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Trivariate Poisson Processes for Modeling the Stage Dependent Cancer Cell Growth

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Abstract: Studying the cancer cell growth through trivariate Poisson processes is the core objective of this paper. The parameters on growth, transitions and loss processes at different independent and inter dependent stages are considered for stochastic modeling of cancer growth in a human body. Formulation of joint probability functions and deriving statistical measures were carried out through differential equations. Model behaviour was analyzed with numerical data.

Keywords: Trivariate Poisson Processes, Stochastic Modeling, Differential Equations and state dependent Cancer Growth

I. INTRODUCTION

Cancer is due to the failure of regulating mechanism on cell division, leads to continuous proliferation and growth of cells. The deviation in the growth and division programming of normal cells will initiate the cancer formations and its invasion. This may be due to several unexplained reasons. Cancer cells have different DNA compared to normal/healthy cells. The division of normal cell is in standard pace and it is governed by DNA, proto-oncogenes, tumor suppressor gene, repair gene, etc. The state of repair gene fails/turned off/unable to fix the problem in the cells will generate rapid cell division in the organ. These factors will provoke rapid and uncontrolled cell division is a prime characteristic of cancer.

Assessment of cancer status through mathematical modeling is a fit in approach of understanding its growth. It has attracted good attention of researchers in mathematical biology. Counting the number of cancer causing cells in the tumor of different categories through manual methods is hypothetical and beyond experimentations. The numbers of cells in different categories of human body are variables and influenced by several uncertainties. Hence, there is a need in understanding the cancer growth with stochastic modeling of biological issues.

The pioneering work on quantification of cancer growth was done by Mayneord [1]. Kendall [2] has given a breakthrough in modeling a cell growth using the uni-variate birth and death process. Neyman et al. [3] have used linear birth and death process to describe the tumor growth as density dependent. First order partial differential equations have been used by Macro et al. [4], Murray [5] and Dewanji et al. [6] to develop mathematical models for studying the cancer growth. The limitations on the deterministic assumptions of biological issues in modeling the cancer growth leads to development of many models based on stochastic assumptions by Neymann [7]; Wette et al. [8]; Dubin [9]; Serio [10]; Tan et al. [11]; Moolgovkar et al. [12]; Hanin et al. [13]; Rinaldo [14], etc., Studies of two stage stochastic modeling of cancer growth with linear birth and death processes was initiated by Birkhead [15] Later on Tirupathi Rao et al. [16], Madhavi et al. [17], Tirupathi Rao et al. [18], [19], [20] and [21] have developed several two stage stochastic models for cancer cell growth. The above reported research work has focused up to the two stage stochastic modeling for studying the growth of cancer cell. However, three stage stochastic modeling is considered to be more appropriate and will provide suitable insights of the cancer growth.

This study is focused on modeling the three stage cancer growth using trivariate Poisson processes. The first stage is considered to be the cell is in normal status. The existing normal cells may generate some more normal cells, some of them may be transformed in to mutant cells or a part of them may be exposed to the risk of death. The second stage is considered to be a cell is in the status of mutant (transformed from normal). These cells may generate some more

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mutant cells (benign cells) with the same intensity of growth, some of the mutant cells may further transformed into a cancerous cell (malignant cell) or a part of the mutant cells may exposed to the event of death. The third stage is considered to be the cell is in malignant state. These cells may further produce some more malignant cells with faster rate or a part of them may be exposed to the event of death. Stochastic modeling is carried out under the biological and theoretical assumptions of cancer pathophysiology as the happenings of the cell division are purely random and influenced by chance factors. The following is a schematic diagram for cancer growth in three stages.

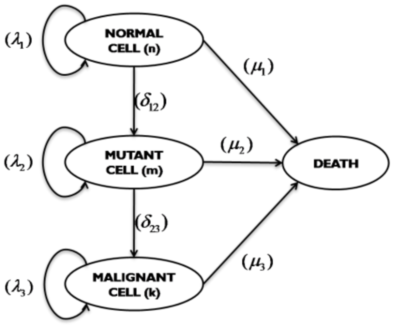

Figure-1: Schematic Diagram for Three Stage Cancer Growth

II. STOCHASTIC MODEL FOR CANCER GROWTH

A Stochastic model for three stage cancer cell growth 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' for any n, m, k>0.

Let λ_i be the rate of growth of cells in ith stage from the same stage; μ_i be the rate of loss of cells in the ith stage from the same stage; δ_{jk} be the rate of transformation of cells from the jth stage to kth stage. Where, 'i' be the stage of cancer cell, i=1,2,3 denoted by normal, mutant and malignant stage respectively; 'j' be the transformation of cells to the kth stage, j=1,2 and k=2,3 denoted by from normal to mutant and from mutant to malignant.

Let $\{N(t), t \geq 0\}$, $\{M(t), t \geq 0\}$, $\{N(t), t \geq 0\}$ 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 the joint processes will be $P\{(N(t), M(t), K(t)) = (n, m, k)\} = P_{n,m,k}(t)$.

Let

$$
\begin{aligned}
P_{n,u} &= P\{N(\Delta t) = u / N(t) = n\} \\
&= n\lambda_1 \Delta t + o(\Delta t) && ; u = n+1 \\
&= n\mu_1 \Delta t + o(\Delta t) && ; u = n-1 \\
&= 1 - \{n(\lambda_1 + \mu_1)\Delta t + o(\Delta t)\} && ; u = n \\
&= o(\Delta t)^2 && ; u = n \pm 2
\end{aligned}
$$

$$
\begin{aligned}
P_{m,v} &= P\{M(\Delta t) = v / M(t) = m\} \\
&= m\lambda_2 \Delta t + o(\Delta t) && ; v = m+1 \\
&= m\mu_2 \Delta t + o(\Delta t) && ; v = m-1 \\
&= 1 - \{m(\lambda_2 + \mu_2)\Delta t + o(\Delta t)\} && ; v = m \\
&= o(\Delta t)^2 && ; v = m \pm 2
\end{aligned}
$$

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$$
\begin{aligned}
P_{\mathrm{k,w}} &= P\{\mathrm{K}(\Delta\,\mathrm{t}) = w / \mathrm{K}(\mathrm{t}) = k\} \\
&= k\,\lambda_3 \Delta t + o(\Delta\,\mathrm{t}) && ; w = k+1 \\
&= k\mu_3 \Delta t + o(\Delta t) && ; w = k-1 \\
&= 1 - \{\mathrm{k}(\lambda_3 + \mu_3)\Delta\,\mathrm{t} + \mathrm{o}(\Delta\,\mathrm{t})\} && ; w = k \\
&= o(\Delta t)^2 && ; w = k \pm 2
\end{aligned}
$$

for any n,m,k >0.

$$
\begin{aligned}
P_{nu,mv,kw} &= P\{[(\mathrm{N}(\Delta\,\mathrm{t}), \mathrm{M}(\Delta\,\mathrm{t}), \mathrm{K}(\Delta\,\mathrm{t})) = (u, v, w)] / [((\mathrm{N}(\mathrm{t}), \mathrm{M}(\mathrm{t}), \mathrm{K}(\mathrm{t})) = (\mathrm{n}, \mathrm{m}, \mathrm{k})]\} \\
&= n\lambda_1 \Delta t + o(\Delta t) \quad ; u = n+1, v = m, w = k \\
&= n\,\mu_1 \Delta t + o(\Delta t) \quad ; \mathrm{u} = n-1, v = m, w = k \\
&= m\lambda_2 \Delta t + o(\Delta t) \quad ; \mathrm{u} = n, v = m+1, w = k \\
&= m\mu_2 \Delta t + o(\Delta t) \quad ; \mathrm{u} = n, v = m-1, w = k \\
&= k\lambda_3 \Delta t + o(\Delta t) \quad ; u = n, v = m, w = k+1 \\
&= k\,\mu_3 \Delta t + o(\Delta t) \quad ; \mathrm{u} = n, v = m, w = k-1 \\
&= n\delta_{12} \Delta t + o(\Delta t) \quad ; u = n, v = m+1, w = k \\
&= m\delta_{23} \Delta t + o(\Delta t) \quad ; u = n, v = m, w = k+1 \\
&= 1 - \{[\mathrm{n}(\lambda_1 + \mu_1 + \delta_{12}) + \mathrm{m}(\lambda_2 + \mu_2 + \delta_{23}) \\
&\qquad + \mathrm{k}(\lambda_3 + \mu_3)]\Delta t + o(\Delta t)\}; u = n, v = m, w = k \\
&= o(\Delta t)^2; \; u = n \pm 2, v = m \pm 2, w = k \pm 2
\end{aligned}
$$

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 per unit time't'. Then Differential difference equations of the model are:

$$
\begin{aligned}
P'_{n,m,k}(t) &= -[n\{\lambda_1 + \delta_{12} + \mu_1\} + m\{\lambda_2 + \delta_{23} + \mu_2\} + k\{\lambda_3 + \mu_3\}]P_{n,m,k}(t) \\
&+ [(n-1).\lambda_1]P_{n-1,m,k}(t) + [(n+1).\mu_1]P_{n+1,m,k}(t) + [(m-1).\lambda_2]P_{n,m-1,k}(t) \\
&+ [(m+1).\mu_2]P_{n,m+1,k}(t) + [(k-1).\lambda_3]P_{n,m,k-1}(t) + [(k+1).\mu_3]P_{n,m,k+1}(t) \\
&+ [(n+1).\delta_{12}]P_{n+1,m-1,k}(t) + [(m+1).\delta_{23}]P_{n,m+1,k-1}(t)
\end{aligned}
$$

for n,m,k≥1 (2.1)

$$P'_{1,0,0}(t) = -\mu_1 P_{1,0,0}(t) + 2\mu_1 P_{2,0,0}(t) + \mu_2 P_{1,1,0}(t) + \mu_3 P_{1,0,1}(t) \tag{2.2}$$

$$P'_{0,1,0}(t) = -\mu_2 P_{0,1,0}(t) + 2\mu_2 P_{0,2,0}(t) + \mu_1 P_{1,1,0}(t) + \mu_3 P_{0,1,1}(t) \tag{2.3}$$

$$P'_{0,0,1}(t) = -\mu_3 P_{0,0,1}(t) + 2\mu_3 P_{0,0,2}(t) + \mu_2 P_{0,1,1}(t) + \mu_1 P_{1,0,1}(t) \tag{2.4}$$

$$P'_{1,1,0}(t) = -(\mu_1 + \mu_2) P_{1,1,0}(t) + 2\mu_2 P_{1,2,0}(t) + 2\mu_1 P_{2,1,0}(t) + \mu_3 P_{1,1,1}(t) + 2\delta_{12} P_{2,0,0}(t) \tag{2.5}$$

$$P'_{1,0,1}(t) = -(\mu_1 + \mu_3) P_{1,0,1}(t) + \mu_2 P_{1,1,1}(t) + 2\mu_1 P_{2,0,1}(t) + 2\mu_3 P_{1,0,2}(t) + \delta_{23} P_{1,1,0}(t) \tag{2.6}$$

$$P'_{0,1,1}(t) = -(\mu_2 + \mu_3) P_{0,1,1}(t) + \mu_1 P_{1,1,1}(t) + 2\mu_2 P_{0,2,1}(t) + 2\mu_3 P_{0,1,2}(t) + 2\delta_{23} P_{0,2,0}(t) \tag{2.7}$$

$$P'_{0,0,0}(t) = \mu_3 P_{0,0,1}(t) + \mu_2 P_{0,1,0}(t) + \mu_1 P_{1,0,0}(t) \tag{2.8}$$

With the initial condition

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

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Where, N_0 normal cells, M_0 mutant cells and K_0 malignant cells in the tumor.

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

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

$$\begin{aligned}\sum_{k=0}^{\infty}\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}x^n y^m z^k P'_{n,m,k}(t) &= \sum_{k=0}^{\infty}\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}-[n\{\lambda_1+\delta_{12}+\mu_1\}+m\{\lambda_2+\delta_{23}+\mu_2\}+k\{\lambda_3+\mu_3\}]x^n y^m z^k P_{n,m,k}(t)\\
&+\sum_{k=0}^{\infty}\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}[(n-1).\lambda_1]x^n y^m z^k P_{n-1,m,k}(t)+\sum_{k=0}^{\infty}\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}[(n+1).\mu_1]x^n y^m z^k P_{n+1,m,k}(t)\\
&+\sum_{k=0}^{\infty}\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}[(m-1).\lambda_2]x^n y^m z^k P_{n,m-1,k}(t)+\sum_{k=0}^{\infty}\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}[(m+1).\mu_2]x^n y^m z^k P_{n,m+1,k}(t)\\
&+\sum_{k=0}^{\infty}\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}[(k-1).\lambda_3]x^n y^m z^k P_{n,m,k-1}(t)+\sum_{k=0}^{\infty}\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}[(k+1).\mu_3]x^n y^m z^k P_{n,m,k+1}(t)\\
&+\sum_{k=0}^{\infty}\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}x^n y^m z^k[(n+1).\delta_{12}]P_{n+1,m-1,k}(t)+\sum_{k=0}^{\infty}\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}x^n y^m z^k[(m+1).\delta_{23}]P_{n,m+1,k-1}(t)\end{aligned}$$

(2.10)

Simplifying and rearranging the terms in the equation (2.10) we arrive to the following,

$$\begin{aligned}\frac{\partial}{\partial t}p(x,y,z:t) &= [-\{\lambda_1+\delta_{12}+\mu_1\}x+\lambda_1 x^2+\mu_1+\delta_{12}\ y]\frac{\partial}{\partial x}p(x,y,z;t)\\
&+[-\{\lambda_2+\delta_{23}+\mu_2\}y+\lambda_2 y^2+\mu_2+\delta_{23}\ z]\frac{\partial}{\partial y}p(x,y,z;t)\\
&+[-\{\lambda_3+\mu_3\}z+\lambda_3 z^2+\mu_3)\frac{\partial}{\partial z}p(x,y,z;t)\end{aligned}$$

(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 $p_{n,m,k}(t)$, eq. (2.11) becomes

$$\begin{aligned}\frac{\partial}{\partial t}c(x,y,z:t) &= [-\{\lambda_1+\delta_{12}+\mu_1\}+\lambda_1 e^u+\mu_1 e^{-u}+\delta_{12}e^{v-u}]\frac{\partial}{\partial u}c(x,y,z;t)\\
&+[-\{\lambda_2+\delta_{23}+\mu_2\}+\lambda_2 e^v+\mu_2 e^{-v}+\delta_{23}e^{w-v}]\frac{\partial}{\partial v}c(x,y,z;t)\\
&+[-\{\lambda_3+\mu_3\}+\lambda_3 e^w+\mu_3 e^{-w})\frac{\partial}{\partial w}c(x,y,z;t)\end{aligned}$$

(2.12)

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III. 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:

$$\frac{\partial}{\partial t} m_{1,0,0}(t) = (\lambda_1 - \mu_1 - \delta_{12}) m_{1,0,0}(t) \quad (3.1)$$

$$\frac{\partial}{\partial t} m_{0,1,0}(t) = \delta_{12} m_{1,0,0}(t) + (\lambda_2 - \mu_2 - \delta_{23}) m_{0,1,0}(t) \quad (3.2)$$

$$\frac{\partial}{\partial t} m_{0,0,1}(t) = \delta_{23} m_{0,1,0}(t) + (\lambda_3 - \mu_3) m_{0,0,1}(t) \quad (3.3)$$

$$\frac{\partial}{\partial t} m_{1,1,0}(t) = -\delta_{12} m_{1,0,0}(t) + \delta_{12} m_{2,0,0}(t) + (\lambda_1 - \mu_1 - \delta_{12}) m_{1,1,0}(t) + (\lambda_2 - \mu_2 - \delta_{23}) m_{1,1,0}(t) \quad (3.4)$$

$$\frac{\partial}{\partial t} m_{1,0,1}(t) = (\lambda_1 - \mu_1 - \delta_{12}) m_{1,0,1}(t) + (\lambda_3 - \mu_3) m_{1,0.1}(t) + \delta_{23} m_{1,1,0}(t) \quad (3.5)$$

$$\frac{\partial}{\partial t} m_{0,1,1}(t) = \delta_{12} m_{1,0,1}(t) - \delta_{23} m_{0,1,0}(t) + \delta_{23} m_{0,2,0}(t) + (\lambda_2 - \mu_2 - \delta_{23}) m_{0,1,1}(t) + (\lambda_3 - \mu_3) m_{0,1,1}(t) \quad (3.6)$$

$$\frac{\partial}{\partial t} m_{2,0,0}(t) = (\lambda_1 + \delta_{12} + \mu_1) m_{1,0,0}(t) + 2(\lambda_1 - \mu_1 - \delta_{12}) m_{2,0,0}(t) \quad (3.7)$$

$$\frac{\partial}{\partial t} m_{0,2,0}(t) = \delta_{12} m_{1,0,0}(t) + 2\delta_{12} m_{1,1,0}(t) + (\lambda_2 + \mu_2 + \delta_{23}) m_{0,1,0}(t) + 2(\lambda_2 - \mu_2 - \delta_{23}) m_{0,2,0}(t) \quad (3.8)$$

$$\frac{\partial}{\partial t} m_{0,0,2}(t) = \delta_{23} m_{0,1,0}(t) + 2\delta_{23} m_{0,1,1}(t) + (\lambda_3 + \mu_3) m_{0,0,1}(t) + 2(\lambda_3 - \mu_3) m_{0,0,2}(t) \quad (3.9)$$

Solving the above relations shall provide the following statistical measures.
Expected number of normal cells at time't' is

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

Expected number of mutant cells at time't' is

$$m_{0,1,0}(t) = \frac{\delta_{12} N_0}{(A-B)} [e^{At} - e^{Bt}] + \ M_0 e^{Bt} \quad (3.11)$$

Expected number of malignant cells during time't' is

$$m_{0,0,1}(t) = De^{Ct} \left(\frac{e^{(A-C)t}}{(A-C)} - \frac{e^{(B-C)t}}{(B-C)} \right) + \frac{\delta_{23} M_0}{(B-C)} e^{Bt} \ + \ E.e^{Ct} \quad (3.12)$$

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

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

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

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$$m_{0,0,2}(t) = \frac{R_1 e^{At}}{(A-2C)} + \frac{R_2 e^{Bt}}{(B-2C)} + 2\delta_{23}\left\{\frac{A_2 e^{2At}}{2(A-C)} + \frac{A_4 e^{2Bt}}{2(B-C)} + \frac{A_5 e^{(B-C)t}}{(B-3C)} - \frac{A_6 e^{(A+C)t}}{(A-C)} - \frac{\delta_2 G_0 e^{(A+B)t}}{(A+B-2C)} - \frac{J_0 e^{(B+C)t}}{(B-C)}\right\} - \frac{PEe^{Ct}}{C} - S_0.e^{2ct} \quad (3.15)$$

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

$$m_{1,1,0}(t) = \frac{\delta_{12} N_0 H}{A(A-B)} e^{2At} + \frac{\delta_{12} N_0}{B}\left(1+\frac{H}{A}\right) e^{At} - I.e^{(A+B)t} \quad (3.16)$$

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

$$m_{0,1,1}(t) = A_1.e^{2At} + A_2.e^{At} - A_3.e^{Bt} + A_4.e^{2Bt} + A_5.e^{(B-C)t} - A_6.e^{(A+C)t} - \delta_{23} G_0.e^{(A+B)t} + J_0.e^{(B+C)t} \quad (3.17)$$

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

$$A = (\lambda_1 - \mu_1 - \delta_{12})\ ;\ B = (\lambda_2 - \mu_2 - \delta_{23})\ ;\ C = (\lambda_3 - \mu_3)\ ;\ D = \frac{\delta_{12}\delta_{23}}{A-B} N_0;$$

$$E = K_0 \frac{D(B-A)}{(A-C)(B-C)} + \frac{M_0}{(B-C)}\delta_{23}\ ;\ H = (\lambda_1 + \mu_1 + \delta_{12})\ ;\ I = \frac{\delta_{12} N_0 H}{A(A-B)} + \frac{\delta_{12} N_0}{B}(1+\frac{H}{A})\ ;$$

$$J = (\lambda_2 + \mu_2 + \delta_{23})\ ;\ D_0 = \frac{\delta_{12} N_0}{(A-2B)} + \frac{2\delta_{12}{}^2 N_0}{B(A-2B)} + \frac{J\delta_{12} N_0}{(A-B)(A-2B)}\ ;\ E_0 = \frac{J\delta_{12} N_0}{B(A-B)} - \frac{M_0}{B}$$

$$F_0 = \frac{2\delta_{12}{}^2 N_0 H}{2A(A-B)^2}\ ;\ G_0 = \frac{I}{(A-B)}\ ;\ H_0 = G_0 - D_0 - E_0 - F_0\ ;\ A_0 = \frac{\delta_{12} N_0 H}{A(A-B)(A-C)}$$

$$B_0 = \frac{\delta_{12} N_0}{BC}(1+\frac{H}{A})\ ;\ C_0 = \frac{I}{(B-C)}\ ;\ A_1 = \frac{\delta_{12} A_0 + \delta_{23} F_0}{2A-B-C}\ ;\ A_2 = \frac{\delta_{23} D_0 - \delta_{12} B_0 - \frac{\delta_{12} N_0}{A-B}}{A-B-C}$$

$$A_3 = \frac{\delta_{23} E_0 - M_0 + \frac{\delta_{12} N_0}{A-B}}{C}\ ;\ A_4 = \frac{\delta_{12} H_0}{B-C}\ ;\ A_5 = \frac{\delta_{12} C_0}{2C}\ ;\ A_6 = \frac{\delta_{12} I_0}{A-B}\ ;\ P = (\lambda_3 + \mu_3)$$

$$R_1 = \frac{\delta_{12}\delta_{23} N_0}{A-B} + 2A_2\delta_{23} + \frac{PD}{(A-C)}\ ;\ R_2 = \delta_{23} M_0 - \frac{\delta_{12}\delta_{23} M_0 N_0}{(A-B)} + \frac{P\delta_{23} M_0}{(B-C)} - \frac{PD}{(B-C)}$$

$$S_0 = \frac{R_1}{(A-2C)} + \frac{R_2}{(B-2C)} + 2\delta_{23}\left\{\frac{A_2}{2(A-C)} + \frac{A_4}{2(B-C)} + \frac{A_5}{(B-3C)} - \frac{A_6}{(A-C)} - \frac{\delta_{23} G_0}{(A+B-2C)} - \frac{J_0}{(B-C)}\right\} - \frac{PE}{C}\ ;$$

$$I_0 = \frac{\delta_{12} N_0}{BC}\left(1+\frac{H}{A}\right) + \frac{I}{(B-C)} - \frac{\delta_{12} N_0 H}{A(A-B)(A-C)}\ ;$$

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$$J_0 = \frac{\delta_{12}A_0 + \delta_{23}F_0}{(2A-B-C)} + \frac{\delta_{23}D_0 - \delta_{12}B_0 - \left(\frac{\delta_{12}N_0}{(A-B)}\right)}{(A-B-C)} - \frac{\delta_{23}\left(E_0 - M_0 + \frac{\delta_{12}N_0}{(A-B)}\right)}{C}$$
$$\frac{\delta_{12}N_0}{(B-C)} + \frac{\delta_{12}C_0}{2C} - \frac{\delta_{12}I_0}{(A-B)} - \delta_{23}G_0 \quad ;$$

IV. NUMERICAL ILLUSTRATION AND SENSITIVITY ANALYSIS

In order to understand the model behavior on more detailed way, simulated data sets 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).

V. FINDINGS

The changing patterns of statistical measures with respect to the study parameters are presented in table 4.1 and the following findings are observed. The findings were made by varying a single parameter and keeping other parameters are constant.

- m_{100}, m_{010}, m_{001} m_{110}, m_{101}, m_{011} m_{200}, m_{020}, and m_{002} are increasing with λ_1.
- m_{100} is invariant and m_{010}, m_{001} are increasing; m_{110} is invariant, m_{101} is increasing and m_{011} is negative & decreasing; m_{200} is invariant, m_{020} is increasing and m_{002} is decreasing with λ_2.
- m_{100}, m_{010} are invariant and m_{001} is increasing; m_{110} is invariant, m_{101} and m_{011} are decreasing; m_{200}, m_{020} are invariant and m_{002} is increasing with λ_3.
- m_{100} is decreasing function, m_{010} and m_{001} are increasing; m_{110}, m_{011} are decreasing and m_{101} is increasing; m_{200} is decreasing, m_{020} and m_{002} are increasing with δ_1.
- m_{100} is invariant, m_{010} is decreasing and m_{001} is increasing; m_{110} is invariant, m_{101} and m_{011} are decreasing; m_{200} is invariant, m_{020} is decreasing and m_{002} is increasing with δ_{23}.
- m_{100}, m_{010}, m_{001} m_{110}, m_{101}, m_{011} m_{200}, m_{020}, and m_{002} are decreasing with time t.

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}, m_{001} m_{110}, m_{101}, m_{011} m_{200}, m_{020}, and m_{002} are decreasing with μ_1.
- m_{100} is invariant, m_{010} and m_{001} are decreasing; m_{110} is invariant, m_{101} and m_{011} are decreasing; m_{200} is invariant, m_{020} is decreasing function and m_{002} is increasing with μ_2.
- It is observed that m_{100}, m_{010} are invariant and m_{001} is decreasing function of μ_3 m_{110} is invariant and m_{101}, m_{011} are increasing functions of μ_3; m_{200}, m_{020} are invariant and m_{002} is decreasing function of μ_3.
- 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.
- m_{100} is invariant, m_{010} and m_{001} are increasing; m_{110}, m_{101} are invariant and m_{011} is decreasing; m_{200} is invariant, m_{020} and m_{002} are increasing with M_0.
- m_{100}, m_{010} are invariant and m_{001} is increasing; m_{110}, m_{101}, and m_{011} are invariant; m_{200}, m_{020} are invariant and m_{002} is increasing with K_0.

VI. ACKNOWLEDGEMENTS

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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_1, λ_2, λ_3, δ_1, δ_2 and t, when the remaining are constants.

λ_1	λ_2	λ_3	δ_{12}	δ_{23}	t	m_{100}	m_{010}	m_{001}	m_{110}	m_{101}	m_{011}	m_{200}	m_{020}	m_{002}
0.4	1	2	2	1	1	0.544	8.980	75.806	0.024	6.118	2.835	0.609	7.890	3805
0.5	1	2	2	1	1	0.601	9.043	76.063	0.036	6.631	3.363	0.693	8.084	3950
0.6	1	2	2	1	1	0.665	9.214	76.327	0.050	7.187	3.898	0.788	8.286	4107
0.7	1	2	2	1	1	0.735	9.395	76.599	0.067	7.793	4.444	0.896	8.499	4278
0.8	1	2	2	1	1	0.812	9.585	76.880	0.088	8.454	5.004	1.019	8.722	4463
0.9	1	2	2	1	1	0.897	9.786	77.169	0.112	9.178	5.581	1.159	8.957	4665
0.3	**1.1**	2	2	1	1	0.492	9.480	76.635	0.015	6.242	2.081	0.536	8.609	3656
0.3	**1.2**	2	2	1	1	0.492	10.306	77.763	0.015	6.924	1.388	0.536	9.624	3644
0.3	**1.3**	2	2	1	1	0.492	11.209	78.946	0.015	7.700	-0.294	0.536	10.765	3627
0.3	**1.4**	2	2	1	1	0.492	12.198	80.187	0.015	8.586	-4.379	0.536	12.050	3591
0.3	**1.5**	2	2	1	1	0.492	13.281	81.490	0.015	9.600	-16.146	0.536	13.496	3484
0.3	**1.6**	2	2	1	1	0.492	14.467	82.858	0.015	10.764	-83.479	0.536	15.124	2841
0.3	1	**2.1**	2	1	1	0.492	8.725	82.108	0.015	4.939	1.854	0.536	7.706	4192
0.3	1	**2.2**	2	1	1	0.492	8.725	89.277	0.015	4.327	1.429	0.536	7.706	4801
0.3	1	**2.3**	2	1	1	0.492	8.725	97.125	0.015	3.794	1.032	0.536	7.706	5512
0.3	1	**2.4**	2	1	1	0.492	8.725	105.720	0.015	3.329	0.668	0.536	7.706	6345
0.3	1	**2.5**	2	1	1	0.492	8.725	115.134	0.015	2.923	0.347	0.536	7.706	7320
0.3	1	**2.6**	2	1	1	0.492	8.725	125.449	0.015	2.568	0.098	0.536	7.706	8643
0.3	1	2	**2.1**	1	1	0.446	8.824	76.078	0.014	5.714	2.330	0.484	7.838	3708
0.3	1	2	**2.2**	1	1	0.403	8.915	76.581	0.013	5.781	2.269	0.438	7.962	3741
0.3	1	2	**2.3**	1	1	0.365	9.000	77.069	0.012	5.843	2.100	0.396	8.078	3770
0.3	1	2	**2.4**	1	1	0.330	9.080	77.542	0.012	5.901	1.786	0.358	8.186	3792
0.3	1	2	**2.5**	1	1	0.299	9.153	78.000	0.011	5.956	1.275	0.323	8.288	3808
0.3	1	2	**2.6**	1	1	0.270	9.222	78.445	0.010	6.007	0.482	0.292	8.383	3816
0.3	1	2	2	**1.1**	1	0.492	8.035	78.304	0.015	5.114	2.386	0.536	7.108	4035
0.3	1	2	2	**1.2**	1	0.492	7.404	80.900	0.015	4.648	2.386	0.536	6.561	4411
0.3	1	2	2	**1.3**	1	0.492	6.826	83.355	0.015	4.235	2.335	0.536	6.062	4798
0.3	1	2	2	**1.4**	1	0.492	6.298	85.680	0.015	3.870	2.249	0.536	5.605	5202
0.3	1	2	2	**1.5**	1	0.492	5.814	87.883	0.015	3.546	2.136	0.536	5.186	5626
0.3	1	2	2	**1.6**	1	0.492	5.371	89.972	0.014	3.259	2.004	0.536	4.804	6074
0.3	1	2	2	1	**2**	6.06E-04	0.166	28.832	2.70E-05	0.282	0.256	6.60E-04	0.164	651.414
0.3	1	2	2	1	**3**	7.46E-07	3.05E-03	10.626	3.34E-08	1.40E-02	1.40E-02	8.13E-07	3.04E-03	1.23E+02
0.3	1	2	2	1	**4**	9.18E-10	5.59E-05	3.909	4.11E-11	6.98E-04	6.97E-04	1.10E-09	5.56E-05	2.90E+01

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λ_1	λ_2	λ_3	δ_{12}	δ_{23}	t	m_{100}	m_{010}	m_{001}	m_{110}	m_{101}	m_{011}	m_{200}	m_{020}	m_{002}
0.3	1	2	2	1	**5**	1.13E-12	1.02E-06	1.438	5.06E-14	3.47E-05	3.47E-05	1.23E-12	1.02E-06	8.47E+00
0.3	1	2	2	1	**6**	1.39E-15	1.87E-08	0.529	0.00E+00	1.73E-06	1.73E-06	1.52E-15	1.87E-08	2.82E+00
0.3	1	2	2	1	**7**	0.00E+00	3.43E-10	0.195	0.00E+00	8.61E-08	8.61E-08	0.00E+00	3.42E-10	9.97E-01

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_1, μ_2, μ_3, N_0, M_0 and K_0, when the remaining are constant.

μ_1	μ_2	μ_3	N_0	M_0	K_0	m_{100}	m_{010}	m_{001}	m_{110}	m_{101}	m_{011}	m_{200}	m_{020}	m_{002}
5	4	3	400	200	100	0.446	8.578	75.317	0.013	5.442	2.019	0.484	7.530	3543
5	4	3	400	200	100	0.403	8.438	75.082	0.012	5.256	1.700	0.438	7.362	3425
5	4	3	400	200	100	0.365	8.304	74.855	0.011	5.081	1.342	0.396	7.201	3314
5	4	3	400	200	100	0.330	8.177	74.634	0.010	4.918	0.932	0.358	7.046	3209
6	4	3	400	200	100	0.299	8.055	74.419	0.009	4.765	0.446	0.323	6.898	3109
6	4	3	400	200	100	0.270	7.940	74.210	0.008	4.621	0.332	0.292	6.757	3013
5	**4.1**	3	400	200	100	0.492	8.035	74.530	0.015	5.114	2.333	0.536	7.108	3685
5	**4.2**	3	400	200	100	0.492	7.404	73.548	0.015	4.648	2.252	0.536	6.561	3705
5	**4.3**	3	400	200	100	0.492	6.826	72.609	0.015	4.235	2.118	0.536	6.602	3733
5	**4.4**	3	400	200	100	0.492	6.298	71.711	0.015	3.870	1.957	0.536	5.605	3769
5	**4.5**	3	400	200	100	0.492	5.814	70.851	0.015	3.546	1.788	0.536	5.186	3814
5	**4.6**	3	400	200	100	0.492	5.371	70.028	0.015	3.259	1.617	0.536	4.804	3869
5	4	**3.1**	400	200	100	0.492	8.725	69.572	0.015	6.454	2.794	0.536	7.706	3228
5	4	**3.2**	400	200	100	0.492	8.725	64.100	0.015	7.390	3.316	0.536	7.706	2848
5	4	**3.3**	400	200	100	0.492	8.725	59.095	0.015	8.471	3.880	0.536	7.706	2520
5	4	**3.4**	400	200	100	0.492	8.725	54.518	0.015	9.724	4.492	0.536	7.706	2237
5	4	**3.5**	400	200	100	0.492	8.725	50.329	0.015	11.179	5.163	0.536	7.706	1991
5	4	**3.6**	400	200	100	0.492	8.725	46.494	0.015	12.871	5.902	0.536	7.706	1778
5	4	3	**410**	200	100	0.505	8.852	75.945	0.015	5.784	2.409	0.549	7.876	3756
5	4	3	**420**	200	100	0.517	8.978	76.331	0.016	5.925	2.510	0.563	8.046	3843
5	4	3	**430**	200	100	0.529	9.105	76.718	0.016	6.066	2.611	0.576	8.217	3930
5	4	3	**440**	200	100	0.542	9.231	77.105	0.016	6.207	2.712	0.589	8.387	4016
5	4	3	**450**	200	100	0.554	9.358	77.491	0.017	6.348	2.813	0.603	8.557	4103
5	4	3	**460**	200	100	0.566	9.485	77.878	0.017	6.489	2.914	0.616	8.727	4190
5	4	3	400	**210**	100	0.492	8.908	76.723	0.015	5.643	2.222	0.536	7.751	3847
5	4	3	400	**220**	100	0.492	9.092	77.888	0.015	5.643	2.136	0.536	7.796	4025
5	4	3	400	**230**	100	0.492	9.275	79.054	0.015	5.643	2.050	0.536	7.841	4202
5	4	3	400	**240**	100	0.492	9.458	80.219	0.015	5.643	1.964	0.536	7.886	4380
5	4	3	400	**250**	100	0.492	9.641	81.384	0.015	5.643	1.877	0.536	7.931	4557
5	4	3	400	**260**	100	0.492	9.824	82.549	0.015	5.643	1.791	0.536	7.976	4735
5	4	3	400	200	**110**	0.492	8.725	79.237	0.015	5.643	2.309	0.536	7.706	3681
5	4	3	400	200	**120**	0.492	8.725	82.916	0.015	5.643	2.309	0.536	7.706	3693
5	4	3	400	200	**130**	0.492	8.725	86.594	0.015	5.643	2.309	0.536	7.706	3704
5	4	3	400	200	**140**	0.492	8.725	90.273	0.015	5.643	2.309	0.536	7.706	3716
5	4	3	400	200	**150**	0.492	8.725	93.952	0.015	5.643	2.309	0.536	7.706	3728
5	4	3	400	200	**160**	0.492	8.725	97.631	0.015	5.643	2.309	0.536	7.706	3739