t, y(t)),called as state dependent delays.

1.12 BASIC PROPERTIES OF DELAY DIFFERENTIAL EQUATIONS:

Ordinary differential equations (ODE) and delay differential equations (DDE) are helpful in framing many physical phenomena [29]. Although delay differential equations are similar to ordinary differential equations in many respects, but they possess several features which make their analysis more complicated. [30]. ODEs contain derivative which depend on the solution at present value of the independent variable ("time"). Whereas DDEs contain additionally contain derivatives which depend on solution at previous times. The most prominent difference between the ODE and DDE is the initial data. The solution of an ODE is determined by its value at the initial point $t=a$. However, for the interval $a \leq t \leq b$, the presence of term like $y(t-\tau_j)$ requires the value of solution at points prior to the initial point [29].

1.13 METHODS TO SOLVE DDEs:

Since there are many analytical as well as numerical methods available for solving ODEs but DDEs lack in availability of such methods to solve them. Various analytical methods such as *variational iteration method* are available to solve DDEs [30, 31]. Successful attempts have been made in calculating the exact solution of delay differential equations [32].

The analytical solution of DDEs is not as easy as the ODEs, but they can be solved with the help of numerical methods using softwares like MATLAB, FORTRAN, MAPLE etc. The first mathematical software ever developed for solving DDEs is dmrode [34]. The FORTRAN codes available for solving DDEs are comparatively less user-friendly. As a result of which, amongst a number of available computational methods we have

chosen Matlab solver dde23 to ease the purpose. This solver follows the approach of explicit Runge-Kutta method by extending the method of MATLAB ODE solver ode23. The fundamental method of solving DDEs is "the method of steps" [29]. This method is actually the basic technique for solving DDE that reduces them it to a sequence of ODEs [35]. The solver dde23 allows only constant delays, so before starting the integration, it determines all the discontinuities in the interval of interest and arranges for these points to be included in the mesh $t_0; t_1;$.....Similar approach can be followed for time dependent delays. But this approach is not applicable to problems with state dependent delays [34, 36]. For time varying delays and state dependent delays, ddesd solver can be used, since dde23 works with constant delays only.

1.2 DELAY DIFFERENTIAL EQUATIONS IN MATHEMATICAL BIOLOGY:

The biological system modelling has been using the ordinary and the partial differential equations since a long period, dating too *Malthius*, *Verhulst*, *Lotka* and *Volterra* etc. These models provide us a better understanding into the complex phenomenon, but these simple models may not cope with the variety of dynamics observed in natural systems. These complexities can be broadly handled into two ways, one, increasing the number of ordinary or partial differential equations i.e. a larger system systems with more differential equations. With the help of these, the observed behavior of natural systems can be approximated well. But the presence of many parameters makes it difficult, most of which cannot be determined experimentally [33].

Second approach that can be followed is the presence of delay terms in differential equations. The delays or lags may here refer to the time required for some biological processes to occur. These biological processes may be related to gestation times, incubation period, transport delays or simply lump complicated biological processes. Possessing richer mathematical framework as compared to ordinary differential equations and having better consistency with the nature of certain biological processes, models based on delay differential equations are more preferred [21]. But on the negative side, the detailed workings of complex biological systems is been hidden in these models. Delay models are becoming very common, playing an inevitable part in biological modelling [33].

In the work by *Liu e.t al.* the effect of M-phase specific drug on the growth of cancer has been considered [37]. It is known that the cancer propagation takes place via a cell cycle having different stages, viz. the mitotic-phase(M-phase), the quiescent phase(Go-phase) and the inter-phase(G1,s,G2 phase).A time delay has been included for the situation when the cell passes through the interphase. Their work includes the extended version of model presented by *Villasana* and *Radunskaya* [42]. The inclusion of immune system and quiescent cells has been done in their work. The numerical and analytical study of cancer free equilibrium is been done that has resulted in the fact that the quiescent cells can escape through the M-phase drug i.e. the cancer cells in the resting stage can survive through the drug and may contribute to further tumor growth on the failure of chemotherapeutic drug. The role of time delays in physiological systems is greatly explained in the work by *Batzel* [38] et al. Their work describes the presence of delays in human physiological systems, counting from delays in respiratory system, cardiovascular system, insulin-glucose control system, hormonal control systems, neuron system functions, to name a few and explaining delays in working mechanism of organs like heart, kidney etc. the clinical diagnosis also encounters some delays during treatment regimens, for example in Cancer, Renal disease, AIDS, Immuno response.

In the work by *F.A. Rihan* [39] et al., the interaction between the tumor cells and the immune cells has been studied with the help of a delay differential equation model. The type of delay incorporated in their work is the time needed by the immune system to show some response on the recognition of some foreign bodies. Least squares approach is used for the parameter estimation for real observations. The steady state solutions for the model are found and their stability has been checked using the Hopf-bifurcation method, theoretically and numerically both.

Another work discusses the numerical algorithm for approximate solution of threshold problems in population dynamics and epidemics. The value of the delay, incorporated here, is not known explicitly and is determined from threshold conditions. These threshold conditions are defined by some integral operators which depend on history of solution. Their theoretical analysis is in total agreement with the numerical experiments on threshold problems from theory of population dynamics and from epidemics [40].

Various successful models have been proposed by various people based on delay differential equations(DDE) and retarded delay differential equations(RDDE), having

applications in various fields of biology. For instance the role of DDEs in diabetes is well formulated in the work by *Emma Geraghty*, taking into consideration the DDEs to understand the mechanisms of glucose insulin regulatory system [20]. The results have come to be in agreement with the existing literature.

In the works by *Borges et. al*., the tumor growth is studied with a mathematical model considering the delay time. This delay time is the duration within which the resting cells convert to hunting cells. The highlight of the model is the introduction of the chemotherapy and the adjustment in the values of the parameters with respect to the recent experimental evidences. Stable solutions are obtained with continuous drug regimens and pulsed chemotherapy [41].

Mammat et. al., have proposed a mathematical model based on coupled ordinary differential equations for modelling the growth of tumor cells in the presence of tumor cells and under bio-chemotherapy. Numerical simulations have been tested for variation in tumor size and variation of parameters among two patients. Finally, biochemotherapy has been declared more effective [3].

The models proposed in [15, 42, 44] forms the basis of our work. However further modification has been introduced in them so as to achieve refined result. A glimpse of these models and the further work is discussed in chapter 2.

CHAPTER 2

CANCER MODELS: A MATHEMATICAL APPROACH

2.1 INTRODUCTION:

In this chapter, we discuss the models that form the basis of our study [15, 42, 43]. The combined effect of interaction of immune cells and quiescent cells with the tumor cells has been taken into consideration in MODEL 3. The mathematical ability of this model has been explored by applying diverse strategies e.g. manipulation of drug delivery maps and improved drug delivery system. A brief outlook of both the models has been given in the following sections. Further MODEL 3 is described in detail and after that the modified MODEL 3 is discussed in following section.

2.2 MODEL 1: TUMOR CELLS DURING MITOSIS AND INTERPHASE

The model 1 is an extended piece of work done by Villasana and Radunskya [42]. A different approach has been followed in [39], i.e. by subdividing the cycling tumor population into phases, without considering the cells in quiescent phase. The area of interest lies in the interaction of tumor cells and drug with the immune cells. The cycle specific drugs (like Paclitaxel) used in this model, interfere with the cell proliferation during mitosis, thereby stopping the multiplication of tumor cells and allowing their natural death.

Following equations represent the mathematical model from based on *Vilasana and Ochoa's* work:

$T_I(t)$ denotes the population of tumor cells during interphase at time t, $T_M(t)$ be the tumor Population during mitosis at time *t*, $I(t)$ be the immune system population at time *t*, τ be the resident time of cells in interphase. The governing equations for the system are:

$$T_I'(t) = 2a_4 T_M(t) - c_1 T_I(t) I(t) - d_2 T_I(t) - a_1 T_I(t-\tau) \tag{2.1}$$

$$T_M'(t) = a_1 T_I(t-\tau) - d_3 T_M(t) - a_4 T_M(t) - c_3 T_I(t) I(t) - k_1(1 - e^{-k_2 \omega(t)}) T_M(t) \tag{2.2}$$

$$I'(t) = k + \frac{\rho I(t)(T_I(t) + T_M(t))^n}{\alpha + (T_I(t) + T_M(t))^n} - c_2 I(t) T_I(t) - c_4 T_M(t) I(t) - d_1 I(t) - k_3(1 - e^{-k_4 \omega(t)}) I(t) \tag{2.3}$$

$$\omega_1'(t) = -\lambda_1 \omega_1(t) + c(t) \tag{2.4}$$

$$\omega_2'(t) = -\lambda_2 \omega_2(t) + c(t) \tag{2.5}$$

With initial conditions

$$T_I(s) = \phi(s) \equiv T_{I_0} \quad ; \qquad -\tau < s \leq 0 \tag{2.6}$$

$$T_M(s) = \phi_2(s) \equiv T_{M_0} \; ; \qquad -\tau < s \leq 0 \tag{2.7}$$

$$I(s) = \phi_3(s) \equiv I_0 \quad ; \qquad -\tau < s \leq 0 \tag{2.8}$$

And

$$\omega_1(0) = 0 \tag{2.9}$$

$$\omega_2(0) = 0 \tag{2.10}$$

Here,

$$\omega(t) = r_1 \omega_1(t) + r_2 \omega_2(t)$$

is a linear combination of "states" $\omega_1(t)$ and $\omega_2(t)$ and $c(t)$ represents the concentration of drug (paclitaxel) that is given to the system at time t. The "kill" terms $k_1(1 - e^{-k_2 \omega(t)}) T_M(t)$ and $k_3(1 - e^{-k_4 \omega(t)}) I(t)$ represent the impact of the drug on mitosis and the immune T-cells, respectively [15]. It has been assumed that the drug arrests the tumor cell during Mitosis and has an exponential decay. The drug is cytotoxic to both immune cells and tumor cells; hence the two kill terms exist.

$T_M(t) I(t)$ and $T_I(t) I(t)$ represent the loss of immune cells due to tumor cells. The immune cells grow non-linearly due to the presence of tumor cells in agreement with the following expression:

$$\frac{\rho I(t)(T_I(t)+T_M(t))^n}{\alpha+(T_I(t)+T_M(t))^n} \tag{2.12}$$

a_1 and a_4 represent the different rates at which cells cycle or reproduce, c_i represent the losses from interactions of tumor cells with immune cells. The parameters ρ, α and n depends on the type of tumor being considered and the health of the immune system, specifically its ability to produce certain cytokines [15]. The term ρ represents the increase in immune cells due to a stimulus and α represents the half of the value of immune response. The presence of the term $T_I(t-\tau)$ indicates that the tumor cells which were in interphase for time τ, are the same cells that move forward into the mitosis i.e. the same cells move into mitosis which were present τ time before in. k is the constant rate at which the immune cells grow when no tumor cells are present. The parameter values are well explained in [42]. The parameters have been non-dimensionlized so that the model constants are as close to unity as possible and in the same range of values and are listed as under:

Parameter	Identity	Values	Logic/ Meaning
T	Delay time	0.92	Time for which the cell reside in the interphase stage
a_1	Rates of cell reproduction	0.98	Fraction of cells which cycle from interphase to mitosis and from mitosis to interphase respectively
a_4		0.8	
d_1	Rate of cell death	0.29	Fractions of natural cell death
d_2		0.11	
d_3		0.4	
c_1	Loss terms	0.9	Losses from interaction of tumor cells with immune cells
c_2		0.085	
c_3		0.9	
c_4		0.085	
α	Half the value of immune response	0.2	ρ, α, n depend on the health of the individual; Larger the value of n, more time will be taken to recognize the tumor
ρ	Increase in immune cells due to presence of stimulus	0.1	
N	Response time taken to recognize the presence of tumor	3	
λ_1	Constant	126.12	-
λ_2	Constant	0.85	-
K	Birth rate of immune cells in absence of tumor cells	0.036	Its value is small in absence of tumor cells
k_1	Components of 'kill' terms	0.47	Combined with the exponential terms, represents the impact of drug on mitosis and immune cells
k_2		0.57	
k_3		0.49	
k_4		0.061	
r_1	Real a-dimensional constants	0.73	-
r_2		0.27	-

Table1. *List of Parameters used*

We have improved this model on the basis of improved drug delivery schedule. The improvement in the model is being done by adding a new parameter and a small change in the drug concentration term in equations (2.4)-(2.5). The details of this improvement and its results have been discussed in chapter 3.

2.3 MODEL 2: MODEL OF QUIESCENT TUMOR CELLS

The model 2 comes from the work by *Yafia* [43]. This model incorporates the quiescent cells which were however not included in MODEL 1. Including quiescent cells in the model makes it more realistic and could provide additional insight into the complex system.

Let $P(t)$ and $Q(t)$ represent the number of proliferating tumor cells and quiescent tumor cells respectively. The total number of tumor cells is given by $N(t) = P(t) + Q(t)$.
Yafia's model is described by the following delay differential equations:

$$P'(t) = bP(t-\tau) - r_P(N(t))P(t) + r_Q(N(t))Q(t) \tag{2.13}$$

$$Q'(t) = r_P(N(t))P(t) - \mu_Q Q(t) - r_Q(N(t))Q(t) \tag{2.14}$$

With constant initial functions

$$P(s) \equiv P_0, Q(s) \equiv Q_0, \quad -\tau < s \leq 0 \tag{2.15}$$

$b = \beta - \mu_P > 0$ is the intrinsic growth rate of proliferating cells , where $\beta>0$ is the division rate of the proliferating cells and μ_P is the death rate of the proliferating cells;μ_Q represents the mortality rate of quiescent cells.
The terms $r_P(N)$ and $r_Q(N)$ signify the transition of proliferating cells to quiescent cells and quiescent cells to proliferating cells respectively. Finally τ is the time it takes proliferating cells to divide.
If the delay is set to zero, the above set of equations get reduced to the ODEs.

2.4 MODEL 3: THE INTEGRATED MODEL

The third model is a combination of model 1 and model 2, taking into consideration tumor cells, immune cells and quiescent cells. Combining equations (2.1)-(2.5) and (2.13)-(2.14) and some additional terms, comprise the model 3. The presence of quiescent cells produces drug resistance in the model because they are resistant to cytotoxic agents. The presence of these cells becomes a matter of curiosity. Hence this model includes the equations containing population levels of immune cells, tumor cells and quiescent cells.

$T_Q(t)$ denotes the population of cells that are in quiescent phase of cell cycle and $N(t) = T_Q(t) + T_I(t) + T_M(t)$ be the total cancer cell population. The transition rates $r_P(N) = a_5$ and $r_Q(N) = a_6$ are taken as constants.

The equations governing this model are as follows:

$$T_Q'(t) = a_5 T_I(t-\tau) - a_6 T_Q(t) - d_4 T_Q(t) - c_5 I(t) T_Q(t) - u_1(t) T_Q(t) \tag{2.16}$$

$$T_I'(t) = 2a_4 T_M(t) - a_5 T_I(t-\tau) + a_6 T_Q(t) - c_1 T_I(t) I(t) - d_2 T_I(t) - a_1 T_I(t-\tau) \tag{2.17}$$

$$T_M'(t) = a_1 T_1(t-\tau) - d_3 T_M(t) - a_4 T_M(t) - c_3 T_M(t) I(t) - u_2(t) T_M(t) \tag{2.18}$$

$$I'(t) = k + \frac{\rho I(t)(T_I(t) + T_M(t))^n}{\alpha + (T_Q(t) + T_I(t) + T_M(t))^n} - c_2 I(t) T_I(t) - c_4 T_M(t) I(t) - d_1 I(t) - c_6 T_Q(t) I(t) - u_3(t) I(t) \tag{2.19}$$

the initial conditions remaining similar as in [39].

$$T_Q(s) \equiv 0.8, -\tau < s \le 0 \tag{2.20}$$

$$T_I(s) \equiv 1.3, -\tau < s \le 0 \tag{2.21}$$

$$T_M(t) \equiv 1.2, \ -\tau < s \le 0 \tag{2.22}$$

$$I(s) \equiv 0.9, \ -\tau < s \le 0 \tag{2.23}$$

All parameter values are in fractional amounts per day. The constants a_1 and a_4 represent the fraction of cells which cycle from interphase to mitosis and from mitosis to interphase, respectively [15]. The constant d_1, d_2 and d_3 represents the fractions of natural cell death, or apoptosis. Again the non-linear growth of immune cells is governed by the term

$$\frac{\rho I(t)(T_I(t)+T_M(t))^n}{\alpha+(T_I(t)+T_M(t))^n} \tag{2.12}$$

In addition to the previous model equations, few more control terms have been added viz. $u_1(t)$, $u_2(t)$, $u_3(t)$ whose general expressions are as follows:

$$u_1(t)=k_5(1-e^{-k_6\omega(t)}) \tag{2.24}$$

$$u_2(t)=k_1(1-e^{-k_2\omega(t)})$$

$$u_3(t)=k_3(1-e^{-k_4\omega(t)})$$

where, as before,

$$\omega_1'(t)=-\lambda_1\omega_1(t)+c(t)\,;\omega_1(0)=0 \tag{2.25}$$

$$\omega_2'(t)=-\lambda_2\omega_2(t)+c(t)\,;\omega_2(0)=0 \tag{2.26}$$

And

$$\omega(t)=r_1\omega_1(t)+r_2\omega_2(t) \tag{2.27}$$

The equations from (3.1)-(3.12) forms the model III. The values of all the parameters a_1, a_4, a_5, a_6, d_1, d_2, d_3, d_4, c_1, c_2, c_3, c_4, c_5 and c_6 are all positive and less than 1. Following table contains all values of the parameters used in the numerical run.

Parameter	**Value**
a_5	0.0001
a_6	0.00015
d_4	0.1
c_5	$50\text{x}10^{-3}$
c_6	$85\text{x}10^{-5}$
k_5	0.47
k_6	0.47

Table2. *List of Parameters*

The interphase tumor cells that become quiescent cells may also get affected by the drug although these cells have shown drug resistant behavior, thus the term $u_1(t)T_Q(t)$ accounts for the loss of quiescent cells due to drugs. If $k_5 = 0$, the quiescent cells remain unaffected by the drug. The immune cells annihilates the quiescent cells also, the term $c_5T_I(t)T_Q(t)$ denotes the losses of quiescent tumor cells caused by the immune system. The term $c_6I(t)T_Q(t)$ denotes the deactivation of immune cells by quiescent tumor cells. Setting $c_6 = 0$ predicts the situation when quiescent cells do not deactivate the immune cells. The term $bP(t-\tau)$, where b is the intrinsic rate of proliferation, so b = birth-death. Due to non-delay in birth, the birth death rate has been separated. That is the rate of change of tumor cells or proliferation of cells during mitosis is represented by the term $a_6T_I(t-\tau)$, with the delay corresponding to the time the cells spend in interphase.

2.5 STABILITY ANALYSIS:

The significance of the solution of a differential equation lies in the ability of the solution to be physically interpretable. The stability of a system depends on the nature of the equilibrium points in phase diagrams [45]. The trajectory of the solution may either converge to an attractor or diverge to infinity. The knowledge of conditions for which these types of solutions are obtained, helps us to understand the long term behavior of the system [48].

To analyze the stability of the system, we consider four cases:

I. Drug free system with no delay ($\tau=0$) and no immune response.

II. Drug free system with delay ($\tau>0$**)** and no immune response.

III. System with immune response, drug activity and no delay ($\tau=0$).

IV. System with immune response, drug activity and positive delay ($\tau>0$).

A detailed discussion of above cases is given below.

2.5.1 DRUG FREE SYSTEM WITH NO DELAY i.e. τ=0 AND NO IMMUNE RESPONSE:

Since we are considering the drug free system with no delay, the terms involving $u_1(t)$ and $u_2(t)$ will vanish. Moreover the effect of immune cells is neglected to ease the study. Following these constraints, the set of equations (2.16)-(2.18) reduces to:

$$T_Q'(t) = a_5 T_I(t) - a_6 T_Q(t) - d_4 T_Q(t) \tag{2.28}$$

$$T_I'(t) = 2a_4 T_M(t) - a_5 T_I(t) + a_6 T_Q(t) - d_2 T_I(t) - a_1 T_I(t) \tag{2.29}$$

$$T_M'(t) = a_1 T_I(t) - d_3 T_M(t) - a_4 T_M(t) \tag{2.30}$$

$$\begin{vmatrix} -d_3 - a_4 & a_1 & 0 \\ 2a_4 & -d_2 - a_1 - a_5 & a_6 \\ 0 & a_5 & -a_6 - d_4 \end{vmatrix} = 0 \tag{2.30 (a))}$$

The discriminant for above equations for non-delay system (for $\tau = 0$) is:

$$\Delta_1 = -d(d_2 a_6 + d_4 a_5) + (a_4 - d_3)(a_1 a_6 + d_4 a_1) \tag{2.31}$$

Where $d = d_3 + a_4$.

2.5.2 DRUG FREE SYSTEM WITH DELAY i.e. τ > 0 AND NO IMMUNE RESPONSE:

When we add the effect of delay in the simple system of equations (2.16) – (2.18), we get the following system

$$T_Q'(t) = a_5 T_I(t-\tau) - a_6 T_Q(t) - d_4 T_Q(t) \tag{2.32}$$

$$T_I'(t) = 2a_4 T_M(t) - a_5 T_I(t-\tau) + a_6 T_Q(t) - a_1 T_I(t-\tau) \tag{2.33}$$

$$T_M'(t) = a_1 T_I(t-\tau) - d_3 T_M(t) - a_4 T_M(t) \tag{2.34}$$

The point of interest lies in studying the growth of tumor when the conditions are varied for a positive value of delay τ about the previously used fixed point (0, 0).

The eigen value equation for the above equations is:

$$-(d_3 + a_4 + \lambda)(d_2 + \lambda)(a_6 + d_4 + \lambda) + 2a_1 a_4 (a_6 + d_4 + \lambda) - (t-\tau)(d_3 + a_4 + \lambda)(a_5 + a_1 - a_5 a_6) \tag{2.35}$$

The characteristic equation for this system around the fixed point (0, 0) is given by

$$F(\lambda) = -(d_3 + a_4 + \lambda)(d_2 + \lambda)(a_6 + d_4 + \lambda) + 2a_1a_4(a_6 + d_4 + \lambda) - e^{-\tau\lambda}(d_3 + a_4 + \lambda)(a_5 + a_1 - a_5a_6) \tag{2.36}$$

We can write eq. (2.36) in this form,

$$F(\lambda) = P(\lambda) + e^{-\tau\lambda}Q(\lambda) \tag{2.37}$$

Where $P(\lambda) = -(d_3 + a_4 + \lambda)(d_2 + \lambda)(a_6 + d_4 + \lambda) + 2a_1a_4(a_6 + d_4 + \lambda)$ (2.38)

$$Q(\lambda) = (d_3 + a_4 + \lambda)(a_5 + a_1 - a_5a_6) \tag{2.39}$$

Using the results of theorem 1 stated by Cooke and P. van den Driessche in [52],

$$F_1(y) = |P(iy)|^2 - |Q(iy)|^2 \text{ where } \lambda = iy \tag{2.40}$$

We obtain the following equation:

$$F_1(y) = y^6 + (\beta^2 + 4a_1a_4 + d^2 + {d_2}^2)y^4 + [(4a_1a_4 + d^2 + {d_2}^2)\beta^2 + (2a_1a_4 - dd_2)^2 - (a_5 + a_1 - a_5a_6)]y^2 + \beta^2(2a_1a_4 - dd_2)^2 - (a_5 + a_1 - a_5a_6)^2d^2 \tag{2.41}$$

Substituting $y^2 = x$, in above equation, we obtain the following equation

$$\alpha_1x^3 + \beta_1x^2 + \gamma_1x + \delta_1 = 0 \tag{2.42}$$

where, $\alpha_1 = 1$, (2.43)

$$\beta_1 = (\beta^2 + 4a_1a_4 + d^2 + {d_2}^2) \tag{2.44}$$

$$\gamma_1 = [(4a_1a_4 + d_2 + {d_2}^2)\beta^2 + (2a_1a_4 - dd_2)^2 - (a_5 + a_1 - a_5a_6)] \tag{2.45}$$

$$\delta_1 = \beta^2(2a_1a_4 - dd_2)^2 - (a_5 + a_1 - a_5a_6)^2d^2 \tag{2.46}$$

The value of discriminant for above system is

$$\Delta_2 = 18\beta_1\gamma\delta - 4{\beta_1}^2\delta + {\beta_1}^2\gamma^2 - 4\gamma^3 - 27\delta^2 \tag{2.47}$$

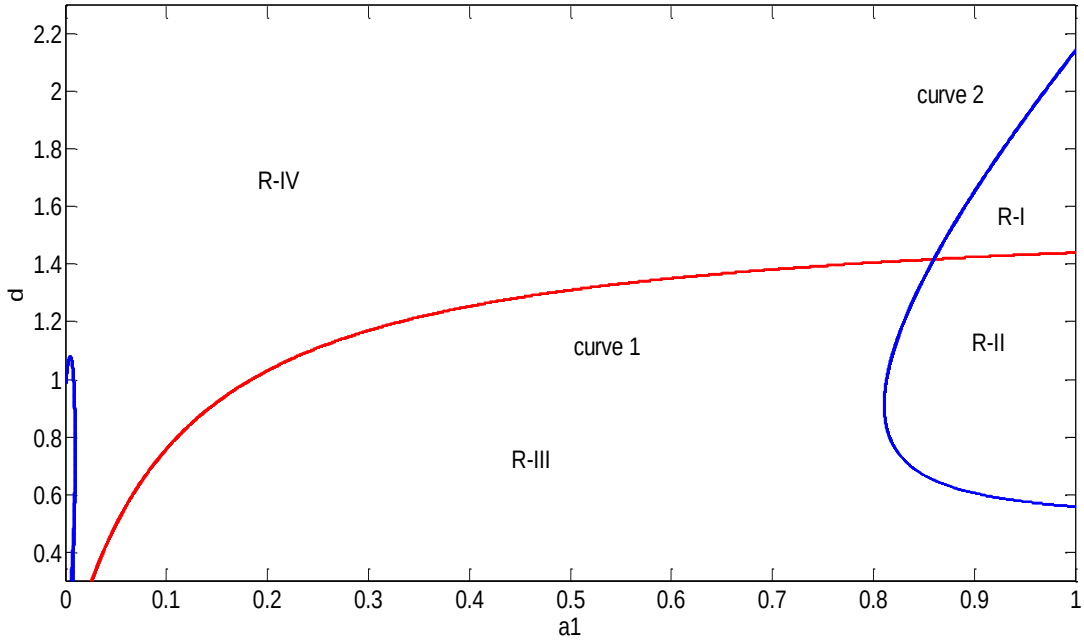

Fig. 2.1 *Variation of space parameters a_1 and d, plotted for $\Delta_1 = 0$ and $\Delta_2 = 0$*

Figure 2.1 depicts the variation of system parameters space with a_1 and d, keeping all other parameters constant, where $a_4 = 0.8$, $d_2 = 0.11$, $a_5 = 0.0001$, $a_6 = 0.00015$, $d_4 = 0.1$.Curve 1 corresponds to $\Delta_1 = 0$ for $\tau = 0$, and it divides the parameter space in R-III and R-IV, where R-III corresponds to $\Delta_1 > 0$ and R-IV corresponds to $\Delta_1 < 0$. As $\Delta_1 < 0$ in R-IV, the system becomes unstable, thus makes the system suitable for growth of tumor. Curve 2 corresponds to $\Delta_2 = 0$ for $\tau > 0$, and divides the parameter space in R-I and R-II where R-I corresponds to $\Delta_2 < 0$ and R-II corresponds to $\Delta_2 > 0$. For $\Delta_2 < 0$, R-I become an unstable region and tumor growth is encouraged in this region. The overlapping region formed by R-I and R-IV gives the region where tumor growth is supported.

2.5.3 SYSTEM WITH IMMUNE RESPONSE, DRUG ACTIVITY AND NO DELAY (τ = 0):

In case **(a)**, we discussed the drug free system with no delay and no immune response. In this case, we add the effect of drug activity and immune response without delay (τ=0). Thus the system equations get modified as following:

$$T_M'(t) = a_1 T_I(t) - d_3 T_M(t) - a_4 T_M(t) - c_3 T_M(t) I(t) - u_2(t) T_M(t) \tag{2.48}$$

$$T_I'(t) = 2a_4 T_M(t) - a_5 T_I(t) + a_6 T_Q(t) - c_1 T_I(t) I(t) - d_2 T_I(t) - a_1 T_I(t) \tag{2.49}$$

$$T_Q'(t) = a_5 T_I(t) - a_6 T_Q(t) - d_4 T_Q(t) - c_5 T_Q(t) I(t) - u_1(t) T_Q(t) \tag{2.50}$$

$$I'(t) = k + \frac{\rho I(t)(T_I(t) + T_M(t))^n}{\alpha + (T_Q(t) + T_I(t) + T_M(t))^n} - c_2 I(t) T_I(t) - c_4 T_M(t) I(t) - d_1 I(t) - c_6 T_Q(t) I(t) - u_3(t) I(t) \tag{2.51}$$

where, the control terms $u_1(t)$, $u_2(t)$ and $u_3(t)$ are given by

$$u_1(t) = k_5(1 - e^{-k_6 \omega(t)}); \quad u_2(t) = k_1(1 - e^{-k_2 \omega(t)}); \quad u_3(t) = k_3(1 - e^{-k_4 \omega(t)}) \tag{2.52}$$

And

$$\omega(t) = r_1 \omega_1(t) + r_2 \omega_2(t) \tag{2.53}$$

$$\omega_1'(t) = -\lambda_1 \omega_1(t) + c(t) \tag{2.54}$$

$$\omega_2'(t) = -\lambda_2 \omega_2(t) + c(t) \tag{2.55}$$

We consider the solution of above equations (2.48)-(2.55) around the fixed point (0, 0, 0, k/D) for the system with zero tumor level and a positive immune level, where D= d_1+u_3.

The eigen value matrix for above system of equations is given as:

$$\begin{bmatrix} -d_3 - a_4 - c_3\frac{k}{D} - u_2 - \lambda & a_1 & 0 & 0 \\ 2a_4 & -a_5 - c_1\frac{k}{D} - d_2 - a_1 - \lambda & a_6 & 0 \\ 0 & a_5 & -a_6 - d_4 - u_1 - c_5\frac{k}{D} - \lambda & 0 \\ -c_4\frac{k}{D} & -c_2\frac{k}{D} & -c_6\frac{k}{D} & -\lambda - d_1 \end{bmatrix} = 0$$

(2.56)

On solving, we obtain the following relations:

$$\lambda = -d_1 \tag{2.57}$$

or

$$-\left(d_3 + a_4 + c_3\frac{k}{D} + u_2 + \lambda\right)\left[\left(a_5 + c_1\frac{k}{D} + d_2 + a_1 + \lambda\right)\left(a_6 + d_4 + u_1 + c_5\frac{k}{D} + \lambda\right) - a_5 a_6\right] + 2a_1 a_4\left(a_6 + d_4 + u_1 + c_5\frac{k}{D} + \lambda\right) = 0 \tag{2.58}$$

Consider $A = d_3 + a_4 + c_3\frac{k}{D} + u_2$ (2.59)

$$B = a_6 + c_1\frac{k}{D} + d_2 + a_1 \tag{2.60}$$

$$C = a_6 + d_4 + u_1 + c_5\frac{k}{D} \tag{2.61}$$

Thus the above eqn. (2.58) gets transformed as:

$$-(A+\lambda)\left[(B+\lambda)(C+\lambda) - a_5 a_6\right] + 2a_1 a_4(C+\lambda) = 0 \tag{2.62}$$

On solving eqn. (2.62) we obtain the following equation:

$$-\left[\lambda^3 + (A+B+C)\lambda^2 + (AB + AC + BC - a_5 a_6 - 2a_1 a_4)\lambda + ABC - a_5 a_6 A - 2a_1 a_4 c\right] = 0 \tag{2.63}$$

Discriminant for eqn. (2.63) is given by:

$$\Delta_3 = 18\alpha_3.\beta_3\gamma_3\delta_3 - 4\beta_3^{\,2}\delta_3 + \beta_3^{\,2}\gamma_3^{\,2} - 4\alpha_3\gamma_3^{\,3} - 27\alpha_3^{\,2}\delta_3^{\,2} \tag{2.64}$$

Where $\alpha_3 = 1,$ (2.65)

$$\beta_3 = A + B + C, \tag{2.66}$$

$$\gamma_3 = AB + AC + BC - a_5 a_6 - 2a_1 a_4, \tag{2.67}$$

$$\delta_3 = ABC - a_5 a_6 A - 2a_1 a_4 C \tag{2.68}$$

2.5.4 SYSTEM WITH IMMUNE RESPONSE, DRUG ACTIVITY AND POSITIVE DELAY i.e. τ>0:

Considering the combined effect of immune response, drug activity and positive delay, we study the system of equations (2.16) to (2.27). The eigen value matrix of system around the fixed point (0, 0, 0, k/D) takes the form as follows:

$$\begin{bmatrix} -d_3 - a_4 - c_3\frac{k}{D} - u_2 - \lambda & a_1(t-\tau) & 0 & 0 \\ 2a_4 & -a_5(t-\tau) - c_1\frac{k}{D} - d_2 - a_1(t-\tau) - \lambda & a_6 & 0 \\ 0 & a_5(t-\tau) & -a_6 - d_4 - u_1 - c_5\frac{k}{D} - \lambda & 0 \\ -c_4\frac{k}{D} & -c_2\frac{k}{D} & -c_6\frac{k}{D} & -\lambda - d_1 \end{bmatrix} = 0 \tag{2.69}$$

Which gives,

$$\lambda = -d_1 \tag{2.70}$$

$$-\left(d_3 + a_4 + c_3\frac{k}{D} + u_2 + \lambda\right)\left[\left(c_1\frac{k}{D} + d_2 + \lambda + (a_5 + a_6)(t-\tau)\right)\left(a_6 + d_4 + u_1 + c_5\frac{k}{D} + \lambda\right) - a_5 a_6 (t-\tau)\right] + 2a_1 a_4 (t-\tau)\left(a_6 + d_4 + u_1 + c_5\frac{k}{D} + \lambda\right) = 0 \tag{2.71}$$

$$A = d_3 + a_4 + c_3\frac{k}{D} + u_2 \tag{2.72}$$

$$C = a_6 + d_4 + u_1 + c_5\frac{k}{D} \tag{2.73}$$

Or

The Characteristic equation for the system is:

$$F(\lambda) = -(A+\lambda)\left\{\left(c_1\frac{k}{D} + d_2 + \lambda\right)(C+\lambda)\right\} + e^{-\tau\lambda}\left[-\{(a_5 + a_1)(C+\lambda) - a_5 a_6\}(A+\lambda) + 2a_1 a_4 (C+\lambda)\right] \tag{2.74}$$

where $$P(\lambda) = -(A+\lambda)\left\{\left(c_1\frac{k}{D}+d_2+\lambda\right)(C+\lambda)\right\} \quad (2.75)$$

$$Q(y) = \left[-\{(a_5+a_1)(C+\lambda)-a_5a_6\}(A+\lambda)+2a_1a_4(C+\lambda)\right] \quad (2.76)$$

Using the results of theorem 1 stated by Cooke and P. van den Driessche in [52],

$$F_1(y) = |P(iy)|^2 - |Q(iy)|^2 \text{ where } \lambda = iy \quad (2.77)$$

We obtain the the following equation:

$$F_1(y) = (A^2+y^2)(C^2+y^2)\left(\left(c_1\frac{k}{D}+d_2\right)^2+y^2\right)-\{-(a_5+a_1)AC+(a_5+a_1)y^2+a_5a_6A+2a_1a_4C\}^2 + \{a_5a_6+2a_1a_4-(A+C)(a_5+a_1)\}y^2$$

substituting $y^2=x$ and rearranging, we get

$$x^3+\left(A^2+C^2+\left(c_1\frac{k}{D}+d_2\right)^2-(a_5+a_1)^2\right)x^2+$$
$$\left\{A^2C^2+(A^2+C^2)\left(c_1\frac{k}{D}+d_2\right)^2-2(a_5a_6A+2a_1a_4C-(a_5+a_1)AC)(a_5+a_1)+a_5a_6+2a_1a_4-(A+C)(a_5+\right.$$
$$\left.+A^2C^2\left(c_1\frac{k}{D}+d_2\right)^2-\{a_5a_6A+2a_1a_4C-(a_5+a_1)AC\}^2=0\right. \quad (2.78)$$

the discriminant for the general cubic equation

$$\alpha_3x^3+\beta_3x^{2\cdot}+\gamma_3x+\delta_3=0 \quad (2.79)$$

is

$$\Delta_4 = 18\alpha_{4.}\beta_4\gamma_4\delta_4-4{\beta_4}^2\delta_4+{\beta_4}^2{\gamma_4}^2-4\alpha_4{\gamma_4}^3-27{\alpha_4}^2{\delta_4}^2 \quad (2.80)$$

The variation of parameter space with d_3 and a_1 has been studied for the cases $\tau=0$ and $\tau>0$. The curves I and II have been plotted for $\Delta_3=0$ and $\Delta_4=0$.

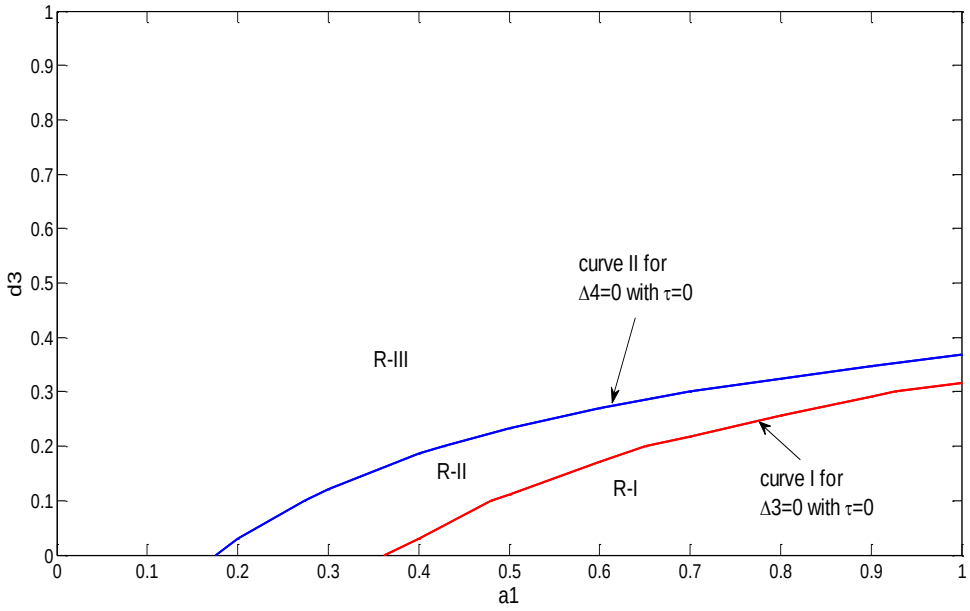

fig. 2.2 *Variation of parameter space with a_1 and d_3 for the case (c) and (d).*

Fig. 2.2 represents the variation of parameter space with a_1 and d_3 for $\tau = 0$ and $\tau > 0$. The curve I corresponds to $\Delta_3 = 0$; τ=0 and curve II corresponds to $\Delta_4 = 0$; $\tau > 0$. Curve I divides the parameter space in R-I and R-II U R-III and curve II corresponds to R-II and R-III. For $\tau = 0$, the region R-I signifies the unstable region i.e. for the condition $\Delta_3 < 0$ and stable region ($\Delta_3 > 0$) is represented by R-II U R-III. Whereas for the curve II, for R-I U R-II depicts the unstable region ($\Delta_3 < 0$) and R-III shows the stable region ($\Delta_3 > 0$). The tumor growth is favourable in the unstable region which is shown by R-I.

Thus the stability analysis as discussed above, gives the region of tumor growth. The study of the region obtained can be helpful for exploring the tumor growth and control dynamics.

2.6 METHODOLOGY:

The delay differential equations are the system governing which can be solved analytically and numerically. As the analytical approach is cumbersome and relatively tougher, so we have followed the numerical approach to solve DDEs. Since, we are

dealing with the constant delays, so, the in-built MATLAB solver dde23 has been used to solve delay differential equations and ode23 is used to solve ordinary differential equations. Further the stability analysis is done using the eigen-values and characteristic values of system equations.

CHAPTER 3

RESULTS AND CONCLUSIONS

We discuss here the results obtained for different testing conditions viz. variation of cell population with delay, drug delivery regimen. Primarily, the variation in the population of the tumor cells has been studied. Further, modification of drug delivery function has been introduced in MODEL 1 and MODEL 3. Finally, the DDE approach has been discussed for Colon Cancer.

3.1 VARIATION OF TUMOR CELL POPULATION WITH DELAY:

The variation of population of tumor cells present in different phases of the cell cycle has been studied with time (in days). The delay time present in the model has been varied gradually and the corresponding outputs have been studied. The initial conditions are kept fixed as 0.8, 1.3, 1.2, 0.9, 0, 0 and the whole variation is based on the regular drug delivery regimen.

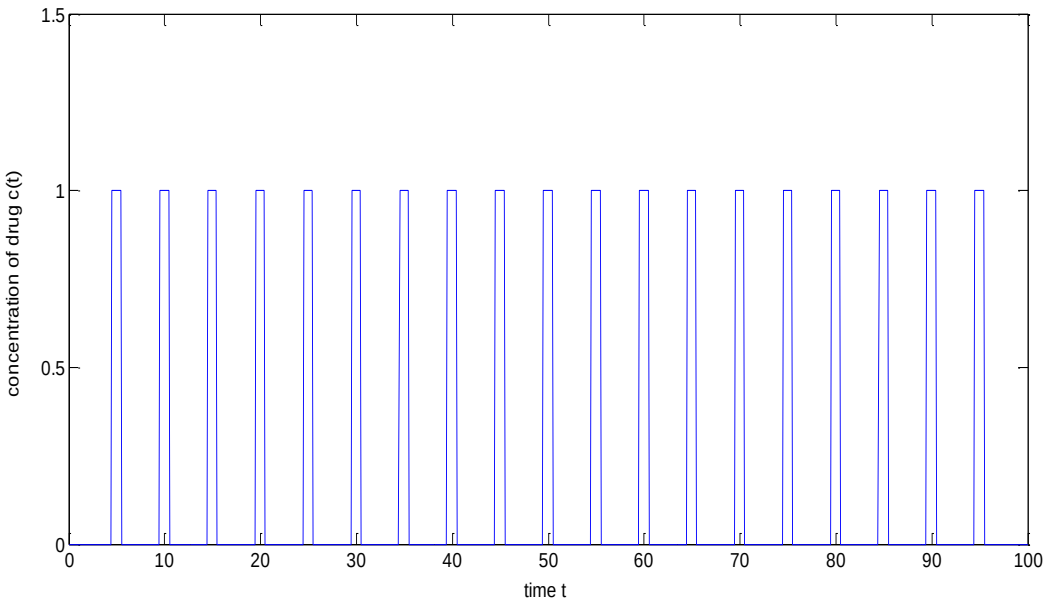

Fig. 3.1 *regular drug delivery map*

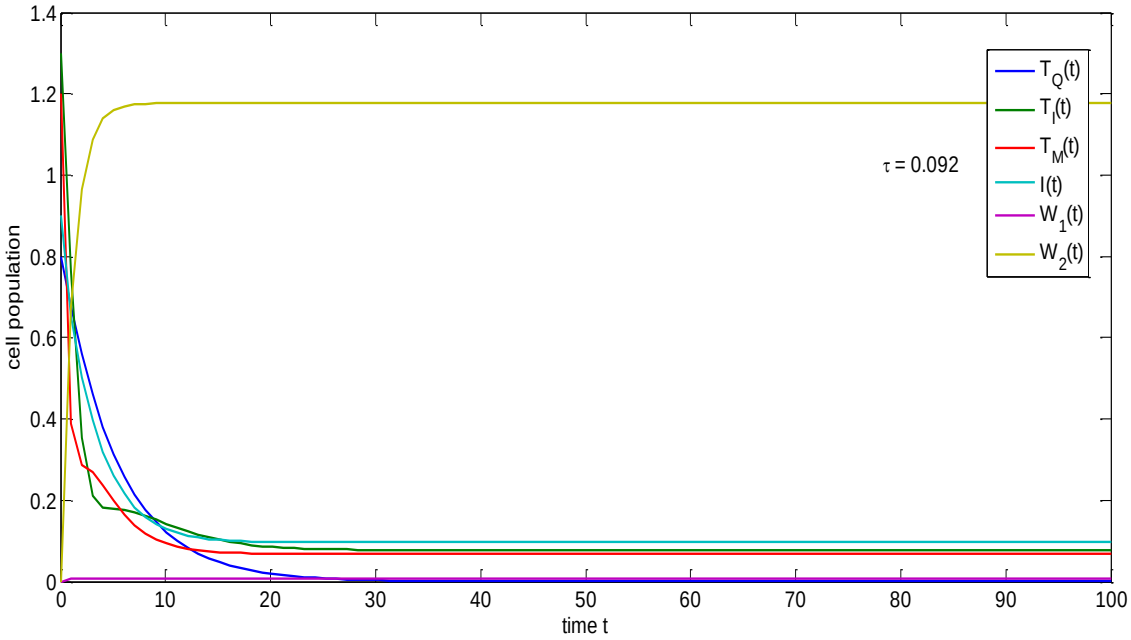

Fig. 3.2 *Variation of cell population with time when delay = 0.092*

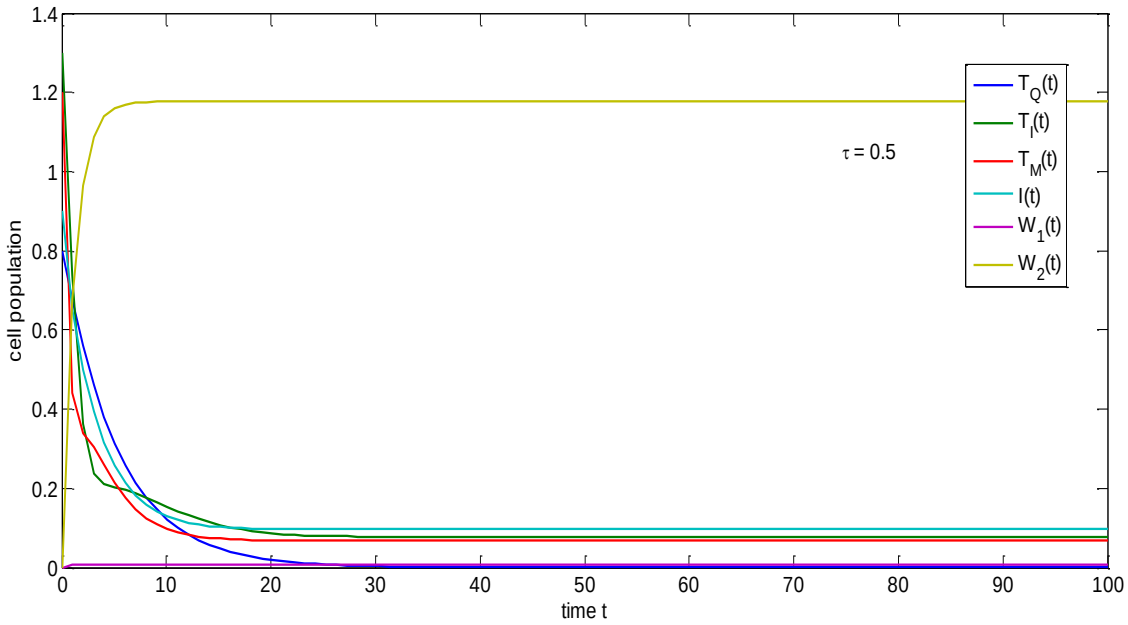

Fig. 3.3 *Variation of tumor cell population with time when delay = 0.5*

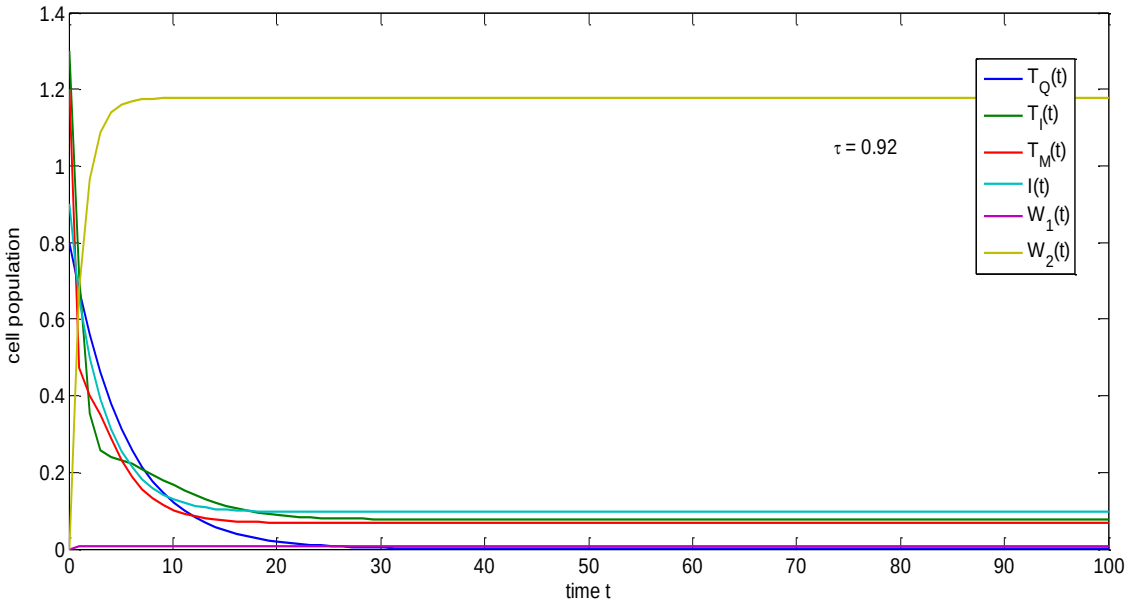

Fig. 3.4 *Variation of tumor cell population with time when delay = 0.92*

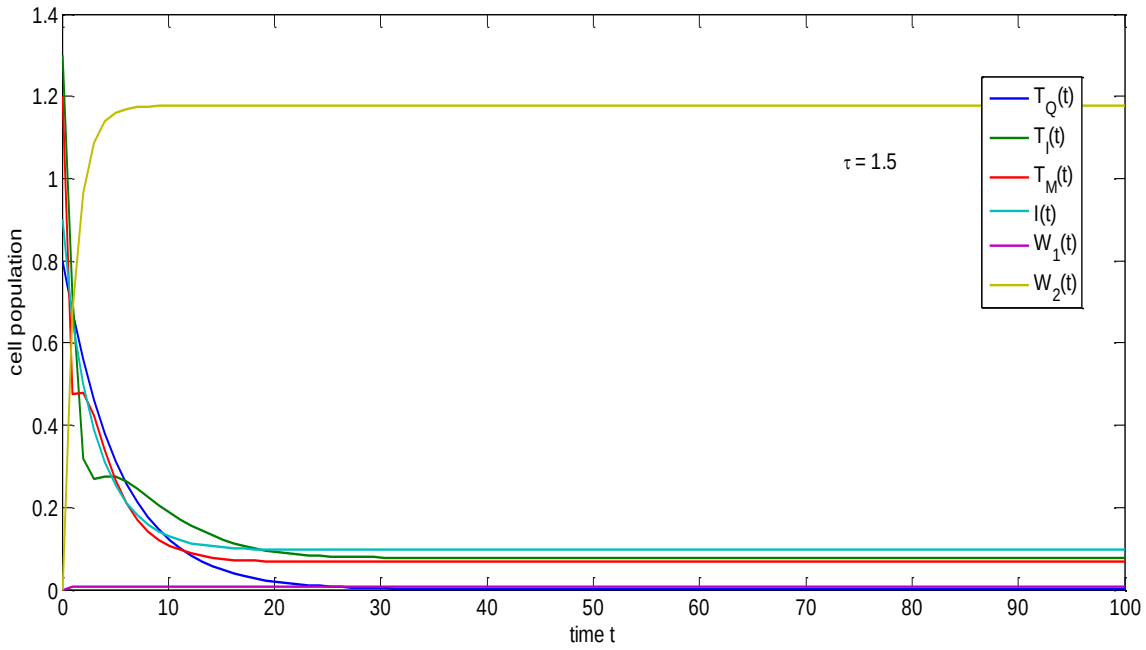

Fig. 3.5 *Variation of tumor cell population with time when delay term = 1.5*

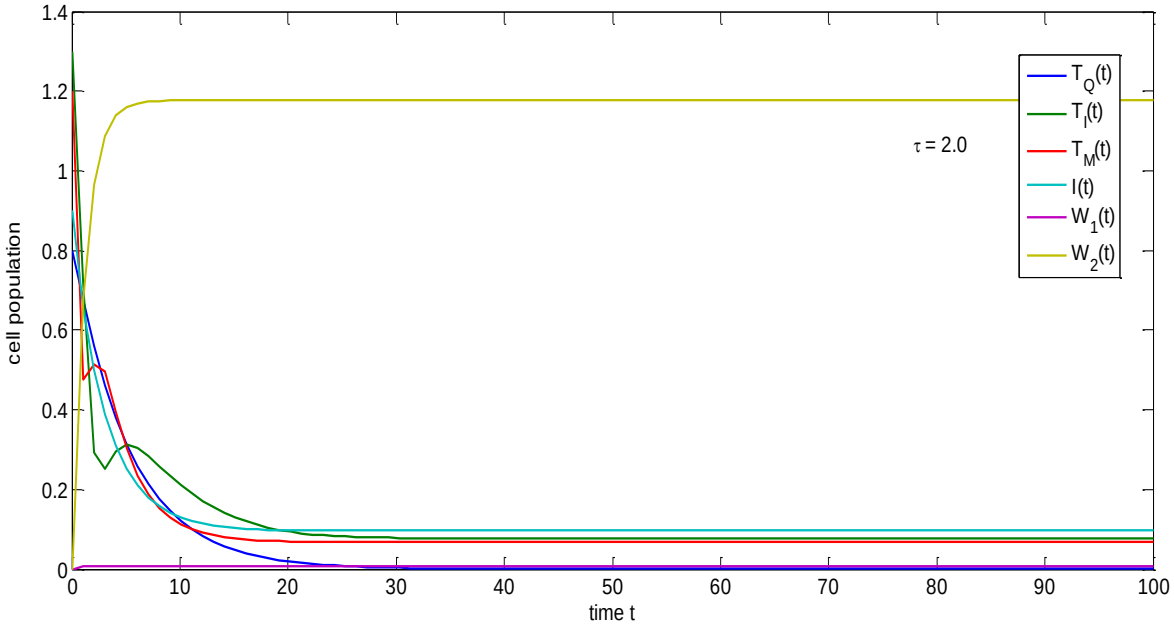

Fig. 3.6 *Variation of tumor cell population with time when delay time = 2*

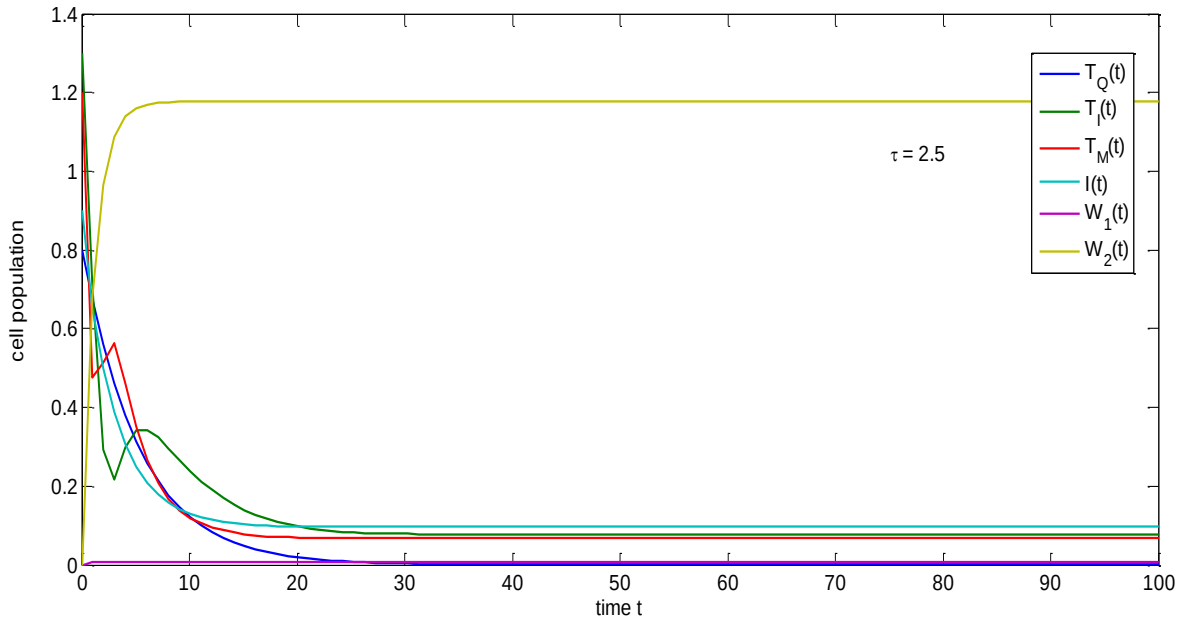

Fig. 3.7 *Variation of tumor cell population with time when delay = 2.5*

From figures (3.1)-(3.6), we observe that the as the delay time increases, there is a gradual increase in the population of tumor cells. The variation in population of tumor cells present in interphase, mitosis and quiescent phase has been plotted for different values of delay time in figure 3.7, 3.8 and 3.9 respectively. There is a visible variation in the population of tumor cells in interphase, mitosis and quiescent phrase as shown in figures.

Population dynamics of $T_{I,}$ T_M and T_Q has been studied individually for different values of delay times. Following graphs (3.7)-(3.9) show the variation of tumor cell population for interphase stage, mitosis and quiescent stage respectively, with time.

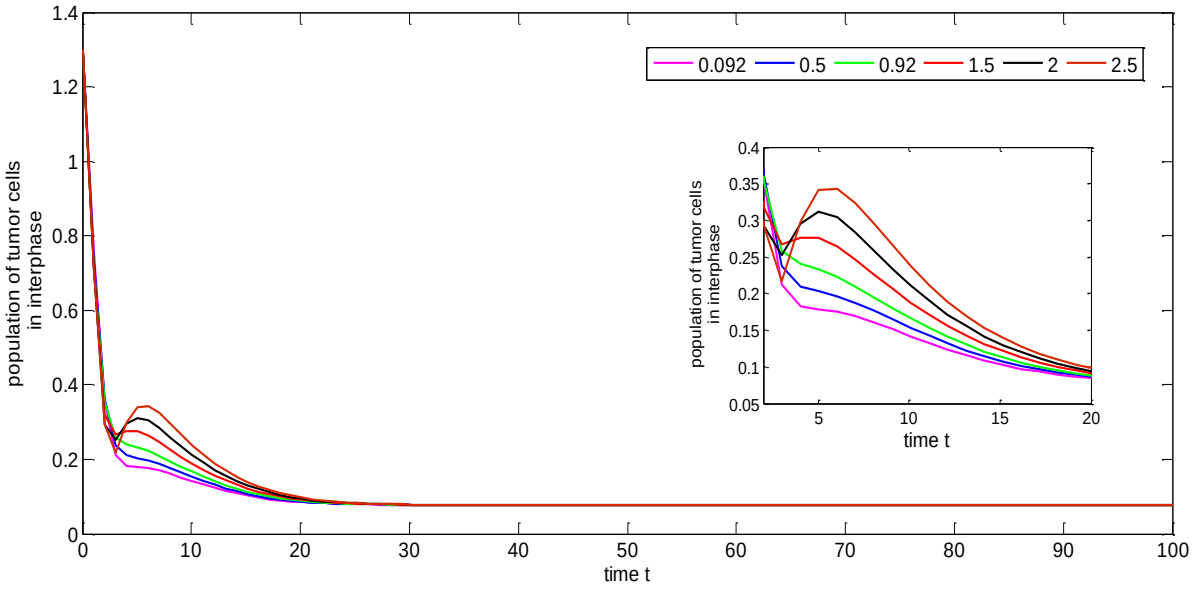

Fig.3.8 *Variation of population of tumor cells present in interphase $T_I(t)$ at different delay times with time*

Above figure shows the variation of tumor cell population in interphase for different values of delay times. Since delay time is the time for which the tumor cell resides in the interphase stage. We can observe that with increase in the delay time the population of tumor cell increases. For delay term = 2.5, there is a sudden fall in the concentration of the tumor cells and with increase in time the population again increases.

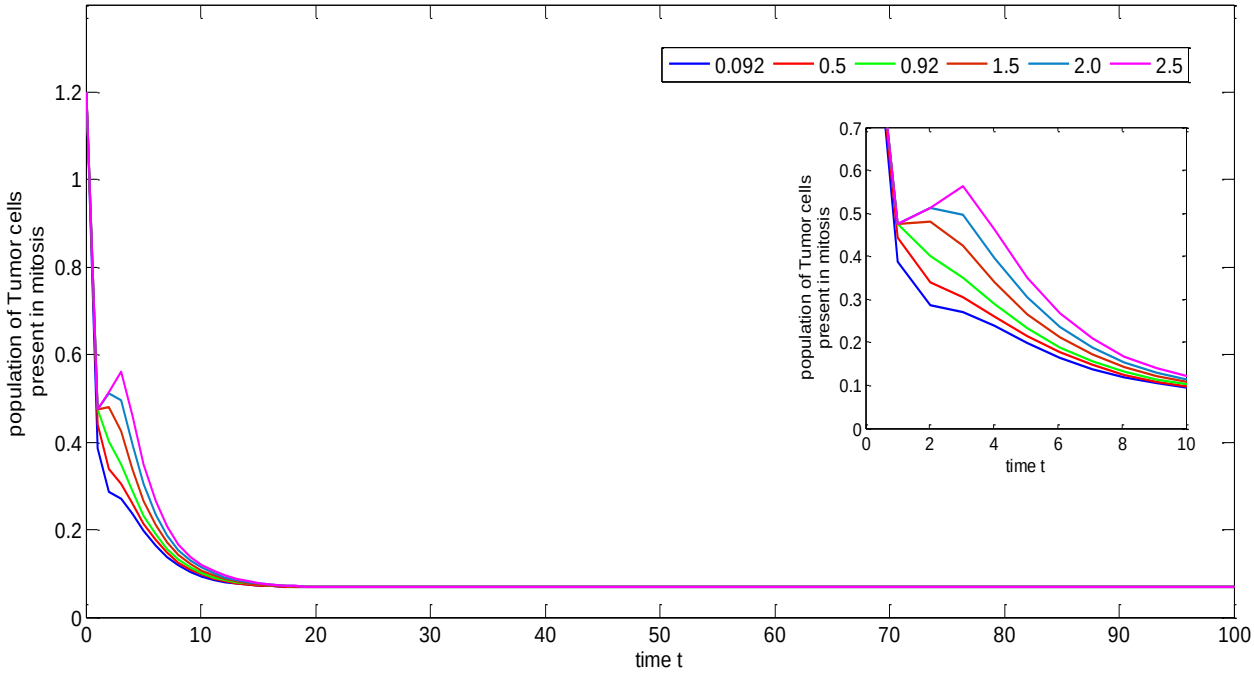

Fig. 3.9 *Variation of population of tumor cells present during Mitosis T_M (t) at different delay times with time t.*

Similar behavior is shown by tumor cells in mitosis. Increase in delay increases the population of tumor cells during mitosis.

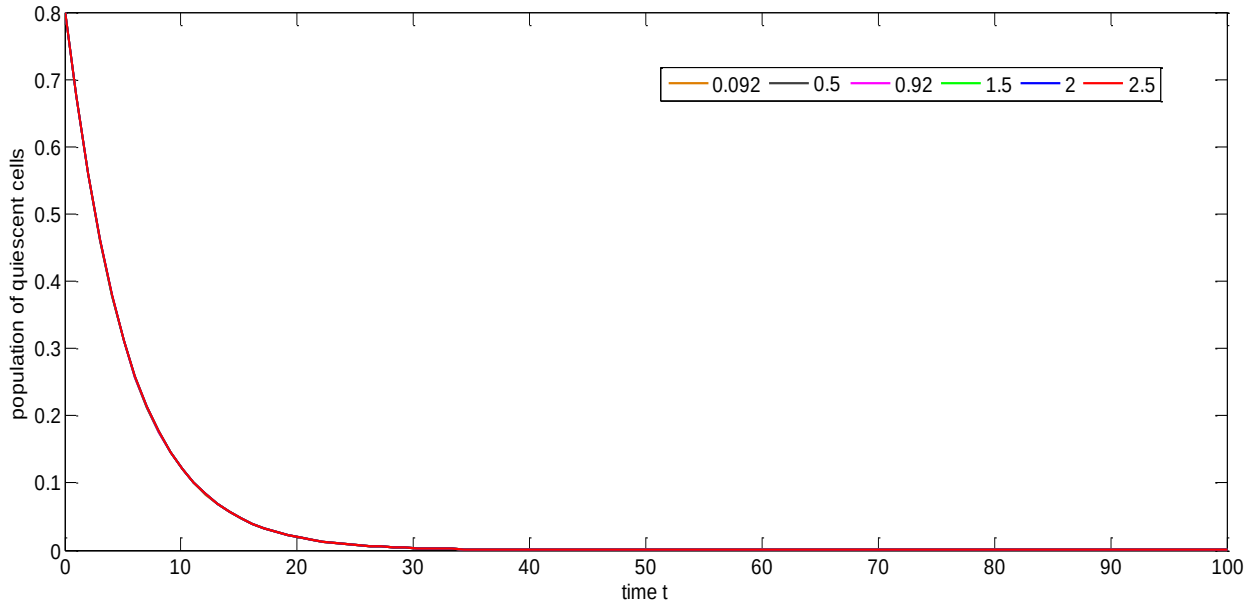

Fig. 3.10 *Variation of population of tumor cells T_Q (t) present in quiescent phase at different delay times with time t.*

Unlike tumor cells in interphase stage and mitosis, the tumor cells in quiescent stage show a nominal change in population with change in delay term. Thus we can say that the quiescent cells bear a little effect of change in delay term.

3.2 VARIATION OF TUMOR CELL POPULATION WITH DRUG DELIVERY REGIMEN:

We have tried to incorporate different types of drug delivery regimens for better insight into drug scheduling mechanism. Fig. 3.11 represents a random drug regimen with three pulses of drug at day 1, day 10 and day 15. Figure 3.12 represents the drug schedule for a regular regimen i.e. drug has been given at equal intervals and of equal concentration for 100 days. The figure 3.13 shows the drug schedule similar to Gaussian distribution, the frequency of drug delivery being higher in the middle. Whereas figure 3.14, is a type of drug profile having high drug delivery frequency during the initial days. Fig. 3.15 is a drug map with drug delivery for unequal and unequal intervals.

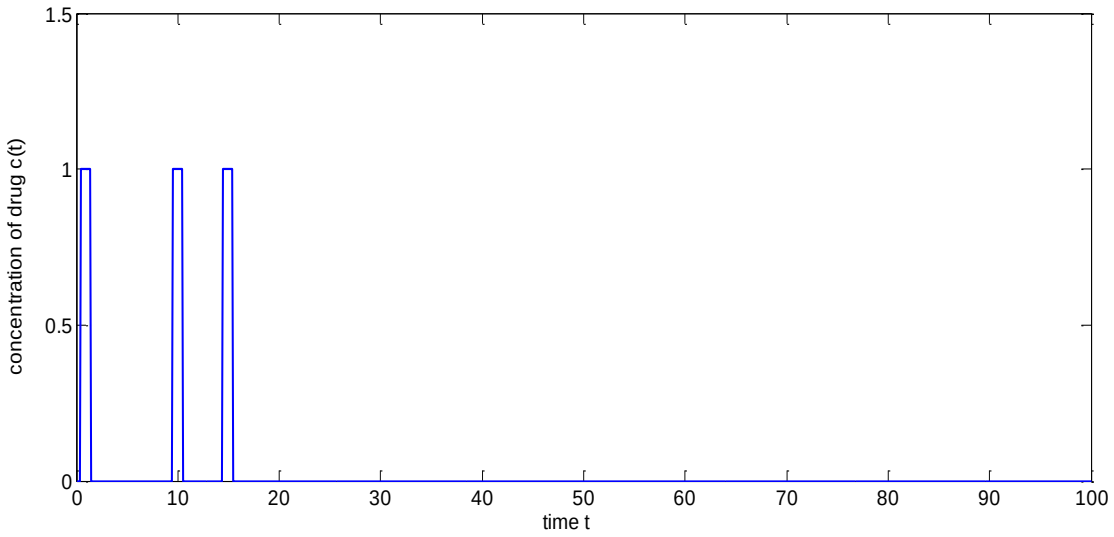

Fig. 3.11 *Random drug regimen with three pulses at day 1, day 10 and day 15*

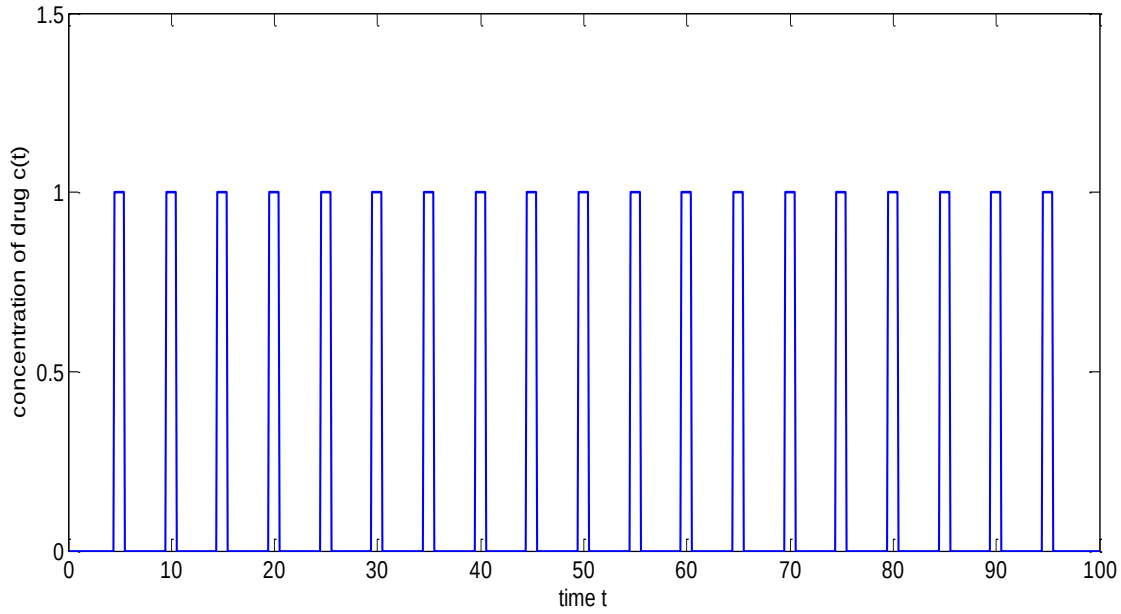

Fig. 3.12 *Drug delivery at regular intervals of time and of equal concentration*

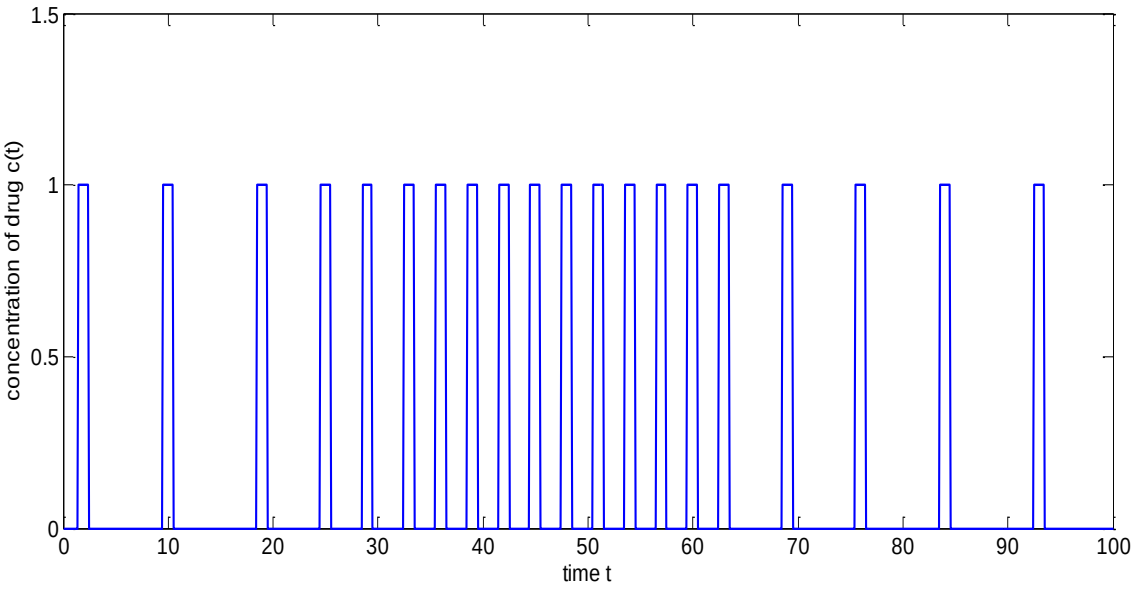

Fig. 3.13 *Gaussian form drug delivery*

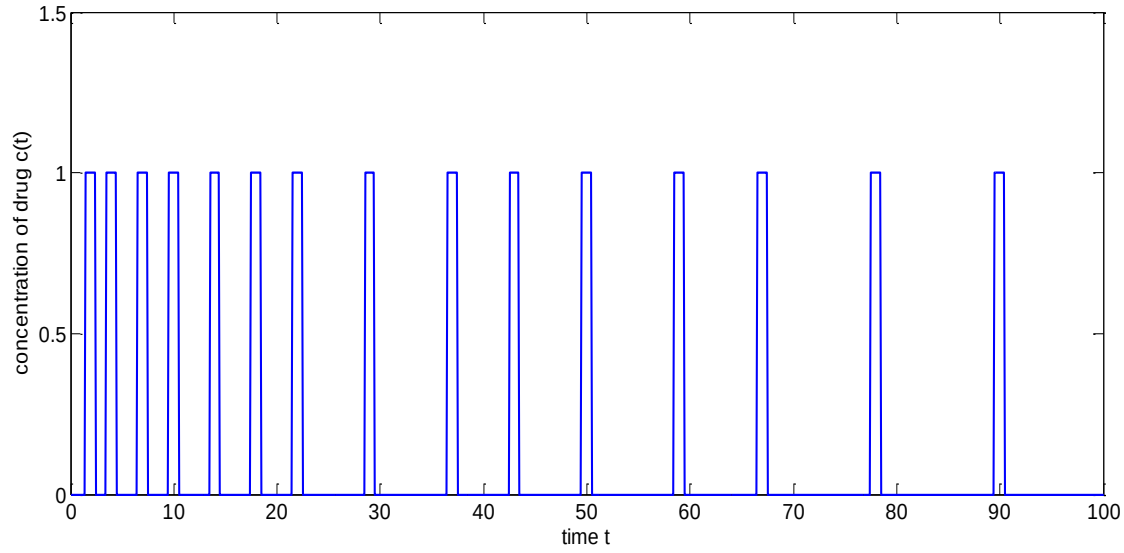

Fig. 3.14 *Drug delivery having initial dense profile*

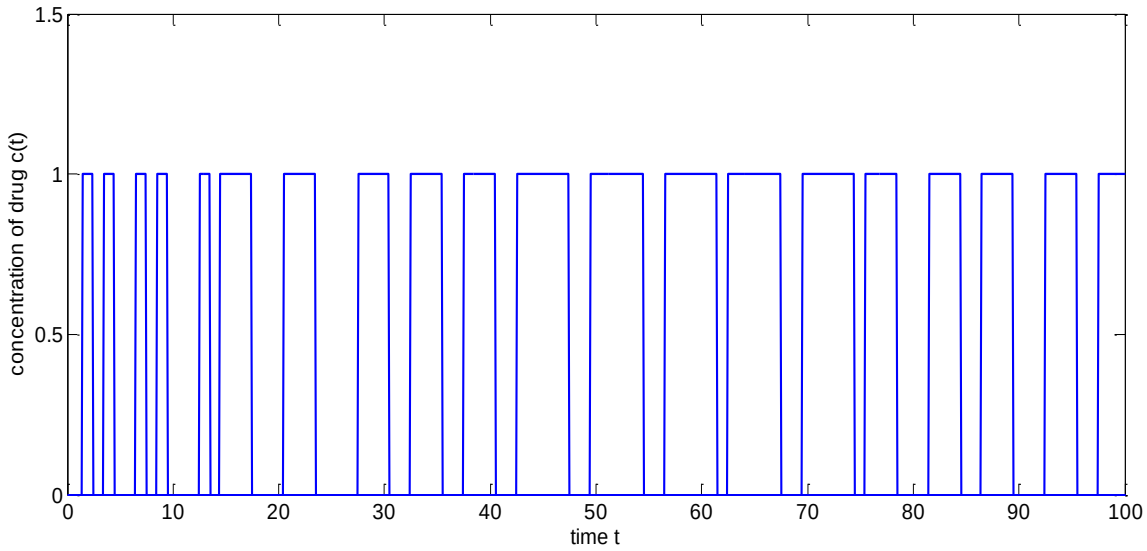

Fig. 3.15 *Drug delivery regimen at irregular intervals and for unequal span of time*

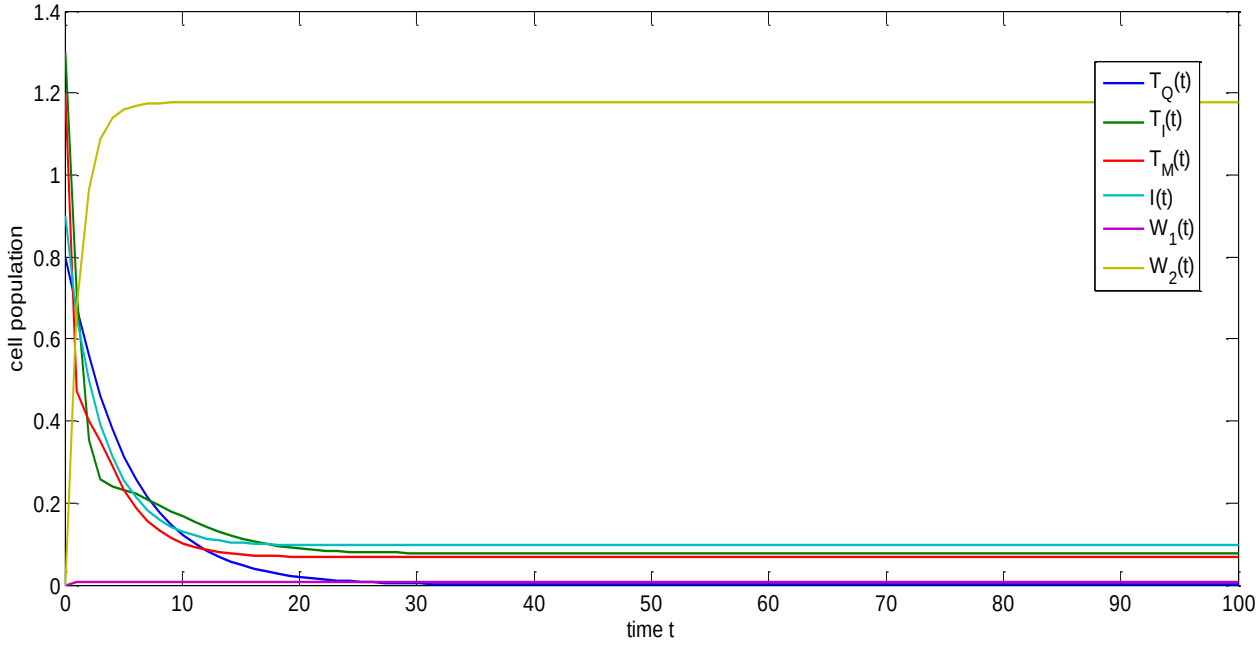

Fig. 3.16 *Variation of tumor cell population for different drug maps*

For the above shown input drug delivery maps (3.11-3.15), nearly similar results are obtained for cell population dynamics. Figure (3.16) depicts the resultant variation of the population of tumor cells with time for different drug maps. There is a very nominal change in the tumor cell population for each drug delivery map considered.

3.3 IMPROVEMENT IN MODEL 1 & MODEL 2:

The MODEL 1 and MODEL 2 discussed in chapter 2 have been improved by modifying the drug delivery function *c(t)*. The effect of modified drug delivery function is studied on the tumor cell growth. The non-linear drug delivery function is introduced in the system in the form $C(t) = c(t) + hc^2(t)$, where h is the control parameter for the non-linear drug delivery term. There is a shocking response by the native cells of the body when a relatively larger amount of drug is given in a single dose. On the other hand, when a meagre amount of dose is given, the native cells get adapted to the effect of the drug. Followed by which a dose with larger amount of drug ($hc^2(t)$), given in one shot, results in prominent decrease in the tumor cell population [48]. The value of $hc^2(t)$ varies with

value of *h*. Increase in *h* results in larger value of amount of drug dose. The improved model 1 and model 2 with modification in drug delivery function have been discussed as follows:

3.3.1 IMPROVED MODEL 1:

The governing equations of MODEL 1 get modified as under:

$$T_I'(t) = 2a_4 T_M(t) - c_1 T_I(t) I(t) - d_2 T_I(t) - a_1 T_I(t-\tau) \tag{3.1}$$

$$T_M'(t) = a_1 T_I(t-\tau) - d_3 T_M(t) - a_4 T_M(t) - c_3 T_I(t) I(t) - k_1(1-e^{-k_2\omega(t)}) T_M(t) \tag{3.2}$$

$$I'(t) = k + \frac{\rho I(t)(T_I(t)+T_M(t))^n}{\alpha + (T_I(t)+T_M(t))^n} - c_2 I(t) T_I(t) - c_4 T_M(t) I(t) - d_1 I(t) - k_3(1-e^{-k_4\omega(t)}) I(t) \tag{3.3}$$

$$\omega_1'(t) = -\lambda_1 \omega_1(t) + c(t) + hc^2(t) \tag{3.4}$$

$$\omega_2'(t) = -\lambda_2 \omega_2(t) + c(t) + hc^2(t) \tag{3.5}$$

$$\omega(t) = r_1 \omega_1(t) + r_2 \omega_2(t) \tag{3.6}$$

All the initial conditions and parameter values are kept same as in MODEL 1. The drug delivery function $c(t)$ is of the form of regular map. The variation in population of tumor cells present in different stages has been studied. The value of the new parameter *h* has been taken nearly small, further its effect on the population of tumor cells is studied for values 0, 0.5, 1.0, 1.5 and 2.0.

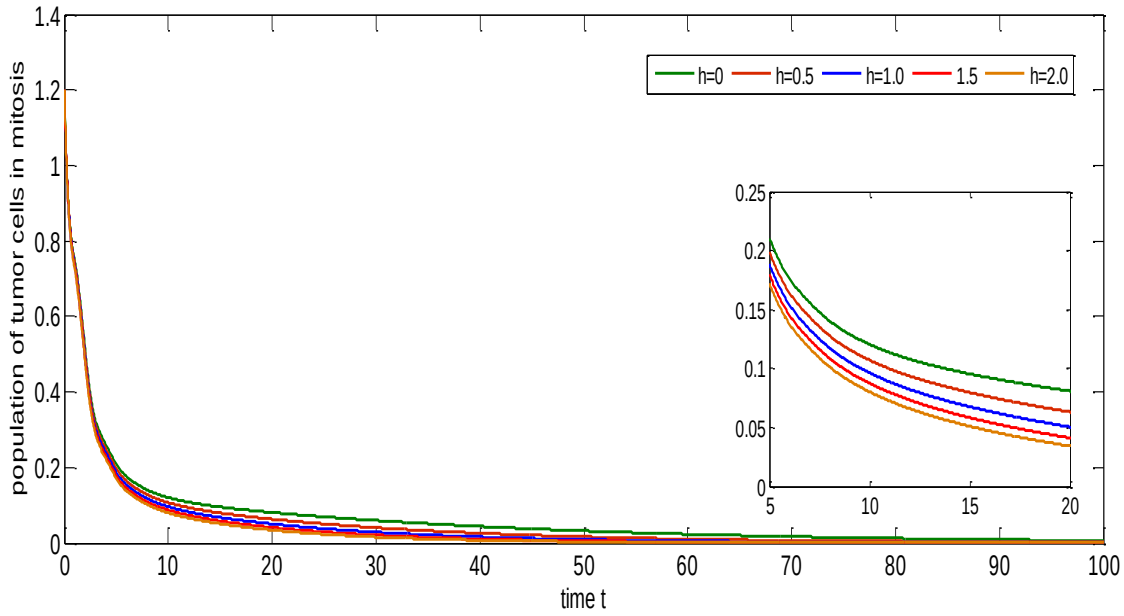

Fig. 3.17 *Variation of population of tumor cells in mitosis with different values of h*

It can be observed from above figure that as we increase the value of *h*, there is a significant decrease in population of tumor cells in mitosis stage. Thus the parameter *h* indirectly controls the population of tumor cells in mitosis phase.

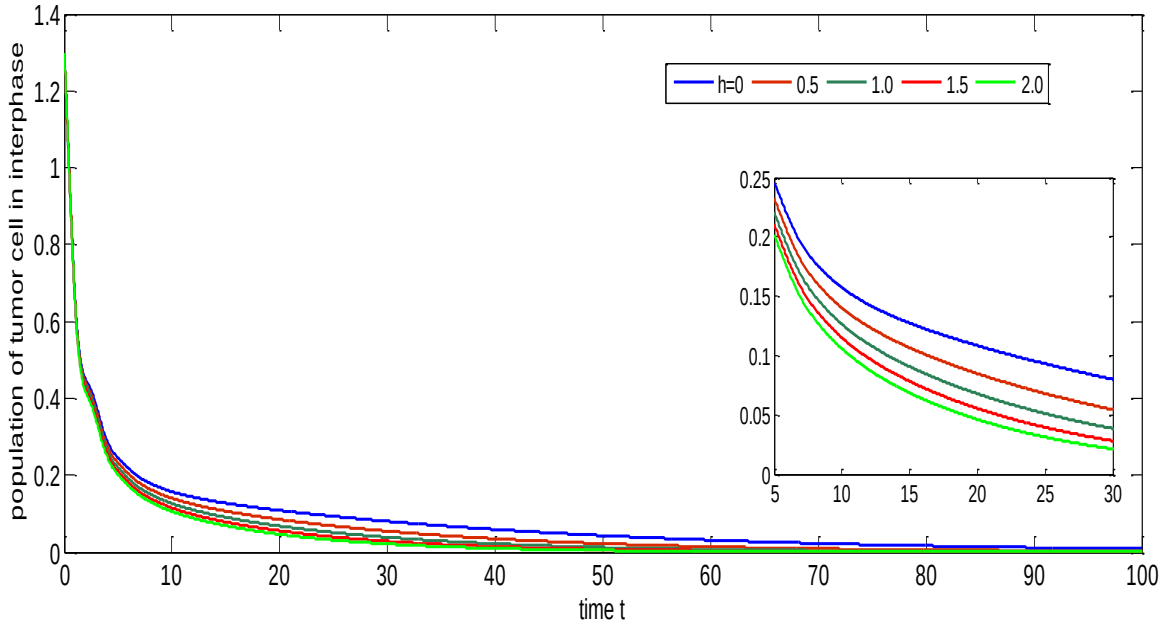

Fig. 3.18 *Variation of population of tumor cells in interphase for different values of h*

Similar variation can be observed in case of tumor cells resting in interphase. With the increase in values of *h*, there is a subsequent decrease in population of tumor cells in interphase stage.

3.3.2 IMPROVED MODEL 3:

The improved MODEL 3, for a regular drug delivery regimen is governed by the following set of equations:

$$T_Q'(t) = a_5 T_I(t-\tau) - a_6 T_Q(t) - d_4 T_Q(t) - c_5 I(t) T_Q(t) - u_1(t) T_Q(t) \tag{3.7}$$

$$T_{I'}(t) = 2a_4 T_M(t) - a_5 T_I(t-\tau) + a_6 T_Q(t) - c_1 T_I(t) I(t) - d_2 T_I(t) - a_1 T_I(t-\tau) \tag{3.8}$$

$$T_M'(t) = a_1 T_1(t-\tau) - d_3 T_M(t) - a_4 T_M(t) - c_3 T_M(t) I(t) - u_2(t) T_M(t) \tag{3.9}$$

$$I'(t) = k + \frac{\rho I(t)(T_I(t) + T_M(t))^n}{\alpha + (T_Q(t) + T_I(t) + T_M(t))^n} - c_2 I(t) T_I(t) - c_4 T_M(t) I(t) - d_1 I(t) - c_6 T_Q(t) I(t) - u_3(t) I(t) \tag{3.10}$$

$$u_1(t) = k_5(1 - e^{-k_6 \omega(t)}) \tag{3.11}$$

$$u_2(t) = k_1(1 - e^{-k_2 \omega(t)}) \tag{3.12}$$

$$u_3(t) = k_3(1 - e^{-k_4 \omega(t)}) \tag{3.13}$$

$$\omega_1'(t) = -\lambda_1 \omega_1(t) + C(t) + hC^2(t) \tag{3.14}$$

$$\omega_2'(t) = -\lambda_2 \omega_2(t) + C(t) + hC^2(t) \tag{3.15}$$

$$\omega(t) = r_1 \omega_1(t) + r_2 \omega_2(t) \tag{3.16}$$

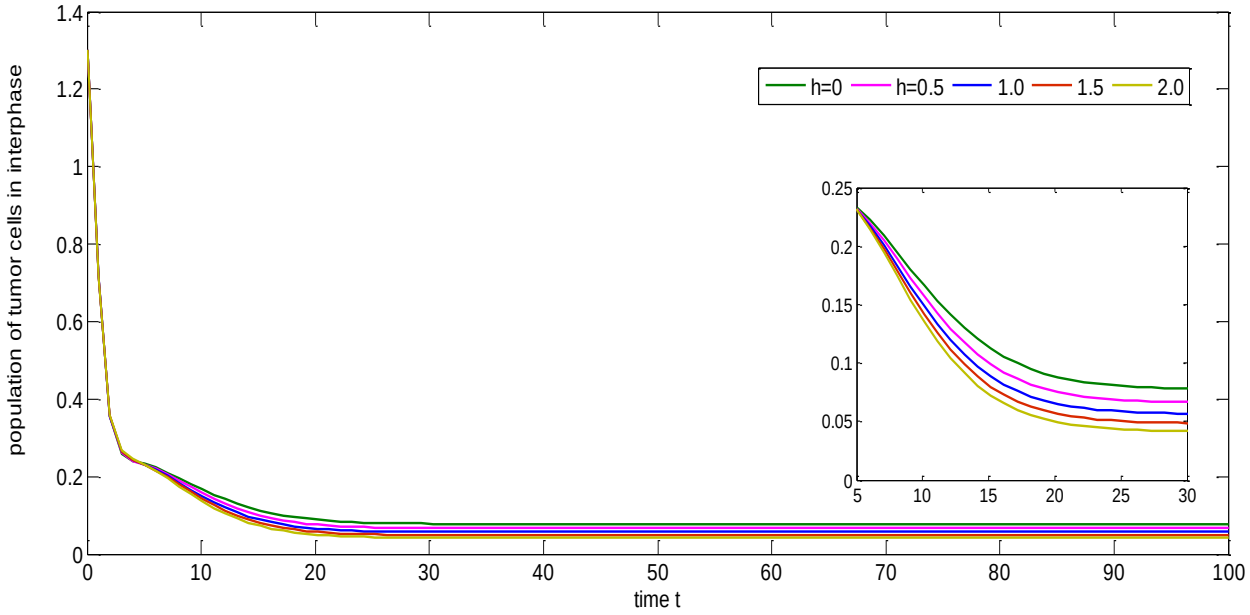

Figure 3.19 *Variation of population of tumor cells in interphase stage with different values of h*

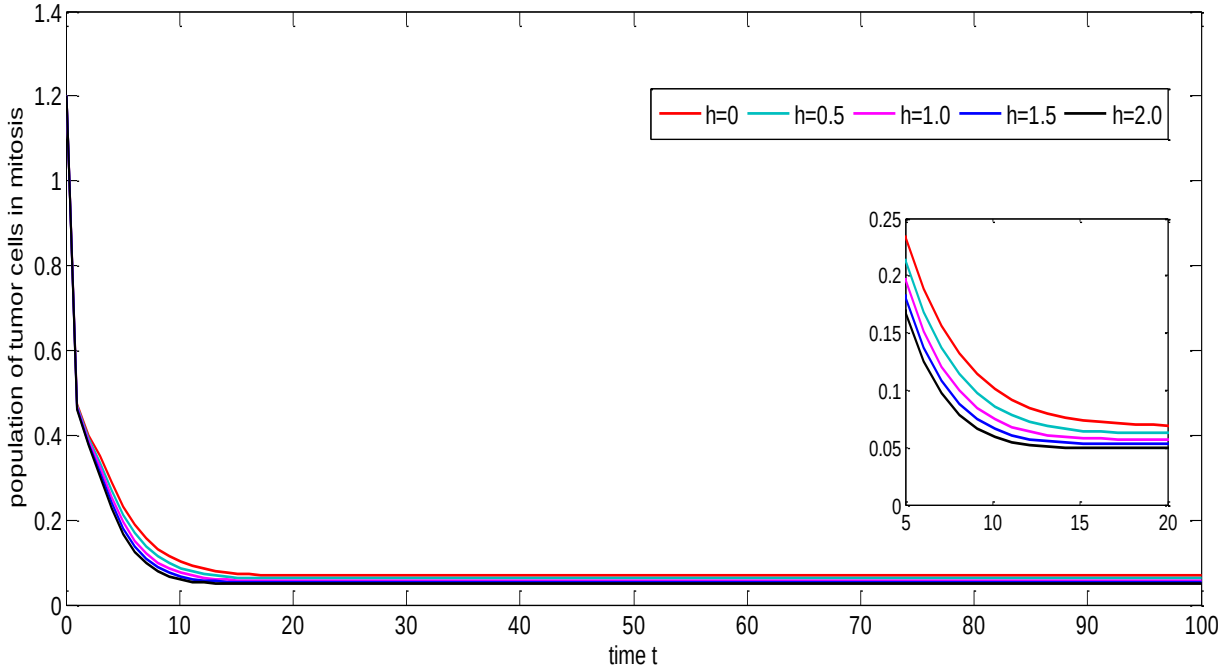

Figure 2.20 *Variation of population of tumor cells in mitosis stage with different values of h*

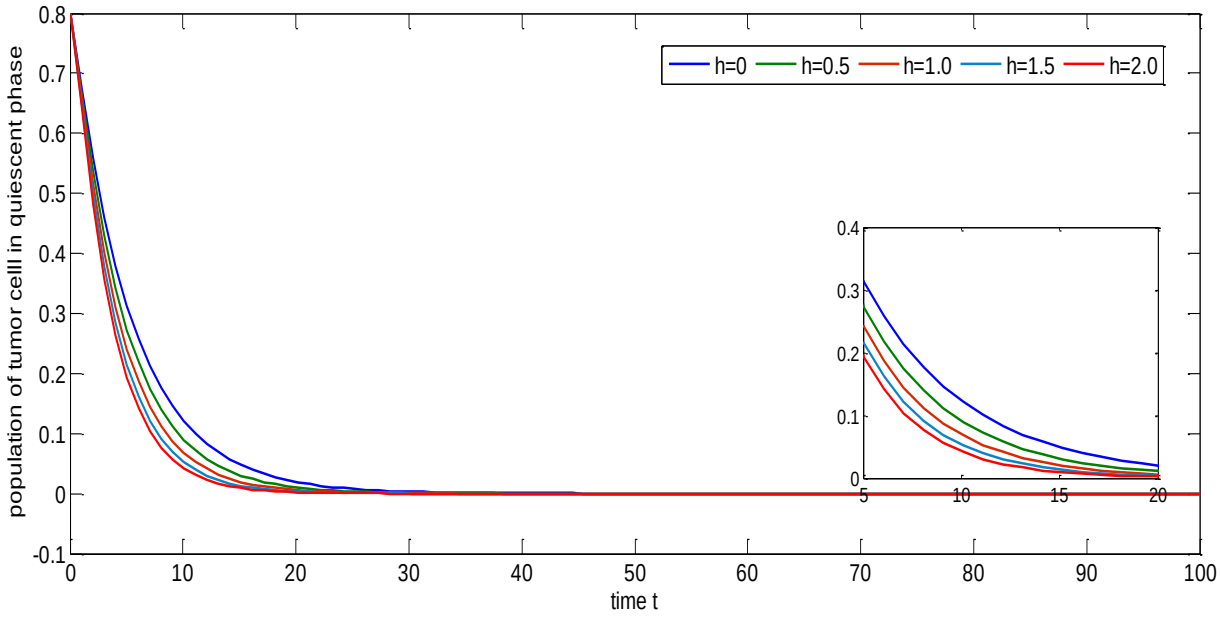

Figure 3.21 *Variation of population of tumor cells in quiescent stage with different values of h*

Fig. (3.19)-(3.21) indicates the variation in tumor cell population present in different stages of cell cycle. It can be observed that with increase in value of *h*, the tumor population T_I, T_M and T_Q decrease significantly. The decrease in quiescent cell population T_Q with *h*, is a notable result, as these cells showed a nominal decrease with increase in delay term.

2.7 APPLICATION OF DDE TO COLON CANCER:

In this section we give a theoretical model based on DDEs for Colon Cancer. The drug term introduced in the model gives a continuous decrease in the thickness of the epithelium tissue.

2.7.1 COLON CANCER:

Colon cancer is formed when the uncontrolled cell growth takes place in the colon i.e. the in the large intestine. The existence of the precancerous polyps in the large intestine is responsible for the colon cancer. One type of polyps is the inflammatory polyp which develops due to the inflammation of the colon [49,50]. The cells of the inflamed colonic mucosa have more probability of undergoing genetic alterations and becoming cancerous. The damage of the oncogenes and tumor suppressor genes is mainly responsible for the cancer growth.

The colonic epithelium is protected from the bacterial infection by the colonic mucosa. It consists of a number of mucins, primarily mucin 2 (MUC2), released from epical membrane and mucin 1 (MUC1) which is a transmembrane mucin lining the surface of the epithelial cells [51]. The inflammation in the intestinal tract is reduced with the help of MUC1 and MUC2, mainly MUC2 and inhibits the development of colon cancer. The mutation in TP53 results in down-regulation of MUC2 that leads to colon cancer. MUC2 is a major secreted mucin that is released form the epical membrane to the region above $\chi = 0$ and below some level $\chi = \chi_t$ MUC1 is a type of protective gel that suppresses the inflammatory response.

2.7.2 MATHEMATICAL MODEL OF COLON CANCER:

We have constructed a mathematical model for colon cancer taking into account the drug effect and the delay time i.e. the time taken by the drug to complete its action on the tumor cells. The model is based on the geometry shown in figure (3.22 (a)). Here, one-dimensional geometry has been considered, where the apical membrane of the epithelium is a flat surface $\chi = 0$, above which the mucus layer is present i.e. in $0 < \chi < \chi_t$ and the surface below i.e. $-\chi_m < \chi < 0$ shows the epithelium tissue.

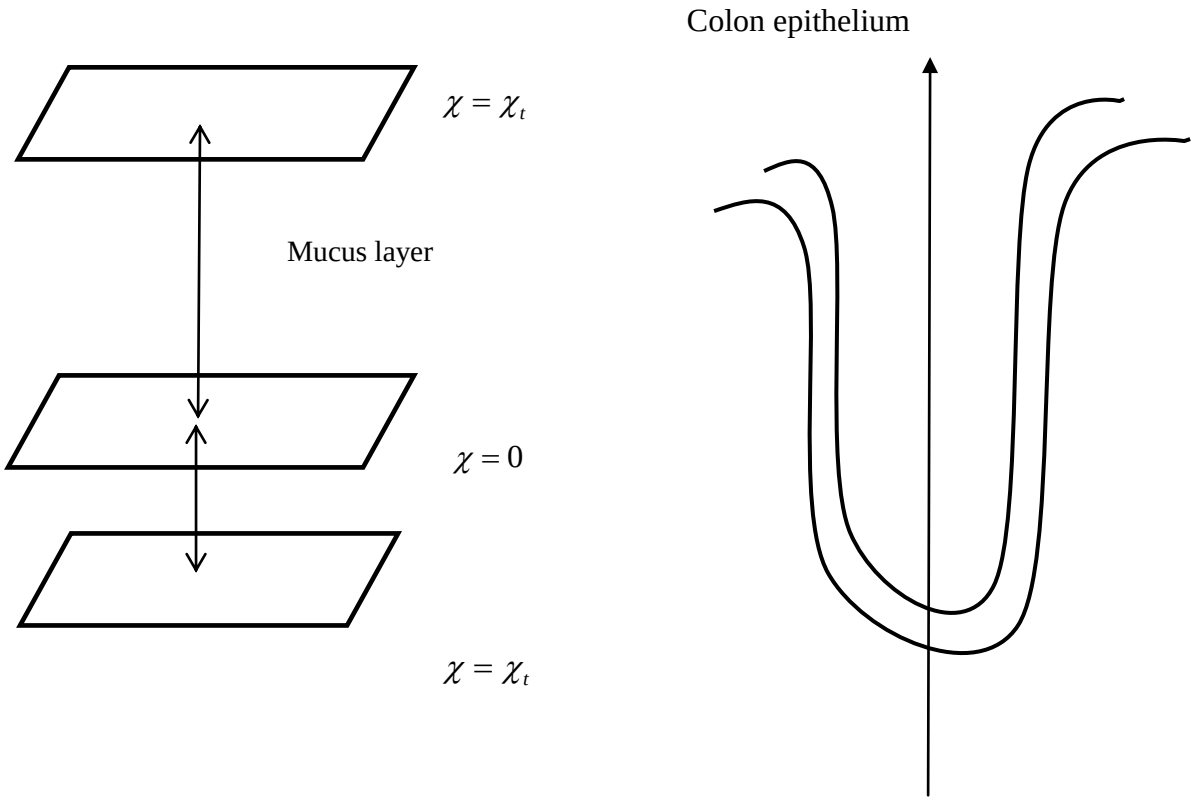

Figure 3.22 *(a) one-dimensional geometry of the model (b) the colonic crypt and the basement membrane*

$$M_1'(t) = \lambda_{11} + \alpha \frac{N(t-\tau)}{N(t-\tau)+K_1} - \lambda_{12} M_1 \tag{3.17}$$

$$M_2'(t) = D_M \left(\lambda_{21}(p) + \beta \frac{N}{N+K_2} \right) - \lambda_{22} M_2 \tag{3.18}$$

$$N'(t) = \lambda_{41} \left(1 + \gamma \frac{(I/K_N)}{(I/K_N)+1} \right) - \lambda_{32} N(t-\tau) - k_5 \left(1 - e^{-k_6 \omega(t)}\right) N(t-\tau) \tag{3.19}$$

$$B'(t) = \lambda_{41} - \lambda_{42} \left(1 + \frac{\nu_1}{1+(M_1/K_{B1})} + \frac{\nu_2}{1+\eta_A (I/K_{B2})} \right) B \tag{3.20}$$

$$\chi_m'(t) = \lambda_c(B,N)\chi_m \tag{3.21}$$

$$\omega(t) = r_1 \omega_1(t) + r_2 \omega_2(t) \tag{3.22}$$

$$\omega_1'(t) = -\lambda_1 \omega_1(t) + c(t);\ \omega_1(0) = 0 \tag{3.23}$$

$$\omega_2'(t) = -\lambda_2 \omega_2(t) + c(t)\ \omega_2(0) = 0 \tag{3.24}$$

$$I = \left(1 - M_1 / \mu_1 - M_2 / \mu_2\right)^+ \tag{3.25}$$

$$\lambda_C(B,N) = \lambda_{51} \frac{\left(0.8B / B_{ss} + N / N_{ss} - K_C\right)}{\left(0.8B / B_{ss} + N / N_{ss} = K_C\right)^+ + 1} \tag{3.26}$$

The term $\alpha \dfrac{N(t-\tau)}{N(t-\tau)+K_1}$ in eqn. (3.17), represent the production of MUC1 by NF-*k*B, λ_{11} is the basel production rate of MUC1 and λ_{12} is the degradation rate of MUC1, $\lambda_{12}M_1$ represents the degradation of MUC 1.. Eqn. (3.18) represents the diffusion equation of MUC1 in the region $0 < \chi < \chi_t$, above the epical surface with diffusion coefficient D_M. The term $\lambda_{21}(p) + \beta \dfrac{N}{N + K_2}$ represents the combined production rate of MUC1, where the value of $\lambda_{21}(p)$ decreases as the number of cells producing TP53 mutation increases. λ_{22} is the degradation coefficient of MUC2 and $\lambda_{22}M_2$ represents the degradation of MUC2.

The equation of NF-*k*B and *β*-catenin are represented by equation (3.19) and (3.20). The first term in eqn. (3.19) represents the activation term for NF-*k*B and the second term is the deactivation term for NF-*k*B; λ_{31} and λ_{32} being the basal growth rate and the deactivation rate respectively. The first term in eqn. (3.20) is the production rate of *β*-catenin per cell and the second term represents the degradation of *β*-catenin; λ_{42} being the degradation coefficient. η_A is the parameter for controlling the level of APC mutation; K_{B1} and K_{B2} are the normalizing factors of M_I and *I*.

Further λ_C is the proliferation rate of cancer cells. This rate depends on the concentration of active NF-*k*B and active *β*-catenin. The expression of λ_C depicts that cancer cells do not proliferate if the sum of the normalized B and N is less than a threshold K_C; N_{SS} and B_{SS} are the steady state concentration of NF-*k*B and *β*-catenin respectively, in healthy tissue. The tumor thickness χ_m is a function of the proliferation rate of cancer cells, represented by equation (3.21). The second term in this equation represents the kill term having an exponential variation. *C (t)* is the concentration of drug given for the treatment and $\chi_m(t-\tau)$ is the increased tumor thickness present before the action of the drug takes place.

The effect of drug on tumor thickness χ_m is studied with time. The values of all the parameters have been taken as same in [49].the value of the kill term has been calculated from MODEL3 [15], taking *c(t)=0*. The following graph was plotted for *c(t)=0* in equation (3.23) and (3.24) keeping the positive value of delay 0.1. An exponential decrease is witnessed in the tumor thickness with time.

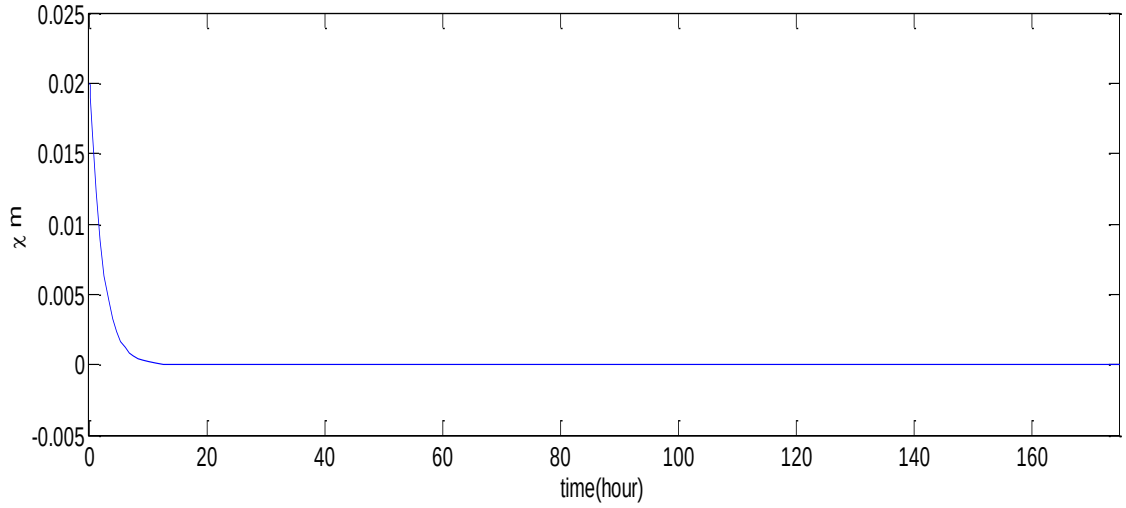

Fig. 23 *Variation of tumor cell thickness with time*

The above discussed model has been solved for no drug and hence without the presence of any delay term by *W..c Lo et. al.* in [51].

Thus we have applied the concept of Delay in Colon cancer, resulting in decrement in tumor thickness. The model can be verified for different parameter variation and can be explored further for future study.

CONCLUSION:

A visible variation in the population dynamics of tumor cells is observed for different delay times. The various drug delivery regimens show a marginal effect on the tumor population. An improvement in the drug delivery system shows a significant decrease in the tumor cell population. The stability analysis was performed for drug free and drug incorporated system with and without the inclusion of delay factor. Finally, the

delay approach was applied to colon cancer. The results obtained can be helpful to provide a better insight into the cancer treatment strategies. The aim of the fundamental research has been fulfilled and the practicality of the results can be taken into account. The improvement in drug delivery system has shown subsequent decrement in tumor cell population and may even lead to the better treatment. All biological processes involve delays in one form or the other, e.g. gestation and maturation etc. The delay incorporating approach can be applied to other biological systems also. The improved model discussed can be further modified for other types of cancer and cell abnormalities. However, there lies an open scope of research into this field. The results obtained may vary from patient to patient depending on a number of factors like health of immune cells, risk factor like uncertainty in death time of the patient and other health factors also. The consideration of such factors in the model discussed may provide an opportunity for future research in this field. Moreover, the range of drug control parameter h needs to be identified for the optimal cancer treatment.

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