BIVARIATE STOCHASTIC MODELING FOR MUTANT CELL GROWTH UNDER CHEMOTHERAPY

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ABSTRACT: Studying cancer growth problems through mathematical modeling is a conventional approach which may have some limitations on the validity of assumptions. Due to changing physiological and environmental factors, cancer cell growth modeling with stochasticity is more appropriate. In this paper we develop a stochastic model for cancer growth under the environment of chemotherapy. A Bivariate probability function for number of normal and mutant cells in a tumor is developed through difference differential equations. The arrival and death rates of normal and mutant cells during drug administration and drug vacation period are assumed to follow time dependent Poisson process. Expressions for different statistical measures are derived. Sensitivity analysis is carried out so as model behavior is analyzed. This model can assess different statistical measures at a point of time \( t \). Developing Computer automation calculator will provide a suitable decision support system.

Keywords: Stochastic modeling, Bivariate poisson process, Cancer chemotherapy, Drug sensitivity analysis.

1. INTRODUCTION

Human system has a mechanism of cell growth and its regulation with alleles of a gene. The failure of growth control or regulation mechanism due to inactivation of alleles is one of the reasons for getting cancer. The body system has a cell growth process as a measure of compensation to wear, tear and the death of a cell after a specified period of time. Usually a normal cell which is under regulation of control mechanism deviates due to unspecified reasons usually named as mutancy. When a normal cell change into a mutant cell then it may be further transformed into a malignant cell. Once malignancy was formulated to the cell then the cell growth will be at faster rate and it behaves beyond the control of natural mechanism.

Cancer is a Disease in which cell in a body divide without any control. The cells are not normal and could invade to other tissues of the body. They also may immigrate to other parts of the body through blood vessels. The cells within malignant tumors have the ability to invade neighboring tissues and organs, thus spreading the disease. It is also possible for cancerous cells to break free from the tumor site and enter the blood stream, spreading the disease to other organs. This process of spreading is called metastasis. (Mehardad et al.)

Chemotherapy is a kind of treatment that uses drugs to treat cancer cells. It is called a ‘systemic treatment’ since the drug, entering through the blood stream, travels throughout the body and kills cancer cells at their sites. Chemotherapeutic drugs are chemically designed to target cells that are dividing and growing rapidly. Once they reach the cancer cells, they
act to retard their growth, eventually resulting in their destruction. The frequency of chemotherapy can be daily, weekly, monthly or on off schedule depending on the type of drug, the body response and the type of cancer. The chemotherapy is decided on the basis of the type of cancer. The dosage is calculated on the basis of the patient’s body weight and the drug’s toxicity.

In order to understand the behavioural pattern from initial formation of mutancy to final stage of cancer cell growth, a well defined model structure is required. Conventional researchers have suggested number of mathematical/deterministic models to assess the cancer situation. The assumption considering the deterministic situations in modeling makes the mathematical models confined to very limited applications. The behaviour of cell division and tumor growth reveals that cell division in a tumor is purely random and it will have complete stochastic behavior.

Modeling Cancer growth has initiated with Mayneord (1932) by assuming the growth of tumor is random. Iverson and Arley(1950) have described the growth of tumor as pure linear birth process by assuming the probability of a birth is analogous to a constant specific growth rate. Kendal (1960) 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. Density Dependent Birth and Death process was developed by Dubin (1976). Hanson and Charles Tier (1982) have developed a stochastic model for tumor growth as the diffusion limit of a continuous time density dependent branching process. Serio (1984) developed a two stage stochastic model with time dependent parameters for carcinogenesis. Stochastic model using birth and death processes with spontaneous mutation is developed by Birkhead (1986). Rao K. S. and Rao P. T., (2004, 2006) have developed different types of stochastic models for cancer growth with the assumption of spontaneous mutation and proliferation; under chemotherapy; Proliferation with inactivation of allele genes etc. Alphano F. D., (2006) developed a stochastic model on Gene Expression Relevant to cancer therapy. Rinaldo (2006) considered two successive mutation hypothesis to develop a stochastic model for cancer cells. LO C. F., (2009) developed a stochastic non-linear model of tumor growth for size dependent tumors.

In the paper of Rao K. S. and Rao P. T., (2004), they have developed stochastic model for cancer cell growth under chemotherapy with the assumption of the growth process of cancer cell is Poisson with growth rate ‘0’ during the presence of chemotherapy and \( n\lambda \) during the absence of chemotherapy. Further they have considered the time for which the patient is in absence of chemotherapy is exponential time of excess time. When we observe the chemotherapy administration. The growth of Normal cell and Mutant cell will be effected some extent by the administered drug. The drug may target to killing the malignant cell once the mutant cell is transformed into full pledged cancer (malignant) cell. The growth of mutant (not completely transformed malignant) cell during drug presence need not be equal to zero. Similarly the growth of normal cell during the drug presence also not equal to zero. In this paper we have assumed the growth rates of normal and mutant cells are
having different rates of growth during the presence and absence of drug during a period of time \( t \). The similar argument can also be extended to the death of Normal and Mutant cells. The rates of death are varying during the absence and presence of drug. A stochastic model for growth of Mutant and Normal cells is developed by assuming the impact of drug has different effectiveness scales and purely stochastic during \( t \) due to various accounts. We may consider \( a_i, b_i, c_i, d_i, g_i \) are equal to zero for \( i = 0 \) when the patient is under drug administration and similarly \( a_i, b_i, c_i, d_i, g_i \) are equal to zero for \( i = 1 \); when the patient is under the recovery state of drug administration.

### 2. Stochastic Model

The following assumptions are considered to develop a stochastic model. Let the events occurred in non-overlapping intervals of time are statistically independent. Let \( \Delta t \) be an infinitesimal interval of time. Let there be \( n \)’ normal cells and \( m \)’ mutant cells initially at time \( t \). Let \( a_0, b_0, c_0, d_0, g_0 \) respectively be the rate of generation of normal cell from normal cell, rate of generation of mutant cell from normal cell, rate of generation of mutant cell from mutant cell, rate of death of normal cell, rate of death of mutant cell under the absence of drug. Let \( a_1, b_1, c_1, d_1, g_1 \) respectively be the rate of generation of normal cell from normal cell, rate of generation of mutant cell from normal cell, rate of generation of mutant cell from mutant cell, rate of death of normal cell, rate of death of mutant cell under the presence of drug. The presence and absence of drug at an instance of time are exclusive. Hence also assumed that all the above mentioned events follows Poisson process.

The probability of generation of one normal cell during \( \Delta t \) from \( n \) normal cells in the presence of drug = \( n \cdot a_0 \Delta t + 0(\Delta t) \). The probability of generation of one normal cell during \( \Delta t \) from \( n \) normal cells in the absence of drug = \( n \cdot a_1 \Delta t + 0(\Delta t) \). The probability of generation of one normal cell from \( n \)’ normal cells either in the presence or in absence of drug is \([n \cdot a_0 \Delta t + 0(\Delta t)] + [n \cdot a_1 \Delta t + 0(\Delta t)] = n(a_0 + a_1) \Delta t + 0(\Delta t)\) = The postulates of the model are, The probability of generation of one normal cell during \( \Delta t \), provided \( \exists n \)’ normal cells during \( t \) is \( n(a_0 + a_1) \Delta t + 0(\Delta t) \); The probability of generation of one mutant cell from a normal cell during \( \Delta t \) provided \( \exists n \)’ normal cells during \( t \) is \( n(b_0 + b_1) \Delta t + 0(\Delta t) \); The probability of generation of one mutant cell from a mutant cell during \( \Delta t \) provided \( \exists m \)’ mutant cells during \( t \) is \( m(c_0 + c_1) \Delta t + 0(\Delta t) \); The probability of death of one normal cell during \( \Delta t \) provided \( \exists n \)’ normal cells at \( t \)’ is \( n(d_0 + d_1) \Delta t + 0(\Delta t) \); The probability of death of one mutant cell during \( \Delta t \) provided \( \exists m \)’ mutant cells at time \( t \)’ is \( m(g_0 + g_1) \Delta t + 0(\Delta t) \); The probability of no generation of normal cell from a normal cell, no formation of mutant cell from normal cell, no generation of mutant cell from mutant cell, no death of normal cell, no death of mutant cell during an infinitesimal interval of time \( \Delta t \) is \( 1 - [n(a_0 + a_1 + b_0 + b_1 + d_0 + d_1) + m(c_0 + c_1 + g_0 + g_1)] \Delta t + 0(\Delta t) \); The probability of occurrence of other than the above events during the above mentioned events follows Poisson process.

Let \( p_n,m(t) \) be the joint probability of existing of \( n \)’ normal cells and \( m \)’ mutant cells in a tumor per unit time \( t \). Then the difference-differential equations of the model are:
\[
\begin{align*}
\frac{dp'_{n,m}(t)}{dt} &= [n(a_0 + a_1 + b_0 + b_1 + d_0 + d_1) + m(c_0 + c_1 + g_0 + g_1)] (-1) p_{n,m}(t) \\
&+ (n-1) (a_0 + a_1) p_{n-1,m}(t) + [(n+1) (d_0 + d_1)] p_{n+1,m}(t) \\
&+ [n(b_0 + b_1) + (m-1)(c_0 + c_1)] p_{n,m-1}(t) \\
&+ (m+1)(g_0 + g_1) p_{n,m+1}(t) \quad \text{for} \quad n, m \geq 1 \quad (2.1)
\end{align*}
\]

\[
\begin{align*}
p'_{1,0}(t) &= (a_0 + a_1 + b_0 + b_1 + d_0 + d_1)(-1)p_{1,0}(t) + 2(d_0 + d_1)p_{2,0}(t) + (g_0 + g_1)p_{1,1}(t) \quad (2.2)
\end{align*}
\]

\[
\begin{align*}
p'_{0,1}(t) &= (c_0 + c_1 + g_0 + g_1)(-1)p_{0,1}(t) + (d_0 + d_1)p_{1,1}(t) + 2(g_0 + g_1)p_{0,2}(t) \quad (2.3)
\end{align*}
\]

\[
\begin{align*}
p'_{0,0}(t) &= (d_0 + d_1)p_{1,0}(t) + (g_0 + g_1)p_{0,1}(t) \quad (2.4)
\end{align*}
\]

With the initial conditions

\[
\begin{align*}
p_{N_0,M_0}(0) &= 1, \quad p_{N_0,M_0}(t) = 0.
\end{align*}
\]

Where \(N_0, M_0\) are the initial sizes of the normal and the mutant cells in the tumor.

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

\[
\begin{align*}
p(x, y; t) &= \sum_{n=0}^{\infty} \sum_{m=0}^{\infty} x^n y^m p_{n,m}(t). \quad (2.5)
\end{align*}
\]

Multiplying the equations (2.1) to (2.4) with \(x^n y^m\) and summing overall \(m\) and \(n\) we get,

\[
\begin{align*}
\frac{\partial}{\partial t} p(x, y; t) &= (a_0 + a_1 + b_0 + b_1 + d_0 + d_1) x \sum_{m=1}^{\infty} \sum_{n=1}^{\infty} -n x^{n-1} y^m p_{n,m}(t) \\
&+ (c_0 + c_1 + g_0 + g_1) y \sum_{m=1}^{\infty} \sum_{n=1}^{\infty} mx^n y^{m-1} p_{n,m}(t) \\
&+ (a_0 + a_1)x^2 \sum_{m=1}^{\infty} \sum_{n=1}^{\infty} (n-1)x^{n-2} y^m p_{n-1,m}(t) \\
&+ (d_0 + d_1) \sum_{m=1}^{\infty} \sum_{n=1}^{\infty} (n+1)x^n y^m p_{n+1,m}(t) \\
&+ (b_0 + b_1)xy \sum_{m=1}^{\infty} \sum_{n=1}^{\infty} nx^{n-1} y^{m-1} p_{n,m-1}(t) \\
&+ (c_0 + c_1)y^2 \sum_{m=1}^{\infty} \sum_{n=1}^{\infty} (m-1)x^n y^{m-2} p_{n,m-1}(t) \\
&+ (g_0 + g_1) \sum_{m=1}^{\infty} \sum_{n=1}^{\infty} (m+1)x^n y^m p_{n,m+1}(t) \quad (2.6)
\end{align*}
\]
Rearranging the terms in the equation (2.6)

\[ t \frac{\partial}{\partial t} p(x, y; t) = -(a_0 + a_1 + b_0 + b_1 + d_0 + d_1)x + (a_0 + a_1)x^2 + (d_0 + d_1) \\
+ (b_0 + b_1)xy \frac{\partial}{\partial x} p(x, y; t) + [- (c_0 + c_1 + g_0 + g_1)y] \\
+ (c_0 + c_1)y^2 + (g_0 + g_1) \frac{\partial}{\partial y} p(x, y; t) \] (2.7)

We can obtain the characteristics of the model by using the joint cumulant generating function of \( p_{n,m}(t) \). Taking \( x = e^u \) and \( y = e^v \) and denoting \( k(u, v; t) \) as the joint cumulant generating function of \( p_{n,m}(t) \), the equation (2.7) becomes

\[ t \frac{\partial}{\partial t} k(u, v; t) = -(a_0 + a_1 + b_0 + b_1 + d_0 + d_1) + (a_0 + a_1)e^u + (b_0 + b_1)e^v + (d_0 + d_1)e^{-u} \frac{\partial k}{\partial u} \]

\[ + [- (c_0 + c_1 + g_0 + g_1) + (c_0 + c_1)e^v + (g_0 + g_1)e^{-v}] \frac{\partial k}{\partial v}. \] (2.8)

3. Differential Equations and Statistical Measures

Let \( m_{i,j}(t) \) denotes the moments of order \((i, j)\) of normal and mutant cells at time \( t' \).

Then the differential equations of the model are:

\[ \frac{\partial}{\partial t} m_{1,0}^{(i)}(t) = (a_0 + a_1 - d_0 - d_1) m_{1,0}^{(i)}(t) \] (3.1)

\[ \frac{\partial}{\partial t} m_{0,1}^{(i)}(t) = (b_0 + b_1) m_{1,0}^{(i)}(t) + (c_0 + c_1 - g_0 - g_1) m_{0,1}^{(i)}(t) \] (3.2)

\[ \frac{\partial}{\partial t} m_{2,0}^{(i)}(t) = (a_0 + a_1 + d_0 + d_1) m_{1,0}^{(i)}(t) + 2(a_0 + a_1 - d_0 - d_1) m_{2,0}^{(i)}(t) \] (3.3)

\[ \frac{\partial}{\partial t} m_{1,1}^{(i)}(t) = (a_0 + a_1 - d_0 - d_1 + c_0 + c_1 - g_0 - g_1) m_{1,1}^{(i)}(t) + (b_0 + b_1) m_{2,0}^{(i)}(t) \] (3.4)

\[ \frac{\partial}{\partial t} m_{0,2}^{(i)} = 2(b_0 + b_1) m_{1,1}^{(i)}(t) + (b_0 + b_1) m_{1,0}^{(i)}(t) + (c_0 + c_1 + g_0 + g_1) m_{0,1}^{(i)}(t) \]
\[ + 2(c_0 + c_1 - g_0 - g_1) m_{0,2}^{(i)}(t) \] (3.5)
We can obtain the characteristics of the model by solving the equations from 3.1 to 3.5

Solving the equation 3.1 we get, expected number of normal cells during chemotherapy at time ‘\(t\)’ is

\[ m_{1,0}(t) = N_0 e^{(a_0 + a_1 - d_0 - d_1)t} \] (3.6)

Where \(N_0\) is the initial size of the normal cells,

Substituting the equation (3.6) in (3.2), we get

\[ \frac{\partial}{\partial t} m_{0,1}(t) + (g_0 + g_1 - c_0 - c_1) m_{0,1}(t) = (b_0 + b_1) N_0 e^{(a_0 + a_1 - d_0 - d_1)t}. \] (3.7)

Solving the equation 3.7 we get expected number of mutant cells during chemotherapy at time ‘\(t\)’ is

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

where

\[ A = \frac{(b_0 + b_1) N_0}{a_0 + a_1 - d_0 - d_1 + g_0 + g_1 - c_0 - c_1} \] (3.8)

and \(M_0\) is the initial size of the mutant cells.

Substituting the equation (3.6) in the equation (3.3) we get,

\[ \frac{\partial}{\partial t} m_{2,0}(t) + 2(d_0 + d_1 - a_0 - a_1) m_{2,0}(t) = (a_0 + a_1 + d_0 + d_1) N_0 e^{(a_0 + a_1 - d_0 - d_1)t}. \] (3.9)

Solving the equation (3.9) we get Variance of normal cells during chemotherapy at time ‘\(t\)’ is

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

where

\[ B = \frac{a_0 + a_1 + d_0 + d_1}{a_0 + a_1 - d_0 - d_1} N_0. \] (3.10)

Substituting the equation (3.10) in (3.4) we get,

\[ \frac{\partial}{\partial t} m_{1,1}(t) - (a_0 + a_1 - d_0 - d_1 + c_0 + c_1 - g_0 - g_1) m_{1,1}(t) \]

\[ = (b_0 + b_1) e^{(a_0 + a_1 - d_0 - d_1)t} \left[ e^{(a_0 + a_1 - d_0 - d_1)t} - 1 \right]. \] (3.11)

Solving the equation (3.11) we get,
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Covariance between normal cells and mutant cells during chemotherapy at time ‘t’ is

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

where

\[ D = \frac{(b_0 + b_1)(a_0 + a_1 + d_0 + d_1)}{(a_0 + a_1 - d_0 - d_1 - c_0 - c_1 + g_0 + g_1)(g_0 + g_1 - c_0 - c_1)} \cdot N_0. \]

Substituting the equations (3.6),(3.8) and (3.12) in the equation (3.5) we get,

\[ \frac{\partial}{\partial t} m_{0,2}(t) + 2(g_0 + g_1 - c_0 - c_1)m_{0,2}(t) \]

\[ = 2(b_0 + b_1) \left[ D e^{(a_0 + a_1 - d_0 - d_1)t} \left[ \frac{(g_0 + g_1 - c_0 - c_1)e^{(a_0 + a_1 - d_0 - d_1)t}}{a_0 + a_1 - d_0 - d_1} + e^{(c_0 + c_1 - g_0 - g_1)t} \right] \right] \]

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

\[ \{ A[e^{(a_0 + a_1 - d_0 - d_1)t} - e^{(c_0 + c_1 - g_0 - g_1)t}] + M_0 e^{(c_0 + c_1 - g_0 - g_1)t} \}. \]

Solving the equation (3.13) we get, Variance of mutant cells during chemotherapy at time ‘t’ is

\[ m_{0,2}(t) = E[e^{2(g_0 + g_1 - c_0 - c_1)t} - e^{2(c_0 + c_1 - g_0 - g_1)t}] + (F + 1 + H)[e^{2(c_0 + c_1 - g_0 - g_1)t} - e^{2(c_0 + c_1 - g_0 - g_1)t}] \]

\[ + G[e^{(a_0 + a_1 - d_0 - d_1)t} - e^{(c_0 + c_1 - g_0 - g_1)t}] + (J + K)[e^{(c_0 + c_1 - g_0 - g_1)t} - e^{(c_0 + c_1 - g_0 - g_1)t}] \]

where

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

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

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

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

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

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

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

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

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

4. **Sensitivity Analysis**

In order to understand the model behavior with more clarity, numerical datasets of simulate data values are calculated using MATHCAD and are presented in Table 1 and Table 2.

From Table 1 and Table 2 it is observed that expected number of normal cells, expected number of mutant cells, variance of normal cells, variance of mutant cells and co-variance of normal and mutant cells are increasing functions of the initial number of normal cells \((N_0)\) when all the other parameters are constants. The expected number of normal cells, variance of normal cells and co-variance of normal and mutant cells are invariant of change of initial number of mutant cells \((M_0)\) when all the other parameters are constants. Further the expected number of mutant cells, variance of mutant cells, are increasing functions of initial number of mutant cells \((M_0)\) when all the other parameters are constants.

The expected number of normal cells and expected number of mutant cells, Variance of normal cells, Variance of mutant cells and co-variance of normal cells and mutant cells are increasing functions of the rate of generation of normal cell from normal cell during the absence of drug \((a_0)\) when all the other parameters are constant. The expected number of normal cells and variance of normal cells are invariant of rate of generation of mutant cell from normal cells during absence of drug \((b_0)\) when all the other parameters are constant. The expected number of mutant cells, covariance of normal and mutant cells, variance of mutant cells are increasing function of rate of generation of mutant cell from normal cell during absence of drug \((b_0)\) when all the other parameters are constant. The expected number of normal cells and variance of normal cells are invariant of rate of generation of mutant cell
Table 1
Statistical Measures For Various Values of the Parameters for 
\( a_1 = 0.2; \ b_1 = 0.3; \ c_1 = 0.3 \ d_1 = 0.5; \ g_1 = 2; \ t = 7 \)

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<th>(c_0)</th>
<th>(d_0)</th>
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Bivariate Stochastic Modeling for Mutant Cell Growth Under Chemotherapy

from mutant cell during the absence of drug \( (c) \) when all the other parameters are constant. The expected number of mutant cells, covariance of normal and mutant cells, Variance of mutant cells are increasing functions of rate of generation of mutant cell from mutant cell during the absence of drug \( (c) \) when all the other parameters are constant. The expected number of normal cells and mutant cells, covariance of normal cells and mutant cells, Variance of normal cells and mutant cells are decreasing functions of rate of death of normal cell during the absence of drug. The expected number of normal cells and variance of number of normal cells are invariant of change of rate death of mutant cell during the absence \( (g) \) when all the other parameters are constant. The expected number of mutant cells, covariance of normal cells and mutant cells, variance of mutant cells are decreasing functions of rate of death of mutant cells during the absence \( (g) \) when all the other parameters are constants.

The expected number of normal cells and mutant cells, Variance of normal cells, Variance of mutant cells, covariance of normal and mutant cells, variance of normal cells, Variance of mutant cells are increasing functions of rate of generation of normal cell from normal cell \( (a) \) during the presence of drug when all the other parameters are constant. The expected number of normal cells, Variance of normal cells are invariant of rate of generation of mutant cell from normal cell during the presence of drug \( (b) \) when all the parameters are constant. The expected number of mutant cells, covariance of normal cells and mutant cells, Variance of mutant cells are increasing functions of rate of generation of mutant cell from normal cell during the presence of drug \( (b) \) when all the parameters are constant. The expected number of mutant cells, covariance of normal and mutant cells, variance of mutant cells are increasing functions of rate of generation of mutant cells from mutant cells during the presence of drug \( (c) \) when all the other parameters are constant. The expected number of normal cells, Expected number of mutant cells, covariance of normal and mutant cells, variance of normal cells, Variance of mutant cells are decreasing functions of rate of death of normal cell during the presence of drug \( (d) \) when all the other parameters are constant. The expected numbers of normal cells, variance of normal cells are invariant of change of rate death of mutant cells during the presence of drug \( (g) \) when all the other parameters are constant. The expected number of mutant cells, covariance of normal cells and mutant cells, variance of mutant cells are decreasing functions of rate of death of mutant cells during the presence of drug \( (g) \) when all the other parameters are constants.

It is observed from Table 2 that expected number of normal cells, Expected number of mutant cells, covariance of normal and mutant cells, variance of normal cells, Variance of mutant cells is decreasing functions of time \( (t) \) when all the other parameters are constant.

REFERENCE

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