Stochastic Modeling for Treatment Dependent Malignancy Growth

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ABSTRACT

In this paper we develop a stochastic model for treatment dependent malignant tumor growth during the presence and absence of drug as a part of cancer treatment with chemotherapy. The cancer cells growth in pre-malignancy and malignancy stages is a resulting effect of treatment with chemotherapy. It has to be considered as a linear combination of the growth during drug absence and its presence. The joint probability function of premalignant and malignant cells is derived under stipulated assumptions and the required postulates of Poisson processes. The statistical measures like averages, variances and co variances of number of cells in malignant and premalignant stages are derived. Model behavior was analyzed with a numerical illustration. This study will be useful in exploring the parameters of malignancy growth during chemotherapy.

Keywords: Treatment dependent malignancy, stochastic modeling, chemotherapy, bivariate linear birth and death process, differential equations.

1. Introduction:

Cancer is a class of diseases characterized as the uncontrolled cell growth beyond the regulatory mechanism of cell division. Cancer harms the body when the damaged cells divide uncontrollably to form lumps or masses of tissue called tumors. Tumors can grow and interfere with various systems of human body. Tumors that stay in one spot and demonstrate limited growth are generally considered to be benign. Cancerous cells manage to move throughout the body using the blood or lymph systems and destroy the healthy tissues in a process called invasion. These cells manages to divide and grow, making new blood vessels to flee themselves in a process called angiogenesis. Normal cells in the body follow an orderly path of growth, division, and death. When this process breaks down, cancer begins to form. Original mass of cells travel through the blood and lymph systems, and lodge in other organs where they can again repeat the uncontrolled growth cycle. In this process, the cancer cells shall move from one area and grow in another area of the body is termed as metastasis spread. Acquired drug resistance is an important reason for the failure of targeted therapy with chemotherapy.

Resistance emerges due to drug metabolism, drug export, and alteration of the drug target by mutation, deletion, or over expression. The effectiveness of chemotherapy depends on many factors like the cancer type, the stage of the disease, the method of therapy, types of drug administration, medical and disease history of the patient, etc. Currently, many targeted drugs are administered continuously at sufficiently low doses so that no drug holidays are necessary to limit the side effects. Alternatively, the drug may be administered at higher doses in short pulses followed by rest periods to allow for recovery from toxicity. One way of combating the slowing rate of tumor regression was to increase the intensity of treatment so as the tumor size became smaller, thus increasing the chance of cure.

A widely used approach on cancer chemotherapy is to give a maximum dosage of drug for some period of time, followed by a period of vacation in which no drug is given. When the cancer reaches the metastasis stage, a transmission of cancerous cells will be taken place from the primary tumor to other parts of the body. A systematic treatment like chemotherapy must be applied to the diffused cancerous cells. Depending on the anti-cancer agents involved, chemotherapy works like a double-edged weapon as it annihilates the cancerous cells while destroying the normal cells also at the same time. The drug resistance has a higher probability to appear with the longer exposure to the chemotherapy drug. Therefore, it is better to annihilate the cancerous cells as soon as possible by higher drug dosage. On the other hand, a high drug dosage will lead to unallowable toxicity.

Ferrante.L, et.al (2000) have estimated the parameters of tumor growth by considering stochastic version of Gompertzian model, which describes in vivo tumor growth and its treatment with antiangiogenic drug. Srinivasa Rao.K. et.al (2004) have developed a stochastic model to study the growth of cancer cell under chemotherapy (i.e. during the presence of drug in the body). Natalia et.al (2006) have formulated a stochastic model for multi-drug resistance and investigated the dependence of treatment outcomes on the initial tumor load, mutation rates and turnover rate of cancerous cell. Raluca Horhat et.al (2009) have investigated a stochastic model for tumor- immune system by using winener process, as the noise has a stabilization effect. Tirupati Rao. P. et.al (2011) have studied the cancer growth by modeling the growth and loss process of normal and mutant cells under chemotherapy using time dependent bivariate poisson process. Madhavi.K. et.al(2012) have developed a stochastic model for stage dependent mutant

cell growth by assuming the growth and loss processes of mutant and normal cells follows time and stage dependent bivariate poisson process.

The above mentioned research works reveals that, the role of cancer growth during the drug administration and vacation periods were not considered with due importance. In order to fill this gap of research, we have developed a stochastic model by considering the growth of cancer is a resulting effect of drug presence and absence. Usually, Chemotherapy is having two fold action on the growth of cancer. Continuous drug administration and drug with high dosage levels may harm the normal cells as the chemical toxicity may kill the healthy cells also in the process of destroying the cancer causing cells. Hence there is a need of drug stoppage to the body so that the patient may get recovery during this period. Therefore chemotherapy has to be implemented in cycles. The large gaps between two drug administrations may re-aggravate the problem of cancer growth. By keeping the above things in mind, a new stochastic model is developed as the rates of growth and losses of healthy cells are influenced by the drug absence and drug presence respectively.

2. Stochastic model:

It is considered that, a mutant cell may divide into either premalignant cell or a malignant cell. The behaviour of the cell division is varying with the influence of drug presence and absence in the body. A high drug dosage level will lead to increase the unwanted toxicity. Similarly low levels of drug or long vacation of drugs may develop drug resistance. As a result, the design of drug administration will be complicated in developing the suitable chemotherapy treatment plan. The behaviors of tumor/cancerous cells are purely stochastic in nature. The dynamics of mutant, pre-malignant and malignant cells on cancer growth is explained through the following schematic diagram.

Let the events like arrivals of premalignant cells through mutations, arrivals of malignant cells either through mutation within malignant cells or from the stage of premalignant cells, The loss of both premalignant and malignant cells occurred in non-overlapping intervals of time are statistically independent. Let Δt be an infinitesimal interval of time 't'. Let there be 'n' premalignant cells and 'm' malignant cells initially at time 't'. Let $\alpha_0, \beta_0, \gamma_0, \delta_0, \theta_0$ be the rate of arrival of mutant cells to pre-malignancy, rate of arrival of mutant cells to malignancy, rate of transformations of cells from pre-malignancy to malignancy, rate of death of premalignant cells

without transforming to malignancy, rate of death of malignant cells respectively during the absence of chemotherapy.
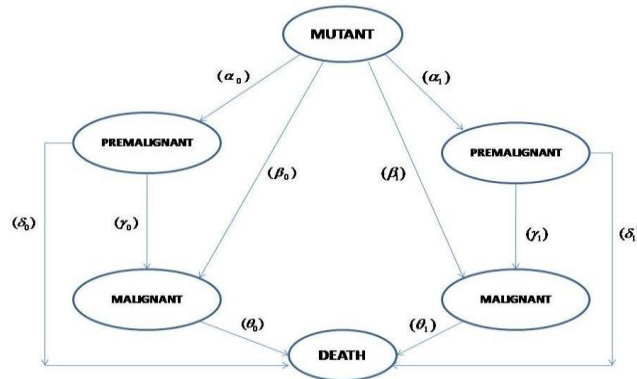
Similarly Let $\alpha_1, \beta_1, \gamma_1, \delta_1, \theta_1$ be the rate of arrival of mutant cells to pre-malignancy, rate of arrival of mutant cells to malignancy, rate of transformations of cells from pre-malignancy to malignancy, rate of death of premalignant cells without transforming to malignancy, rate of death of malignant cells respectively during the presence of chemotherapy. It is further assumed that the parameters of the above mentioned events follow Poisson process. The cell growth of normal and mutant cells are additive in nature with respect to drug absence or presence. The loss and growth rate of mutant cells is a linear combination of drug administration and its vacation on cancer growth.

Since α_0, α_1 are the rates of arrival of premalignant cells during the absence and presence of chemotherapy,   the overall arrival rate of premalignant cells during time 't' is, $[a\alpha_0 + (1-a)\alpha_1]; 0 \le a \le 1$; The overall 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 $[g\theta_0 + (1-g)\theta_1]; 0 \le g \le 1$; The postulates of the model includes (i) The probability of arrival of one premalignant cell from mutant cells during Δt is $[a\alpha_0 + (1-a)\alpha_1]\Delta t + o(\Delta t)$; (ii) The probability   of   arrival   of   one   malignant   cells   from   mutant   cell   during Δt is $[b\beta_0 + (1-b)\beta_1]\Delta t + o(\Delta t)$; (iii)The probability of transformation of premalignant cell to a malignant cell provided $\exists$ 'n' premalignant cells at time 't' is $n[c\gamma_0 + (1-c)\gamma_1]\Delta t + o(\Delta t)$; (iv)

The probability of death of one premalignant cell provided $\exists$ 'n' premalignant cells at time 't' is

$n[d\delta_0 + (1-d)\delta_1]\Delta t + o(\Delta t)$; (v) The probability of death of one malignant cell provided $\exists$ 'm'

malignant cell at time 't' is $m[g\theta_0 + (1-g)\theta_1]\Delta t + o(\Delta t)$; (vi) The probability of no arrival of a

premalignant cell, no arrival of a malignant cell, no transformation of cell from pre-malignancy

to malignancy, no death of premalignant cell, and no death of malignant cell during an

infinitesimal interval of time Δt is $1 - [\{a\alpha_0 + (1-a)\alpha_1\} + \{b\beta_0 + (1-b)\beta_1\} + n\{c\gamma_0 + (1-c)\gamma_1$

$+ d\delta_0 + (1-d)\delta_1\} + m\{g\theta_0 + (1-g)\theta_1\}]\Delta t + o(\Delta t)$; (vii) The probability of occurrence of other

than the above events during an infinitesimal interval of time Δt is $o(\Delta t)^2$.

Let $p_{n,m}(t)$ be the joint probability of existing of 'n' premalignant cells and 'm' malignant cells

in a tumor per unit time 't'.   Then the difference-differential equations of the model are:

$$\begin{aligned}
p'_{n,m}(t) = &[1 - [\{a\alpha_0 + (1-a)\alpha_1 + b\beta_0 + (1-b)\beta_1\} + n\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1\} \\
&+ m\{g\theta_0 + (1-g)\theta_1\}]p_{n,m}(t) + [\{a\alpha_0 + (1-a)\alpha_1\}p_{n-1,m}(t)] \\
&+ [(n+1)\{d\delta_0 + (1-d)\delta_1\}p_{n+1,m}(t)] + [(n+1)\{c\gamma_0 + (1-c)\gamma_1\}p_{n+1,m-1}(t)] \\
&+ [\{b\beta_0 + (1-b)\beta_1\}p_{n,m-1}(t)] + [(m+1)\{g\theta_0 + (1-g)\theta_1\}p_{n,m+1}(t)\}] \quad \text{for n,m} \geq 1 \quad \dots (2.1)
\end{aligned}$$

$$\begin{aligned}
p'_{1,0}(t) = &-[\{a\alpha_0 + (1-a)\alpha_1 + b\beta_0 + (1-b)\beta_1 + c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1\}]p_{1,0}(t) \\
&+ \{a\alpha_0 + (1-a)\alpha_1\}p_{0,0}(t)\} + 2\{d\delta_0 + (1-d)\delta_1\}p_{2,0}(t)] + \{g\theta_0 + (1-g)\theta_1\}p_{1,1}(t) \quad \dots(2.2)
\end{aligned}$$

$$\begin{aligned}
p'_{0,1}(t) = &-\{a\alpha_0 + (1-a)\alpha_1 + b\beta_0 + (1-b)\beta_1 + g\theta_0 + (1-g)\theta_1\}p_{0,1}(t) + \{d\delta_0 + (1-d)\delta_1\}p_{1,1}(t) \\
&+ \{c\gamma_0 + (1-c)\gamma_1\}p_{1,0}(t) + \{b\beta_0 + (1-b)\beta_1\}p_{0,0}(t) + 2\{g\theta_0 + (1-g)\theta_1\}p_{0,2}(t) \quad \dots(2.3)
\end{aligned}$$

$$\begin{aligned}
p'_{0,0}(t) = &-\{a\alpha_0 + (1-a)\alpha_1 + b\beta_0 + (1-b)\beta_1\}p_{0,0}(t) + \{d\delta_0 + (1-d)\delta_1\}p_{1,0}(t) \\
&+ \{g\theta_0 + (1-g)\theta_1\}p_{0,1}(t) \quad \dots(2.4)
\end{aligned}$$

With the initial condition
$p_{N_0,M_0}(0) = 1, \ p_{i,j}(0) = 0 \qquad \forall i \neq N_0, j \neq M_0;$

Let $p(x, y; t)$ be the joint probability generating function of $p_{n,m}(t)$, $p(x, y; t) = \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} x^m y^m p_{n,m}(t)$

Multiplying the equation (2.1) to (2.4) with $x^m y^m$ and summing overall m and n we have

$$\sum_{m=0}^{\infty}\sum_{n=0}^{\infty} x^n y^m p'_{n,m}(t) = \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} -[\{a\alpha_0 + (1-a)\alpha_1 + b\beta_0 + (1-b)\beta_1\} + n\{c\gamma_0 + (1-c)\gamma_1$$

$$+ d\delta_0 + (1-d)\delta_1\} + m\{g\theta_0 + (1-g)\theta_1\}]x^n y^m p_{n,m}(t)$$

$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty}\{a\alpha_0 + (1-a)\alpha_1\}x^n y^m p_{n-1,m}(t)$$

$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty}[(n+1)\{d\delta_0 + (1-d)\delta_1\}]x^n y^m p_{n+1,m}(t)$$

$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty}[(n+1)\{c\gamma_0 + (1-c)\gamma_1\}]x^n y^m p_{n+1,m-1}(t)$$

$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty}\{b\beta_0 + (1-b)\beta_1\}x^n y^m p_{n,m-1}(t)$$

$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty}[(m+1)\{g\theta_0 + (1-g)\theta_1\}]x^n y^m p_{n,m+1}(t)$$

…(2.5)

Simplifying

and rearranging the terms in the equation 2.5 we get

$$\Rightarrow \frac{\partial}{\partial t} p(x,y;t) = [\{a\alpha_0 + (1-a)\alpha_1(x-1) + \{b\beta_0 + (1-b)\beta_1\}(y-1)]p(x,y;t)$$

$$+ [-\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1\}x$$

$$+ \{c\gamma_0 + (1-c)\gamma_1\}y + \{d\delta_0 + (1-d)\delta_1\}]\frac{\partial p}{\partial t}$$

…(2.6)

$$+ [\{g\theta_0 + (1-g)\theta_1\}(1-y)]\frac{\partial}{\partial y} p(x,y;t)$$

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:

$$\Rightarrow \frac{\partial}{\partial t} k(u,v;t) = [-\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1\} + \{c\gamma_0 + (1-c)\gamma_1\}e^{-u+v}$$

$$+ \{d\delta_0 + (1-d)\delta_1\}e^{-u}]\frac{\partial k}{\partial u} + [\{g\theta_0 + (1-g)\theta_1\}(e^{-v}-1)]\frac{\partial k}{\partial v}$$

$$+ [\{a\alpha_0 + (1-a)\alpha_1\}(e^u-1) + \{b\beta_0 + (1-b)\beta_1\}(e^v-1)]k(u,v;t)$$

…(2.7)

3. Differential Equations & Statistical Measures:

If $m_{i,j}(t)$ denotes the moments of order (i,j) of premalignant and malignant cells at time 't', then the differential equations governing $m_{i,j}(t)$ are:

$$\frac{d}{dt}m_{1,0}(t) = -\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1\}m_{1,0}(t) + a\alpha_0 + (1-a)\alpha_1 \qquad \ldots(3.1)$$

$$\frac{d}{dt}m_{0,1}(t) = \{c\gamma_0 + (1-c)\gamma_1\}m_{1,0}(t) - \{g\theta_0 + (1-g)\theta_1\}m_{0,1}(t) + \{b\beta_0 + (1-b)\beta_1\} \qquad \ldots(3.2)$$

$$\frac{d}{dt}m_{2,0}(t) = \{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1\}m_{1,0}(t) - 2\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0$$
$$+ (1-d)\delta_1\}m_{2,0}(t) + \{a\alpha_0 + (1-a)\alpha_1\} \qquad \ldots(3.3)$$

$$\frac{d}{dt}m_{1,1}(t) = -\{c\gamma_0 + (1-c)\gamma_1\}m_{1,0}(t) + \{c\gamma_0 + (1-c)\gamma_1\}m_{2,0}(t)$$
$$- [d\delta_0 + (1-d)\delta_1 + c\gamma_0 + (1-c)\gamma_1 + g\theta_0 + (1-g)\theta_1]m_{1,1}(t) \qquad \ldots(3.4)$$

$$\frac{d}{dt}m_{0,2}(t) = \{c\gamma_0 + (1-c)\gamma_1\}m_{1,0}(t) + 2\{c\gamma_0 + (1-c)\gamma_1\}m_{1,1}(t) + \{g\theta_0 + (1-g)\theta_1\}m_{0,1}(t)$$
$$- 2\{g\theta_0 + (1-g)\theta_1\}m_{0,1}(t) + \{b\beta_0 + (1-b)\beta_1\} \qquad \ldots(3.5)$$

Solving the above relations shall provide the following statistical measures.

Expected number of premalignant cells during the treatment at time 't' is

$$m_{1,0}(t) = \frac{\{a\alpha_0 + (1-a)\alpha_1\}}{\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1\}} . [1 - e^{-\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1\}t}]$$
$$+ N_0 e^{-\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1\}t} \qquad \ldots(3.6)$$

Expected number of malignant cells during the treatment at time 't' is

$$m_{0,1}(t) = \frac{\{a\alpha_0 + (1-a)\alpha_1\}\{c\gamma_0 + (1-c)\gamma_1\}}{\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1\}} . [1 - \frac{e^{-\{g\theta_0 + (1-g)\theta_1\}t}}{\{g\theta_0 + (1-g)\theta_1\}}$$
$$+ \frac{e^{-\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1\}t} - e^{-\{g\theta_0 + (1-g)\theta_1\}t}}{\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1 - g\theta_0 - (1-g)\theta_1\}}]$$
$$- \frac{N_0\{c\gamma_0 + (1-c)\gamma_1\}}{\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1 - g\theta_0 - (1-g)\theta_1\}}$$
$$[e^{-\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1\}t} - e^{-\{g\theta_0 + (1-g)\theta_1\}t}] + \frac{\{b\beta_0 + (1-b)\beta_1\}}{\{g\theta_0 + (1-g)\theta_1\}} \qquad \ldots(3.7)$$
$$[1 - e^{-\{g\theta_0 + (1-g)\theta_1\}t}] + M_0 e^{-\{g\theta_0 + (1-g)\theta_1\}t}$$

Variance of number of premalignant cells during the treatment at time 't' is

$$m_{2,0}(t) = \frac{\{a\alpha_0 + (1-a)\alpha_1\}}{\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1\}}.[1 - e^{-\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1\}t}]$$

$$+ N_0 e^{-\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1\}t}[1 - e^{-\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1\}t}] \qquad \dots(3.8)$$

Covariance of number of premalignant cells and malignant cells during treatment at time 't' is

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

$$[e^{-\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1\}t} - e^{-\{g\theta_0 + (1-g)\theta_1 + c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1\}t}] \qquad \dots(3.9)$$

Variance of number of malignant cells during chemotherapy at time 't' is

$$m_{0,2}(t) = \frac{\{a\alpha_0 + (1-a)\alpha_1\}\{c\gamma_0 + (1-c)\gamma_1\}}{\{g\theta_0 + (1-g)\theta_1\}\{c\gamma_0 + (1-c)\gamma_1 + d\delta_0 + (1-d)\delta_1 - g\theta_0 - (1-g)\theta_1\}}.$$

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

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

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

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

$$- e^{-2\{g\theta_0 + (1-g)\theta_1\}t} + \frac{\{b\beta_0 + (1-b)\beta_1\}}{\{g\theta_0 + (1-g)\theta_1\}}[1 - e^{-\{g\theta_0 + (1-g)\theta_1\}t}]$$

$$+ M_0 e^{-\{g\theta_0 + (1-g)\theta_1\}t}[1 - e^{-\{g\theta_0 + (1-g)\theta_1\}t}] \qquad \dots(3.10)$$

4. Numerical Illustrations and Sensitivity Analysis:

Table 4.1:

Values of (i) Average number of premalignant cells $m_{1,0}$; (ii) The average number of malignant cells $m_{0,1}$; (iii) The variance of number of premalignant cells $m_{2,0}$; (iv) The variance of number of malignant cells $m_{0,2}$; The covariance between the number of premalignant and malignant cells to various values of $\alpha_0, \beta_0, \gamma_0, \delta_0, \theta_0$ and $\alpha_1, \beta_1, \gamma_1, \delta_1, \theta_1$.

α_0	β_0	γ_0	δ_0	θ_0	α_1	β_1	γ_1	δ_1	θ_1	N_0	M_0	t	m_{10}	m_{01}	m_{20}	m_{11}	m_{02}
1	0.6	0.9	0.3	0.8	0.4	0.4	0.1	0.7	0.9	100	50	5	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
0.9	0.6	0.9	0.3	0.8	0.45	0.4	0.1	0.7	0.9	100	50	5	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
0.9	0.7	0.9	0.3	0.8	0.4	0.4	0.1	0.7	0.9	100	50	5	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
0.9	0.6	0.9	0.3	0.8	0.4	0.6	0.1	0.7	0.9	100	50	5	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
0.9	0.6	1	0.3	0.8	0.4	0.4	0.1	0.7	0.9	100	50	5	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
0.9	0.6	0.9	0.3	0.8	0.4	0.4	0.4	0.7	0.9	100	50	5	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
0.9	0.6	0.9	0.32	0.8	0.4	0.4	0.1	0.7	0.9	100	50	5	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
0.9	0.6	0.9	0.3	0.8	0.4	0.4	0.7	0.75	0.9	100	50	5	1.543	2.804	1.533	-0.015	61.027
								0.8					1.34	2.665	1.333	-0.011	59.335

α_0	β_0	γ_0	δ_0	θ_0	α_1	β_1	γ_1	δ_1	θ_1	N_0	M_0	t	m_{10}	m_{01}	m_{20}	m_{11}	m_{02}
								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
0.9	0.6	0.9	0.3	0.82	0.4	0.4	0.1	0.7	0.9	100	50	5	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
0.9	0.6	0.9	0.3	0.8	0.4	0.4	0.1	0.7	0.93	100	50	5	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
0.9	0.6	0.9	0.3	0.8	0.4	0.4	0.1	0.7	0.9	102	50	5	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
0.9	0.6	0.9	0.3	0.8	0.4	0.4	0.1	0.7	0.9	100	55	5	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
0.9	0.6	0.9	0.3	0.8	0.4	0.4	0.1	0.7	0.9	100	50	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 equations 3.6 to 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 varying values of the parameters and they are presented in the table 4.1

It is observed that expected number of premalignant cells and malignant cells, variance of number of premalignant cells and variance of number 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 of number of

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. It is observed that expected number of premalignant cells, variance of number of premalignant cells and co variance of number of 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 number of malignant cells are increasing function of arrival rate of malignant cells under absence of drug (β_0) and presence of drug (β_1) when all other parameters are constant. It is observed that expected number of premalignant cells, variance of number of pre malignant cells and variance number of malignant cells are decreasing functions of rate of transformation of premalignant cells to malignant cells during the drug (γ_0) and the presence of the drug (γ_1) when all the other parameters are constant. Also observed that covariance of number of premalignant cells and malignant cells & expected number of malignant cells are increasing function 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 constant. It is observed that expected number of premalignant cell and expected number of malignant cells, variance of number of premalignant and malignant cells are decreasing functions and co variances of number of premalignant and malignant cells is negative and decreasing function of rate of death of premalignant cells under the absence of drug (δ_0) and presence of drug (δ_1) when all other parameters are constant. It is observed that expected number of premalignant cells $m_{1,0}$ and variance of number of premalignant cells $m_{2,0}$ are invariant of change; expected number of malignant cells $m_{0,1}$ are decreasing functions of death of malignant cells under absence of drug (θ_0) and presence of drug (θ_1) when all other parameters are constant.

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

and covariance of number of 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 and variance of number of malignant cells are increasing functions of initial number of malignant cells (M_0) when all other parameters are constant. It is observed that the expected number of premalignant cells, expected number of malignant cells, variance of number of premalignant cells and variance of number of malignant cells are increasing functions of time 't' when all the other parameters are constant. The covariance of number of premalignant cells and malignant cells is decreasing function of time 't' when all the other parameters are constant.

References:

1. Ferrante. L. et.al (2000) " Parameter Estimation in a Gompertzian Stochastic Model for Tumor Growth" biometrics, Vol 56, Issue 4, pages 1076-1081.

2. Madhavi. K. et.al (2012) "Stochastic Modeling on Stage Dependent Mutant Cell Growth" International Journal of computational Science and Mathematics ISSN 0974-3189 Vol 4, No. 3 (2012), pp. 187-196.

3. Natalia et.al (2006) "Stochastic Modeling of Drug Resistance in Cancer" Journal of Theoretical Biology Vol. 239, Issue 3, (2006), pp. 351-366.

4. Raluca Horhat et.al (2009) "The Simulation of a Stochastic Model for Tumour-Immune System" Proceedings of the 2nd WSEAS International Conference on Biomedical Electronics and Biomedical Infromatics.

5. Srinivasa Rao. K. et.al (2004) "A Stochastic Model for Cancer Cell Growth Under Chemotherapy" Assam Statistical Review, Vol.18, No.1, March 2004, pp. 81-101.

6. Tirupathi Rao.P. et.al (2011) "Bivariate Stochastic Modeling for Mutant Cell Growth under Chemotherapy" International Journal of Mathematics & Applications vol. 4, No. 1, (June 2011), pp. 1-12.

7. www.cancer.org.in/

8. www.cancer.org/cancer/index

9. www.cancer.org/research