Stochastic Modeling of Inter & Intra Stage Dependent Cancer Growth under Chemotherapy through Trivariate Poisson Processes

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ABSTRACT. This study has proposed a Stochastic Model for cancer growth under chemotherapy with the assumptions of the growth, transition and loss parameters of different stages are inter and intra dependent. A trivariate Poisson process approach has been adopted for modeling the three stage cancer growth by considering the stages of cells in the tumor namely normal cell, mutant cell and malignant cell in the presence and absence of chemotherapy during time 't'. Stochastic differential equations were obtained and the three dimensional joint probability functions along with related statistical measures were derived. Model behavior was analysed through numerical data.

1. Introduction

The spread of cancer is more vigorous when a normal cell will transformed in to a mutant and further to a malignant cell. The growth, spread and loss processes of different types of cells are purely random and influenced by many known and unknown factors. The cell division and control mechanism of cancerous cells are out of the genetic instructions of any living body. Continuous proliferation of cells within each stage, transformation of cells from one stage to another stage leads to enormous growth within the limited membrane structures of a tissue may cause the formation of tumours. Development of secondary and invasion of cancerous cells through metastasis is again subject to many random issues and uncertainties. Usually the violation of genetic instruction of the cell will be initiated with conversion of a normal cell in to a typical and erratic behaved cell. Further, this erratic behaved/ mutant cell will have a faster growth of division as well as continuous and unending proliferation leads to formation of malignant cell. Hence, the cell division behaviour is varying from one stage to other stage.

Quantification of cancer growth through the mathematical models was initiated by Mayneord (1932). Tumor resistance to chemotherapy by Coldmann et al. (1983), effects of drug resistance in the presence of chemotherapy by Birkhead et al. (1984), chemotherapy of experimental tumors by Coldman et al. (1986), cancer progression and response of chemotherapy by Sandeep sanga et al. (2006), system of differential equations for the control of tumor cells growth by Costa et al. (1995), Phase-space analysis of tumor growth with an immune response and chemotherapy by De pillis et al. (2003), cancer cell growth with spontaneous mutation and proliferation, inactivation of allele genes and under chemotherapy by Tirupathi Rao et al. (2004a, 2004b, 2004c), cancer growth with and without chemotherapy using bi-variate Poisson process by Madhavi et al. (2011) are some significant contributions in modeling the cancer growth using mathematical and stochastic models.

Stochastic modeling on pathophysiology of cancer and its Biology is more appropriate to study the cancer growth and loss processes as it is influenced by many uncertain factors. This study is on stochastic modeling of cancer cell growth in three stages namely normal cell, mutant cell and malignant cell by using trivariate Poisson process in chemotherapy. The process of presence and absence of drug with indexed variables is introduced by assuming the growth of tumor during drug administration and drug vacations are complementary. This model is useful to study the growth of cancer cell as overall phenomena of chemotherapy.

Figure 1: Schematic Diagram for Cancer Growth Processes during Chemotherapy

2. Stochastic Model for Cancer Growth during Chemotherapy

A Stochastic model for three stage cancer cell growth in chemotherapy is developed with the following assumptions. 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' normal cells, 'm' mutant cells, 'k' malignant cells initially at time 't'. Let a, b, c, d, e, f, g, h assuming 0 and 1 when the patient is in drug presence and absence respectively.

Let λ_{ij} be the rate of growths; μ_{ij} be the rate of death of cells; δ_{ij} be the rate of transformation of cells from k to $k+1$ stage. where, 'i' be the stage of cells, $i=1,2,3$ for normal, mutant, malignant cells respectively; 'j' be the state of drug, $j=0,1$ (absence, presence); 'k' be the transformation of cells k to $k+1$ stage, $k=1,2$. All the parameters follow poisson processes and, let postulates of the model are.

Let $\{N(t), t \geq 0\}$, $\{M(t), t \geq 0\}$, $\{K(t), t \geq 0\}$ be individual stochastic processes of normal cell, mutant cell and malignant cell. Such that, $P\{N(t) = n\} = P_n(t)$, $P\{M(t) = m\} = P_m(t)$, $P\{K(t) = k\} = P_k(t)$ and let $\{N(t), M(t), K(t); t \geq 0\}$ be the tri-variate process such that processes will be $P\{(N(t), M(t), K(t)) = (n, m, k)\} = P_{n,m,k}(t)$. Let us define,

$$\begin{aligned}
 P_{n,u} &= P\{N(\Delta t) = u / N(t) = n\} \\
 &= n\{a\lambda_{11} + (1-a)\lambda_{10}\}\Delta t + o(\Delta t) \quad ; u=n+1 \\
 &= n\{f\mu_{11} + (1-f)\mu_{10}\}\Delta t + o(\Delta t) \quad ; u=n-1 \\
 &= 1 - \{n(\{a\lambda_{11} + (1-a)\lambda_{10}\} + \{f\mu_{11} + (1-f)\mu_{10}\})\Delta t + o(\Delta t)\} \quad ; u=n \\
 &= o(\Delta t)^2 \quad ; u=n \pm 2
 \end{aligned}$$

$$\begin{aligned}
 P_{m,v} &= P\{M(\Delta t) = v / M(t) = m\} \\
 &= m\{b\lambda_{21} + (1-b)\lambda_{20}\}\Delta t + o(\Delta t) \quad ; u=m+1 \\
 &= m\{g\mu_{21} + (1-g)\mu_{20}\}\Delta t + o(\Delta t) \quad ; u=m-1 \\
 &= 1 - \{m(\{b\lambda_{21} + (1-b)\lambda_{20}\} + \{g\mu_{21} + (1-g)\mu_{20}\})\Delta t + o(\Delta t)\} \quad ; u=m \\
 &= o(\Delta t)^2 \quad ; u=m \pm 2
 \end{aligned}$$

$$\begin{aligned}
P_{k,w} &= P\{K(\Delta t) = w/K(t) = k\} \\
&= k\{c\lambda_{31} + (1-c)\lambda_{30}\}\Delta t + o(\Delta t) \quad ; u=k+1 \\
&= k\{h\mu_{31} + (1-h)\mu_{30}\}\Delta t + o(\Delta t) \quad ; u=k-1 \\
&= 1 - \{k\{c\lambda_{31} + (1-c)\lambda_{30}\} + \{h\mu_{31} + (1-h)\mu_{30}\}\}\Delta t + o(\Delta t) \quad ; u=k \\
&= o(\Delta t)^2 \quad ; u=k \pm 2 \\
P_{nu,mv,kw} &= P\{[(N(\Delta t), M(\Delta t), K(\Delta t)) = (u, v, w)] / [(N(\Delta t), M(\Delta t), K(\Delta t)) = (n, m, k)]\} \\
&= n\{a\lambda_{11} + (1-a)\lambda_{10}\}\Delta t + o(\Delta t) \quad ; u=n+1, v=m, w=k \\
&= n\{f\mu_{11} + (1-f)\mu_{10}\}\Delta t + o(\Delta t) \quad ; u=n-1, v=m, w=k \\
&= m\{b\lambda_{21} + (1-b)\lambda_{20}\}\Delta t + o(\Delta t) \quad ; u=n, v=m+1, w=k \\
&= m\{g\mu_{21} + (1-g)\mu_{20}\}\Delta t + o(\Delta t) \quad ; u=n, v=m-1, w=k \\
&= k\{c\lambda_{31} + (1-c)\lambda_{30}\}\Delta t + o(\Delta t) \quad ; u=n, v=m, w=k+1 \\
&= k\{h\mu_{31} + (1-h)\mu_{30}\}\Delta t + o(\Delta t) \quad ; u=n, v=m, w=k-1 \\
&= n\{d\delta_{11} + (1-d)\delta_{10}\}\Delta t + o(\Delta t) \quad ; u=n, v=m+1, w=k \\
&= m\{e\delta_{21} + (1-e)\delta_{20}\}\Delta t + o(\Delta t) \quad ; u=n, v=m, w=k+1 \\
&= 1 - \{[n\{a\lambda_{11} + (1-a)\lambda_{10}\} + \{f\mu_{11} + (1-f)\mu_{10}\} + \{d\delta_{11} + (1-d)\delta_{10}\}] \\
&\quad + m\{b\lambda_{21} + (1-b)\lambda_{20}\} + \{g\mu_{21} + (1-g)\mu_{20}\} + \{e\delta_{21} + (1-e)\delta_{20}\}] \\
&\quad + k\{c\lambda_{31} + (1-c)\lambda_{30}\} + \{h\mu_{31} + (1-h)\mu_{30}\}]\Delta t + o(\Delta t)\} \\
&\quad ; u=n, v=m, w=k \\
&= o(\Delta t)^2 \quad ; u=n \pm 2, v=m \pm 2, w=k \pm 2
\end{aligned}$$

The probability of occurrence of other than the above events during an infinitesimal interval of time Δt is $o(\Delta t)^2$. Let $P_{n,m,k}(t)$ be the joint probability of existence of 'n' normal cells, 'm' mutant cells and 'k' malignant cells in a tumor during chemotherapy per unit time 't'. Then differential-difference equations of the model are:

$$\begin{aligned}
P'_{n,m,k}(t) &= -[n\{a\lambda_{11} + (1-a)\lambda_{10}\} + \{d\delta_{11} + (1-d)\delta_{10}\} + \{f\mu_{11} + (1-f)\mu_{10}\}] + m\{b\lambda_{21} \\
&\quad + (1-b)\lambda_{20}\} + \{e\delta_{21} + (1-e)\delta_{20}\} + \{g\mu_{21} + (1-g)\mu_{20}\} + k\{c\lambda_{31} + (1-c)\lambda_{30}\} \\
&\quad + \{h\mu_{31} + (1-h)\mu_{30}\}]P_{n,m,k}(t) + [(n-1)\{a\lambda_{11} + (1-a)\lambda_{10}\}]P_{n-1,m,k}(t) \\
&\quad + [(n+1)\{f\mu_{11} + (1-f)\mu_{10}\}]P_{n+1,m,k}(t) + [(m-1)\{b\lambda_{21} + (1-b)\lambda_{20}\}]P_{n,m-1,k}(t) \\
&\quad + [(m+1)\{g\mu_{21} + (1-g)\mu_{20}\}]P_{n,m+1,k}(t) + [(k-1)\{c\lambda_{31} + (1-c)\lambda_{30}\}]P_{n,m,k-1}(t) \\
&\quad + [(k+1)\{h\mu_{31} + (1-h)\mu_{30}\}]P_{n,m,k+1}(t) + [(n+1)\{d\delta_{11} + (1-d)\delta_{10}\}]P_{n+1,m-1,k}(t) \\
&\quad + [(m+1)\{e\delta_{21} + (1-e)\delta_{20}\}]P_{n,m+1,k-1}(t)
\end{aligned} \tag{2.1}$$

For $n, m, k \geq 1$

$$\begin{aligned}
P'_{1,0,0}(t) &= -\{f\mu_{11} + (1-f)\mu_{10}\}P_{1,0,0}(t) + 2\{f\mu_{11} + (1-f)\mu_{10}\}P_{2,0,0}(t) \\
&\quad + \{g\mu_{21} + (1-g)\mu_{20}\}P_{1,1,0}(t) + \{h\mu_{31} + (1-h)\mu_{30}\}P_{1,0,1}(t)
\end{aligned} \tag{2.2}$$

$$\begin{aligned}
P'_{0,1,0}(t) &= -\{g\mu_{21} + (1-g)\mu_{20}\}P_{0,1,0}(t) + 2\{g\mu_{21} + (1-g)\mu_{20}\}P_{0,2,0}(t) \\
&\quad + \{f\mu_{11} + (1-f)\mu_{10}\}P_{1,1,0}(t) + \{h\mu_{31} + (1-h)\mu_{30}\}P_{0,1,1}(t)
\end{aligned} \tag{2.3}$$

$$\begin{aligned}
P'_{0,0,1}(t) &= -\{h\mu_{31} + (1-h)\mu_{30}\}P_{0,0,1}(t) + 2\{h\mu_{31} + (1-h)\mu_{30}\}P_{0,0,2}(t) \\
&\quad + \{g\mu_{21} + (1-g)\mu_{20}\}P_{0,1,1}(t) + \{f\mu_{11} + (1-f)\mu_{10}\}P_{1,0,1}(t)
\end{aligned} \tag{2.4}$$

$$\begin{aligned} P'_{1,1,0}(t) = & -(\{f\mu_{11} + (1-f)\mu_{10}\} + \{g\mu_{21} + (1-g)\mu_{20}\})P_{1,1,0}(t) + 2\{g\mu_{21} + (1-g)\mu_{20}\}P_{1,2,0}(t) \\ & + 2\{f\mu_{11} + (1-f)\mu_{10}\}P_{2,1,0}(t) + \{h\mu_{31} + (1-h)\mu_{30}\}P_{1,1,1}(t) + 2\{d\delta_{11} + (1-d)\delta_{10}\}P_{2,0,0}(t) \end{aligned} \quad (2.5)$$

$$\begin{aligned} P'_{1,0,1}(t) = & -(\{f\mu_{11} + (1-f)\mu_{10}\} + \{h\mu_{31} + (1-h)\mu_{30}\})P_{1,0,1}(t) + \{g\mu_{21} + (1-g)\mu_{20}\}P_{1,1,1}(t) \\ & + 2\{f\mu_{11} + (1-f)\mu_{10}\}P_{2,0,1}(t) + 2\{h\mu_{31} + (1-h)\mu_{30}\}P_{1,0,2}(t) + \{e\delta_{21} + (1-e)\delta_{20}\}P_{1,1,0}(t) \end{aligned} \quad (2.6)$$

$$\begin{aligned} P'_{0,1,1}(t) = & -(\{g\mu_{21} + (1-g)\mu_{20}\} + \{h\mu_{31} + (1-h)\mu_{30}\})P_{0,1,1}(t) + \{f\mu_{11} + (1-f)\mu_{10}\}P_{1,1,1}(t) \\ & + 2\{g\mu_{21} + (1-g)\mu_{20}\}P_{0,2,1}(t) + 2\{h\mu_{31} + (1-h)\mu_{30}\}P_{0,1,2}(t) + 2\{e\delta_{21} + (1-e)\delta_{20}\}P_{0,2,0}(t) \end{aligned} \quad (2.7)$$

$$\begin{aligned} P'_{0,0,0}(t) = & \{h\mu_{31} + (1-h)\mu_{30}\}P_{0,0,1}(t) + \{g\mu_{21} + (1-g)\mu_{20}\}P_{0,1,0}(t) \\ & + \{f\mu_{11} + (1-f)\mu_{10}\}P_{1,0,0}(t) \end{aligned} \quad (2.8)$$

With the initial condition

$$P_{N_0, M_0, K_0}(t) = 1, P_{i,j,l}(0) = 0 \quad \forall \quad i \neq N_0, j \neq M_0, l \neq K_0$$

Where N_0 normal cells, M_0 mutant cells and K_0 malignant cells in the tumor under chemotherapy. Let $P(x, y, z; t)$ be the joint probability generating function of $P_{n,m,k}(t)$;

$$P(x, y, z; t) = \sum_{k=0}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} x^n y^m z^k P_{n,m,k}(t)$$

Where

(2.9)

Multiplying the equations (2.1) to (2.8) with $x^n y^m z^k$ and summing overall n, m and k, we obtain

$$\begin{aligned} \sum_{k=0}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} x^n y^m z^k P'_{n,m,k}(t) = & \sum_{k=0}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} -[n(\{a\lambda_{11} + (1-a)\lambda_{10}\} + \{d\delta_{11} + (1-d)\delta_{10}\} + \{f\mu_{11} \\ & + (1-f)\mu_{10}\})]x^n y^m z^k P_{n,m,k}(t) + m(\{b\lambda_{21} + (1-b)\lambda_{20}\} + \{e\delta_{21} \\ & + (1-e)\delta_{20}\} + \{g\mu_{21} + (1-g)\mu_{20}\}) + k(\{c\lambda_{31} + (1-c)\lambda_{30}\} \\ & + \{h\mu_{31} + (1-h)\mu_{30}\})]x^n y^m z^k P_{n,m,k}(t) + \sum_{k=0}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} [(n-1) \cdot \{a\lambda_{11} \\ & + (1-a)\lambda_{10}\}]x^n y^m z^k P_{n-1,m,k}(t) + \sum_{k=0}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} [(n+1) \cdot \{f\mu_{11} \\ & + (1-f)\mu_{10}\}]x^n y^m z^k P_{n+1,m,k}(t) + \sum_{k=0}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} [(m-1) \cdot \{b\lambda_{21} \\ & + (1-b)\lambda_{20}\}]x^n y^m z^k P_{n,m-1,k}(t) + \sum_{k=0}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} [(m+1) \cdot \{g\mu_{21} \\ & + (1-g)\mu_{20}\}]x^n y^m z^k P_{n,m+1,k}(t) + \sum_{k=0}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} [(k-1) \cdot \{c\lambda_{31} \\ & + (1-c)\lambda_{30}\}]x^n y^m z^k P_{n,m,k-1}(t) + \sum_{k=0}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} [(k+1) \cdot \{h\mu_{31} \\ & + (1-h)\mu_{30}\}]x^n y^m z^k P_{n,m,k+1}(t) + \sum_{k=0}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} [(n+1) \cdot \{d\delta_{11} \\ & + (1-d)\delta_{10}\}]x^n y^m z^k P_{n+1,m-1,k}(t) + \sum_{k=0}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} [(m+1) \cdot \{e\delta_{21} \\ & + (1-e)\delta_{20}\}]x^n y^m z^k P_{n,m+1,k-1}(t) \end{aligned} \quad (2.10)$$

Simplifying and rearranging the terms in the equation (2.10) we get,

$$\begin{aligned} \frac{\partial}{\partial t} p(x, y, z; t) = & [-\{a\lambda_{11} + (1-a)\lambda_{10}\} + \{d\delta_{11} + (1-d)\delta_{10}\} + \{f\mu_{11} + (1-f)\mu_{10}\}]x \\ & + \{a\lambda_{11} + (1-a)\lambda_{10}\}x^2 + \{f\mu_{11} + (1-f)\mu_{10}\} + \{d\delta_{11} + (1-d)\delta_{10}\}y] \\ & \frac{\partial}{\partial x} p(x, y, z; t) + [-\{b\lambda_{21} + (1-b)\lambda_{20}\} + \{e\delta_{21} + (1-e)\delta_{20}\} + \{g\mu_{21} \\ & + (1-g)\mu_{20}\}]y + \{b\lambda_{21} + (1-b)\lambda_{20}\}y^2 + \{g\mu_{21} + (1-g)\mu_{20}\} + \{e\delta_{21} \\ & + (1-e)\delta_{20}\}z] \frac{\partial}{\partial y} p(x, y, z; t) + [-\{c\lambda_{31} + (1-c)\lambda_{30}\} + \{h\mu_{31} + (1-h)\mu_{30}\}]z \\ & + \{c\lambda_{31} + (1-c)\lambda_{30}\}z^2 + \{h\mu_{31} + (1-h)\mu_{30}\}] \frac{\partial}{\partial z} p(x, y, z; t) \end{aligned} \quad (2.11)$$

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 $c(u, v, w; t)$ as the joint cumulant generating function of $P_{n,m,k}(t)$, equation. (2.11) becomes

$$\begin{aligned} \frac{\partial}{\partial t} c(x, y, z; t) = & [-\{a\lambda_{11} + (1-a)\lambda_{10}\} + \{d\delta_{11} + (1-d)\delta_{10}\} + \{f\mu_{11} + (1-f)\mu_{10}\}] + \{a\lambda_{11} \\ & + (1-a)\lambda_{10}\}e^u + \{f\mu_{11} + (1-f)\mu_{10}\}e^{-u} + \{d\delta_{11} + (1-d)\delta_{10}\}e^{v-u}] \frac{\partial}{\partial u} c(x, y, z; t) \\ & + [-\{b\lambda_{21} + (1-b)\lambda_{20}\} + \{e\delta_{21} + (1-e)\delta_{20}\} + \{g\mu_{21} + (1-g)\mu_{20}\}] + \{b\lambda_{21} \\ & + (1-b)\lambda_{20}\}e^v + \{g\mu_{21} + (1-g)\mu_{20}\}e^{-v} + \{e\delta_{21} + (1-e)\delta_{20}\}e^{w-v}] \frac{\partial}{\partial v} c(x, y, z; t) \\ & + [-\{c\lambda_{31} + (1-c)\lambda_{30}\} + \{h\mu_{31} + (1-h)\mu_{30}\}] + \{c\lambda_{31} + (1-c)\lambda_{30}\}e^w + \{h\mu_{31} \\ & + (1-h)\mu_{30}\}e^{-w}] \frac{\partial}{\partial w} c(x, y, z; t) \end{aligned} \quad (2.12)$$

3. Differential Equations and Statistical Measures

Let $m_{i,j,l}(t)$ denote the moments of order (i, j, l) of normal cells, mutant cells, malignant cells at time 't'.

Then the differential equation governing $m_{i,j,l}(t)$ are obtain as

$$\frac{\partial}{\partial t} m_{1,0,0}(t) = (\{a\lambda_{11} + (1-a)\lambda_{10}\} - \{f\mu_{11} + (1-f)\mu_{10}\} - \{e\delta_{21} + (1-e)\delta_{20}\})m_{1,0,0}(t) \quad (3.1)$$

$$\begin{aligned} \frac{\partial}{\partial t} m_{0,1,0}(t) = & \{d\delta_{11} + (1-d)\delta_{10}\}m_{1,0,0}(t) + (\{b\lambda_{21} + (1-b)\lambda_{20}\} - \{g\mu_{21} + (1-g)\mu_{20}\} \\ & - \{e\delta_{21} + (1-e)\delta_{20}\})m_{0,1,0}(t) \end{aligned} \quad (3.2)$$

$$\frac{\partial}{\partial t} m_{0,0,1}(t) = \{e\delta_{21} + (1-e)\delta_{20}\}m_{0,1,0}(t) + (\{c\lambda_{31} + (1-c)\lambda_{30}\} - \{h\mu_{31} + (1-h)\mu_{30}\})m_{0,0,1}(t) \quad (3.3)$$

$$\begin{aligned} \frac{\partial}{\partial t} m_{1,1,0}(t) = & -\{d\delta_{11} + (1-d)\delta_{10}\}m_{1,0,0}(t) + \{d\delta_{11} + (1-d)\delta_{10}\}m_{2,0,0}(t) + (\{a\lambda_{11} + (1-a)\lambda_{10}\} \\ & - \{f\mu_{11} + (1-f)\mu_{10}\} - \{d\delta_{11} + (1-d)\delta_{10}\})m_{1,1,0}(t) + (\{b\lambda_{21} + (1-b)\lambda_{20}\} - \{g\mu_{21} \\ & + (1-g)\mu_{20}\} - \{e\delta_{21} + (1-e)\delta_{20}\})m_{1,1,0}(t) \end{aligned} \quad (3.4)$$

$$\begin{aligned} \frac{\partial}{\partial t} m_{1,0,1}(t) = & (\{a\lambda_{11} + (1-a)\lambda_{10}\} - \{f\mu_{11} + (1-f)\mu_{10}\} - \{d\delta_{11} + (1-d)\delta_{10}\})m_{1,0,1}(t) \\ & + (\{c\lambda_{31} + (1-c)\lambda_{30}\} - \{h\mu_{31} + (1-h)\mu_{30}\})m_{1,0,1}(t) + \{e\delta_{21} + (1-e)\delta_{20}\}m_{1,1,0}(t) \end{aligned} \quad (3.5)$$

$$\begin{aligned} \frac{\partial}{\partial t} m_{0,1,1}(t) = & \{d\delta_{11} + (1-d)\delta_{10}\}m_{1,0,1}(t) - \{e\delta_{21} + (1-e)\delta_{20}\}m_{0,1,0}(t) + \{e\delta_{21} + (1-e)\delta_{20}\}m_{0,2,0}(t) \\ & + (\{b\lambda_{21} + (1-b)\lambda_{20}\} - \{g\mu_{21} + (1-g)\mu_{20}\} - \{e\delta_{21} + (1-e)\delta_{20}\})m_{0,1,1}(t) + (\{c\lambda_{31} \\ & + (1-c)\lambda_{30}\} - \{h\mu_{31} + (1-h)\mu_{30}\})m_{0,1,1}(t) \end{aligned} \quad (3.6)$$

$$\begin{aligned} \frac{\partial}{\partial t} m_{2,0,0}(t) = & (\{a\lambda_{11} + (1-a)\lambda_{10}\} + \{d\delta_{11} + (1-d)\delta_{10}\} + \{f\mu_{11} + (1-f)\mu_{10}\})m_{1,0,0}(t) \\ & + 2(\{a\lambda_{11} + (1-a)\lambda_{10}\} - \{f\mu_{11} + (1-f)\mu_{10}\} - \{d\delta_{11} + (1-d)\delta_{10}\})m_{2,0,0}(t) \end{aligned} \quad (3.7)$$

$$\begin{aligned} \frac{\partial}{\partial t} m_{0,2,0}(t) = & \{d\delta_{11} + (1-d)\delta_{10}\}m_{1,0,0}(t) + 2\{d\delta_{11} + (1-d)\delta_{10}\}m_{1,1,0}(t) + (\{b\lambda_{21} + (1-b)\lambda_{20}\} \\ & + \{g\mu_{21} + (1-g)\mu_{20}\} + \{e\delta_{21} + (1-e)\delta_{20}\})m_{0,1,0}(t) + 2(\{b\lambda_{21} + (1-b)\lambda_{20}\} - \{g\mu_{21} \\ & + (1-g)\mu_{20}\} - \{e\delta_{21} + (1-e)\delta_{20}\})m_{0,2,0}(t) \end{aligned} \quad (3.8)$$

$$\begin{aligned} \frac{\partial}{\partial t} m_{0,0,2}(t) = & \{e\delta_{21} + (1-e)\delta_{20}\}m_{0,1,0}(t) + 2\{e\delta_{21} + (1-e)\delta_{20}\}m_{0,1,1}(t) + (\{c\lambda_{31} + (1-c)\lambda_{30}\} \\ & + \{h\mu_{31} + (1-h)\mu_{30}\})m_{0,0,1}(t) + 2(\{c\lambda_{31} + (1-c)\lambda_{30}\} - \{h\mu_{31} + (1-h)\mu_{30}\})m_{0,0,2}(t) \end{aligned} \quad (3.9)$$

Expected number of normal cells at time 't' is

$$m_{1,0,0}(t) = N_0 \cdot e^{At} \quad (3.10)$$

Expected number of mutant cells at time 't' is

$$m_{0,1,0}(t) = \frac{\{d\delta_{11} + (1-d)\delta_{10}\}N_0}{(A-B)}[e^{At} - e^{Bt}] + M_0 e^{Bt} \quad (3.11)$$

Expected number of malignant cells during time 't' is

$$m_{0,0,1}(t) = D e^{Ct} \left(\frac{e^{(A-C)t}}{(A-C)} - \frac{e^{(B-C)t}}{(B-C)} \right) + \frac{\{e\delta_{21} + (1-e)\delta_{20}\}M_0}{(B-C)} e^{Bt} + E \cdot e^{Ct} \quad (3.12)$$

Variance of number of normal cells at time 't' is

$$m_{2,0,0}(t) = \frac{N_0 H}{A} [e^{2At} - e^{At}] \quad (3.13)$$

Variance of number of mutant cells at time 't' is

$$m_{0,2,0}(t) = D_0 \cdot e^{At} + E_0 \cdot e^{Bt} + F_0 \cdot e^{2At} - G_0 \cdot e^{(A+B)t} + H_0 \cdot e^{2Bt} \quad (3.14)$$

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

$$\begin{aligned} m_{0,0,2}(t) = & \frac{R_1 e^{At}}{(A-2C)} + \frac{R_2 e^{Bt}}{(B-2C)} + 2\delta_2 \left\{ \frac{A_2 e^{2At}}{2(A-C)} + \frac{A_4 e^{2Bt}}{2(B-C)} + \frac{A_5 e^{(B-C)t}}{(B-3C)} - \frac{A_6 e^{(A+C)t}}{(A-C)} \right. \\ & \left. - \frac{\delta_2 G_0 e^{(A+B)t}}{(A+B-2C)} - \frac{J_0 e^{(B+C)t}}{(B-C)} \right\} - \frac{P E e^{Ct}}{C} - S_0 \cdot e^{2Ct} \end{aligned} \quad (3.15)$$

Covariance of number of normal and mutant cells at time 't' is

$$m_{1,1,0}(t) = \frac{\{d\delta_{11} + (1-d)\delta_{10}\}N_0H}{A(A-B)}e^{2At} + \frac{\{d\delta_{11} + (1-d)\delta_{10}\}N_0}{B}\left(1 + \frac{H}{A}\right)e^{At} - I.e^{(A+B)t} \quad (3.16)$$

Covariance of number of mutant and malignant cell at time 't' is

$$m_{0,1,1}(t) = A_1.e^{2At} + A_2.e^{At} - A_3.e^{Bt} + A_4.e^{2Bt} + A_5.e^{(B-C)t} - A_6.e^{(A+C)t} \\ - \delta_2 G_0.e^{(A+B)t} - J_0.e^{(B+C)t} \quad (3.17)$$

Covariance of number of normal and malignant cells at time 't' is

$$m_{1,0,1}(t) = A_0.e^{2At} - B_0.e^{At} - C_0.e^{(B-C)t} + I_0.e^{(A+C)t} \quad (3.18)$$

where

$$A = (\{a\lambda_{11} + (1-a)\lambda_{10}\} - \{f\mu_{11} + (1-f)\mu_{10}\} - \{d\delta_{11} + (1-d)\delta_{10}\}) ;$$

$$B = (\{b\lambda_{21} + (1-b)\lambda_{20}\} - \{g\mu_{21} + (1-g)\mu_{20}\} - \{e\delta_{21} + (1-e)\delta_{20}\}) ;$$

$$C = (\{c\lambda_{31} + (1-c)\lambda_{30}\} - \{h\mu_{31} + (1-h)\mu_{30}\}) ; D = \frac{\{d\delta_{11} + (1-d)\delta_{10}\}\{e\delta_{21} + (1-e)\delta_{20}\}}{A-B}N_0 ;$$

$$E = K_0 \frac{D(B-A)}{(A-C)(B-C)} + \frac{M_0}{(B-C)}\{e\delta_{21} + (1-e)\delta_{20}\} ;$$

$$H = (\{a\lambda_{11} + (1-a)\lambda_{10}\} + \{f\mu_{11} + (1-f)\mu_{10}\} + \{d\delta_{11} + (1-d)\delta_{10}\}) ;$$

$$I = \frac{\{d\delta_{11} + (1-d)\delta_{10}\}N_0H}{A(A-B)} + \frac{\{d\delta_{11} + (1-d)\delta_{10}\}N_0}{B}\left(1 + \frac{H}{A}\right) ;$$

$$J = (\{b\lambda_{21} + (1-b)\lambda_{20}\} + \{g\mu_{21} + (1-g)\mu_{20}\} + \{e\delta_{21} + (1-e)\delta_{20}\}) ;$$

$$D_0 = \frac{\{d\delta_{11} + (1-d)\delta_{10}\}N_0}{(A-2B)} + \frac{2\{d\delta_{11} + (1-d)\delta_{10}\}^2N_0}{B(A-2B)} + \frac{J\{d\delta_{11} + (1-d)\delta_{10}\}N_0}{(A-B)(A-2B)} ;$$

$$E_0 = \frac{J\{d\delta_{11} + (1-d)\delta_{10}\}N_0}{B(A-B)} - \frac{M_0}{B} ; F_0 = \frac{2\{d\delta_{11} + (1-d)\delta_{10}\}^2N_0H}{2A(A-B)^2}$$

$$; G_0 = \frac{I}{(A-B)} H_0 = G_0 - D_0 - E_0 - F_0 ;$$

$$A_0 = \frac{\{d\delta_{11} + (1-d)\delta_{10}\}N_0H}{A(A-B)(A-C)} ;$$

$$B_0 = \frac{\{d\delta_{11} + (1-d)\delta_{10}\}N_0}{BC}\left(1 + \frac{H}{A}\right) C_0 = \frac{I}{(B-C)} ;$$

$$A_1 = \frac{\{d\delta_{11} + (1-d)\delta_{10}\}A_0 + \{e\delta_{21} + (1-e)\delta_{20}\}F_0}{2A-B-C}$$

$$A_2 = \frac{\{e\delta_{21} + (1-e)\delta_{20}\}D_0 - \{d\delta_{11} + (1-d)\delta_{10}\}B_0 - \frac{\{d\delta_{11} + (1-d)\delta_{10}\}N_0}{A-B}}{A-B-C} ;$$

$$A_3 = \frac{\{e\delta_{21} + (1-e)\delta_{20}\}E_0 - M_0 + \frac{\{d\delta_{11} + (1-d)\delta_{10}\}N_0}{A-B}}{C} ; A_4 = \frac{\{d\delta_{11} + (1-d)\delta_{10}\}H_0}{B-C}$$

$$A_5 = \frac{\{d\delta_{11} + (1-d)\delta_{10}\}C_0}{2C} ; A_6 = \frac{\{d\delta_{11} + (1-d)\delta_{10}\}I_0}{A-B}$$

$$; P = (\{c\lambda_{31} + (1-c)\lambda_{30}\} + \{h\mu_{31} + (1-h)\mu_{30}\}) ;$$

$$\begin{aligned}
R_1 &= \frac{\{d\delta_{11} + (1-d)\delta_{10}\} \{e\delta_{21} + (1-e)\delta_{20}\} N_0}{A-B} + 2A_2 \{e\delta_{21} + (1-e)\delta_{20}\} + \frac{PD}{(A-C)} \\
R_2 &= \delta_2 M_0 - \frac{\{d\delta_{11} + (1-d)\delta_{10}\} \{e\delta_{21} + (1-e)\delta_{20}\} M_0 N_0}{(A-B)} \\
&\quad + \frac{P\{e\delta_{21} + (1-e)\delta_{20}\} M_0}{(B-C)} - \frac{PD}{(B-C)} \\
S_0 &= \frac{R_1}{(A-2C)} + \frac{R_2}{(B-2C)} + 2\{e\delta_{21} + (1-e)\delta_{20}\} \left\{ \frac{A_2}{2(A-C)} + \frac{A_4}{2(B-C)} + \frac{A_5}{(B-3C)} \right. \\
&\quad \left. - \frac{A_6}{(A-C)} - \frac{\{e\delta_{21} + (1-e)\delta_{20}\} G_0}{(A+B-2C)} - \frac{J_0}{(B-C)} \right\} - \frac{PE}{C} \\
I_0 &= \frac{\{d\delta_{11} + (1-d)\delta_{10}\} N_0}{BC} \left(1 + \frac{H}{A} \right) + \frac{I}{(B-C)} - \frac{\{d\delta_{11} + (1-d)\delta_{10}\} N_0 H}{A(A-B)(A-C)} \\
J_0 &= \frac{\{d\delta_{11} + (1-d)\delta_{10}\} A_0 + \{e\delta_{21} + (1-e)\delta_{20}\} F_0}{(2A-B-C)} \\
&\quad + \frac{\{e\delta_{21} + (1-e)\delta_{20}\} D_0 - \{d\delta_{11} + (1-d)\delta_{10}\} B_0 - \left(\frac{\{d\delta_{11} + (1-d)\delta_{10}\} N_0}{(A-B)} \right)}{(A-B-C)} \\
&\quad - \frac{\{e\delta_{21} + (1-e)\delta_{20}\} \left(E_0 - M_0 + \frac{\{d\delta_{11} + (1-d)\delta_{10}\} N_0}{(A-B)} \right)}{C} \\
&\quad + \frac{\{d\delta_{11} + (1-d)\delta_{10}\} N_0}{(B-C)} + \frac{\{d\delta_{11} + (1-d)\delta_{10}\} C_0}{2C} - \frac{\{d\delta_{11} + (1-d)\delta_{10}\} I_0}{(A-B)} \\
&\quad - \{e\delta_{21} + (1-e)\delta_{20}\} G_0
\end{aligned}$$

4. Numerical Illustration and sensitivity analysis

In order to understand the model behavior on more detailed way, a simulated data set based were obtained. From equations (3.10), (3.11), (3.12), (3.13), (3.14), (3.15), (3.16), (3.17) and (3.18) the values of $m_{1,0,0}(t), m_{0,1,0}(t), m_{0,0,1}(t), m_{1,1,0}(t), m_{1,0,1}(t), m_{0,1,1}(t), m_{2,0,0}(t), m_{0,2,0}(t)$ and $m_{0,0,2}(t)$ are computed and presented in tables (4.1), (4.2), (4.3) and (4.4).

The changing patterns of statistical measures with respect to the study parameters are presented in table 4.1 and the following findings are observed.

- $m_{100}, m_{010},$ and $m_{001}; m_{110}, m_{101}$ and $m_{011}; m_{200}, m_{020}$ and m_{002} are increasing with λ_{11} when all other parameters are constants.
- m_{100} is invariant, m_{010} and m_{001} are increasing; m_{110}, m_{101} and m_{011} are increasing; m_{200} is invariant, m_{020} and m_{002} are increasing with λ_{21} when all other parameters are constants.
- m_{100}, m_{010} are invariant, m_{001} is increasing; m_{110} is invariant, m_{101} is increasing function and m_{011} is decreasing function; m_{200}, m_{020} are invariant and m_{002} is decreasing with λ_{31} when all other parameters are constants.
- m_{100}, m_{010} are decreasing and m_{001} is increasing; m_{110}, m_{101} are decreasing and m_{011} is increasing; m_{200}, m_{002} are decreasing and m_{020} is increasing with δ_{11} when all other parameters are constants.

- m_{100} is invariant, m_{010} is decreasing and m_{001} is increasing; m_{110} , m_{101} and m_{011} are decreasing; m_{200} is invariant, m_{020} and m_{002} are decreasing with δ_{21} when all other parameters are constants.
- m_{100} , m_{010} , and m_{001} are increasing; m_{110} , m_{101} and m_{011} are increasing; m_{200} , m_{020} , and m_{002} are increasing with time t when all other parameters are constants.

The changing patterns of statistical measures with respect to the study parameters are presented in table 4.2 and the following findings are observed.

- m_{100} , m_{010} and m_{001} are decreasing; m_{110} , m_{101} and m_{011} are decreasing; m_{200} , m_{020} and m_{002} are decreasing with μ_{11} when all other parameters are constants.
- m_{100} is invariant, m_{010} and m_{001} are decreasing; m_{110} , m_{101} and m_{011} are decreasing; m_{200} is invariant, m_{020} and m_{002} are decreasing with μ_{21} when all other parameters are constants.
- m_{100} , m_{010} are invariant and m_{001} is decreasing; m_{110} is invariant, m_{101} is decreasing and m_{011} is increasing; m_{200} , m_{020} are invariant and m_{002} is increasing with μ_{31} when all other parameters are constants.
- m_{100} , m_{010} and m_{001} are increasing; m_{110} , m_{101} and m_{011} are increasing; m_{200} , m_{020} and m_{002} are increasing with N_0 when all other parameters are constants.
- m_{100} is invariant, m_{010} and m_{001} are increasing; m_{110} , m_{101} , and m_{011} are invariant; m_{200} , m_{020} are invariant and m_{002} is decreasing with M_0 when all other parameters are constants.
- m_{100} , m_{010} are invariant and m_{001} is increasing; m_{110} , m_{101} and m_{011} are invariant; m_{200} , m_{020} and m_{002} are invariant with K_0 when all other parameters are constants.

The changing patterns of statistical measures with respect to the study parameters are presented in table 4.3 and the following findings are observed.

- m_{100} , m_{010} and m_{001} are increasing; m_{110} is increasing, m_{101} and m_{011} are negative & increasing; m_{200} , m_{020} and m_{002} are increasing with λ_{10} when all other parameters are constants.
- m_{100} is invariant and m_{010} , m_{001} are increasing; m_{110} , m_{011} are decreasing and m_{101} is increasing; m_{200} is invariant, m_{020} is increasing and m_{002} is decreasing with λ_{20} when all other parameters are constants.
- m_{100} , m_{010} are invariant and m_{001} is increasing; m_{110} is invariant, m_{101} and m_{011} are negative & decreasing; m_{200} , m_{020} are invariant and m_{002} is increasing with λ_{30} when all other parameters are constants.
- m_{100} , m_{010} are decreasing and m_{001} is increasing; m_{110} is decreasing, m_{101} and m_{011} are negative & increasing; m_{200} , m_{020} and m_{002} are decreasing with δ_{10} when all other parameters are constants.
- m_{100} is invariant, m_{010} is decreasing and m_{001} is increasing; m_{110} is increasing, m_{101} is negative & decreasing and m_{011} is negative & increasing; m_{200} is invariant, m_{020} is decreasing and m_{002} is increasing with δ_{20} when all other parameters are constants.
- m_{100} , m_{010} are decreasing and m_{001} is increasing; m_{110} is decreasing, m_{101} and m_{011} are negative & increasing; m_{200} , m_{020} are decreasing and m_{002} is increasing with time t when all other parameters are constants.

The changing patterns of statistical measures with respect to the study parameters are presented in table 4.3 and the following findings are observed.

- m_{100} , m_{010} and m_{001} are decreasing; m_{110} is decreasing, m_{101} is negative & increasing function and m_{011} is negative and decreasing function of μ_{10} ; m_{200} , m_{020} and m_{002} are decreasing with μ_{10} when all other parameters are constants.
- m_{100} is invariant, m_{010} and m_{001} are decreasing; m_{110} is increasing, m_{101} is negative & decreasing and m_{011} is negative & increasing; m_{200} is invariant, m_{020} is decreasing and m_{002} is increasing with μ_{20} when all other parameters are constants.
- m_{100} , m_{010} are invariant and m_{001} is decreasing; m_{110} is invariant, m_{101} and m_{011} are negative & increasing; m_{200} , m_{020} are invariant and m_{002} is decreasing with μ_{30} when all other parameters are constants.
- m_{100} , m_{010} and m_{001} are increasing; m_{110} is increasing, m_{101} and m_{011} are negative & decreasing; m_{200} , m_{020} and m_{002} are increasing with N_0 when all other parameters are constants.

- m_{100} is invariant, m_{010} and m_{001} are increasing; m_{110} is invariant, m_{101} is negative & invariant and m_{011} is decreasing; m_{200} is invariant and m_{020} , m_{002} are increasing with M_0 when all other parameters are constants.
- m_{100} , m_{010} are invariant and m_{001} is increasing; m_{110} is invariant and m_{101} , m_{011} are negative & invariant; m_{200} , m_{020} are invariant and m_{002} is increasing with K_0 when all other parameters are constants.

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Appendix

Table 4.1: Values of m_{100} , m_{010} , m_{001} , m_{110} , m_{101} , m_{011} , m_{200} , m_{020} , and m_{002} for varying values of λ_{11} , λ_{21} , λ_{31} , δ_{11} , δ_{21} and t .

λ_{11}	λ_{21}	λ_{31}	δ_{11}	δ_{21}	t	m_{100}	m_{010}	m_{001}	m_{110}	m_{101}	m_{011}	m_{200}	m_{020}	m_{002}
4.02	0.5	1	1	2	1	6711	1471	1440	35790	9413	17780	196000	10560	61810
4.04	0.5	1	1	2	1	6846	1494	1451	37110	9740	18050	203600	10850	63930
4.06	0.5	1	1	2	1	6985	1518	1462	38480	10080	18340	211500	11140	66110
4.08	0.5	1	1	2	1	7126	1542	1474	39900	10430	18620	219700	11450	68340
4.10	0.5	1	1	2	1	7270	1566	1485	41380	10790	18920	228200	11770	70630
4.12	0.5	1	1	2	1	7417	1590	1497	42900	11160	19220	237000	12090	72980
4	0.52	1	1	2	1	6578	1455	1435	34630	9144	17740	188700	10370	60800
4	0.54	1	1	2	1	6578	1462	1440	34750	9192	17980	188700	10460	61880
4	0.56	1	1	2	1	6578	1469	1446	34870	9242	18220	188700	10550	62990
4	0.58	1	1	2	1	6578	1475	1451	34990	9293	18470	188700	10650	64130
4	0.6	1	1	2	1	6578	1482	1457	35110	9345	18720	188700	10740	65300
4	0.62	1	1	2	1	6578	1489	1462	35230	9399	18980	188700	10840	66500
4	0.5	1.02	1	2	1	6578	1449	1442	34520	9125	17230	188700	10280	56730
4	0.5	1.04	1	2	1	6578	1449	1455	34520	9153	16990	188700	10280	53880
4	0.5	1.06	1	2	1	6578	1449	1468	34520	9181	16760	188700	10280	51170
4	0.5	1.08	1	2	1	6578	1449	1481	34520	9209	16560	188700	10280	48580
4	0.5	1.10	1	2	1	6578	1449	1494	34520	9238	16380	188700	10280	46090
4	0.5	1.12	1	2	1	6578	1449	1508	34520	9266	16220	188700	10280	43700
4	0.5	1	1.1	2	1	5952	1472	1473	33030	8848	20150	162200	11080	65570
4	0.5	1	1.2	2	1	5385	1484	1510	31350	8536	22900	139400	11800	71110
4	0.5	1	1.3	2	1	4873	1486	1541	29550	8180	25750	119900	12440	76440
4	0.5	1	1.4	2	1	4409	1481	1567	27690	7793	28730	103100	13010	81630
4	0.5	1	1.5	2	1	3990	1469	1588	25830	7389	31850	88730	13510	86800
4	0.5	1	1.6	2	1	3610	1451	1605	23990	6976	35150	76380	13960	13960
4	0.5	1	1	2.1	1	6578	1417	1465	33940	8880	16600	188700	9882	58040
4	0.5	1	1	2.2	1	6578	1386	1500	33380	8685	15770	188700	9511	56500
4	0.5	1	1	2.3	1	6578	1357	1533	32840	8509	15020	188700	9162	55130
4	0.5	1	1	2.4	1	6578	1329	1564	32310	8349	14330	188700	8834	53890
4	0.5	1	1	2.5	1	6578	1302	1594	31800	8201	13700	188700	8524	52770
4	0.5	1	1	2.6	1	6578	1276	1623	31300	8063	13110	188700	8232	51770
4	0.5	1	1	2	2	1.08E+05	2.35E+04	2.08E+04	1.16E+07	4.64E+06	1.75E+06	5.41E+07	2.58E+06	1.98E+07
4	0.5	1	1	2	3	1.78E+06	3.87E+05	3.37E+05	3.19E+09	1.37E+09	4.09E+08	1.47E+10	6.94E+08	5.23E+09
4	0.5	1	1	2	4	2.93E+07	6.36E+06	5.53E+06	8.64E+11	3.75E+11	1.09E+11	3.97E+12	1.88E+11	1.41E+12
4	0.5	1	1	2	5	4.81E+08	1.05E+08	9.09E+07	2.34E+14	1.02E+14	2.94E+13	1.07E+15	5.08E+13	3.82E+14
4	0.5	1	1	2	6	7.91E+09	1.72E+09	1.50E+09	6.32E+16	2.75E+16	7.96E+15	2.91E+17	1.37E+16	1.03E+17
4	0.5	1	1	2	7	1.30E+11	2.83E+10	2.46E+10	1.71E+19	7.43E+18	2.15E+18	7.86E+19	3.71E+18	2.79E+19

Table 4.2: Values of m_{100} , m_{010} , m_{001} , m_{110} , m_{101} , m_{011} , m_{200} , m_{020} , and m_{002} for varying values of μ_{11} , μ_{21} , μ_{31} , N_0 , M_0 and K_0 .

μ_{11}	μ_{21}	μ_{31}	N_0	M_0	K_0	m_{100}	m_{010}	m_{001}	m_{110}	m_{101}	m_{011}	m_{200}	m_{020}	m_{002}
0.21	0.3	0.5	400	200	100	6512	1437	1424	34040	8986	17430	185800	10180	58960
0.22	0.3	0.5	400	200	100	6448	1426	1419	33570	8876	17350	183000	10080	58180
0.23	0.3	0.5	400	200	100	6383	1415	1413	33100	8767	17270	180300	9979	57410
0.24	0.3	0.5	400	200	100	6320	1405	1408	32640	8660	17190	177600	9882	56650
0.25	0.3	0.5	400	200	100	6257	1394	1403	32190	8554	17110	174900	9786	55890
0.26	0.3	0.5	400	200	100	6195	1383	1398	31750	8450	17040	172300	9692	55150
0.2	0.31	0.5	400	200	100	6578	1445	1427	34460	9074	17400	188700	10240	59250
0.2	0.32	0.5	400	200	100	6578	1442	1424	34400	9052	17290	188700	10200	58760
0.2	0.33	0.5	400	200	100	6578	1439	1422	34340	9029	17180	188700	10160	58270
0.2	0.34	0.5	400	200	100	6578	1436	1419	34280	9007	17070	188700	10120	57790
0.2	0.35	0.5	400	200	100	6578	1433	1416	34230	8985	16960	188700	10080	57320
0.2	0.36	0.5	400	200	100	6578	1429	1414	34170	8964	16850	188700	10040	56850
0.2	0.3	0.51	400	200	100	6578	1449	1423	34520	9084	17660	188700	10280	61330
0.2	0.3	0.52	400	200	100	6578	1449	1417	34520	9070	17810	188700	10280	62970
0.2	0.3	0.53	400	200	100	6578	1449	1411	34520	9057	17980	188700	10280	64660
0.2	0.3	0.54	400	200	100	6578	1449	1405	34520	9043	18150	188700	10280	66400
0.2	0.3	0.55	400	200	100	6578	1449	1399	34520	9030	18340	188700	10280	68210
0.2	0.3	0.56	400	200	100	6578	1449	1393	34520	9016	18530	188700	10280	70080
0.2	0.3	0.5	410	200	100	6742	1484	1455	35380	9325	17950	193400	10530	61440
0.2	0.3	0.5	420	200	100	6907	1519	1480	36240	9552	18380	198100	10790	61440
0.2	0.3	0.5	430	200	100	7071	1555	1505	37110	9780	18820	202800	11050	61440
0.2	0.3	0.5	440	200	100	7236	1590	1530	37970	10010	19260	207500	11300	63490
0.2	0.3	0.5	450	200	100	7400	1626	1555	38830	10230	19700	212300	11560	65540
0.2	0.3	0.5	460	200	100	7565	1661	1580	39690	10460	20140	217000	11820	67580
0.2	0.3	0.5	400	210	100	6578	1450	1442	34520	9097	17510	188700	10280	59390
0.2	0.3	0.5	400	220	100	6578	1452	1455	34520	9097	17510	188700	10280	57340
0.2	0.3	0.5	400	230	100	6578	1454	1468	34520	9097	17510	188700	10280	55300
0.2	0.3	0.5	400	240	100	6578	1455	1481	34520	9097	17510	188700	10280	53250
0.2	0.3	0.5	400	250	100	6578	1457	1494	34520	9097	17510	188700	10280	51200
0.2	0.3	0.5	400	260	100	6578	1459	1507	34520	9097	17510	188700	10280	51200
0.2	0.3	0.5	400	200	110	6578	1449	1446	34520	9097	17510	188700	10280	59390
0.2	0.3	0.5	400	200	120	6578	1449	1462	34520	9097	17510	188700	10280	59390
0.2	0.3	0.5	400	200	130	6578	1449	1479	34520	9097	17510	188700	10280	59390
0.2	0.3	0.5	400	200	140	6578	1449	1495	34520	9097	17510	188700	10280	59390
0.2	0.3	0.5	400	200	150	6578	1449	1512	34520	9097	17510	188700	10280	59390
0.2	0.3	0.5	400	200	160	6578	1449	1528	34520	9097	17510	188700	10280	59390

Table 4.3: Values of m_{100} , m_{010} , m_{001} , m_{110} , m_{101} , m_{011} , m_{200} , m_{020} , and m_{002} for varying values of λ_{10} , λ_{20} , λ_{30} , δ_{10} , δ_{20} and t .

λ_{10}	λ_{20}	λ_{30}	δ_{10}	δ_{20}	t	m_{100}	m_{010}	m_{001}	m_{110}	m_{101}	m_{011}	m_{200}	m_{020}	m_{002}
0.51	1	2	4	3	1	8.178	107.706	2916	1.259	-0.804	-10400	10.111	81.128	3641000
λ_{10}	λ_{20}	λ_{30}	δ_{10}	δ_{20}	t	m_{100}	m_{010}	m_{001}	m_{110}	m_{101}	m_{011}	m_{200}	m_{020}	m_{002}
0.52	1	2	4	3	1	8.26	108.02	2918	1.331	-0.758	-10300	10.258	81.495	3674000
0.53	1	2	4	3	1	8.343	108.335	2920	1.405	-0.71	-10210	10.407	81.869	3707000
0.54	1	2	4	3	1	8.427	108.652	2922	1.48	-0.661	-10120	10.558	82.251	3739000
0.55	1	2	4	3	1	8.512	108.971	2924	1.557	-0.612	-10040	10.711	82.641	3772000
0.56	1	2	4	3	1	8.597	109.292	2926	1.635	-0.561	-9970	10.866	83.038	3804000
5	1.3	2	4	3	1	8.097	133.375	3071	1.086	0.163	68370	9.967	100.738	7854000
5	1.4	2	4	3	1	8.097	143.579	3127	1.04	0.644	26210	9.967	106.693	5247000
5	1.5	2	4	3	1	8.097	154.676	3186	0.988	1.219	18450	9.967	111.474	4685000
5	1.6	2	4	3	1	8.097	166.748	3248	0.929	1.907	15760	9.967	114.234	4427000
5	1.7	2	4	3	1	8.097	179.885	3312	0.861	2.732	14820	9.967	113.743	4282000
5	1.8	2	4	3	1	8.097	194.187	3379	0.785	3.725	14860	9.967	108.211	4197000
5	1	2.1	4	3	1	8.097	107.395	3145	1.189	-1.91	-11380	9.967	80.768	4270000
5	1	2.2	4	3	1	8.097	107.395	3397	1.189	-2.928	-12340	9.967	80.768	5058000
5	1	2.3	4	3	1	8.097	107.395	3670	1.189	-3.915	-13390	9.967	80.768	5999000
5	1	2.4	4	3	1	8.097	107.395	3968	1.189	-4.884	-14540	9.967	80.768	7121000
5	1	2.5	4	3	1	8.097	107.395	4293	1.189	-5.844	-15790	9.967	80.768	8460000
5	1	2.6	4	3	1	8.097	107.395	4646	1.189	-6.806	-17160	9.967	80.768	10060000
5	1	2	4.02	3	1	7.936	107.2	2916	1.172	-0.764	-10860	9.763	80.29	3551000
5	1	2	4.04	3	1	7.779	107.005	2918	1.155	-0.68	-11260	9.564	79.822	3491000
5	1	2	4.06	3	1	7.625	106.812	2921	1.139	-0.598	-11690	9.369	79.365	3429000
5	1	2	4.08	3	1	7.474	106.619	2923	1.122	-0.517	-11280	9.177	78.918	3364000
5	1	2	4.10	3	1	7.326	106.427	2925	1.106	-0.437	-12720	8.99	78.48	3295000
5	1	2	4.12	3	1	7.181	106.236	2927	1.09	-0.359	-13320	8.807	78.052	3221000
5	1	2	4	3.02	1	8.097	105.881	2919	1.194	-0.899	-9734	9.967	80.522	3716000
5	1	2	4	3.04	1	8.097	104.392	2924	1.199	-0.946	-9083	9.967	80.247	3818000
5	1	2	4	3.06	1	8.097	102.927	2929	1.204	-0.992	-8525	9.967	79.945	3917000
5	1	2	4	3.08	1	8.097	101.486	2934	1.209	-1.035	-8043	9.967	79.617	4012000
5	1	2	4	3.10	1	8.097	100.069	2939	1.214	-1.077	-7624	9.967	79.265	4106000
5	1	2	4	3.12	1	8.097	98.674	2944	1.218	-1.117	-7258	9.967	78.892	4197000
5	1	2	4	3	2	0.164	13.625	2.00E+04	0.07	-0.532	-7.66E+03	0.206	18.96	1.61E+08
5	1	2	4	3	3	3.32E-03	1.545	1.34E+05	1.53E-03	-1.78E-01	-5.66E+03	4.17E-03	2.46E+00	7.21E+09
5	1	2	4	3	4	6.72E-05	0.172	8.96E+05	3.13E-05	-1.10E-02	-4.19E+03	8.44E-05	2.82E-01	3.22E+11
5	1	2	4	3	5	1.36E-06	0.019	5.99E+06	6.34E-07	-1.45E-03	-3.10E+03	1.71E-06	3.10E-02	1.44E+13
5	1	2	4	3	6	2.75E-08	2.11E-03	4.00E+07	1.28E-08	-1.96E-04	-2.30E+03	3.46E-08	3.49E-03	6.44E+14
5	1	2	4	3	7	5.57E-10	2.34E-04	2.68E+08	2.60E-10	-2.65E-05	-1.70E+03	7.00E-10	3.87E-04	2.88E+16

Table 4.4: Values of m_{100} , m_{010} , m_{001} , m_{110} , m_{101} , m_{011} , m_{200} , m_{020} , and m_{002} for varying values of μ_{10} , μ_{20} , μ_{30} , N_0 , M_0 and K_0 .

μ_{10}	μ_{20}	μ_{30}	N_0	M_0	K_0	m_{100}	m_{010}	m_{001}	m_{110}	m_{101}	m_{011}	m_{200}	m_{020}	m_{002}
0.41	0.2	0.1	400	200	100	8.016	107.085	2912	1.177	-0.805	-10630	9.865	80.498	3574000
0.42	0.2	0.1	400	200	100	7.936	106.777	2910	1.166	-0.76	-10760	9.763	80.232	3539000
0.43	0.2	0.1	400	200	100	7.857	106.47	2908	1.155	-0.717	-10910	9.663	79.97	3504000
0.44	0.2	0.1	400	200	100	7.779	106.165	2906	1.144	-0.673	-11060	9.564	79.712	3469000
0.45	0.2	0.1	400	200	100	7.702	105.862	2904	1.133	-0.631	-11220	9.466	79.458	3433000
0.46	0.2	0.1	400	200	100	7.625	105.561	2902	1.122	-0.589	-11390	9.369	79.208	3397000
0.4	0.21	0.1	400	200	100	8.097	106.635	2909	1.191	-0.875	-10070	9.967	80.649	3651000
0.4	0.22	0.1	400	200	100	8.097	105.881	2904	1.194	-0.899	-9669	9.967	80.522	3692000
μ_{10}	μ_{20}	μ_{30}	N_0	M_0	K_0	m_{100}	m_{010}	m_{001}	m_{110}	m_{101}	m_{011}	m_{200}	m_{020}	m_{002}
0.4	0.23	0.1	400	200	100	8.097	105.133	2899	1.197	-0.923	-9302	9.967	80.388	3731000
0.4	0.24	0.1	400	200	100	8.097	104.392	2894	1.199	-0.946	-8963	9.967	80.247	3769000
0.4	0.25	0.1	400	200	100	8.097	103.657	2893	1.202	-0.969	-8648	9.967	80.099	3805000
0.4	0.26	0.1	400	200	100	8.097	102.927	2885	1.204	-0.992	-8356	9.967	79.945	3841000
0.4	0.2	0.11	400	200	100	8.097	107.395	2892	1.189	-0.741	-10420	9.967	80.768	3548000
0.4	0.2	0.12	400	200	100	8.097	107.395	2870	1.189	-0.632	-10330	9.967	80.768	3489000
0.4	0.2	0.13	400	200	100	8.097	107.395	2848	1.189	-0.521	-10250	9.967	80.768	3431000
0.4	0.2	0.14	400	200	100	8.097	107.395	2827	1.189	-0.411	-10170	9.967	80.768	3374000
0.4	0.2	0.15	400	200	100	8.097	107.395	2805	1.189	-0.299	-10090	9.967	80.768	3318000
0.4	0.2	0.16	400	200	100	8.097	107.395	2784	1.189	-0.187	-10010	9.967	80.768	3264000
0.4	0.2	0.1	410	200	100	8.299	109.526	2946	1.218	-0.871	-10760	10.216	82.563	3698000
0.4	0.2	0.1	420	200	100	8.502	111.656	2978	1.248	-0.892	-11030	10.465	84.358	3787000
0.4	0.2	0.1	430	200	100	8.704	113.787	3010	1.278	-0.914	-11290	10.714	86.153	3877000
0.4	0.2	0.1	440	200	100	8.906	115.918	3042	1.308	-0.935	-11550	10.964	87.949	3967000
0.4	0.2	0.1	450	200	100	9.109	118.049	3074	1.337	-0.956	-11820	11.213	89.744	4057000
0.4	0.2	0.1	460	200	100	9.311	120.18	3106	1.367	-0.977	-12080	11.462	91.539	4146000
0.4	0.2	0.1	400	210	100	8.097	108.503	2962	1.189	-0.85	-10500	9.967	81.215	3818000
0.4	0.2	0.1	400	220	100	8.097	109.611	3010	1.189	-0.85	-10500	9.967	81.663	4029000
0.4	0.2	0.1	400	230	100	8.097	110.719	3058	1.189	-0.85	-10500	9.967	82.111	4240000
0.4	0.2	0.1	400	240	100	8.097	111.827	3106	1.189	-0.85	-10500	9.967	82.559	4450000
0.4	0.2	0.1	400	250	100	8.097	112.935	3154	1.189	-0.85	-10490	9.967	83.007	4661000
0.4	0.2	0.1	400	260	100	8.097	114.043	3203	1.189	-0.85	-10490	9.967	83.455	4871000
0.4	0.2	0.1	400	200	110	8.097	107.395	2981	1.189	-0.85	-10500	9.967	80.768	3608000
0.4	0.2	0.1	400	200	120	8.097	107.395	3048	1.189	-0.85	-10500	9.967	80.768	3609000
0.4	0.2	0.1	400	200	130	8.097	107.395	3114	1.189	-0.85	-10500	9.967	80.768	3609000
0.4	0.2	0.1	400	200	140	8.097	107.395	3181	1.189	-0.85	-10500	9.967	80.768	3610000
0.4	0.2	0.1	400	200	150	8.097	107.395	3248	1.189	-0.85	-10500	9.967	80.768	3610000
0.4	0.2	0.1	400	200	160	8.097	107.395	3315	1.189	-0.85	-10500	9.967	80.768	3610000

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