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Stochastic Modelling of Tumor Growth within Organ during Chemotherapy Using Bivariate Birth, Death and Migration Processes

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Abstract: *In this paper, a bivariate stochastic model for cancer growth within a specific organ during chemotherapy is developed using the birth, death and migration processes based on pathophysiology and genetic programs of cancerous cell. Joint probability functions and statistical properties of the model are derived with the formulated stochastic differential equations. Model behaviour was analysed with numerical data.*

Keywords*: Stochastic Modelling, Cancer Growth within Organ, Chemotherapy, Generalized Poisson Processes, Differential- difference equations*

I. Introduction

Continuous proliferation with minimum rate of death in such cells will form a mass of accumulation of corrupted cells called tumour. The growth or loss processes of cells are depending on the nature of mutant cell and its stages of transformation. Invasion of cancer cells has a potential to generate new colonies at different sites of the body from the forming or hosting sites. Hence, the growth and spread of cancerous cells will have the random processes such as birth, death and migration. The dynamics of cancer cells spread is influenced by the drug presence and its absence during the treatment with chemotherapy. It is customary to assess the severity of the cancer of the patient through manual methods.

Approach of stochastic modelling for evaluating the health status of the patient will be more beneficial under the uncertain environment. There is much evidence in literature on quantitative approach of cancer growth studies. The colony size distribution of multiple metastatic tumor and their growth is modelled by Wata et al [1]. The cancer chemotherapy treatment with the metastasis is modelled mathematically by Pinho et al [2]. The growth of cancer during and after the chemotherapy is modelled for studying the equilibrium probability of tumor size by Srinivasa Rao et al [3,4]. Various stochastic multistage models were developed for dynamics of cells in the cancer tumor and its behaviour under the presence and absence of chemotherapy by Tirupathi Rao et al [5-7].

This study is focused on developing bi-variate stochastic model for the cancer cells growth in an organ under presence and absence of chemotherapy. The birth, death and migration of cells to the neighbouring parts of an organ have been considered in the model. The migration of cancer cells are happens through the process called metastasis. Initial position of cancer tumor is named as primary tumor and tumor in the neighbouring location due migration process is called secondary tumor. This model is constructed based on the biological and patho-physiological assumptions of cancer and completely randomized cell divisions. The following schematic diagram shall give more clear idea on cancer growth in presence and absence of chemotherapy.

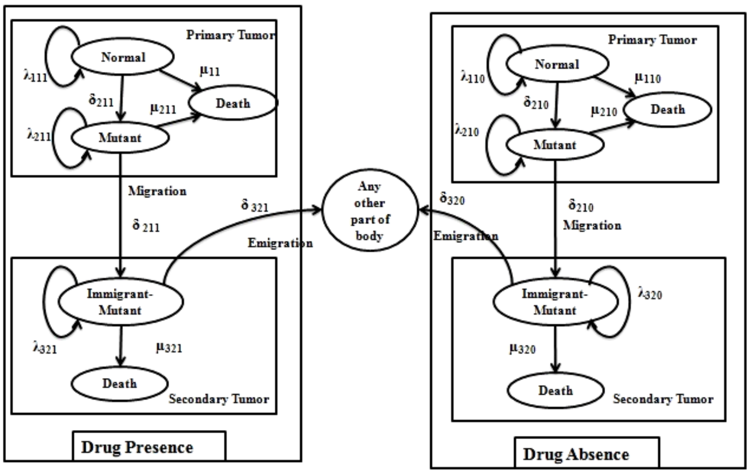

Figure -1: Schematic Diagram of cancer cells growth during chemotherapy.

II. Stochastic Model for growth of cancerous cell during chemotherapy

The mechanisms involved in the cell divisions are purely stochastic in nature. Let the events occurred in non-overlapping interval of time are statistically independent. Let Δt be an infinitesimal interval in the time.

Let λ_{ijl} be the growth rate of i^{th} stage cells in j^{th} stage tumor and l^{th} state of drug in chemotherapy; μ_{ijl} be the loss rate of i^{th} stage cells in j^{th} stage tumor and l^{th} state of drug in chemotherapy;
δ_{ijl} be the transformation rate of i^{th} stage cells to $(i+1)^{th}$ stage in the j^{th} stage tumor to $(j+1)^{th}$ stage of tumor and l^{th} state of drug in chemotherapy.

Where,
i=1, 2, 3 : Normal stage of cell, Mutant stage of cell, Migrant mutant stage of cell.
j=1, 2 : Primary stage of tumor, Secondary stage of tumor.
l=0, 1: Drug Absence , Drug Presence.

Let $a_k = \begin{cases} 1 & \text{Drug Presence} \quad \text{for } k = 1,2,3,4,5,6,7,8,9 \\ 0 & \text{Drug Absence} \\ (0,1) & \text{Partial Presence of drug} \end{cases}$

Let $\{N(t), t \geq 0\}$ be the process of normal cell division (growth/loss) and $\{M(t), t \geq 0\}$ be the process of mutant cell division (growth/loss). Let $\{N(t), M(t), t \geq 0\}$ be a joint bivariate stochastic processes of individual stochastic processes of $\{N(t), t \geq 0\}$ and $\{M(t), t \geq 0\}$. Such that $\Pr\{[N(t), M(t)] = [n, m]\} = P_{n,m}(t)$ and $\Pr\{N(t) = n\} = P_n(t)$, $\Pr\{M(t) = m\} = P_m(t)$.

Further,

$$\Pr\{N(\Delta t) = u / N(t) = n\} = P_{nu} \text{ for } u = n+1, n-1, n, n \pm 2$$

$$\Pr\{M(\Delta t) = v / M(t) = m\} = P_{mv} \text{ for } v = m+1, m-1, m, m \pm 2$$

$$\Pr\left\{\{[N(\Delta t), M(\Delta t)] = (u, v)\} / \{[N(t), M(t) = (n, m)]\}\right\} = P_{nu,mv} \text{ for } v = m+1, m-1, m, m \pm 2$$

Let us now define postulates of the univariate process with respect to normal and mutant growth,

$$\begin{aligned} P_{n,u} &= P\{N(\Delta t) = u / N(t) = n\} \\ &= n(a_1 \lambda_{111} + (1-a_1)\lambda_{110})\Delta t + o(\Delta t) & ; u = n+1 \\ &= n(a_5\mu_{111} + (1-a_5)\mu_{110})\Delta t + o(\Delta t) & ; u = n-1 \\ &= n(a_2\delta_{111} + (1-a_2)\delta_{111})\Delta t + o(\Delta t) & ; u = n-1 \\ &= 1 - \left[n \begin{pmatrix} (a_1 \lambda_{111} + (1-a_1)\lambda_{110}) \\ +(a_5\mu_{111} + (1-a_5)\mu_{110}) \\ +(a_2\delta_{111} + (1-a_2)\delta_{111}) \end{pmatrix} \Delta t + o(\Delta t) \right] & ; u = n \\ &= o(\Delta t)^2 & ; u = n \pm 2 \end{aligned}$$

For mutant growth processes,

$$\begin{aligned} P_{m,v} &= P\{M(\Delta t) = v / M(t) = m\} \\ &= m(a_3\lambda_{211} + (1-a_3)\lambda_{210})\Delta t + o(\Delta t) & ; v = m+1 \\ &= m(a_6\mu_{211} + (1-a_6)\mu_{210})\Delta t + o(\Delta t) & ; v = m-1 \\ &= m(a_7\delta_{211} + (1-a_7)\delta_{210})\Delta t + o(\Delta t) & ; v = m-1 \\ &= (a_4\lambda_{321} + (1-a_4)\lambda_{320})\Delta t + o(\Delta t) & ; v = m+1 \\ &= (a_8\mu_{321} + (1-a_8)\mu_{320})\Delta t + o(\Delta t) & ; v = m-1 \\ &= (a_9\delta_{321} + (1-a_9)\delta_{321})\Delta t + o(\Delta t) & ; v = m-1 \\ &= 1 - \left[\begin{Bmatrix} m((a_3\lambda_{211} + (1-a_3)\lambda_{210}) + (a_6\mu_{211} + (1-a_6)\mu_{210}) \\ +(a_7\delta_{211} + (1-a_7)\delta_{210})) + ((a_4\lambda_{321} + (1-a_4)\lambda_{320}) \\ +(a_8\mu_{321} + (1-a_8)\mu_{320}) + (a_9\delta_{321} + (1-a_9)\delta_{321})) \end{Bmatrix} \Delta t + o(\Delta t) \right] & ; v = m \\ &= o(\Delta t)^2 & ; v = m \pm 2 \end{aligned}$$

Considering the joint stochastic processes, we have

$$
\begin{aligned}
P_{nu,mv} &= P\{[(N(\Delta t), M(\Delta t)] = (u,v)/[(N(t), M(t)] = (n,m)\} \\
&= n(a_1\lambda_{111} + (1-a_1)\lambda_{110})\Delta t + o(\Delta t) && ; u = n+1, v = m \\
&= n\,(a_5\mu_{111} + (1-a_5)\mu_{110})\Delta t + o(\Delta t) && ; u = n-1, v = m \\
&= n(a_2\delta_{111} + (1-a_2)\delta_{111})\Delta t + o(\Delta t) && ; u = n-1, v = m \\
&= m(a_3\lambda_{211} + (1\text{-}a_3)\lambda_{210})\Delta t + o(\Delta t) && ; u = n, v = m+1 \\
&= m(a_6\mu_{211} + (1\text{-}a_6)\mu_{210})\Delta t + o(\Delta t) && ; u = n, v = m\text{-}1 \\
&= m(a_7\delta_{211} + (1\text{-}a_7)\delta_{210})\Delta t + o(\Delta t) && ; u = n, v = m\text{-}1 \\
&= (a_4\lambda_{321} + (1\text{-}a_4)\lambda_{320})\Delta t + o(\Delta t) && ; u = n, v = m+1 \\
&= (a_8\mu_{321} + (1\text{-}a_8)\mu_{320})\Delta t + o(\Delta t) && ; u = n, v = m-1 \\
&= (a_9\delta_{321} + (1\text{-}a_9)\delta_{320})\Delta t + o(\Delta t) && ; u = n, v = m-1 \\
&= 1\text{-}\left[\left\{\begin{array}{l} n((a_1\lambda_{111} + (1\text{-}a_1)\lambda_{110}) + (a_5\mu_{111} + (1\text{-}a_5)\mu_{110}) \\ +(a_2\delta_{111} + (1\text{-}a_2)\delta_{111})) + m((a_3\lambda_{211} + (1\text{-}a_3)\lambda_{210}) \\ +(a_6\mu_{211} + (1\text{-}a_6)\mu_{210}) + (a_7\delta_{211} + (1\text{-}a_7)\delta_{210})) \\ +((a_4\lambda_{321} + (1\text{-}a_4)\lambda_{320}) + (a_8\mu_{321} + (1\text{-}a_8)\mu_{320}) \\ +(a_9\delta_{321} + (1\text{-}a_9)\delta_{320})) \end{array}\right\}\Delta t + o(\Delta t)\right] \\
& && ; u = n, v = m \\
&= o(\Delta t)^2 && ; u = n \pm 2, v = m \pm 2
\end{aligned}
$$

Let $P_{n,m}(t+\Delta t)$ be the probability that happening of an event of one event in an infinitesimal interval Δt, there exists 'n' normal and 'm' mutant cells in the organ upto time 't'. Then the differential - difference equations of the model are:

$$
\begin{aligned}
P'_{n,m}(t) = &-\{n((a_1\lambda_{111} + (1-a_1)\lambda_{110}) + (a_2\delta_{111} + (1-a_2)\delta_{110}) + (a_5\mu_{111} + (1-a_5)\mu_{110})) \\
&+ m((a_3\lambda_{211} + (1-a_3)\lambda_{210}) + (a_6\mu_{211} + (1-a_6)\mu_{210}) + (a_7\delta_{211} + (1-a_7)\delta_{210})) \\
&+ ((a_4\lambda_{41} + (1-a_4)\lambda_{40}) + (a_8\mu_{41} + (1-a_8)\mu_{40}) + (a_9\mu_{51} + (1-a_9)\mu_{50}))\}P_{n,m}(t) \\
&+ P_{n+1,m}(t)[(n-1)(a_1\lambda_{111} + (1-a_1)\lambda_{110})] + P_{n+1,m-1}(t)[(n+1)(a_2\delta_{111} + (1-a_2)\delta_{110})] \\
&+ P_{n,m-1}(t)[(m-1)(a_3\lambda_{211} + (1-a_3)\lambda_{210})] + P_{n+1,m}(t)[(n+1)(a_5\mu_{111} + (1-a_5)\mu_{110})] \\
&+ P_{n,m+1}(t)[(m+1)(a_6\mu_{211} + (1-a_6)\mu_{210})] + P_{n,m+1}(t)[(m+1)(a_7\delta_{211} + (1-a_7)\delta_{210})] \\
&+ P_{n,m-1}(t)[(a_4\lambda_{321} + (1-a_4)\lambda_{320})] + P_{n,m+1}(t)[(a_8\mu_{321} + (1-a_8)\mu_{320})] \\
&+ P_{n,m+1}(t)[(a_9\delta_{321} + (1-a_9)\delta_{320})] \qquad \text{for } n, m \geq 1
\end{aligned} \tag{2.1}
$$

$$
\begin{aligned}
P'_{0,1}(t) = &\text{-}[(a_3\lambda_{211} + (1\text{-}a_3)\lambda_{210}) + (a_4\lambda_{321} + (1\text{-}a_4)\lambda_{320}) + (a_6\mu_{211} + (1\text{-}a_6)\mu_{210}) \\
&+ (a_8\mu_{321} + (1\text{-}a_8)\mu_{320}) + (a_9\delta_{321} + (1\text{-}a_9)\delta_{320})]P_{0,1}(t) + (a_5\mu_{111} + (1\text{-}a_5)\mu_{110})P_{1,1}(t) \\
&+ (a_2\delta_{111} + (1\text{-}a_2)\delta_{110})P_{1,0}(t) + \{2((a_6\mu_{211} + (1\text{-}a_6)\mu_{210}) + (a_7\delta_{211} + (1\text{-}a_7)\delta_{210})) \\
&+ (a_8\mu_{321} + (1\text{-}a_8)\mu_{320}) + (a_9\delta_{321} + (1\text{-}a_9)\delta_{320})\}P_{0,2}(t) + (a_4\lambda_{321} + (1\text{-}a_4)\lambda_{320})P_{0,0}(t)
\end{aligned} \tag{2.2}
$$

$$
\begin{aligned}
P'_{1,0}(t) = &P_{1,0}(t)\{\text{-}((a_1\lambda_{111} + (1\text{-}a_1)\lambda_{110}) + (a_2\delta_{111} + (1\text{-}a_2)\delta_{110}) + (a_4\lambda_{321} + (1\text{-}a_4)\lambda_{320}) \\
&+(a_5\mu_{111} + (1\text{-}a_5)\mu_{110}) + (a_7\delta_{211} + (1\text{-}a_7)\delta_{210}) + (a_8\mu_{321} + (1\text{-}a_8)\mu_{320}) + (a_9\delta_{321} \\
&+(1\text{-}a_9)\delta_{320}))\} + 2(a_5\mu_{111} + (1\text{-}a_5)\mu_{110})P_{2,0}(t) + P_{1,1}(t)\{((a_5\mu_{111} + (1\text{-}a_5)\mu_{110}) \\
&+(a_7\delta_{211} + (1\text{-}a_7)\delta_{210}) + (a_8\mu_{321} + (1\text{-}a_8)\mu_{320}) + (a_9\delta_{321} + (1\text{-}a_9)\delta_{320}))\}
\end{aligned} \tag{2.3}
$$

$$
\begin{aligned}
P'_{0,0}(t) = &\{\text{-}[(a_4\lambda_{321} + (1\text{-}a_4)\lambda_{320}) + (a_8\mu_{321} + (1\text{-}a_8)\mu_{320}) + (a_9\delta_{321} + (1\text{-}a_9)\delta_{320})]\}P_{0,0}(t) \\
&+(a_5\mu_{111} + (1\text{-}a_5)\mu_{110})P_{1,0}(t) + ((a_5\mu_{111} + (1\text{-}a_5)\mu_{110}) + (a_7\delta_{211} + (1\text{-}a_7)\delta_{210}) \\
&+(a_8\mu_{321} + (1\text{-}a_8)\mu_{320}) + (a_9\delta_{321} + (1\text{-}a_9)\delta_{320}))P_{0,1}(t)
\end{aligned} \tag{2.4}
$$

With the initial condition

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

III. Generating Functions and Statistical Measures

Let $P(x,y;t)$ be the probability generating function of $P_{n,m}(t)$.

Where, $P(x,y;t)=\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}x^n y^m\, P_{n,m}(t))\ ;|x|<1,|y|<1$. Multiplying the above differential-difference equations (2.1) to (2.4) with $x^n y^m$ and summing over n, m, we get

$$\begin{aligned}\frac{d}{dx}P(x,y;t)=&-((a_1\lambda_{111}+(1-a_1)\lambda_{110})+(a_2\,\delta_{111}+(1-a_2)\delta_{110})+(a_5\,\mu_{111}+(1-a_5)\mu_{110}))x\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}nx^{n-1}y^mP_{n,m}(t)\\&-((a_3\,\lambda_{211}+(1-a_3)\lambda_{210})+(a_6\,\mu_{211}+(1-a_6)\mu_{210})+(a_7\,\delta_{211}+(1-a_7)\delta_{210}))y\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}mx^ny^{m-1}P_{n,m}(t)\\&-((a_4\,\lambda_{321}+(1-a_4)\lambda_{320})+(a_8\,\mu_{321}+(1-a_8)\mu_{320})+(a_9\,\delta_{321}+(1-a_9)\delta_{320}))\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}x^ny^mP_{n,m}(t)\\&+(a_1\lambda_{111}+(1-a_1)\lambda_{110})x^2\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}(n-1)x^{n-2}y^mP_{n+1,m}(t)+(a_2\,\delta_{111}+(1-a_2)\delta_{110})y\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}(n+1)x^ny^{m-1}\\&P_{n+1,m-1}(t)+(a_3\,\lambda_{211}+(1-a_3)\lambda_{210})y^2\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}(m-1)x^ny^{m-2}P_{n,m-1}(t)+(a_5\,\mu_{111}+(1-a_5)\mu_{110})\\&\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}(n+1)x^ny^mP_{n+1,m}(t)+((a_6\,\mu_{211}+(1-a_6)\mu_{210})+(a_7\,\delta_{211}+(1-a_7)\delta_{210}))\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}(m+1)x^ny^m\\&P_{n+1,m-1}(t)+(a_3\,\lambda_{211}+(1-a_3)\lambda_{210})y^2\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}(m-1)x^ny^{m-2}P_{n,m-1}(t)+(a_5\,\mu_{111}+(1-a_5)\mu_{110})\\&\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}(n+1)x^ny^mP_{n+1,m}(t)+((a_6\,\mu_{211}+(1-a_6)\mu_{210})+(a_7\,\delta_{211}+(1-a_7)\delta_{210}))\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}(m+1)x^ny^m\end{aligned}\tag{3.1}$$

On simplification, we obtain the differential equation of the form as follows,

$$\begin{aligned}\frac{\partial}{\partial t}P(x,y;t)=&\{-((a_1\lambda_{111}+(1-a_1)\lambda_{110})+(a_2\delta_{111}+(1-a_2)\delta_{110})+(a_5\mu_{111}+(1-a_5)\mu_{110}))x+(a_5\mu_{111}\\&+(1-a_5)\mu_{110})+(a_1\lambda_{111}+(1-a_1)\lambda_{110})x^2+(a_2\delta_{111}+(1-a_2)\delta_{110})y\}\frac{\partial}{\partial x}P(x,y;t)\\&+\{-((a_3\lambda_{211}+(1-a_3)\lambda_{210})+(a_6\mu_{211}+(1-a_6)\mu_{210})+(a_7\delta_{211}+(1-a_7)\delta_{210}))y\\&+(a_3\lambda_{211}+(1-a_3)\lambda_{210})y^2+((a_6\mu_{211}+(1-a_6)\mu_{210})+(a_7\delta_{211}+(1-a_7)\delta_{210}))\}\\&\frac{\partial}{\partial y}P(x,y;t)+\{-((a_4\lambda_{321}+(1-a_4)\lambda_{320})+(a_8\mu_{321}+(1-a_8)\mu_{320})\\&+(a_9\delta_{321}+(1-a_9)\delta_{320}))+\frac{[(a_8\mu_{321}+(1-a_8)\mu_{320})+(a_9\delta_{321}+(1-a_9)\delta_{320})]}{y}\\&+(a_4\lambda_{321}+(1-a_4)\lambda_{320})y\}P(x,y;t)\end{aligned}\tag{3.2}$$

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

$$\begin{aligned}\frac{\partial}{\partial t}k(u,v;t)=&\{-((a_1\lambda_{111}+(1-a_1)\lambda_{110})+(a_2\,\delta_{111}+(1-a_2)\delta_{110})+(a_5\,\mu_{111}+(1-a_5)\mu_{110}))+(a_5\,\mu_{111}\\&+(1-a_5)\mu_{110})+(a_1\lambda_{111}+(1-a_1)\lambda_{110})e^u+(a_2\,\delta_{111}+(1-a_2)\delta_{110})e^{v-u}\}\frac{\partial}{\partial u}k(u,v;t)\\&+\{-((a_3\,\lambda_{211}+(1-a_3)\lambda_{210})+(a_6\,\mu_{211}+(1-a_6)\mu_{210})+(a_7\,\delta_{211}+(1-a_7)\delta_{210}))\end{aligned}$$

$$+(a_3\lambda_{211}+(1-a_3)\lambda_{210})e^{v}+((a_6\mu_{211}+(1-a_6)\mu_{210})+(a_7\delta_{211}+(1-a_7)\delta_{210}))e^{-v}\}$$
$$\frac{\partial}{\partial v}k(u,v;t)+\{-((a_4\lambda_{321}+(1-a_4)\lambda_{320})+(a_8\mu_{321}+(1-a_8)\mu_{320})+(a_9\delta_{321}+(1-a_9)\delta_{320}))$$
$$+\frac{[(a_8\mu_{321}+(1-a_8)\mu_{320})+(a_9\delta_{321}+(1-a_9)\delta_{320})]}{e^{v}}+(a_4\lambda_{321}+(1-a_4)\lambda_{320})e^{v}\}k(u,v;t) \tag{3.3}$$

Comparing the coefficient of the power of u's and v's in the above equations, we get the following

$$\frac{\partial}{\partial t}m_{1,0}(t)=(\lambda_1^*-\lambda_2^*-\mu_1^*)\,m_{1,0}(t) \tag{3.4}$$

$$\frac{\partial}{\partial t}m_{0,1}(t)=\lambda_2^*m_{1,0}(t)+(\lambda_3^*-\mu_2^*-\mu_3^*)m_{0,1}(t) \tag{3.5}$$

$$\frac{\partial}{\partial t}m_{2,0}(t)=2(\lambda_1^*-\lambda_2^*-\mu_1^*)m_{2,0}(t)+(\lambda_1^*+\lambda_2^*+\mu_1^*)\,m_{1,0}(t) \tag{3.6}$$

$$\frac{\partial}{\partial t}m_{0,2}(t)=\lambda_2^*m_{1,0}(t)+(\lambda_3^*+\mu_2^*+\mu_3^*)m_{0,1}(t)+2(\lambda_3^*-\mu_2^*-\mu_3^*)m_{0,2}(t)$$
$$+2(\lambda_4^*-\mu_4^*-\mu_5^*)m_{0,1}(t)+\lambda_2^*m_{1,1}(t) \tag{3.7}$$

$$\frac{\partial}{\partial t}m_{1,1}(t)=(\lambda_1^*-\lambda_2^*-\mu_1^*)m_{1,1}(t)+\lambda_2^*m_{2,0}(t)-\lambda_2^*m_{1,0}(t)+(\lambda_3^*-\mu_2^*-\mu_3^*)m_{1,1}(t)$$
$$+(\lambda_4^*-\mu_4^*-\mu_5^*)m_{1,0}(t)+\lambda_2^*m_{2,0}(t) \tag{3.8}$$

Let $m_{i,j}(t)$ denotes the moments of order (i, j) of the normal cells, mutant cells in an organ at time t. Then the characteristics of the model are obtained by solving the above ordinary linear differential equations, which are as follows

Expected number of normal cells in an organ at time 't'

$$m_{1,0}(t)=N_0\,e^{At} \tag{3.9}$$

Expected number of mutant cells in an organ at time 't'

$$m_{0,1}(t)=\frac{\lambda_2^*N_0e^{At}}{A-B}+\left(M_0-\frac{\lambda_2^*N_0}{A-B}\right)e^{Bt} \tag{3.10}$$

Variance of number of normal cells in the organ at time't'

$$m_{2,0}(t)=\frac{DN_0e^{At}}{A}\left(e^{At}-1\right) \tag{3.11}$$

Variance of number of mutant cells in the organ at time't'

$$m_{0,2}(t)=\frac{\lambda_2^*N_0e^{At}}{A-2B}+(F+2E)\left\{\frac{\lambda_2^*N_0e^{At}}{(A-2B)(A-B)}-\left(M_0-\frac{\lambda_2^*N_0}{A-B}\right)\frac{e^{Bt}}{B}\right\}$$
$$+\lambda_2^*\left\{\begin{array}{l}\dfrac{\lambda_2^*N_0D}{A}\left(\dfrac{e^{2At}}{2(A-B)^2}+\dfrac{e^{At}}{(A-2B)B}\right)-\dfrac{(E-\lambda_2^*)N_0e^{At}}{(A-2B)B}\\ -\left(\dfrac{\lambda_2^*N_0D-(A-B)\left(E-\lambda_2^*\right)N_0}{(A-B)B}\right)\dfrac{e^{(A+B)t}}{(A-B)}\end{array}\right\}$$
$$-\left\{\begin{array}{l}\dfrac{\lambda_2^*N_0}{(A-2B)}+(F+2E)\left(\dfrac{\lambda_2^*N_0-(A-2B)M_0}{2(A-2B)(A-B)^2B}\right)\\ +\lambda_2^{*2}N_0\left(\dfrac{2(A-B)(\lambda_2^*-E)+D\lambda_2^*}{2(A-2B)(A-B)^2}\right)\end{array}\right\}e^{2Bt} \tag{3.12}$$

Covariance of number of normal and mutant cells in an organ at time 't'

$$m_{1,1}(t)=\left\{\frac{(E-\lambda_2^*)N_0e^{-Bt}}{-B}+\frac{\lambda_2^*DN_0}{A}\left(\frac{e^{2At}}{(A-B)}+\frac{e^{At}}{B}\right)\right\}+\left\{\frac{\lambda_2^*DN_0-(A-B)(E-\lambda_2^*)N_0}{(A-B)B}\right\}e^{(A+B)t} \tag{3.13}$$

Where, N_0 & M_0 – Initial number of normal and mutant cells in an organ

$A=\lambda_1^*-\lambda_2^*-\mu_1^*$ $\quad B=\lambda_3^*-\mu_2^*-\mu_3^*$ $\quad D=\lambda_1^*+\lambda_2^*+\mu_1^*$

$E=\lambda_4^*-\mu_4^*-\mu_5^*$ $\quad F=\lambda_3^*+\mu_2^*+\mu_3^*$ $\quad$ -

$\lambda_1^*=a_1\lambda_{111}+(1-a_1)\lambda_{110}$ $\quad \lambda_2^*=a_2\delta_{111}+(1-a_2)\delta_{110}$ $\quad \lambda_3^*=a_3\lambda_{211}+(1-a_3)\lambda_{210}$

$\lambda_4^*=a_4\lambda_{321}+(1-a_4)\lambda_{320}$ $\quad \mu_1^*=a_5\mu_{111}+(1-a_5)\mu_{110}$ $\quad \mu_2^*=a_6\mu_{211}+(1-a_6)\mu_{210}$

$\mu_3^*=a_7\delta_{211}+(1-a_7)\delta_{210}$ $\quad \mu_4^*=a_8\mu_{321}+(1-a_8)\mu_{320}$ $\quad \mu_5^*=a_9\delta_{321}+(1-a_9)\delta_{320}$

IV. Numerical Illustration

The computed values of the characteristics of the model $m_{1,0}(t), m_{0,1}(t), m_{2,0}(t), m_{0,2}(t)$ and $m_{1,1}(t)$ mentioned above from equation (3.9) to (3.13) for the parameters are presented in the tables for changing values of λ_{111}, λ_{110}, δ_{111}, δ_{110}, λ_{211}, λ_{210}, λ_{321}, λ_{320}, μ_{111}, μ_{110}, μ_{211}, μ_{210}, δ_{211}, δ_{210}, μ_{321}, μ_{320}, δ_{321}, δ_{320} and t in the appendix-I. The linear function is defined to connection the kinetics of cells in the tumor under presence and vacation period of drug therapy.

V. Findings

The findings were made by changing one decision parameter while fixing other parameters are constant.

- m_{10}, m_{01}, m_{20}, m_{02} and m_{11} are the increasing function of initial size normal cells N_0.
- m_{10}, m_{20}, m_{11} are invariant and m_{01}, m_{02} are increasing function of initial number of mutant cells M_0.
- m_{10}, m_{01}, m_{20}, m_{02} and m_{11} are the increasing function arrival of normal cells λ_{111} and λ_{110}.
- m_{10}, m_{20}, m_{02} and m_{11} are decreasing and m_{01} is an increasing function of transformation rate of normal cells to mutant cells δ_{111} and δ_{110}.
- m_{10}, m_{20} are invariant and, m_{01}, m_{02} and m_{11} are the increasing function arrival of mutant cells λ_{211} and λ_{210}.
- m_{10}, m_{01}, m_{20} are invariant and, m_{02} and m_{11} are the increasing function growth rate of mutant cells in secondary tumor λ_{321} and λ_{320}.
- m_{10}, m_{01}, m_{20}, m_{02} and m_{11} are decreasing function of death rate of normal cells μ_{111} and μ_{110}.
- m_{10}, m_{20} are invariant and m_{01}, m_{02} and m_{11} are decreasing function death rate of mutant cells μ_{211} and μ_{210}.
- m_{10}, m_{01}, m_{20} are invariant and, m_{02} and m_{11} are the decreasing function migration rate of mutant cells to in secondary tumor δ_{211} and δ_{210}.
- m_{10}, m_{01}, m_{20} are invariant and, m_{02} and m_{11} are the decreasing function death rate of mutant cells in secondary tumor μ_{321} and μ_{320}.
- m_{10}, m_{01}, m_{20} are invariant and, m_{02} and m_{11} are the decreasing function migration rate of mutant cells in secondary tumor μ_{321} and μ_{320}.
- m_{10}, m_{01}, m_{20}, m_{02} and m_{11} are the increasing function of time t.

The above findings are describing dynamics of the measures derived from the developed stochastic model and a_k is assumed as the partial presence of drug.

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Appendix-1: Table for all statistical measures with varying values of one parameter when other parameters are fixed

N_0	M_0	λ	λ	δ	δ	λ	λ	λ	λ	μ	μ	μ	μ	δ	δ	μ	μ	δ	δ	t	m_{10}	m_{01}	m_{20}	m_{02}	m_{11}
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	602.919	6599	1484	11110	498.333
400	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	803.892	6647	1979	11420	664.444
500	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	1005	6695	2474	11730	830.555
600	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	1206	6743	2969	12050	996.666
700	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	1407	6791	3464	12360	1163
300	**550**	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	7497	989.639	11830	332.222
300	**600**	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	7842	989.639	12830	332.222
300	**650**	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	8488	989.639	13850	332.222
300	**700**	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	9133	989.639	14870	332.222
300	**750**	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	9779	989.639	15890	332.222
300	500	**2.1**	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	410.066	6552	1033	11280	340.668
300	500	**2.2**	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	418.36	6552	1078	11790	349.329
300	500	**2.3**	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	426.801	6553	1125	12300	358.241
300	500	**2.4**	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	435.423	6554	1174	12840	367.381
300	500	**2.5**	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	444.219	6555	1225	13390	376.765
300	500	2	**1.2**	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	471.668	6557	1391	15170	406.45
300	500	2	**1.3**	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	510.973	6560	1645	17860	449.888
300	500	2	**1.4**	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	553.973	6563	1943	20980	498.209
300	500	2	**1.5**	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	599.633	6566	2294	24620	551.992
300	500	2	**1.6**	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	649.574	6570	2705	28920	611.887
300	500	2	1	**0.02**	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	648.277	6573	2698	28820	610.331
300	500	2	1	**0.04**	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	645.689	6578	2686	28630	607.239
300	500	2	1	**0.06**	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	643.11	6583	2674	28440	604.703
300	500	2	1	**0.08**	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	640.544	6589	2662	28250	601.037
300	500	2	1	**0.1**	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	637.987	6594	2650	28060	598.127
300	500	2	1	0.01	**0.2**	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	599.633	6.68E+03	2.47E+03	2.54E+04	554.712
300	500	2	1	0.01	**0.3**	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	553.531	6.77E+03	2.25E+03	2.24E+04	506.62
300	500	2	1	0.01	**0.4**	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	510.973	6.87E+03	2.05E+03	1.98E+04	465.861
300	500	2	1	0.01	**0.5**	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	471.688	6.95E+03	1.87E+03	1.76E+04	431.017
300	500	2	1	0.01	**0.6**	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	435.423	7.04E+03	1.70E+03	1.58E+04	409.94
300	500	2	1	0.01	0.1	**1.2**	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	6817	989.639	11120	340.688
300	500	2	1	0.01	0.1	**1.3**	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	6954	989.639	11300	345.012
300	500	2	1	0.01	0.1	**1.4**	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	7094	989.639	11480	349.404
300	500	2	1	0.01	0.1	**1.5**	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	7236	989.639	11670	352.862
300	500	2	1	0.01	0.1	**1.6**	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	7382	989.639	11880	358.388
300	500	2	1	0.01	0.1	1	**4.1**	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	7094	989.639	11480	349.404
300	500	2	1	0.01	0.1	1	**4.2**	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	7682	989.639	12300	367.644
300	500	2	1	0.01	0.1	1	**4.3**	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	8318	989.639	13280	387.014
300	500	2	1	0.01	0.1	1	**4.4**	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	9008	989.639	14430	407.588
300	500	2	1	0.01	0.1	1	**4.5**	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	9755	989.639	15770	429.446
300	500	2	1	0.01	0.1	1	4	**0.3**	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	6551	989.639	10980	407.08
300	500	2	1	0.01	0.1	1	4	**0.4**	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	6551	989.639	11080	444.509
300	500	2	1	0.01	0.1	1	4	**0.5**	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	6551	989.639	11170	481.938
300	500	2	1	0.01	0.1	1	4	**0.6**	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	6551	989.639	11260	519.367
300	500	2	1	0.01	0.1	1	4	**0.7**	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	6551	989.639	11350	556.796
300	500	2	1	0.01	0.1	1	4	0.1	**0.4**	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	6551	989.639	11170	481.939
300	500	2	1	0.01	0.1	1	4	0.1	**0.5**	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	6551	989.639	11540	631.654
300	500	2	1	0.01	0.1	1	4	0.1	**0.6**	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	6551	989.639	11900	781.369
300	500	2	1	0.01	0.1	1	4	0.1	**0.7**	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	6551	989.639	12270	931.085
300	500	2	1	0.01	0.1	1	4	0.1	**0.8**	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	6551	989.639	12640	1081
300	500	2	1	0.01	0.1	1	4	0.1	0.3	**0.3**	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	386.185	6550	951.773	9875	320.301
300	500	2	1	0.01	0.1	1	4	0.1	0.3	**0.4**	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	378.528	6549	933.247	9434	314.489
300	500	2	1	0.01	0.1	1	4	0.1	0.3	**0.5**	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	371.043	6548	914.933	9007	308.776
300	500	2	1	0.01	0.1	1	4	0.1	0.3	**0.6**	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	363.696	6548	897.013	8593	303.158
300	500	2	1	0.01	0.1	1	4	0.1	0.3	**0.7**	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	356.494	6547	879.307	8191	297.635
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	**0.6**	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	371.043	6548	914.993	9007	308.776
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	**0.7**	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	342.516	6546	844.715	7423	286.869
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	**0.8**	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	316.182	6543	778.805	6016	266.416
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	**0.9**	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	291.873	6541	717.197	4760	247.336

No	Mo	λ_{111}	λ_{110}	δ_{111}	δ_{110}	λ_{211}	λ_{210}	λ_{221}	λ_{220}	μ_{111}	μ_{110}	μ_{211}	μ_{210}	δ_{211}	δ_{210}	μ_{221}	μ_{220}	δ_{221}	δ_{220}	t	m_{10}	m_{01}	m_{20}	m_{02}	m_{11}
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	**1.3**	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	6172	989.639	10630	319.99
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	**1.4**	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	6050	989.639	10580	316.033
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	**1.5**	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	5931	989.639	10540	312.133
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	**1.6**	0.5	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	5814	989.639	10510	308.291
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	**0.6**	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	6050	989.639	10580	316.033
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	**0.7**	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	5587	989.639	10470	300.39
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	**0.8**	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	5160	989.639	10460	286.39
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	**0.9**	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	4766	989.639	10560	272.826
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	**1.1**	0.01	0.3	0.1	0.03	0.001	0.01	1	401.946	4065	989.639	11150	247.958
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	**0.04**	0.3	0.1	0.03	0.001	0.01	1	401.946	6512	989.639	10780	330.805
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	**0.06**	0.3	0.1	0.03	0.001	0.01	1	401.946	6486	989.639	10770	330.145
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	**0.08**	0.3	0.1	0.03	0.001	0.01	1	401.946	6460	989.639	10750	329.319
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	**0.1**	0.3	0.1	0.03	0.001	0.01	1	401.946	6435	989.639	10740	328.495
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	**0.12**	0.3	0.1	0.03	0.001	0.01	1	401.946	6409	989.639	10730	327.674
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	**0.4**	0.1	0.03	0.001	0.01	1	401.946	6050	989.639	10580	316.033
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	**0.5**	0.1	0.03	0.001	0.01	1	401.946	5587	989.639	10470	300.775
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	**0.6**	0.1	0.03	0.001	0.01	1	401.946	5160	989.639	10460	286.39
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	**0.7**	0.1	0.03	0.001	0.01	1	401.946	4766	989.639	10560	276.826
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	**0.8**	0.1	0.03	0.001	0.01	1	401.946	4402	989.639	10790	260.031
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	**0.3**	0.03	0.001	0.01	1	401.946	6551	989.639	10620	257.364
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	**0.4**	0.03	0.001	0.01	1	401.946	6551	989.639	10520	219.935
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	**0.5**	0.03	0.001	0.01	1	401.946	6551	989.639	10430	182.506
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	**0.6**	0.03	0.001	0.01	1	401.946	6551	989.639	10340	145.077
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	**0.7**	0.03	0.001	0.01	1	401.946	6551	989.639	10250	107.648
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	**0.05**	0.001	0.01	1	401.946	6551	989.639	10370	302.279
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	**0.07**	0.001	0.01	1	401.946	6551	989.639	10650	272.336
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	**0.09**	0.001	0.01	1	401.946	6551	989.639	10580	242.392
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	**0.11**	0.001	0.01	1	401.946	6551	989.639	10500	212.449
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	**0.13**	0.001	0.01	1	401.946	6551	989.639	10430	182.506
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	**0.004**	0.01	1	401.946	6551	989.639	10800	331.009
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	**0.006**	0.01	1	401.946	6551	989.639	10800	330.35
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	**0.008**	0.01	1	401.946	6551	989.639	10790	329.602
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	**0.01**	0.01	1	401.946	6551	989.639	10790	328.853
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	**0.012**	0.01	1	401.946	6551	989.639	10790	328.105
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	**0.02**	1	401.946	6551	989.639	10760	317.25
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	**0.04**	1	401.946	6551	989.639	10690	287.307
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	**0.06**	1	401.946	6551	989.639	10620	257.364
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	**0.08**	1	401.946	6551	989.639	10540	227.421
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	**0.1**	1	401.946	6551	989.639	10470	197.478
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	**3**	1623	1.10E+06	2.82E+04	6.31E+08	2.73E+05
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	**4**	3263	1.41E+07	1.22E+05	1.05E+11	7.11E+06
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	**5**	6557	1.83E+08	5.08E+05	1.76E+13	1.85E+08
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	**6**	13180	2.36E+09	2.19E+06	2.93E+15	4.79E+09
300	500	2	1	0.01	0.1	1	4	0.1	0.3	0.1	0.5	1	0.5	0.01	0.3	0.1	0.03	0.001	0.01	**7**	26480	3.04E+10	8.49E+06	4.88E+17	1.24E+11