

## A TWO PHASE AGE DEPENDENT AND TWO-MUTATION STOCHASTIC MODEL OF CARCINOGENESIS

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**ABSTRACT.** An age dependent and two-mutation stochastic model of carcinogenesis is formulated and studied. In this model, we introduce a fitness age  $T$ , (a positive constant) for each cell to divide into two cells. A normal cell if its age is not greater than  $T$  either divides into two normal cells or divides into one normal cell and one intermediate cell or dies. A normal cell if its age is greater than  $T$  either divides into one normal cell and one intermediate cell, or divides into two intermediate cells or dies. An intermediate cell if its age is not greater than  $T$  divides into two intermediate cells or divides into one intermediate cell and one malignant cell or dies. An intermediate cell if its age is greater than  $T$  divides into one intermediate cell and one malignant cell or divides into two malignant cells or dies. It is assumed that, once a malignant cell is produced, it generates a malignant tumor with probability 1. We obtain the mean numbers of normal, intermediate and malignant cells. It is shown that the production of malignant cells in one-mutation model is faster than that in two-mutation model. A numerical illustration is presented to highlight the performance of the model.

**Keywords:** Carcinogenesis, Fitness age, Malignant cell, Age-dependence, Two-stage mutation.

**AMS Subject Classification:** 92-10, 92B05, 92D25.

### 1. INTRODUCTION

Cancer is the result of accumulation of genetic and epigenetic mutations in genes which regulate cell proliferation (see You and Jones [1]). Mutations in the genes occur spontaneously or due to DNA-damage when exposed to environment. The mutations are irreversible and the mutated cells have increased rate of growth and increased probability of survival over the normal cells which lead to the above mentioned accumulation, called

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the evolution of a tumor (tumorigenesis) (see Rivlin et al. [2]).

Mathematical models of cancer growth were first developed by Nordling [3], and Armitage and Doll ([4],[5],[6]). These models were laid down on the assumption that the degeneration of a normal cell to a malignant cell occurs as a result of a finite number of intermediate stages. A series of papers (Knudson et al. [7], Moolgavkar and Venzon [8], Moolgavkar and Knudson [9]) emerged emphasizing that at least two mutations are needed to adequately explain the qualitative and epidemiological features of many tumors such as breast cancer, colorectal cancer and retinoblastoma occurring in human populations. An excellent and exhaustive review of mathematical models of carcinogenesis can be found in Whittemore and Keller [10]. Serio [11] did a generalization of Moolgavkar-Venzon model (see Moolgavkar and Venzon [8]) by considering time-dependent parameters.

In recent times, the studies on carcinogenesis have digressed towards evolutionary models. Sun et al. [12] have observed that tumorigenesis can be regarded as an evolutionary process and they have formulated a new model of time scheme for progression of colorectal cancer based upon maturity. Random mutations arising during DNA replication in normal, noncancerous stem cells have been taken into account by Tomasetti and Vogelstein [13] in their studies on cancer risk. Rozhok and DeGregori [14] have considered evolution of lifespan and age-dependent cancer risk. Rozhok et al. [15] have studied age-dependent incidence of cancer. Rozhok and DeGregori [16] have made simulation studies on a generalized theory of age-dependent carcinogenesis to demonstrate the impact of key somatic evolutionary parameters on the performance of multistage model of carcinogenesis. Wolf et al. [17] have considered multi-stage carcinogenesis models to assess the effect of carcinogenicity of chemicals in the production of malignant cells.

To our knowledge, age-dependent modeling of cell division has not been taken into account in the study of carcinogenesis. Accordingly, we are motivated to propose an age dependent two-mutation model of cell division process and provide mean analysis of carcinogenesis. To be specific, we present a two phase age-dependent and two-stage stochastic model of carcinogenesis. In this model, a normal cell if its age is not greater than a positive constant  $T$  either divides into two normal cells with rate  $l_{11}$ , or divides into one normal cell and one intermediate cell with rate  $l_{12}$  or dies with rate  $d_1$ . A normal cell if its age is greater than  $T$  either divides into one normal cell and one intermediate cell with rate  $l_{21}$ , or divides into two intermediate cells with rate  $l_{22}$  or dies with rate  $d_2$ . An intermediate cell if its age is not greater than  $T$  either divides into two intermediate cells with rate  $\alpha_{11}$ , or divides into one intermediate cell and one malignant cell with rate  $\alpha_{12}$ , or dies with rate  $\mu_1$ . An intermediate cell if its age is greater than  $T$  either divides into one intermediate cell and one malignant cell with rate  $\alpha_{21}$ , or divides into two malignant cells with rate  $\alpha_{22}$ , or dies with rate  $\mu_2$ . It is assumed that, once a malignant cell is produced, it generates a malignant tumor with probability 1. Based upon the model, we obtain the mean numbers of normal, intermediate and malignant cells.

The paper is organized as follows: In section 2, we describe the two phase age-dependent and two stage mutation model of carcinogenesis. In section 3, we write the integral equations satisfied by the conditional probability generating functions of the number of normal, intermediate and malignant cells. Section 4 obtains the mean number of normal, intermediate and malignant cells in the population. In section 5, a numerical illustration is provided. Section 6 provides conclusion.

## 2. MODEL FORMULATION

We begin with a single normal cell at time  $t = 0$ . As time progresses, stochastic mutation and cell division processes take place and a cell population consisting of normal, intermediate and malignant cells is generated. Let  $X(t)$ ,  $Y(t)$  and  $Z(t)$  be the random variables denoting the number of normal, intermediate and malignant cells at time  $t$ .

**2.1. Assumptions.** The following assumptions are made. In what follows,  $o(h)$  denotes a function of  $h$  satisfying  $\lim_{h \rightarrow 0} \frac{o(h)}{h} = 0$ .

- (i) The age of a cell at time  $t$  is the time elapsed since the time of its birth.
- (ii) A normal cell existing at time  $t$  splits into two normal cells in a small interval  $(t, t + \Delta t)$  with probability  $l_{11}\Delta t + o(\Delta t)$ , if the age of the cell is not greater than a positive constant  $T$ .
- (iii) A normal cell existing at time  $t$  splits into one normal cell and one intermediate cell in a small interval  $(t, t + \Delta t)$  with probability  $l_{12}\Delta t + o(\Delta t)$ , if the age of the cell is not greater than a positive constant  $T$ .
- (iv) A normal cell existing at time  $t$  dies in a small interval  $(t, t + \Delta t)$  with probability  $d_1\Delta t + o(\Delta t)$ , if the age of the cell is not greater than a positive constant  $T$ .
- (v) A normal cell existing at time  $t$  splits into one normal cell and one intermediate cell in a small interval  $(t, t + \Delta t)$  with probability  $l_{21}\Delta t + o(\Delta t)$ , if the age of the cell is greater than a positive constant  $T$ .
- (vi) A normal cell existing at time  $t$  splits into two intermediate cells in a small interval  $(t, t + \Delta t)$  with probability  $l_{22}\Delta t + o(\Delta t)$ , if the age of the cell is greater than a positive constant  $T$ .
- (vii) A normal cell existing at time  $t$  dies in a small interval  $(t, t + \Delta t)$  with probability  $d_2\Delta t + o(\Delta t)$ , if the age of the cell is greater than a positive constant  $T$ .
- (viii) An intermediate cell existing at time  $t$  splits into two intermediate cells in a small interval  $(t, t + \Delta t)$  with probability  $\alpha_{11}\Delta t + o(\Delta t)$ , if the age of the cell is not greater than a positive constant  $T$ .
- (ix) An intermediate cell existing at time  $t$  splits into one intermediate cell and one malignant cell in a small interval  $(t, t + \Delta t)$  with probability  $\alpha_{12}\Delta t + o(\Delta t)$ , if the age of the cell is not greater than a positive constant  $T$ .
- (x) An intermediate cell existing at time  $t$  dies in a small interval  $(t, t + \Delta t)$  with probability  $\mu_1\Delta t + o(\Delta t)$ , if the age of the cell is not greater than a positive constant  $T$ .
- (xi) An intermediate cell existing at time  $t$  splits into one intermediate cell and one malignant cell in a small interval  $(t, t + \Delta t)$  with probability  $\alpha_{21}\Delta t + o(\Delta t)$ , if the age of the cell is greater than a positive constant  $T$ .
- (xii) An intermediate cell existing at time  $t$  splits into two malignant cells in a small interval  $(t, t + \Delta t)$  with probability  $\alpha_{22}\Delta t + o(\Delta t)$ , if the age of the cell is greater than a positive constant  $T$ .
- (xiii) An intermediate cell existing at time  $t$  dies in a small interval  $(t, t + \Delta t)$  with probability  $\mu_2\Delta t + o(\Delta t)$ , if the age of the cell is greater than a positive constant  $T$ .
- (xiv) Once a malignant cell is born, it generates a malignant tumor with probability 1.
- (xv) All events are independent.
- (xvi) The probability of occurrence of more than one event in a small interval  $(t, t + \Delta t)$  is  $o(\Delta t)$ .

In the above assumptions, the parameters  $l_{11}, l_{12}, l_{21}, l_{22}, d_1$ , and  $d_2$  are positive constants and they are rates for a normal cell to divide. Similarly,  $\alpha_{11}, \alpha_{12}, \alpha_{21}, \alpha_{22}, \mu_1$ , and  $\mu_2$

are positive constants and they are rates for an intermediate cell to divide. Further, the parameters  $l_{12}, l_{21}, \alpha_{12}$  and  $\alpha_{21}$  arise due to cross mutations. Estimated values of these parameters have been reported (see Tomasetti et al. [18]).

### 3. GOVERNING EQUATIONS

We begin our study with 1 newly born normal cell and no other cells. Then, we have the condition  $X(0) = 1, Y(0) = 0, Z(0) = 0$ . We define the conditional probability generating function for the number of normal, intermediate and malignant cells at time  $t$  as follows:

$$\psi(x, y, z, t) = \mathbb{E} \left[ x^{X(t)} y^{Y(t)} z^{Z(t)} | X(0) = 1, Y(0) = 0, Z(0) = 0 \right]. \tag{1}$$

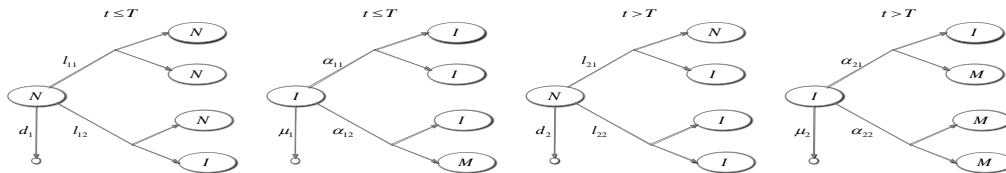
The above function describes the two-mutation model.

In the same manner, we define the conditional probability generating function for the number of intermediate and malignant cells at time  $t$  as follows:

$$\phi(y, z, t) = \mathbb{E} \left[ y^{Y(t)} z^{Z(t)} | Y(0) = 1, Z(0) = 0 \right]. \tag{2}$$

The above function describes one-mutation model.

Considering various possible events happening in the time interval  $(0, t]$  and using the invariant imbedding technique (see Bellmann et al. [19]), we obtain an integral equations for  $\psi(x, y, z, t)$  and  $\phi(y, z, t)$ . As a short-hand notation, we denote  $\psi(x, y, z, t)$  and  $\phi(y, z, t)$  respectively by  $\psi(t)$  and  $\phi(t)$ . The following diagrams clarify the mechanism of cancer progression ( $N, I$  and  $M$  denote respectively normal, intermediate and malignant cells):



**Case  $t \leq T$ :** The following mutually exclusive and exhaustive events occur. The normal cell with which we started at time  $t = 0$

- (i) neither splits nor dies before  $t$ .
- (ii) splits before  $t$ .
- (iii) dies before  $t$ .

Consequently, we have

$$\psi(t) = x e^{-at} + l_{11} \int_0^t e^{-au} \{\psi(t-u)\}^2 du + l_{12} \int_0^t e^{-au} \psi(t-u) \phi(t-u) du + \frac{d_1}{a} (1 - e^{-at}), \tag{3}$$

where  $a = l_{11} + l_{12} + d_1$ . The term  $x e^{-at}$  corresponds to the possible event (i). The event (ii) leads to the term,  $l_{11} \int_0^t e^{-au} \{\psi(t-u)\}^2 du + l_{12} \int_0^t e^{-au} \psi(t-u) \phi(t-u) du$ . The term  $\frac{d_1}{a} (1 - e^{-at})$  is the contribution of the occurrence of the event (iii).

Similarly, the following mutually exclusive and exhaustive events occur. The intermediate cell with which we started at time  $t = 0$

- (iv) neither splits nor dies before  $t$ .

- (v) splits before  $t$ .
- (vi) dies before  $t$ .

Consequently, we have

$$\begin{aligned} \phi(t) = ye^{-bt} + \alpha_{11} \int_0^t e^{-bu} \{\phi(t-u)\}^2 du + \alpha_{12} z \int_0^t e^{-bu} \phi(t-u) du \\ + \frac{\mu_1}{b} (1 - e^{-bt}), \end{aligned} \quad (4)$$

where  $b = \alpha_{11} + \alpha_{12} + \mu_1$ . The term  $ye^{-bt}$  corresponds to the possible event (iv). The event (v) leads to the term,  $\alpha_{11} \int_0^t e^{-bu} \{\phi(t-u)\}^2 du + \alpha_{12} z \int_0^t e^{-bu} \phi(t-u) du$ . The term  $\frac{\mu_1}{b} (1 - e^{-bt})$  is the contribution by the occurrence of the event (vi).

**Case  $t > T$ :** The following mutually exclusive and exhaustive events occur. The normal cell with which we started at time  $t = 0$

- (vii) neither split nor die before  $t$ .
- (viii) splits before  $t$ .
- (ix) dies before  $t$ .

Consequently, we have

$$\begin{aligned} \psi(t) = xe^{-aT} e^{-A(t-T)} + l_{11} \int_0^T e^{-au} \{\psi(t-u)\}^2 du + l_{12} \int_0^T e^{-au} \psi(t-u) \phi(t-u) du \\ + e^{-aT} l_{21} \int_T^t e^{-A(u-T)} \psi(t-u) \phi(t-u) du + e^{-aT} l_{22} \int_T^t e^{-A(u-T)} \{\phi(t-u)\}^2 du \\ + \frac{d_1}{a} (1 - e^{-aT}) + e^{-aT} \frac{d_2}{A} (1 - e^{-A(t-T)}), \end{aligned} \quad (5)$$

where  $A = l_{21} + l_{22} + d_2$ . The term  $xe^{-aT} e^{-A(t-T)}$  arises due to the occurrence of the possible event (vii). The event (viii) leads to the term,

$$\begin{aligned} l_{11} \int_0^T e^{-au} \{\psi(t-u)\}^2 du + l_{12} \int_0^T e^{-au} \psi(t-u) \phi(t-u) du \\ + e^{-aT} l_{21} \int_T^t e^{-A(u-T)} \psi(t-u) \phi(t-u) du + e^{-aT} l_{22} \int_T^t e^{-A(u-T)} \{\phi(t-u)\}^2 du. \end{aligned}$$

The term  $\frac{d_1}{a} (1 - e^{-aT}) + e^{-aT} \frac{d_2}{A} (1 - e^{-A(t-T)})$  is the contribution by the occurrence of the event (ix).

Similarly, the following mutually exclusive and exhaustive events occur. The intermediate cell with which we started at time  $t = 0$

- (x) neither splits nor dies before  $t$ .
- (xi) splits before  $t$ .
- (xii) dies before  $t$ .

Consequently, we have

$$\begin{aligned} \phi(t) = ye^{-bT} e^{-B(t-T)} + \alpha_{11} \int_0^T e^{-bu} \{\phi(t-u)\}^2 du + \alpha_{12} z \int_0^T e^{-bu} \phi(t-u) du \\ + \alpha_{21} e^{-bT} z \int_T^t e^{-B(u-T)} \phi(t-u) du + e^{-bT} \frac{\alpha_{22}}{B} z^2 (1 - e^{-B(t-T)}) \\ + \frac{\mu_1}{b} (1 - e^{-bT}) + e^{-bT} \frac{\mu_2}{B} (1 - e^{-B(t-T)}), \end{aligned} \quad (6)$$

where  $B = \alpha_{21} + \alpha_{22} + \mu_2$ . The term  $ye^{-bT}e^{-B(t-T)}$  arises due to the occurrence of the possible event (x). The event (xi) leads to the term,

$$\alpha_{11} \int_0^T e^{-bu} \{\phi(t-u)\}^2 du + \alpha_{12} z \int_0^T e^{-bu} \{\phi(t-u)\} du + \alpha_{21} e^{-bT} z \int_T^t e^{-B(u-T)} \phi(t-u) du + e^{-bT} \frac{\alpha_{22}}{B} z^2 (1 - e^{-B(t-T)}).$$

The term  $\frac{\mu_1}{b} (1 - e^{-bT}) + e^{-bT} \frac{\mu_2}{B} (1 - e^{-B(t-T)})$  is the contribution by the occurrence of the event (xii).

#### 4. MEAN NUMBER OF CELLS

We define the mean numbers of normal, intermediate and malignant cells in the two-stage model respectively as follows:

$$\begin{aligned} m_X^{(2)}(t) &= E[X(t)|X(0) = 1, Y(0) = 0, Z(0) = 0], \\ m_Y^{(2)}(t) &= E[Y(t)|X(0) = 1, Y(0) = 0, Z(0) = 0], \\ m_Z^{(2)}(t) &= E[Z(t)|X(0) = 1, Y(0) = 0, Z(0) = 0]. \end{aligned}$$

We define the mean numbers of normal (intermediate) and malignant cells in the one-stage model as follows:

$$\begin{aligned} m_Y^{(1)}(t) &= E[Y(t)|Y(0) = 1, Z(0) = 0], \\ m_Z^{(1)}(t) &= E[Z(t)|Y(0) = 1, Z(0) = 0]. \end{aligned}$$

The probability generating function of a random variable  $X$  is defined by  $H_X(x) = E[x^X]$  and so,

$$E(X) = [E(Xx^{X-1})]_{x=1} = \left[ \frac{\partial}{\partial x} (H_X(x)) \right]_{x=1}.$$

Applying the above result with  $\psi(x, y, z, t)$  and  $\phi(y, z, t)$ , we get

$$\begin{aligned} m_X^{(2)}(t) &= \left[ \frac{\partial \psi(t)}{\partial x} \right]_{x=1, y=1, z=1}, m_Y^{(2)}(t) = \left[ \frac{\partial \psi(t)}{\partial y} \right]_{x=1, y=1, z=1}, \\ m_Z^{(2)}(t) &= \left[ \frac{\partial \psi(t)}{\partial z} \right]_{x=1, y=1, z=1}, \\ m_Y^{(1)}(t) &= \left[ \frac{\partial \phi(t)}{\partial y} \right]_{y=1, z=1}, m_Z^{(1)}(t) = \left[ \frac{\partial \phi(t)}{\partial z} \right]_{y=1, z=1}. \end{aligned}$$

Differentiating (3) with respect to  $x$  and putting  $x = 1, y = 1, z = 1$ , we get

$$m_X^{(2)}(t) = e^{-at} + (2l_{11} + l_{12}) \int_0^t e^{-au} m_X^{(2)}(t-u) du, t \leq T. \tag{7}$$

Similarly, differentiating (5) with respect to  $x$  and putting  $x = 1, y = 1, z = 1$ , we get

$$\begin{aligned} m_X^{(2)}(t) &= e^{-aT} e^{-A(t-T)} + (2l_{11} + l_{12}) \int_0^T e^{-au} m_X^{(2)}(t-u) du \\ &+ e^{-aT} l_{21} \int_T^t e^{-A(u-T)} m_X^{(2)}(t-u) du, t > T. \end{aligned} \tag{8}$$

Using Heaviside function, equations (7) and (8) are clubbed as follows:

$$m_X^{(2)}(t) = e^{-at} [1 - H(t - T)] + e^{(A-a)T} e^{-At} H(t - T)$$

$$\begin{aligned}
& + (2l_{11} + l_{12}) \int_0^t e^{-au} [1 - H(u - T)] m_X^{(2)}(t - u) du \\
& + e^{-aT} l_{21} \int_0^t e^{-A(u-T)} H(u - T) m_X^{(2)}(t - u) du, t > 0.
\end{aligned} \tag{9}$$

Proceeding in similar lines, equations (3) and (5) lead to the following equations.

$$\begin{aligned}
m_Y^{(2)}(t) & = (2l_{11} + l_{12}) \int_0^t e^{-au} [1 - H(u - T)] m_Y^{(2)}(t - u) du \\
& + l_{12} \int_0^t e^{-au} [1 - H(u - T)] m_Y^{(1)}(t - u) du + e^{-aT} l_{21} \int_0^t e^{-A(u-T)} H(u - T) m_Y^{(2)}(t - u) du \\
& + e^{-aT} (l_{21} + 2l_{22}) \int_0^t e^{-A(u-T)} H(u - T) m_Y^{(1)}(t - u) du,
\end{aligned} \tag{10}$$

$$\begin{aligned}
m_Z^{(2)}(t) & = (2l_{11} + l_{12}) \int_0^t e^{-au} [1 - H(u - T)] m_Z^{(2)}(t - u) du \\
& + l_{12} \int_0^t e^{-au} [1 - H(u - T)] m_Z^{(1)}(t - u) du + e^{-aT} l_{21} \int_0^t e^{-A(u-T)} H(u - T) m_Z^{(2)}(t - u) du \\
& + e^{-aT} (l_{21} + 2l_{22}) \int_0^t e^{-A(u-T)} H(u - T) m_Z^{(1)}(t - u) du.
\end{aligned} \tag{11}$$

In the same manner, equations (4) and (6) give

$$\begin{aligned}
m_Y^{(1)}(t) & = e^{-bt} [1 - H(t - T)] + e^{-bT} e^{-B(t-T)} H(t - T) \\
& + (2\alpha_{11} + \alpha_{12}) \int_0^t e^{-bu} [1 - H(u - T)] m_Y^{(1)}(t - u) du \\
& + e^{-bT} \alpha_{21} \int_0^t e^{-B(u-T)} H(u - T) m_Y^{(1)}(t - u) du, \\
m_Z^{(1)}(t) & = (2\alpha_{11} + \alpha_{12}) \int_0^t e^{-bu} [1 - H(u - T)] m_Z^{(1)}(t - u) du \\
& + e^{-bT} \alpha_{21} \int_0^t e^{-B(u-T)} H(u - T) m_Z^{(1)}(t - u) du \\
& + \alpha_{12} \left( \frac{1 - e^{-bt}}{b} \right) [1 - H(t - T)] + \alpha_{12} \left( \frac{1 - e^{-bT}}{b} \right) H(t - T) \\
& + (\alpha_{21} + 2\alpha_{22}) e^{-bT} \left( \frac{1 - e^{-B(t-T)}}{B} \right) H(t - T).
\end{aligned} \tag{12}$$

Equations (9)- (13) can be solved explicitly by using Laplace transform technique. Denoting the Laplace transform of a function  $\eta(t)$  by  $\eta^*(s)$ , equations (9)- (13) lead to

$$m_X^{(2)*}(s) = \frac{\frac{1 - e^{-(s+a)T}}{s+a} + \frac{e^{-(s+a)T}}{s+A}}{1 - y_3 \left( \frac{1 - e^{-(s+a)T}}{s+a} \right) - y_4 \frac{e^{-(s+a)T}}{s+A}}, \tag{14}$$

$$m_Y^{(2)*}(s) = \frac{\left[ y_1 \left( \frac{1 - e^{-(s+a)T}}{s+a} \right) + y_2 \frac{e^{-(s+a)T}}{s+A} \right] m_Y^{(1)*}(s)}{1 - y_3 \left( \frac{1 - e^{-(s+a)T}}{s+a} \right) - y_4 \frac{e^{-(s+a)T}}{s+A}}, \tag{15}$$

$$m_Z^{(2)*}(s) = \frac{\left[ y_1 \left( \frac{1 - e^{-(s+a)T}}{s+a} \right) + y_2 \frac{e^{-(s+a)T}}{s+A} \right] m_Z^{(1)*}(s)}{1 - y_3 \left( \frac{1 - e^{-(s+a)T}}{s+a} \right) - y_4 \frac{e^{-(s+a)T}}{s+A}}, \tag{16}$$

$$m_Y^{(1)*}(s) = \frac{\frac{1-e^{-(s+b)T}}{s+b} + \frac{e^{-(s+b)T}}{s+B}}{1 - z_3 \left( \frac{1-e^{-(s+b)T}}{s+b} \right) - z_4 \frac{e^{-(s+b)T}}{s+B}}, \tag{17}$$

$$m_Z^{(1)*}(s) = \frac{z_1 \left( \frac{1-e^{-(s+b)T}}{s(s+b)} \right) + z_2 \frac{e^{-(s+b)T}}{s(s+B)}}{1 - z_3 \left( \frac{1-e^{-(s+b)T}}{s+b} \right) - z_4 \frac{e^{-(s+b)T}}{s+B}}, \tag{18}$$

where

$$y_1 = l_{12}, y_2 = l_{21} + 2l_{22}, y_3 = 2l_{11} + l_{12}, y_4 = l_{21},$$

$$z_1 = \alpha_{12}, z_2 = \alpha_{21} + 2\alpha_{22}, z_3 = 2\alpha_{11} + \alpha_{12}, z_4 = \alpha_{21}.$$

Expanding (18) as a power series, we get

$$m_Z^{(1)*}(s) = z_1 \sum_{r=0}^{\infty} \sum_{m=0}^r \sum_{i=0}^{m+1} \sum_{k=0}^{\infty} \sum_{n=0}^{\infty} E_{i,k,m,r} b^n \frac{e^{-(s+b)(i+r-m)T}}{(s+b)^{r+k+n+2}}$$

$$+ z_2 \sum_{r=0}^{\infty} \sum_{m=0}^r \sum_{i=0}^m \sum_{k=0}^{\infty} \sum_{n=0}^{\infty} F_{i,k,m,r} b^n \frac{e^{-(s+b)(i+r-m+1)T}}{(s+b)^{r+k+n+2}}, \tag{19}$$

where

$$E_{i,k,m,r} = (-1)^i \binom{r}{m} \binom{m+1}{i} \binom{-(r-m)}{k} z_3^m z_4^{r-m} (B-b)^k,$$

$$F_{i,k,m,r} = (-1)^i \binom{r}{m} \binom{m}{i} \binom{-(r-m+1)}{k} z_3^m z_4^{r-m} (B-b)^k.$$

By inverse Laplace transform, equation (19) leads explicitly

$$m_Z^{(1)}(t) = e^{-bt} \left[ z_1 \sum_{r=0}^{\infty} \sum_{m=0}^r \sum_{i=0}^{m+1} \sum_{k=0}^{\infty} \sum_{n=0}^{\infty} E_{i,k,m,r} b^n \times \right.$$

$$\frac{[t - (i+r-m)T]^{r+k+n+1}}{(r+k+n+1)!} H[t - (i+r-m)T]$$

$$+ z_2 \sum_{r=0}^{\infty} \sum_{m=0}^r \sum_{i=0}^m \sum_{k=0}^{\infty} \sum_{n=0}^{\infty} F_{i,k,m,r} b^n \times$$

$$\left. \frac{[t - (i+r-m+1)T]^{r+k+n+1}}{(r+k+n+1)!} H[t - (i+r-m+1)T] \right]. \tag{20}$$

Substituting (18) into (16) and then expanding (16) as a power series, we obtain

$$m_Z^{(2)*}(s) = y_1 z_1 \sum_{r=0}^{\infty} \sum_{m=0}^r \sum_{i=0}^{m+1} \sum_{k=0}^{\infty} \sum_{r_1=0}^{\infty} \sum_{m_1=0}^{m_1+1} \sum_{i_1=0}^{\infty} \sum_{k_1=0}^{\infty} \sum_{n_1=0}^{\infty} \sum_{n_2=0}^{\infty} (-1)^i \times$$

$$P_{i,k,m,r} E_{i_1,k_1,m_1,r_1} e^{-(a-b)(r-m+i)T} b^{n_1} (a-b)^{n_2} \binom{-(r+k+1)}{n_2} \times$$

$$\frac{e^{-(s+b)((r-m+i+i_1+r_1-m_1)T}}{(s+b)^{r+k+r_1+k_1+n_1+n_2+3}}$$

$$+ y_1 z_2 \sum_{r=0}^{\infty} \sum_{m=0}^r \sum_{i=0}^{m+1} \sum_{k=0}^{\infty} \sum_{r_1=0}^{\infty} \sum_{m_1=0}^{m_1} \sum_{i_1=0}^{\infty} \sum_{k_1=0}^{\infty} \sum_{n_1=0}^{\infty} \sum_{n_2=0}^{\infty} (-1)^i \times$$

$$P_{i,k,m,r} F_{i_1,k_1,m_1,r_1} e^{-(a-b)(r-m+i)T} b^{n_1} (a-b)^{n_2} \binom{-(r+k+1)}{n_2} \times$$



$$\begin{aligned}
 & \frac{e^{-(s+b)(r-m+i+i_1+r_1-m_1+1)T}}{(s+b)^{r+k+r_1+k_1+n_1+n_2+3}} \\
 & + y_2 z_1 \sum_{r=0}^{\infty} \sum_{m=0}^r \sum_{i=0}^m \sum_{k=0}^{\infty} \sum_{r_1=0}^{\infty} \sum_{m_1=0}^{r_1} \sum_{i_1=0}^{m_1+1} \sum_{k_1=0}^{\infty} \sum_{n_1=0}^{\infty} \sum_{n_2=0}^{\infty} (-1)^i \times \\
 & Q_{i,k,m,r} E_{i_1,k_1,m_1,r_1} e^{-(a-b)(r-m+i+1)T} b^{n_1} (a-b)^{n_2} \binom{-(r+k+1)}{n_2} \times \\
 & \frac{e^{-(s+b)(r-m+i+i_1+r_1-m_1+1)T}}{(s+b)^{r+k+r_1+k_1+n_1+n_2+3}} \\
 & + y_2 z_2 \sum_{r=0}^{\infty} \sum_{m=0}^r \sum_{i=0}^m \sum_{k=0}^{\infty} \sum_{r_1=0}^{\infty} \sum_{m_1=0}^{r_1} \sum_{i_1=0}^{m_1} \sum_{k_1=0}^{\infty} \sum_{n_1=0}^{\infty} \sum_{n_2=0}^{\infty} (-1)^i \times \\
 & Q_{i,k,m,r} F_{i_1,k_1,m_1,r_1} e^{-(a-b)(r-m+i+1)T} b^{n_1} (a-b)^{n_2} \binom{-(r+k+1)}{n_2} \times \\
 & \frac{e^{-(s+b)(r-m+i+i_1+r_1-m_1+2)T}}{(s+b)^{r+k+r_1+k_1+n_1+n_2+3}}, \tag{21}
 \end{aligned}$$

where

$$\begin{aligned}
 P_{i,k,m,r} &= \binom{m+1}{i} \binom{r}{m} \binom{-(r-m)}{k} y_3^m y_4^{r-m} (A-a)^k, \\
 Q_{i,k,m,r} &= \binom{m}{i} \binom{r}{m} \binom{-(r-m+1)}{k} y_3^m y_4^{r-m} (A-a)^k.
 \end{aligned}$$

By inverse Laplace transform, equation (21) gives

$$\begin{aligned}
 m_Z^{(2)}(t) &= e^{-bt} \left[ y_1 z_1 \sum_{r=0}^{\infty} \sum_{m=0}^r \sum_{i=0}^{m+1} \sum_{k=0}^{\infty} \sum_{r_1=0}^{\infty} \sum_{m_1=0}^{r_1} \sum_{i_1=0}^{m_1+1} \sum_{k_1=0}^{\infty} \sum_{n_1=0}^{\infty} \sum_{n_2=0}^{\infty} (-1)^i \times \right. \\
 & P_{i,k,m,r} E_{i_1,k_1,m_1,r_1} e^{-(a-b)(r-m+i)T} b^{n_1} (a-b)^{n_2} \times \\
 & H[t - (r-m+i+i_1+r_1-m_1)T] \times \\
 & \left. \binom{-(r+k+1)}{n_2} \frac{[t - (r-m+i+i_1+r_1-m_1)T]^{r+k+r_1+k_1+n_1+n_2+2}}{(r+k+r_1+k_1+n_1+n_2+2)!} \right. \\
 & + y_1 z_2 \sum_{r=0}^{\infty} \sum_{m=0}^r \sum_{i=0}^{m+1} \sum_{k=0}^{\infty} \sum_{r_1=0}^{\infty} \sum_{m_1=0}^{r_1} \sum_{i_1=0}^{m_1} \sum_{k_1=0}^{\infty} \sum_{n_1=0}^{\infty} \sum_{n_2=0}^{\infty} (-1)^i \times \\
 & P_{i,k,m,r} F_{i_1,k_1,m_1,r_1} e^{-(a-b)(r-m+i)T} b^{n_1} (a-b)^{n_2} \times \\
 & H[t - (r-m+i+i_1+r_1-m_1+1)T] \times \\
 & \left. \binom{-(r+k+1)}{n_2} \frac{[t - (r-m+i+i_1+r_1-m_1+1)T]^{r+k+r_1+k_1+n_1+n_2+2}}{(r+k+r_1+k_1+n_1+n_2+2)!} \right. \\
 & + y_2 z_1 \sum_{r=0}^{\infty} \sum_{m=0}^r \sum_{i=0}^m \sum_{k=0}^{\infty} \sum_{r_1=0}^{\infty} \sum_{m_1=0}^{r_1} \sum_{i_1=0}^{m_1+1} \sum_{k_1=0}^{\infty} \sum_{n_1=0}^{\infty} \sum_{n_2=0}^{\infty} (-1)^i \times \\
 & Q_{i,k,m,r} E_{i_1,k_1,m_1,r_1} e^{-(a-b)(r-m+i+1)T} b^{n_1} (a-b)^{n_2} \times \\
 & H[t - (r-m+i+i_1+r_1-m_1+1)T] \times \\
 & \left. \binom{-(r+k+1)}{n_2} \frac{[t - (r-m+i+i_1+r_1-m_1+1)T]^{r+k+r_1+k_1+n_1+n_2+2}}{(r+k+r_1+k_1+n_1+n_2+2)!} \right]
 \end{aligned}$$

$$\begin{aligned}
 &+y_2z_2 \sum_{r=0}^{\infty} \sum_{m=0}^r \sum_{i=0}^m \sum_{k=0}^{\infty} \sum_{r_1=0}^{\infty} \sum_{m_1=0}^{r_1} \sum_{i_1=0}^{m_1} \sum_{k_1=0}^{\infty} \sum_{n_1=0}^{\infty} \sum_{n_2=0}^{\infty} (-1)^i \times \\
 &Q_{i,k,m,r} F_{i_1,k_1,m_1,r_1} e^{-(a-b)(r-m+i+1)T} b^{n_1} (a-b)^{n_2} \times \\
 &H[t - (r - m + i + i_1 + r_1 - m_1 + 2)T] \times \\
 &\binom{-(r+k+1)}{n_2} \frac{[t - (r - m + i + i_1 + r_1 - m_1 + 2)T]^{r+k+r_1+k_1+n_1+n_2+2}}{(r+k+r_1+k_1+n_1+n_2+2)!} \Big]. \tag{22}
 \end{aligned}$$

Equations (20) and (22) provide the mean structure of the production of malignant cells in one-mutation model and two-mutation model respectively.

It is to be noted that the expressions for the means of cells are in closed form, and they are given as infinite series. These series have been obtained after invoking the convergence conditions in equations (14)- (18):

$$\begin{aligned}
 &\left| y_3 \left( \frac{1 - e^{-(s+a)T}}{s+a} \right) + y_4 \frac{e^{-(s+a)T}}{s+A} \right| < 1, \\
 &\left| z_3 \left( \frac{1 - e^{-(s+b)T}}{s+b} \right) + z_4 \frac{e^{-(s+b)T}}{s+B} \right| < 1.
 \end{aligned}$$

### 5. A NUMERICAL ILLUSTRATION

For the purpose of illustration, we assume  $T = 0.5$  and the following values for the other parameters of the stochastic model:

$$\begin{aligned}
 &l_{11} = 0.3, l_{12} = 0, d_1 = 0.5, l_{21} = 0, l_{22} = 0.5, d_2 = 0.5, \\
 &\alpha_{11} = 0.6, \alpha_{12} = 0, \mu_1 = 0.2, \alpha_{21} = 0, \alpha_{22} = 0.7, \mu_2 = 0.2.
 \end{aligned}$$

We have assumed that an intermediate cell has an higher rate of splitting into malignant cells when its age exceeds  $T$  and also there is perfect splitting in the cell-division process. That is,  $0.6 = \alpha_{11} < \alpha_{22} = 0.7$  and we have excluded cross-mutations ( $l_{12} = l_{21} = \alpha_{12} = \alpha_{21} = 0$ ). Then, equations (20) and (22) become

$$\begin{aligned}
 m_Z^{(1)}(t) = z_2 e^{-bt} &\left[ \sum_{r=0}^{\infty} \sum_{i=0}^r \sum_{k=0}^{\infty} \sum_{n=0}^{\infty} (-1)^i \binom{r}{i} z_3^r (b-B)^k b^n \times \right. \\
 &\left. \frac{[t - (i+1)T]^{r+k+n+1}}{(r+k+n+1)!} H[t - (i+1)T] \right], \tag{23}
 \end{aligned}$$

$$\begin{aligned}
 m_Z^{(2)}(t) = y_2 z_2 e^{-bt} &\sum_{r=0}^{\infty} \sum_{i=0}^r \sum_{k=0}^{\infty} \sum_{r_1=0}^{\infty} \sum_{i_1=0}^{r_1} \sum_{k_1=0}^{\infty} \sum_{n_1=0}^{\infty} \sum_{n_2=0}^{\infty} \left[ (-1)^i \binom{r}{i} \binom{r_1}{i_1} \times \right. \\
 &y_3^r (a-A)^k (-1)^{i_1} z_3^{r_1} (b-B)^{k_1} e^{-(a-b)(i+1)T} b^{n_1} (a-b)^{n_2} H[t - (i+i_1+2)T] \times \\
 &\left. \binom{-(r+k+1)}{n_2} \frac{[t - (i+i_1+2)T]^{r+k+r_1+k_1+n_1+n_2+2}}{(r+k+r_1+k_1+n_1+n_2+2)!} \right]. \tag{24}
 \end{aligned}$$

We have computed  $m_Z^{(1)}(t)$  with (23) for  $t$  varying from 0.0 to 5.0 and the variation is exhibited in Figure 1. This corresponds to one-mutation model.

When  $t = 1.4$ , we computed  $m_Z^{(1)}(t) = 0.9165$  and when  $t = 1.5$ , we computed  $m_Z^{(1)}(t) = 1.0063$ . Since the occurrence of first malignant cell leads to a certain tumor, we find that in the one-mutation model, for the given values of the parameters, the mean value of the

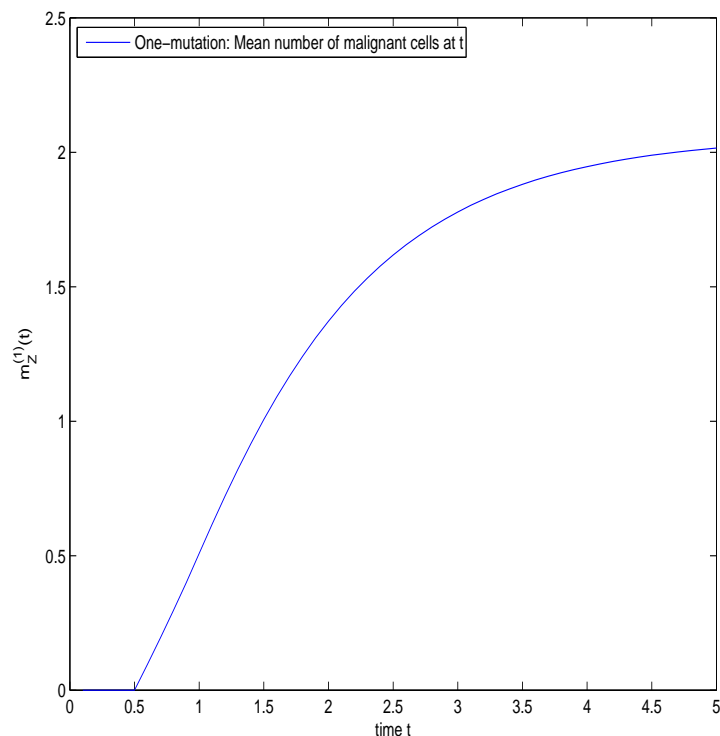


FIGURE 1. Graph of  $m_Z^{(1)}(t)$

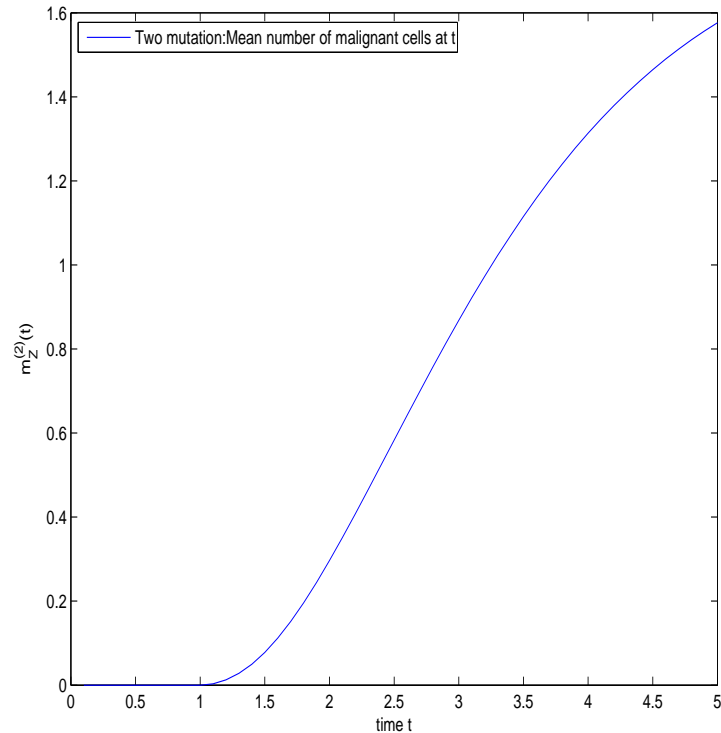
number of malignant cells crosses the threshold value 1 in the time interval (1.4, 1.5).

We have computed  $m_Z^{(2)}(t)$  with (24) for  $t$  varying from 0.0 to 5.0 and the variation is exhibited in Figure 2. This corresponds to two-mutation model.

When  $t = 3.2$ , we have computed  $m_Z^{(2)}(t) = 0.9727$  and when  $t = 3.3$ , we have computed  $m_Z^{(2)}(t) = 1.0222$ . Since the occurrence of first malignant cell leads to a certain tumor, we find that in the two-mutation model, for the given values of the parameters, the mean value of the number of malignant cells crosses the threshold value 1 in the time interval (3.2, 3.3). This justifies that in the two-mutation model, there is a more delay in the production of malignant cells than in one-mutation model.

## 6. CONCLUSION

We introduced age-dependence in the cell-division process and the dependence has affected the production of malignant cells. We found that the production of malignant cells in one-mutation model is faster than that in two-mutation model. We justified that the behaviour is attributed to the phase type mutation of intermediate cells. If we extend our model to multi-stage age-dependant models with three-stage, four-stage and then multiple-stages, then the production of malignant cells will be delayed in time. In the numerical illustration, we assumed that no cross-mutations could occur. Even if the cross-mutations are allowed to take place, these would further delay the production of malignant cells. The present model enhances the literature on multi-stage modeling of carcinogenesis and it opens a new-direction by considering age-dependent mutation.

FIGURE 2. Graph of  $m_Z^{(2)}(t)$ 

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