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THREE STAGE STOCHASTIC MODELING FOR CANCER CELL GROWTH UNDER CHEMOTHERAPY

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ABSTRACT

In this paper a stochastic model is developed for studying the behaviour of cancer cell growth in 3 stages namely mutant (stage-1), pre- malignant (stage-2) and malignant (stage-3) during the chemotherapy. Difference differential equations were developed for all the stages by assuming rates of arrivals, death rates of cells and the rate of transformations of cells from one stage to the next stage are follows Poisson processes. A tri-variate probability function was obtained through the developed differential equations. The statistical measures such as means, variances and co – variances of mutant cells, pre- malignant cells and malignant cells were derived. Analysis on Model behaviour was carried out through numerical data sets. This model is useful to health care industries for developing suitable decision support systems in evolution of health status of a patient under chemotherapy.

Keywords: Stochastic model, chemotherapy, drug administration, Poisson process, tri-variate Poisson probability function.

1. INTRODUCTION

Continuous Proliferation with uninterrupted cell division leads to Cancer. The normal or healthy cells used to behave as per the regulatory mechanism of cell division based on genetical aspects. Whereas mutant cells used to behave with different mechanism, the growth of them does not obey the physiological or genetical regulatory conditions. All the mutant cells need not have the same mechanism of cell division. The growths of different mutant cells have different rates of due to the stochastic nature of cell division. The cancer growth problems is a resultant effect of conversion of normal cell in to malignant cell in stages, which includes the stage of mutancy (stage-1), transformed into pre malignancy (stage-2), and further transformed in to malignancy (stage-3). If a mutant cell is transformed to a malignant cell, then with the cell division is at faster growth rate. In this study we considered a Tri-variate stochastic model with three variables namely number of mutant cells, number of premalignant cells and number of malignant cells. The parameters related

to growth and loss rates at different stages are assumed to follow Poisson process. Treatment with chemicals with an objective of killing cancer causing cells in spells is considered as chemotherapy. Long spells of drug administration will cause harm to the normal cells. Contrary, long spells of drug vacation leads to aggravation of mutant cell growth. Malignancy is a resulting stage of a normal cell converted to mutant cell, then mutant cell converted to premalignant cell and further premalignant cell to malignant cell.

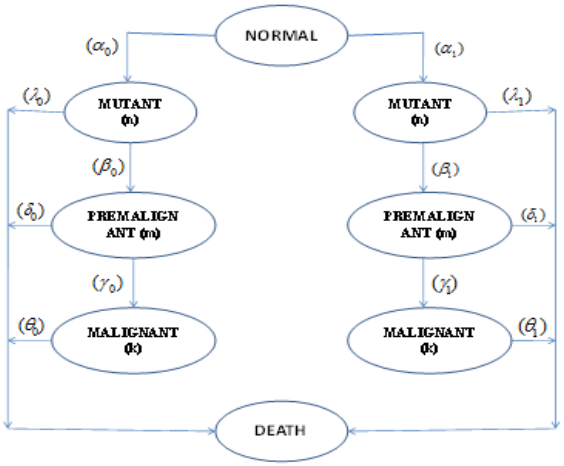
Understanding a disease like cancer requires much attention on conventional means. Measuring the severity of a cancer is possible when it is supported by a proper structure of mathematical model by incorporating all assumption related physiological factors of the body. Iverson et.al [4] have described the growth of tumor as pure linear birth process by assuming the probability of a birth is constant and analogous to specific growth rate. Neyman et.al [7] have used a linear birth and death process to describe a growth of tumor by assuming the probabilities of birth and death are constant and density independent. Witte et.al [15] have developed a stochastic model for growth of solid tumors by considering the physical characteristics of a tumor growth are dependent and stochastic. Density dependent birth and death process was developed by Dubin [2]. A two stage stochastic model for carcinogenesis with time dependent parameters was developed by Gabriella Serio [3]. Tirupathi Rao. P. et.al [12] have developed a stochastic model for tumor growth with spontaneous mutation and proliferation by assuming the mutation and loss processes of normal and mutant cells are Poisson with various parameters. Srinivasa Rao. K. et.al [9,10] have developed a stochastic model for mutant cell growth under the condition of inactivation of allele genes by assuming the growth and loss of mutant cell follows Poisson processes. They have also 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 [6] have formulated and analyzed a stochastic model for multi-drug resistance and also investigated the dependence of treatment results based on the initial tumor size, rates of mutation and the turnover rate of cancerous cells. Srinivasa Rao, K.[11] have developed a two stage stochastic model to study the growth of cancer cell. The size of the malignant tumor is heavily influenced by the growth kinetics of malignant cell, that make up foci within the foci, so as the growth, mutation and losses of premalignant and malignant cells are random and follows bivariate Poisson processes. C.F.LO [1] developed a stochastic non-linear model of tumor growth for size dependent tumors. Multistage tumor growth with continuous time was modeled through a non-homogeneous Poisson processes by Tirupathi Rao, P. et.al [13,14]. They have modeled the tumor growth on natural environment without considering the impact of chemotherapy on the disease. A Bi-variate stochastic modeling for mutant cell growth under chemotherapy was also developed. Stage dependent mutant cell growth was studied through a stochastic model by Madhavi. K. et.al [5].

Observing the mentioned works, most of the authors have considered the growth of cancer is as homogeneous and in non-treatment environments. The health status of the patient under drug administration has to be considered as different and heterogeneous during drug administration and its vacation. The factor like individual physiology, environmental and other extraneous conditions have influence on the growth of cancer because they are heterogeneous and time dependent. The variables like growth and loss rates of mutant cells, premalignant cells and malignant cells are varying subject to many unexplained reasons. The processes of cell division, growth and loss of mutant cells have to be studied by obtaining suitable stochastic processes. Therefore the theme of division process is probabilistic rather than deterministic. The pathological aspects of cancer

reveal that the growth stage of cancer cell depends on the growth status of previous stages. Assuming dependence between mutant and malignant stages is rational. Therefore, two stage transformations among cancer cell growth may not sufficient in understanding the tumor dynamics properly. By considering the above mentioned gap in the research, we have developed a three stage treatment dependent stochastic model under the environment of cancer chemotherapy. Drug administration and vacation periods are considered separately while fixing the assumptions in the development of model.

2. Stochastic Model:

The mechanism of cell division may includes that a mutant cell may be divide into premalignant cell then it is into malignant cell; and mutant cells once formulated from normal cells, they will generate further malignant cells. The behaviour of the cell division is varying with the influence of drug presence and absence in the body etc. In the presence of drug administration, it is assumed that a normal cell may contribute the generation of mutant cell at the rate of α_1. Regarding the mutant cell division during drug administration, it may contribute in producing some premalignant cells with rate of β_1 and the premalignant cell further divides in to malignant cells with rates of γ_1. The death rates of mutant cells, premalignant cells and malignant cells during drug administration are assumed as λ_1,δ_1 and θ_1 respectively. When drug is absent the behaviour of the cell division among the mutant cells, premalignant cells and malignant cells will be on different rates from a drug presence. Hence, we further assume that the contribution of normal cells division as mutant cells is in the rate of α_0, division of mutant cell into a premalignant cell is with a rate of β_0 and division of premalignant cell in to a malignant cell is with a rate of γ_0. The death rates of mutant cells, premalignant cells and malignant cells are λ_0, δ_0 and θ_0 respectively. Assuming all the said mechanisms are stochastic in nature, the patterns of cell growth and loss may be clarified from the following schematic diagram.



Let the events occurred in non-overlapping intervals of time are statistically independent. Let Δt be an infinitesimal interval of time. Let there be 'n' mutant cells 'm' pre-malignant cells, 'k' malignant cells initially at time 't'. Let $\alpha_0, \beta_0, \gamma_0, \lambda_0, \delta_0, \theta_0$ respectively be the rate of generation of mutant cell, rate of transformation of mutant cell to premalignant cell, rate of cell transformations from pre-malignancy to malignancy, rate of death of mutant cell without transforming to premalignant stage, rate of death of premalignant cell without transforming to malignant stage, rate of death of malignant cell during the absence of chemotherapy. Similarly Let $\alpha_1, \beta_1, \gamma_1, \lambda_1, \delta_1, \theta_1$ respectively be the rate of generation of mutant cell, rate of transformation of mutant cell to premalignant cell, rate of cell transformations from pre-malignancy to malignancy, rate of death of mutant cell without transforming to premalignant stage, rate of death of premalignant cell without transforming to malignant stage, rate of death of malignant cell during the presence of chemotherapy. Let a, b, c, d, f, g be the impact coefficients on the rates of arrivals and rates of losses during the drug absence (i.e in recovery period of chemotherapy). Usually these coefficients are non-negative and representing as a proper fraction, so as lies

between 0 and 1. Also it is assumed that all the parameters follow Poisson processes. The postulate of the model includes, The probability of arrival of one mutant cell during an infinitesimal interval of time Δt is $\{a\alpha_0 + (1-a)\alpha_1\}\Delta t + o(\Delta t)$; The probability of transformation from mutant cell to premalignant cell during an infinitesimal interval of time Δt provided $\exists$ 'n' mutant cells during 't' is $n\{b\beta_0 + (1-b)\beta_1\}\Delta t + o(\Delta t)$; The probability of transformation of premalignant cell to mutant cell during an infinitesimal interval of time Δt provided $\exists$ 'm' premalignant cells during 't' is $m\{c\gamma_0 + (1-c)\gamma_1\}\Delta t + o(\Delta t)$; The probability of death of a mutant cell without transforming to pre-malignancy during an infinitesimal interval of time Δt provided $\exists$ 'n' mutant cells during 't' is $n\{d\lambda_0 + (1-d)\lambda_1\}\Delta t + o(\Delta t)$; The probability of death of a premalignant cell without transforming to malignancy during an infinitesimal interval of time Δt provided $\exists$ 'm' premalignant cells during 't' is $m\{f\delta_0 + (1-f)\delta_1\}\Delta t + o(\Delta t)$; The probability of death of a malignant cell during an infinitesimal interval of time Δt provided $\exists$ 'k' premalignant cells during 't' is $k\{g\theta_0 + (1-g)\theta_1\}\Delta t + o(\Delta t)$; The probability of no arrival to mutant cell, no transformation from mutancy to pre-malignancy, no transformation from pre-malignancy to malignancy, no death of mutant cell without transforming to pre-malignancy, no death of premalignant cell without transforming to malignancy, no death of malignant cell during an infinitesimal interval of time Δt is $1-[\{a\alpha_0 + (1-a)\alpha_1\} + n\{b\beta_0 + (1-b)\beta_1 + d\lambda_0 + (1-d)\lambda_1\} + m\{c\gamma_0 + (1-c)\gamma_1 + f\delta_0 + (1-f)\delta_1\} + k\{g\theta_0 + (1-g)\theta_1\}]\Delta t + o(\Delta t)$; The probability of occurrence of other than the above said events during an infinitesimal interval of time Δt is $o(\Delta t)^2$.

Let $P_{n,m,k}(t)$ be the probability that there 'n' mutant cells, 'm' premalignant cells and 'k' malignant cells at time 't'. Then difference-differential equations of the model are:

$$\begin{aligned} p'_{n,m,k}(t) = &-[\{a\alpha_0 + (1-a)\alpha_1\} + n\{b\beta_0 + (1-b)\beta_1 + d\lambda_0 + (1-d)\lambda_1\} \\ &+ m\{c\gamma_0 + (1-c)\gamma_1 + f\delta_0 + (1-f)\delta_1\} + k\{g\theta_0 + (1-g)\theta_1\}]p_{n,m,k}(t) \\ &+ [\{a\alpha_0 + (1-a)\alpha_1\}p_{n-1,m}(t)] + [(n+1)\{b\beta_0 + (1-b)\beta_1\}p_{n+1,m-1,k}(t)] \\ &+ [(m+1)\{f\delta_0 + (1-f)\delta_1\}p_{n,m+1,k}(t)] + [(m+1)\{c\gamma_0 + (1-c)\gamma_1\}p_{n,m+1,k-1}(t)] \\ &+ [(k+1)\{g\theta_0 + (1-g)\theta_1\}p_{n,m,k+1}(t)] \qquad \text{for n,m} \geq 1 \end{aligned} \quad \ldots(2.1)$$

$$\begin{aligned} p'_{1,0,0}(t) = &-[\{a\alpha_0 + (1-a)\alpha_1\} + b\beta_0 + (1-b)\beta_1 + d\lambda_0 + (1-d)\lambda_1\}]p_{1,0,0}(t) \\ &+ \{a\alpha_0 + (1-a)\alpha_1\}p_{1,0,0}(t) + 2\{d\lambda_0 + (1-d)\lambda_1\}p_{2,0,0}(t) \\ &+ \{f\delta_0 + (1-f)\delta_1\}p_{1,0,0}(t) + \{g\theta_0 + (1-g)\theta_1\}p_{1,0,1}(t) \end{aligned} \quad (2.2)$$

$$\begin{aligned} p'_{0,1,0}(t) = &-[\{a\alpha_0 + (1-a)\alpha_1 + c\gamma_0 + (1-c)\gamma_1 + f\delta_0 + (1-f)\delta_1\}p_{0,1,0}(t) \\ &+ \{d\lambda_0 + (1-d)\lambda_1\}p_{1,1,0}(t) + \{b\beta_0 + (1-b)\beta_1\}p_{1,0,0}(t) \\ &+ 2\{f\delta_0 + (1-f)\delta_1\}p_{0,2,0}(t) + \{g\theta_0 + (1-g)\theta_1\}p_{0,1,1}(t) \end{aligned} \quad \ldots(2.3)$$

$$\begin{aligned} p'_{0,0,1}(t) = &-[\{a\alpha_0 + (1-a)\alpha_1 + c\gamma_0 + (1-c)\gamma_1 + g\theta_0 + (1-g)\theta_1\}p_{0,0,1}(t) \\ &+ \{d\lambda_0 + (1-d)\lambda_1\}p_{1,0,1}(t) + \{f\delta_0 + (1-f)\delta_1\}p_{0,1,1}(t) \\ &+ \{c\gamma_0 + (1-c)\gamma_1\}p_{0,1,0}(t) + 2\{g\theta_0 + (1-g)\theta_1\}p_{0,0,2}(t) \end{aligned} \quad (2.4)$$

$$p'_{1,1,0}(t) = -[\{a\alpha_0 + (1-a)\alpha_1 + b\beta_0 + (1-b)\beta_1 + d\lambda_0 + (1-d)\lambda_1 + c\gamma_0 + (1-c)\gamma_1 + f\delta_0 + (1-f)\delta_1\}p_{1,1,0}(t) + \{a\alpha_0 + (1-a)\alpha_1\}p_{0,1,0}(t) + 2\{d\lambda_0 + (1-d)\lambda_1\}p_{2,1,0}(t) + 2\{b\beta_0 + (1-b)\beta_1\}p_{2,0,0}(t) + 2\{f\delta_0 + (1-f)\delta_1\}p_{1,2,0}(t) + \{g\theta_0 + (1-g)\theta_1\}p_{1,1,1}(t) \quad (2.5)$$

$$p'_{1,0,1}(t) = -[\{a\alpha_0 + (1-a)\alpha_1 + c\gamma_0 + (1-c)\gamma_1 + f\delta_0 + (1-f)\delta_1 + g\theta_0 + (1-g)\theta_1\}p_{0,1,0}(t) + \{d\lambda_0 + (1-d)\lambda_1\}p_{1,1,1}(t) + \{b\beta_0 + (1-b)\beta_1\}p_{1,0,1}(t) + 2\{f\delta_0 + (1-f)\delta_1\}p_{0,2,1}(t) + 2\{c\gamma_0 + (1-c)\gamma_1\}p_{0,2,0}(t) + 2\{g\theta_0 + (1-g)\theta_1\}p_{0,1,2}(t) \quad ...(2.7)$$

$$p'_{0,0,0}(t) = -\{a\alpha_0 + (1-a)\alpha_1\}p_{0,0,0}(t) + \{d\lambda_0 + (1-d)\lambda_1\}p_{1,0,0}(t) + \{f\delta_0 + (1-f)\delta_1\}p_{0,1,0}(t) + \{g\theta_0 + (1-g)\theta_1\}p_{0,0,1}(t) \quad ...(2.8)$$

With the initial condition

$p_{N_0,M_0,K_0}(t) = 1,\ p_{i,j,k}(0) = 0 \ \ \forall \ \ i \neq N_0\ j \neq M_0\ k \neq K_0$

3. Generating Functions and Statistical Measures:

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

Where $P(x, y, z; t) = \sum_{k=0}\sum_{m=0}\sum_{n=0} x^n y^m z^k p_{n,m,k}(t)$ Multiplying the equation (2.1) to (2.8) with $x^n y^m z^k$ and summing overall n, m and k, and on simplification we obtain

$$\frac{\partial}{\partial t}p(x, y, z : t) = [-\{b\beta_0 + (1-b)\beta_1 + d\lambda_0 + (1-d)\lambda_1\}]x + \{d\lambda_0 + (1-d)\lambda_1\} + [\{b\beta_0 + (1-b)\beta_1\}y]\frac{\partial p}{\partial x} + [-\{c\gamma_0 + (1-c)\gamma_1 + f\delta_0 + (1-f)\delta_1\}]y + \{f\delta_0 + (1-f)\delta_1\} + [\{c\gamma_0 + (1-c)\gamma_1\}z]\frac{\partial p}{\partial y} + [\{g\theta_0 + (1-g)\theta_1\}](1-z)\frac{\partial p}{\partial z} + [\{a\alpha_0 + (1-a)\alpha_1\}](x-1)p(x, y, z; t) \quad ...(3.1)$$

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

$$\frac{\partial}{\partial t}k(u, v, w; t) = [-\{b\beta_0 + (1-b)\beta_1 + d\lambda_0 + (1-d)\lambda_1\} + \{d\lambda_0 + (1-d)\lambda_1\}e^{-u} + \{b\beta_0 + (1-b)\beta_1\}e^{-u+v}]\frac{\partial k}{\partial u} + [-\{c\gamma_0 + (1-c)\gamma_1 + d\lambda_0 + (1-d)\lambda_1\} + \{d\lambda_0 + (1-d)\lambda_1\}e^{-v} + \{c\gamma_0 + (1-c)\gamma_1\}e^{-v+w}]\frac{\partial k}{\partial v} + [\{g\theta_0 + (1-g)\theta_1\}](e^{-w} - 1)\frac{\partial k}{\partial w} + [\{a\alpha_0 + (1-a)\alpha_1\}](e^u - 1).k(u, v, w; t) \quad ...(3.2)$$

Let $m_{i,j,k}(t)$ denote the moments of order (i, j, k) of mutant cells, premalignant cells, malignant cells during chemotherapy at time 't'. Then the characteristics of the model by considering

$\alpha = \{a\alpha_0 + (1-a)\alpha_1\}$, $\beta = \{b\beta_0 + (1-b)\beta_1\}$, $\gamma = \{c\gamma_0 + (1-c)\gamma_1\}$,

$\lambda = \{d\lambda_0 + (1-d)\lambda_1\}$, $\delta = f\delta_0 + (1-f)\delta_1\}$, and $\theta = \{g\theta_0 + (1-g)\theta_1\}$ are,

Average number of mutant cells during time 't'

$$m_{1,0,0}(t) = \frac{\alpha}{\lambda+\beta}[1-e^{-(\lambda+\beta)t}(1-N_0)] \quad ...(3.3)$$

Average number of premalignant cells at time 't'

$$m_{0,1,0}(t) = [\frac{\alpha\beta}{(\lambda+\beta)(\lambda+\beta-\delta-\gamma)} - \frac{N_0\beta}{(\lambda+\beta-\delta-\gamma)}]e^{-(\lambda+\beta)t}$$
$$-[\frac{\alpha\beta}{(\delta+\gamma)(\lambda+\beta-\delta-\gamma)} - \frac{N_0\beta}{(\lambda+\beta-\delta-\gamma)} - M_0]e^{-(\delta+\gamma)t} + \frac{\alpha\beta}{(\delta+\gamma)(\lambda+\beta)}] \quad ...(3.4)$$

Average number of malignant cells at time 't'

$$m_{0,0,1}(t) = [\frac{\alpha\beta\gamma}{(\delta+\gamma)(\lambda+\beta-\delta-\gamma)} - \frac{N_0\beta\gamma}{(\lambda+\beta-\delta-\gamma)} - M_0\gamma]\frac{e^{-(\delta+\gamma)t}}{(\delta+\gamma-\theta)}$$
$$-[\frac{\alpha\beta\gamma}{\theta(\lambda+\beta-\theta)} - \frac{N_0\beta\gamma}{(\lambda+\beta-\delta-\gamma)(\lambda+\beta-\theta)} - M_0\gamma]\frac{e^{-\theta t}}{(\delta+\gamma-\theta)}$$
$$+K_0\frac{e^{-\theta t}}{(\delta+\gamma-\theta)} + [N_0\beta - \frac{\alpha\beta\gamma}{\lambda+\beta}][\frac{e^{-(\lambda+\beta)t}}{(\lambda+\beta-\delta-\gamma)(\lambda+\beta-\theta)}] + \frac{\alpha\beta\gamma}{(\delta+\gamma)(\lambda+\beta)}] \quad ...(3.5)$$

Covariance of number of mutant and premalignant cell

$$m_{1,1,0}(t) = \frac{N_0\beta}{(\lambda+\beta-\delta-\gamma)}[e^{-2(\lambda+\beta)t} - e^{-(\lambda+\beta+\delta+\gamma)t}] \quad ...(3.6)$$

Covariance of number of mutant and malignant cell

$$m_{1,0,1}(t) = \frac{N_0\beta\gamma}{(\lambda+\beta-\delta-\gamma)}[(\frac{e^{-(\lambda+\beta+\delta+\gamma)t} - e^{-(\lambda+\beta+\theta)t}}{(\delta+\gamma-\theta)}) - (\frac{e^{-2(\lambda+\beta)t} - e^{-(\lambda+\beta+\theta)t}}{(\lambda+\beta+\theta)})] \quad ...(3.7)$$

Covariance of number of premalignant and malignant cell

$$m_{0,1,1}(t) = \frac{N_0\beta^2\gamma}{(\lambda+\beta-\delta-\gamma)^2}[\frac{1}{(\delta+\gamma+\theta)}(\frac{e^{-(\lambda+\beta+\theta)t}}{(\lambda+\beta-\delta-\gamma)} - \frac{e^{-(\lambda+\beta-\delta-\gamma)t}}{(\lambda+\beta-\theta)}) - \frac{1}{(\lambda+\beta-\theta)}$$
$$(\frac{e^{-(\lambda+\beta+\theta)t}}{(\lambda+\beta-\delta-\gamma)} - \frac{e^{-2(\lambda+\beta)t}}{(2\lambda+2\beta-\delta-\gamma-\theta)})].[e^{-2(\delta+\gamma)t} - e^{-(\delta+\gamma+\theta)t}$$
$$+\frac{1}{(\lambda+\beta-\delta-\gamma)} - (e^{-2(\delta+\gamma)t} - e^{-(\delta+\gamma+\theta)t})] - \frac{N_0\beta}{(\lambda+\beta-\delta-\gamma)(\lambda+\beta-\delta-\gamma-\theta)}$$
$$[e^{-(\lambda+\beta)t} - e^{-(\delta+\gamma)t}] - \frac{M_0}{(\delta+\gamma-\theta)}[(e^{-2(\delta+\gamma)t} - e^{-(\delta+\gamma+\theta)})]$$
$$-\frac{N_0\beta^2\gamma}{(\lambda+\beta-\delta-\gamma)(\lambda+\beta-\theta)(2\lambda+2\beta-\delta-\gamma-\theta)}e^{-(\delta+\gamma+\theta)t} \quad ...(3.8)$$

Variance of number of Mutant cell

$$m_{2,0,0}(t)=\frac{\alpha}{\lambda+\beta}[1-e^{-(\lambda+\beta)t}]N_0e^{-(\lambda+\beta)t}(1-e^{-(\lambda+\beta)t}) \quad ...(3.9)$$

Variance of number of premalignant cell

$$\begin{aligned}m_{0,2,0}(t)=&[\frac{N_0\beta}{(\lambda+\beta-\delta-\gamma)}-\frac{\alpha\beta}{(\delta+\gamma)(\lambda+\beta-\delta-\gamma)}M_0]e^{-(\delta+\gamma)t}-[\frac{N_0\beta^2}{(\lambda+\beta-\delta-\gamma)^2}+M_0]e^{-2(\delta+\gamma)t}\\&\cdot\frac{N_0\beta^2}{(\lambda+\beta-\delta-\gamma)^2}e^{-2(\lambda+\beta)t}\cdot\frac{\alpha\beta}{(\lambda+\beta)(\delta+\gamma)}+\frac{2N_0\beta^2}{(\lambda+\beta-\delta-\gamma)}+e^{-(\lambda+\beta+\delta+\gamma)t}\\&+[\frac{\alpha\beta}{(\lambda+\beta)}-N_0\beta]\frac{e^{-2(\lambda+\beta)t}}{(\lambda+\beta-\delta-\gamma)} \quad ...(3.10)\end{aligned}$$

Variance of number of malignant cell

$$\begin{aligned}m_{0,0,2}(t)=&[\frac{\alpha\beta\gamma}{(\delta+\gamma)(\lambda+\beta-\delta-\gamma)}\frac{N_0\beta\gamma}{(\lambda+\beta-\delta-\gamma)}-M_0\gamma][1-M_0].[\frac{e^{-(\delta+\gamma)t}-e^{-2\theta t}}{(\delta+\gamma-2\theta)}]\\&+[\frac{N_0\beta\gamma}{(\lambda+\beta-\delta-\gamma)}-\frac{\alpha\beta\gamma}{(\lambda+\beta)(\lambda+\beta-\delta-\gamma)}].[1-\frac{\theta}{(\lambda+\beta-\theta)}][\frac{e^{-(\lambda+\beta)t}-e^{-2\theta t}}{(\lambda+\beta-2\theta)}]\\&+\frac{\alpha\beta\gamma}{(\lambda+\beta)(\delta+\gamma)}[1-\frac{e^{-2\theta t}}{\theta}]\frac{\alpha\beta\gamma}{\theta(\lambda+\beta-\theta)}-\frac{N_0\beta\gamma}{(\lambda+\beta-\delta-\gamma)(\lambda+\beta-\theta)}-M_0\gamma-K_0].\\&[\frac{e^{-\theta t}-e^{-2\theta t}}{(\delta+\gamma-\theta)}][\frac{e^{-2(\lambda+\beta)t}}{2(\lambda+\beta-\theta)}]+[\frac{N_0\beta^2\gamma^2}{(\lambda+\beta-\delta-\gamma)^2}+M_0\gamma][\frac{e^{-(\delta+\gamma)t}-e^{-2\theta t}}{(\delta+\gamma-\theta)}]\\&-\frac{2N_0\beta^2\gamma^2}{(\lambda+\beta-\theta)(\delta+\gamma-\theta)(\lambda+\beta-\delta-\gamma)}[\frac{e^{-(\lambda+\beta+\theta)t}-e^{-2\theta t}}{(\lambda+\beta-\theta)}].[\frac{e^{-(\lambda+\beta+\delta+\gamma)t}-e^{-2\theta t}}{(\lambda+\beta+\delta+\gamma-2\theta)}]\\&+\frac{M_0}{(\delta+\gamma-\theta)}[\frac{e^{-(\delta+\gamma+\theta)t}-e^{-2\theta t}}{(\delta+\gamma-\theta)}+\frac{2N_0\beta^2\gamma^2}{(\lambda+\beta-\delta-\theta)}[\frac{e^{-(\delta+\gamma+\theta)t}-e^{-2\theta t}}{(\delta+\gamma-\theta)}].[\frac{1}{2(\lambda+\beta-\theta)(\lambda+\beta-\delta-\gamma)}\\&+\frac{1}{(\lambda+\beta-\delta-\gamma)(\delta+\gamma-\theta)}+\frac{1}{(\lambda+\beta-\delta-\gamma)(2\lambda+2\beta-\delta-\gamma-\theta)} \quad ...(3.11)\end{aligned}$$

4. Numerical Illustration and Sensitivity Analysis

From equations 3.2 to 3.11 the values of $m_{1,0,0}(t), m_{0,0,1}(t), m_{2,0,0}(t), m_{1,1,0}(t), m_{1,0,1}(t), m_{0,1,1}(t)$, $m_{0,2,0}(t)$ and $m_{0,0,2}(t)$ are computed values of the parameters and presented in the tables for varying values of $\alpha_0, \beta_0, \gamma_0, \lambda_0, \delta_0, \theta_0$ and $\alpha_1, \beta_1, \gamma_1, \lambda_1, \delta_1, \theta_1$ N_0, M_0, K_0, t and presented in Tables 4.1 to 4.8

Table 4.1:
For varying values of α_0 , α_1 & fixed values of other parameters say β_0=0.4; β_1=0.3; γ_0=0.3; γ_1=0.2; λ_0=0.2; λ_1=0.1; δ_0=0.05; δ_1=0.10; θ_0=0.02; θ_1=0.04 ; N_0=1000; M_0=500; K_0=100 t=15

α_0	α_1	m_{100}	m_{010}	m_{001}	m_{110}	m_{101}	m_{011}	m_{200}	m_{020}	m_{002}
0.6	0.1	1.499	22.233	3820	-0.028	-0.542	283.264	2.159	9.773	96770
0.8		1.859	22.362	3820	-0.028	-0.542	283.264	2.298	7.826	96660
1		2.219	22.492	3820	-0.028	-0.542	283.264	2.437	5.879	96540
1.2		2.579	22.622	3820	-0.028	-0.542	283.264	2.576	3.932	96430
1.4		2.939	22.751	3821	-0.028	-0.542	283.264	2.716	1.985	96320
0.4	0.2	1.559	22.254	3820	-0.028	-0.542	283.264	2.182	9.449	96750
	0.3	1.979	22.406	3820	-0.028	-0.542	283.264	2.344	7.177	96620
	0.4	2.399	22.557	3820	-0.028	-0.542	283.264	2.507	4.906	96490
	0.5	2.819	22.708	3821	-0.028	-0.542	283.264	2.669	2.634	96350
	0.6	3.239	22.859	3821	-0.028	-0.542	283.264	2.832	0.363	96220

It is observed that Expected number of mutant, premalignant and malignant cells and variance of number of mutant cells are increasing functions of arrival rate of mutant cells under absence of drug and presences of drug when all other parameters are constant. Further it is also observed that covariance of number of mutant and premalignant cells; covariance of number of mutant and malignant cells; covariance of number of premalignant and malignant cells are invariant of α_0 , α_1, whereas the variance of number of premalignant cells and variance of number of malignant cells are decreasing functions of arrival rate of mutant cells under absence of drug and presence of drug when all other parameters are constant.

Table 4.2:
For varying values of β_0, β_1 & fixed values of other parameters say α_0 =0.4; α_1=0.1; γ_0=0.3; γ_1=0.2; λ_0=0.2; λ_1=0.1; δ_0=0.05; δ_1=0.10; θ_0=0.02; θ_1=0.04 ; N_0=1000; M_0=500; K_0=100 t=15

β_0	β_1	m_{100}	m_{010}	m_{001}	m_{110}	m_{101}	m_{011}	m_{200}	m_{020}	m_{002}
0.6	0.3	0.916	21.301	3311	-0.02	-0.408	207.53	1.591	11.615	80160
0.8		0.755	20.579	2940	-0.014	-0.307	161.45	1.271	11.394	68880
1		0.637	19.93	2657	-0.01	-0.23	130.87	1.03	11.125	60800
1.2		0.55	19.348	2433	-0.007	-0.172	109.33	0.848	10.84	54730
1.4		0.485	18.826	2252	-0.005	-0.129	93.479	0.711	10.558	50000
0.4	0.6	0.279	16.061	1471	-0.0003	-0.011	41.086	0.299	8.799	31360
	0.9	0.196	14.385	1054	-5E-06	-0.0002	23.24	0.196	7.632	21890
	1.2	0.153	13.686	875.71	-8E-08	-3E-06	17.542	0.153	7.142	17510
	1.5	0.126	13.306	775.69	-1E-09	-6E-08	14.815	0.126	6.876	14830
	1.8	0.107	13.068	711.58	-2E-11	-1E-09	13.23	0.107	6.71	12970

It is observed that Expected number of mutant, premalignant and malignant cells, variances of number of mutant, premalignant and malignant cells and co-variance of number of mutant cells with premalignant cells are negatively decreasing functions of arrival rate of premalignant cells from formed mutant cells under absence and presence of drug, when all other parameters are constant.

Table 4.3:
For varying values of γ_0 , γ_1 & the fixed values of other parameters say α_0 =0.4; α_1=0.1; β_0=0.4; β_1=0.3; λ_0=0.2; λ_1=0.1; δ_0=0.05; δ_1=0.10; θ_0=0.02; θ_1=0.04 ; N_0=1000; M_0=500; K_0=100 t=15

γ_0	γ_1	m_{100}	m_{010}	m_{001}	m_{110}	m_{101}	m_{011}	m_{200}	m_{020}	m_{002}
0.4	0.2	1.14	16.402	5288	-0.021	-0.561	394.051	2.019	8.595	209700
0.42		1.14	15.486	5733	-0.02	-0.564	447.027	2.019	8.01	251900
0.44		1.14	14.632	6263	-0.019	-0.567	526.551	2.019	7.424	306900
0.46		1.14	13.835	6903	-0.018	-0.57	656.833	2.019	6.828	380300
0.48		1.14	13.092	7694	-0.017	-0.573	905.992	2.019	6.21	481200
0.3	0.22	1.14	19.188	4386	-0.025	-0.551	315.66	2.019	10.204	135500
	0.23	1.14	17.904	4738	-0.023	-0.555	342.224	2.019	9.488	162700
	0.24	1.14	16.722	5155	-0.022	-0.559	380.23	2.019	8.792	197800
	0.25	1.14	15.634	5654	-0.021	-0.563	436.745	2.019	8.107	244100
	0.26	1.14	14.632	6263	-0.019	-0.567	526.551	2.019	7.424	306900

It is observed that average number of mutant cells and Variance of number of mutant cells are invariant of change of γ_0 , γ_1. The expected number of malignant cells; variance of number of malignant cells and co-variance of number of premalignant and malignant are increasing functions of arrival rate of malignant cells transformed from premalignant cells during the absence of drug and presence of drug, when all other parameters are constant. It is also observed that Expected number of premalignant cells and Variance of number of premalignant cells are decreasing function, co-variance of number of mutant cells and premalignant cells is negative and decreasing function; co-variance of number mutant cells and malignant cells are negative and increasing functions of arrival of malignant cells transformed from premalignant cells during the absence of drug and presence of drug when all other parameters are constant.

Table 4.4:
For varying values of λ_0 , λ_1 & the fixed values of other parameters say α_0 =0.4; α_1=0.1; β_0=0.4; β_1=0.3; γ_0=0.3; γ_1=0.2; δ_0=0.05; δ_1=0.10; θ_0=0.02; θ_1=0.04 ; N_0=1000; M_0=500; K_0=100 t=15

λ_0	λ_1	m_{100}	m_{010}	m_{001}	m_{110}	m_{101}	m_{011}	m_{200}	m_{020}	m_{002}
0.4	0.1	0.755	18.663	2652	-0.013	-0.272	143.71	1.271	10.092	87360
0.6		0.55	16.162	2020	-5.71E-03	-0.137	88.548	0.848	8.616	67790
0.8		0.436	14.301	1633	-2.65E-03	-0.07	61.044	0.607	7.416	52060
1		0.368	12.883	1375	-1.26E-03	-0.035	45.388	0.465	6.461	40570
1.2		0.325	11.781	1193	-0.001	-0.018	35.66	0.38	5.7	32240
0.2	0.2	0.55	16.162	2020	-0.006	-0.137	88.548	0.848	8.616	67790
	0.4	0.296	10.906	1060	-0.0003	-0.0094	29.22	0.327	5.087	26140
	0.6	0.23	8.718	768.55	-1.8E-05	-0.0007	17.269	0.233	3.533	13340
	0.8	0.192	7.558	640.03	-1.3E-06	-5E-05	13.004	0.192	2.702	8288
	1	0.165	6.842	571.76	-9E-08	-4E-06	11.013	0.165	2.188	5865

It is observed that expected numbers of mutant cells, premalignant cells and malignant cells; Variances of number of mutant cells, premalignant cells and malignant cells; Co-variance of number of premalignant cells and malignant cells are decreasing functions of death of mutant cells during absence of drug and presence of drug, when all other parameters are constant. Further it is also observed that the covariance between the number of mutant cells and premalignant cells; The covariance between the number of mutant cells and malignant cells are negative and decreasing functions of death of mutant cells during absences of drug and presence of drug, when all other parameters are constant.

Table 4.5:

For varying values of δ_0 , δ_1 & the fixed values of other parameters say α_0 =0.4; α_1=0.1; β_0=0.4; β_1=0.3; γ_0=0.3; γ_1=0.2; λ_0=0.2; λ_1=0.1; θ_0=0.02; θ_1=0.04 ; N_0=1000; M_0=500; K_0=100 t=15

δ_0	δ_1	m_{100}	m_{010}	m_{001}	m_{110}	m_{101}	m_{011}	m_{200}	m_{020}	m_{002}
0.06	0.1	1.14	21.878	3839	-0.028	-0.541	284.875	2.019	11.608	100800
0.07		1.14	21.656	3859	-0.028	-0.539	286.57	2.019	11.496	104800
0.08		1.14	21.437	3880	-0.027	-0.537	288.352	2.019	11.384	108900
0.09		1.14	21.22	3901	-0.027	-0.536	290.223	2.019	11.274	113100
0.1		1.14	21.005	3923	-0.027	-0.534	292.189	2.019	11.164	117500
0.05	0.11	1.14	20.173	4015	-0.026	-0.528	301.074	2.019	10.731	136200
	0.12	1.14	18.441	4261	-0.024	-0.514	328.587	2.019	9.792	187600
	0.13	1.14	16.885	4575	-0.022	-0.5	371.744	2.019	8.89	257200
	0.14	1.14	15.486	4981	-0.02	-0.487	443.32	2.019	8.01	355400
	0.15	1.14	14.226	5520	-0.019	-0.475	576.64	2.019	7.128	501100

It is observed that Expected number of mutant cells and Variance of number mutant cells are invariant of change of δ_0 , δ_1. The Expected number of premalignant cells and Variance of number of premalignant cells are decreasing functions and Co-Variance between the number of mutant cells and premalignant and the covariance between mutant cells and malignant cells are negative and decreasing functions of death of premalignant cells during absence of drug and presence of drug when all other parameters are constant.

Further it is also observed that Expected number of malignant cells; Variance of number of malignant cells; Co-Variance between number of premalignant cells and malignant cells are increasing functions of death of premalignant cells during absence of drug and presence of drug when all other parameters are constant.

Table 4.6:

For varying values of θ_0 , θ_1 & the fixed values of other parameters say α_0 =0.4; α_1=0.1; β_0=0.4; β_1=0.3; γ_0=0.3; γ_1=0.2; λ_0=0.2; λ_1=0.1; δ_0=0.05; δ_1=0.10; N_0=1000; M_0=500; K_0=100 t=15

θ_0	θ_1	m_{100}	m_{010}	m_{001}	m_{110}	m_{101}	m_{011}	m_{200}	m_{020}	m_{002}
0.04	0.04	1.14	22.103	3749	-0.028	-0.532	290.984	2.019	11.72	96500
0.06		1.14	22.103	3680	-0.028	-0.522	299.24	2.019	11.72	95560
0.08		1.14	22.103	3613	-0.028	-0.512	308.084	2.019	11.72	94160
0.1		1.14	22.103	3547	-0.028	-0.503	317.572	2.019	11.72	92360
0.12		1.14	22.103	3483	-0.028	-0.493	327.771	2.019	11.72	90230
0.02	0.06	1.14	22.103	3240	-0.028	-0.458	377.372	2.019	11.72	79450
	0.07	1.14	22.103	2991	-0.028	-0.421	457.873	2.019	11.72	65170
	0.08	1.14	22.103	2766	-0.028	-0.388	586.238	2.019	11.72	50500
	0.09	1.14	22.103	2563	-0.028	-0.357	820.931	2.019	11.72	36240
	0.1	1.14	22.103	2379	-0.028	-0.33	1382	2.019	11.72	22440

It is observed that, The expected number of mutant cells; Expected number of malignant cells; Variance of number of mutant cells; Variance of number of premalignant cells; The covariance between the number of mutant cells and number of premalignant cells are invariant of change of death

of malignant cells under absence of drug and presence of drug when all other parameters are constant. Further it is also observed that expected number of malignant cells and Variance of number of malignant cells are decreasing functions; whereas Co-variance between number of mutant cells and malignant cells is negative, decreasing function and Co-variance between the number of premalignant cells and malignant cells is increasing function of death of malignant cells during absence of drug and presence of drug when all other parameters are constant.

Table 4.7:
For varying values of $\mathbf{N_0}$, $\mathbf{M_0}$, $\mathbf{K_0}$ & the fixed values of other parameters say α_0 =0.4; α_1=0.1; β_0=0.4; β_1=0.3; γ_0=0.3; γ_1=0.2; λ_0=0.2; λ_1=0.1; δ_0=0.05; δ_1=0.10; θ_0=0.02; θ_1=0.02; t=15

N_0	M_0	K_0	m_{100}	m_{010}	m_{001}	m_{110}	m_{101}	m_{011}	m_{200}	m_{020}	m_{002}
1002	500	100	1.141	22.139	3826	-0.028	-0.543	283.82	2.022	11.756	97150
1004			1.142	22.175	3833	-0.028	-0.544	284.367	2.025	11.792	97430
1006			1.144	22.211	3840	-0.028	-0.545	284.919	2.029	11.827	97700
1008			1.145	22.246	3847	-0.028	-0.547	285.47	2.032	11.863	97970
1010			1.147	22.282	3853	-0.029	-0.548	286.022	2.035	11.899	98250
1000	502	100	1.14	22.119	3820	-0.028	-0.542	283.293	2.019	11.694	97110
	512		1.14	22.195	3825	-0.028	-0.542	283.442	2.019	11.562	98240
	522		1.14	22.271	3829	-0.028	-0.542	283.59	2.019	11.43	99370
	532		1.14	22.348	3834	-0.028	-0.542	283.738	2.019	11.298	100500
	542		1.14	22.424	3838	-0.028	-0.542	283.887	2.019	11.167	101600
1000	500	110	1.14	22.103	3839	-0.028	-0.542	283.264	2.019	11.72	96880
		120	1.14	22.103	3859	-0.028	-0.542	283.264	2.019	11.72	96880
		130	1.14	22.103	3879	-0.028	-0.542	283.264	2.019	11.72	96880
		140	1.14	22.103	3898	-0.028	-0.542	283.264	2.019	11.72	96880
		150	1.14	22.103	3918	-0.028	-0.542	283.264	2.019	11.72	96880

It is observed that The expected number of mutant cells; Expected number of premalignant cells; Expected number of malignant cells; Variance of number of mutant cells; Variance of number of premalignant cells; Variance of number of malignant cells; Covariance between the number of premalignant cells and malignant cells are increasing functions. Whereas Co-Variance between the number of mutant cells and premalignant cells; Covariance between number of mutant and malignant cells are negative, increasing functions of initial number of mutant cells (N_0) when all other parameters are constant. The expected number of premalignant cells, the average number of malignant cells; The covariance between the number of premalignant cells and malignant cells; The variance of number of malignant cells are increasing functions if initial number of premalignant cells (M_0). The average number of mutant cells; The covariance between the number of mutant cells and premalignant cells; the covariance between the number of mutant cells and malignant cells; The variance of number of mutant cells are invariant of change of initial number of premalignant cells (M_0); However, the variance of number of premalignant cells is a decreasing function of initial number of premalignant cells (M_0) when all other parameters are constant. It is observed that Expected number of mutant cells and the expected number of premalignant cells, The variance number of mutant cells; Variance of number of premalignant cells and variance of number of malignant cells; The covariance between the number of mutant cells and premalignant cells; The covariance between the number of mutant cells and malignant

cells; The covariance between the number of premalignant cells and malignant cells are invariant of change of initial number of malignant cells (K_0) when other parameters are constant. However the expected number of malignant cells is a increasing function of initial number of malignant cells when all other parameters are constant.

Table 4.8:
For varying values of **'t'** & fixed values of other parameters say α_0 =0.4; α_1=0.1; β_0=0.4; β_1=0.3; γ_0=0.3; γ_1=0.2; λ_0=0.2; λ_1=0.1; δ_0=0.05; δ_1=0.10; θ_0=0.02; N_0=1000; M_0=500; K_0=100 ;θ_1=0.02

t	m_{100}	m_{010}	m_{001}	m_{110}	m_{101}	m_{011}	m_{200}	m_{020}	m_{002}
16	0.896	16.423	3681.00	-0.014	-0.343	208.337	1.468	8.921	109600
17	0.737	12.202	3547.00	-0.0066	-0.217	152.935	1.11	6.78	118600
18	0.634	9.075	3417.00	-0.0031	-0.136	112.076	0.877	5.157	124400
19	0.567	6.766	3292.00	-0.0015	-0.086	82.012	0.725	3.935	127800
20	0.523	5.066	3170.00	-0.0007	-0.054	59.934	0.626	3.02	129100

It is observed that The expected number of mutant cells; Average number of premalignant cells; The average number of malignant cells; The variance of number of mutant cells; The variance of number of premalignant cells; The variance of number of malignant cells; The covariance between the number of premalignant cells and malignant cells are decreasing functions time period. Whereas the covariance between the number of mutant cells and premalignant cells; The covariance between the number of mutant and malignant cells are negative and increasing functions of time 't' when all other parameters are constant.

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