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Two Stage Mutant Cell Growth through Stochastic Modeling

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Abstract

Modeling cancer cell growth with stochasticity has attracted the attention of good number of researchers as the complexity of the problem. In this paper we develop a stochastic model for cancer growth as Malignancy in a stepwise transformation of a normal cell to cancer cell. A Bivariate time dependent Poisson process is considered to develop the joint probability function of pre-malignant and malignant cells. Statistical measures are derived and the model behaviour is analyzed thorough sensitivity analysis. This study provides some theoretical aspects on modeling the stepwise cancer growth. Appropriate software development to this study will enhance the work to a potential user friendly decision support system for cancer health care management.

Keywords: Stochastic modeling, Bivaraite Poisson Process, Cancer chemotherapy, drug sensitivity analysis.

Introduction

Cancer is a disease in which a group of abnormal cells grow uncontrollably by disregarding the normal rules of cell division. Normal cells are constantly subject to signals that dictate whether the cell should divide, differentiate into another cell or die. But cancer cells develop a degree of autonomy (Independence) from these signals, resulting in uncontrolled continuous and spread, it can be serious.(Momna Hejmadi, 2010). All cancers have only one feature in common: are diseases of

uncontrolled cell division. Under normal circumstances, the body regulates the production of new cells very precisely. In cancer cells, particular defects in deoxyribonucleic acid (DNA), lead to breakdowns in the cell communication and growth control that are normal in healthy cells. Having escaped these controls, cancer cells can become invasive and spread to other parts of the body. The formation of the cancer has some connections with Genes and Mutations. The environmental factors suggest that some cancers could originate from agents that change a cell's genetic material (mutation). Each of the more than 100 trillion cells in a human body carries its genetic information in DNA, composed of long double-helical strands made of sequences of four building blocks (bases) linked in pairs. It is packaged in 23 pairs of chromosomes. Genes are sequences of DNA that code for individual proteins. And Mutations are errors in DNA structure that alter this genetic information. Most mutations arise spontaneously, possibly from mistakes that arise while DNA duplicates during cell growth. If cell growth is stopped when molecular mechanisms termed checkpoints sense the damage, recruit the molecules to rectify the problem, and give time for corrections to be made. Then enzymes for repair are activated, and the cell may recover if the damage was not too severe. Genes designated BRCA1 and BRCA2 are involved in DNA repair, the inability to repair damaged DNA may result in cancer. (B. Pardee and Gary S. Stein 2009)

In this paper we propose a two stage stochastic model for cancer cell growth. A mutant cell, after required stages of transformation will be converted into a malignant, from then the cell division is at faster growth. The mutant cell is transformed into premalignant cell and then it will be converted into malignant cell as a fully fledged cancerous cell. The rates of arrivals to the premalignancy and malignant stages from mutant stage are assumed as bivariate Poisson parameters. The death rates of premalignant and malignant cells are assumed as bivariate Poisson parameters. The rate of conversion of premalignant cell to malignant cell is also a bivariate Poisson parameter. Statistical measures are derived from the developed model. In order to observe the model behavior during chemotherapy, a state dependent bivariate Poison process along with time dependency is developed by incorporating the stages of drug absence and drug presence. Difference differential equations of the model are derived from the developed bivariate Poisson process. Intensity of cancer problem can be assessed through suitable designing and development of structural Mathematical models of Cancer growth. Proper understanding of Physiological and Environmental factors will help in the construction of suitable mathematical model. We have considered the growth of cancer cell as stochastic rather than deterministic.

It is established that the growth of tumor is a random variable and not a constant. With reference to the pioneering work of Mayneord (1932), much work has been reported on tumor growth. Iverson and Arley(1950) have described the growth of tumor as pure linear birth process. Kendal (1960), Neyman and Scott (1967) have used a linear birth and death process to describe a growth of tumor. Witte et al (1974)

have developed a stochastic model for growth of solid tumors as the physical characteristics of a tumor growth are dependent and stochastic. Density dependent birth and death process was developed by Dubin (1976). Hanson and Charles Tier (1982) have developed stochastic model for tumor growth as the diffusion limit of a continuous time density dependent branching process. Serio (1984) developed a two stage stochastic model with time dependent parameters for carcinogensis. Gerd Rosenkarinz (1985) developed tumor immunology growth model using stochastic differential equations. Stochastic model using birth and death processes with spontaneous mutation is developed by Birkhead (1986). Coldman, A.J. and Murray, J.M. (2000) developed a stochastic model of Chemotherapy for cancer includes the drug resistance and the concomitant effect on normal system. Rao, P.T. and Rao, K. S. (2004, 2006) have developed various stochastic models for cancer growth under spontaneous mutation and proliferation; under chemotherapy; Proliferation with inactivation of allele genes and also in two stage of pre-malignancy and malignancy. Rinaldo (2006) considered two successive mutation hypothesis to develop a stochastic model for cancer cells. LO, C.F. (2009) developed a stochastic non-linear model of tumor growth for size dependent tumors.

In all the above mentioned works almost all have considered the growth of cancer is homogeneous irrespective of environment in which the patient is living whereas the health status of the cancer patient has to be considered as heterogeneous due to the factors like individual, environmental and other extraneous conditions. While developing a two stage stochastic model by Rao K.S and Rao P.T (2006) they have considered the rates of arrivals to premalignant stage, arrivals to malignant stage from premalignant stage(as transformed cells from premalignant to malignant). Where as they have ignored the arrivals of cells to Malignant stage directly from Mutancy. When we observe the behavior of mutant cell, it may be converted to second stage mutancy even without taking the intermediate stage of premalignancy. In this model we have assumed that there are some arrivals directly to second stage of cancer from the stage of mutancy.

Stochastic Model

A stochastic model for two 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' premalignant cells and 'm' malignant cells initially at time't'. Let 'α','β','γ','δ','θ' be the rates of arrival to premalignancy, rate of arrival to malignancy, rate of transformation from premalignancy to malignancy, rate of death of premalignant cell without transforming to malignancy, rate of death of malignant cells respectively and they are all poisson parameters. The probability of arrival of one premalignant cell during Δt is $\alpha\,\Delta t + 0(\Delta t)$; The probability of arrival of one malignant cell during Δt

is $\beta\,\Delta t + 0(\Delta t)$; The probability of transformation of premalignant cell to malignant cell provided there exists 'n' premalignant cells already at time 't' is $n\gamma\,\Delta t + 0(\Delta t)$; The probability of death of one premalignant cell provided ∃ 'n' premalignant cells already at time't' is $n\delta\Delta t + 0(\Delta t)$; The probability of death of one malignant cell provided ∃ 'm' malignant cells at time't' is $m\theta\Delta t + 0(\Delta t)$; The probability of no arrival of premalignant cell, no arrival of malignant, no transformation from premalignancy to malignancy, no death of premalignant cell and no death of malignant cell during an infinitesimal interval of time Δt is $1 - [\alpha + \beta + n(\gamma + \delta) + m\theta]\Delta t + 0(\Delta t)$; The probability of occurrence of other than the above events during an infinitesimal interval of time Δt is $0(\Delta t)^2$;

Let $p_{n,m}(t)$ be the joint probability of existence of 'n' premalignant cells and 'm' malignant cells in a tumor per unit time't' ,Then the difference differential equations of the model are:

$$p'_{n,m}(t) = -\,[\alpha + \beta + n(\gamma + \delta) + m\theta]\,p_{n,m}(t) + (\alpha)\,p_{n-1,m}(t) + (n+1)\delta p_{n+1,m}(t) + (n+1)\gamma\,p_{n+1,m-1}(t) + (\beta)p_{n,m-1}(t) + (m+1)\theta\,p_{n,m+1}(t)$$

for n,m≥1 (2.1)

$$p'_{1,0}(t) = -\,(\alpha + \beta + \gamma + \delta)p_{1,0}(t) + \alpha\,p_{0,0}(t) + 2\delta\,p_{2,0}(t) + \theta\,p_{1,1}(t) \quad (2.2)$$

$$p'_{0,1}(t) = -\,(\alpha + \beta + \gamma)p_{0,1}(t) + \delta\,p_{1,1}(t) + \gamma\,p_{1,0}(t) + \beta\,p_{0,0}(t) + 2\theta\,p_{0,2}(t) \quad (2.3)$$

$$p'_{0,0}(t) = -\,(\alpha + \beta)p_{0,0}(t) + \delta\,p_{1,0}(t) + \theta\,p_{0,1}(t) \quad (2.4)$$

With the initial conditions

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

i.e., initially there are N_0 premalignant cells and M_0 malignant cells.

Where N_0, M_0 are the initial sizes of the premalignant and the malignant cells in the tumor.

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

Where

$$p(x, y; t) = \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} x^n y^m\,p_{n,m}(t) \quad (2.5)$$

Multiplying the equation (2.1) to (2.4) with $x^n y^m$ and summing overall m and n, we obtain

$$\sum_{m=0}^{\infty}\sum_{n=0}^{\infty} x^n y^m\, p'_{n,m}(t)$$

$$= \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} \left[-[\alpha+\beta+n(\gamma+\delta)+m\theta]x^n y^m\, p_{n,m}(t)\right]$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} \alpha\, x^n y^m\, p_{n-1,m}(t)$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (n+1)\delta\, x^n y^m\, p_{n+1,m+1}(t)$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (n+1)\gamma\, x^n y^m\, p_{n+1,m-1}(t)$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} \beta\, x^n y^m\, p_{n,m-1}(t)$$
$$+ \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} (m+1)\theta\, x^n y^m\, p_{n,m+1}(t) \qquad (2.6)$$

On simplifying the equation (2.6) we get,

$$\frac{\partial}{\partial t}p(x,y;t) = [\alpha(x-1)+\beta(y-1)]\,p(x,y;t)] + [-(\gamma+\delta)\,x+\delta$$
$$+ \gamma y\,\frac{\partial}{\partial x}\,p(x,y;t) + [\theta(1-y)]\frac{\partial}{\partial y}p(x,y;t) \qquad (2.7)$$

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

$$\frac{\partial}{\partial t}k(u,v;t) = [-(\gamma+\delta)+\gamma\, e^{-u+v} + \delta\, e^{-u}]\frac{\partial k}{\partial u} + \theta(\, e^{-v}-1)\frac{\partial k}{\partial v}$$
$$+ [\alpha(\, e^u-1)\, e^v + \beta(\, e^v-1)]\, k(u,v;t) \qquad (2.8)$$

Differential Equations & Statistical Measures

Let $m_{i,j}(t)$ denotes the moments of order (i,j) of premalignant and malignant cells at time 't'

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

$$\frac{d}{dt}m_{1,0}(t) = -(\gamma+\delta)m_{1,0}(t) + \alpha \quad (3.1)\quad \frac{d}{dt}m_{0,1}(t) = \gamma\, m_{1,0}(t) - \theta\, m_{0,1}(t) \qquad (3.2)$$

$$\frac{d}{dt}m_{2,0}(t) = (\delta+\gamma)m_{1,0}(t) - 2(\delta+\gamma)m_{2,0}(t) \qquad (3.3)$$

$$\frac{d}{dt}m_{1,1}(t) = -\gamma\, m_{1,0}(t) + \gamma\, m_{2,0}(t) - (\delta+\gamma+\theta)m_{1,1}(t) \qquad (3.4)$$

$$\frac{d}{dt}m_{0,2}(t) = \gamma\, m_{1,0}(t) + 2\,\gamma\, m_{1,1}(t) + \theta\, m_{0,1}(t) - 2\theta\, m_{0,2}(t) + \beta \qquad (3.5)$$

Solving the equation 3.1 we get,

$$m_{1,0}(t) = \frac{\alpha}{\gamma+\delta} + \left[N_0 - \frac{\alpha}{\gamma+\delta}\right] e^{-(\gamma+\delta)t} \qquad (3.6)$$

On simplifying the equation 3.6 we get,
Expected number of premalignant cells at time't' is

$$m_{1,0}(t) = \frac{\alpha}{\gamma+\delta} + \left[1 - e^{-(\gamma+\delta)t}\right] + + N_0 e^{-(\gamma+\delta)t} \qquad (3.7)$$

Substituting the equation 3.7 in the equation 3.2 and on solving the resultant we get,

$$m_{0,1}(t) = \frac{\alpha\,\gamma}{\gamma+\delta}\frac{1}{\theta} + \frac{\alpha\,\gamma}{\gamma+\delta}\frac{e^{-(\gamma+\delta)t}}{(\gamma+\delta)-\theta} - N_0\gamma\,\frac{e^{-(\gamma+\delta)t}}{(\gamma+\delta)-\theta} + \frac{\beta}{\theta} + \left[M_0 - \frac{\alpha\,\gamma}{\gamma+\delta}\frac{1}{\theta} - \frac{\alpha\,\gamma}{\gamma+\delta}\frac{1}{(\gamma+\delta)-\theta} + N_0\gamma\,\frac{1}{(\gamma+\delta)-\theta} - \frac{\beta}{\theta}\right] e^{-\theta t} \qquad (3.8)$$

On simplifying the equation 3.8 we get, Expected number of malignant cells at time 't' is

$$m_{0,1}(t) = \frac{\alpha\,\gamma}{\gamma+\delta}\left[\frac{1-e^{-\theta t}}{\theta} + \frac{e^{-(\gamma+\delta)t} - e^{-\theta t}}{(\gamma+\delta)-\theta}\right] - \frac{N_0\gamma}{(\gamma+\delta)-\theta}\left[e^{-(\gamma+\delta)t} - e^{-\theta t}\right] + \frac{\beta}{\theta}\left(1 - e^{-\theta t}\right) + M_0 e^{-\theta t} \qquad (3.9)$$

Substituting the equation 3.6 in the equation 3.3 we get,

$$\frac{d}{dt}m_{2,0}(t) + 2(\delta+\gamma)m_{2,0}(t) = (\delta+\gamma)\left[\left[\frac{\alpha}{\gamma+\delta} + \left[N_0 - \frac{\alpha}{\gamma+\delta}\right]\right] e^{-(\gamma+\delta)t}\right] + \alpha \qquad (3.10)$$

Solving the equation 3.10 we get, Variance of number of premalignant cells at time 't' is

$$m_{2,0}(t) = \frac{\alpha}{\gamma+\delta}\left[1 - e^{-(\gamma+\delta)t}\right] + N_0 e^{-(\gamma+\delta)t}\left[1 - e^{-(\gamma+\delta)t}\right] \qquad (3.11)$$

Substituting the equation 3.6 and 3.4 and solving the equation we get,
Covariance of number of premalignant cells and malignant cells at time 't' is

$$m_{1,1}(t) = \frac{N_0\gamma}{(\gamma+\delta)-\theta}\left[e^{-2(\gamma+\delta)t} - e^{-(\theta+\gamma+\delta)t}\right] \qquad (3.12)$$

Substituting the equation (3.12), (3.9) and (3.12) in the equation (3.5) and solving

we get

$$\Rightarrow m_{0,2}(t) = \frac{\alpha\,\gamma}{\gamma+\delta}\left[\frac{1}{\theta} + \frac{\mathrm{e}^{-(\gamma+\delta)\mathrm{t}}}{(\gamma+\delta)-\theta} - \frac{\gamma+\delta}{\theta(\gamma+\delta-\theta)}\mathrm{e}^{-\theta\mathrm{t}}\right] + \frac{N_0\gamma}{(\gamma+\delta)-\theta}\left[\mathrm{e}^{-\theta\mathrm{t}} - \mathrm{e}^{-(\gamma+\delta)\mathrm{t}}\right] + \frac{\gamma^2}{(\gamma+\delta-\theta)^2}\left[\left(2\mathrm{e}^{-\theta\mathrm{t}} - \mathrm{e}^{-(\gamma+\delta)\mathrm{t}}\right)\mathrm{e}^{-(\gamma+\delta)\mathrm{t}}\right] + \frac{\beta}{\theta}\left(1-\mathrm{e}^{-\theta\mathrm{t}}\right) + M_0\mathrm{e}^{-\theta\mathrm{t}} + const\ \mathrm{e}^{-2\theta\mathrm{t}} \quad (3.13)$$

On simplifying the equation 3.13 we get, Variance of number of malignant cells at time 't' is

$$m_{0,2}(t) = \frac{\alpha\,\gamma}{\theta(\gamma+\delta-\theta)}\left(1-\mathrm{e}^{-\theta\mathrm{t}}\right) + \frac{\alpha\,\gamma}{\gamma+\delta}.\frac{\mathrm{e}^{-(\gamma+\delta)\mathrm{t}}-1}{(\gamma+\delta)-\theta} + \frac{N_0\gamma}{(\gamma+\delta)-\theta}\left[\mathrm{e}^{-\theta\mathrm{t}} - \mathrm{e}^{-(\gamma+\delta)\mathrm{t}}\right] + \frac{\gamma^2\,N_0}{(\gamma+\delta-\theta)^2}\left[\left(2\mathrm{e}^{-(\theta+\gamma+\delta)\mathrm{t}} - \mathrm{e}^{-2(\gamma+\delta)\mathrm{t}} - \mathrm{e}^{-2\theta\mathrm{t}}\right] + \frac{\beta}{\theta}\left(1-\mathrm{e}^{-\theta\mathrm{t}}\right) + M_0\mathrm{e}^{-\theta\mathrm{t}}\left(1-\mathrm{e}^{-\theta\mathrm{t}}\right) \quad (3.14)$$

Sensitivity Analysis

From equations (3.7), (3.9), (3.11), (3.12) and (3.14) the values of $m_{1,0}(t)$ $m_{0,1}(t)$, $m_{2,0}(t)$, $m_{1,1}(t)$ and $m_{0,2}(t)$ are computed respectively for various values of the parameters and presented in the table –I.

Table I: values of $m_{1,0}$, $m_{0,1}$, $m_{2,0}$, $m_{1,1}$, $m_{0,2}$ for varing values of the parameters like α, β, γ, δ, θ and t and also the initial sizes of Normal cells (N_o) and Mutant cells (M_o).

N_o	M_0	α	β	γ	δ	θ	t	m_{10}	m_{01}	m_{20}	m_{11}	m_{02}
102	50	0.9	0.5	0.4	1	5	2	6.806	0.838	6.429	-0.042	0.833
104								6.928	0.852	6.543	-0.043	0.847
106								7.05	0.865	6.658	-0.044	0.86
108								7.171	0.879	6.772	-0.044	0.874
110								7.293	0.892	6.886	-0.045	0.887
100	100	0.9	0.5	0.4	1	5	2	6.685	0.827	6.315	-0.041	0.822
	150							6.685	0.829	6.315	-0.041	0.824
	200							6.685	0.831	6.315	-0.041	0.827
	250							6.685	0.834	6.315	-0.041	0.829
	300							6.685	0.836	6.315	-0.041	0.831
100	50	1	0.5	0.4	1	5	2	6.752	0.83	6.382	-0.041	0.825
		1.5						7.087	0.856	6.717	-0.041	0.851
		2						7.423	0.882	7.053	-0.041	0.878

		2.5						7.758	0.908	7.388	-0.041	0.904
		3						8.094	0.934	7.724	-0.041	0.93
100	50	0.9	0.55	0.4	1	5	2	6.685	0.835	6.315	-0.041	0.83
			0.6					6.685	0.845	6.315	-0.041	0.84
			0.65					6.685	0.855	6.315	-0.041	0.85
			0.7					6.685	0.865	6.315	-0.041	0.86
			0.75					6.685	0.875	6.315	-0.041	0.87
100	50	0.9	0.5	0.44	1	5	2	6.203	0.846	5.888	-0.039	0.841
				0.48				5.758	0.862	5.49	-0.037	0.857
				0.52				5.347	0.874	5.118	-0.034	0.869
				0.56				4.967	0.881	4.772	-0.032	0.876
				0.6				4.616	0.884	4.45	-0.029	0.879
100	50	0.9	0.5	0.4	1.2	5	2	4.616	0.624	4.45	-0.02	0.621
					1.3			3.849	0.546	3.738	-0.013	0.545
					1.4			3.219	0.482	3.144	-0.01	0.48
					1.5			2.7	0.427	2.65	-0.01	0.426
					1.6			2.273	0.381	2.24	-0.004	0.38
100	50	0.9	0.5	0.4	1	6	2	6.685	0.652	6.315	-0.032	0.649
						7		6.685	0.54	6.315	-0.026	0.538
						8		6.685	0.461	6.315	-0.022	0.459
						9		6.685	0.402	6.315	-0.019	0.401
						10		6.685	0.357	6.315	-0.017	0.356
100	50	0.9	0.5	0.4	1	5	3	2.133	0.317	2.11	-0.0025	0.317
							4	1.01	0.192	1.009	-0.00015	0.192
							5	0.733	0.161	0.733	-0.00001	0.161
							6	0.665	0.154	0.665	0	0.154
							7	0.648	0.152	0.648	0	0.152

It is observed from table 1 that, expected number of premalignant cells; expected number of malignant cells; covariance of premalignant and malignant cells ; variance of premalignant cells and variance of malignant cells are increasing functions of initial number of premalignant cells (N_0) when all other parameters are constant. It is also observed that expected number of premalignant cells; variance of premalignant cells and co-variances of premalignant and malignant cells are invariant of change of initial number of malignant cells (M_0) when all other parameters are constant. It is further observed that expected number of malignant cells and variance of malignant cells are increasing functions of initial number of malignant cells (M_0) when all other parameters are constant.

It is observed that expected number of premalignant cells; variance of premalignant cells and variance of malignant cells are increasing functions and co-variance of premalignant cells and malignant cells are invariant of rate of generation of premalignant cells (α) when all the other parameters are constant. It is observed that expected number of premalignant cells; variance of pre malignant cells and co-

variance of premalignant and malignant cells are invariant of rate of generation of malignant cells (β) when all other parameters are constant. It is also observed that expected no of malignant cells and variances of malignant cells are increasing functions of rate of generation of malignant cells (β) when all the other parameters are constant. It is observed that expected number of premalignant cells; expected number of malignant cells; variance of premalignant cells; co-variance of premalignant and malignant cells are decreasing functions of rate of transformation malignant cells from premalignant cells (γ) when all other parameters are constant. It is also observed that variance of malignant cells is an increasing function of rate of transformation of malignant cells from premalignant cell (γ) when all other parameters are constant.

It is observed that the expected numbers of premalignant cells; expected numbers of malignant cells; variance of premalignant and malignant cells; co-variance of premalignant and malignant cells are decreasing functions of rate of death of pre malignant cells (δ) when all other parameters are constant. It is observed that expected no of premalignant cells and variance of premalignant cells are invariant of rate of death of malignant cells (θ) when all other parameters are constant. It is also observed that expected number of malignant cells; variance of malignant cells and co-variance of premalignant and malignant cells are decreasing functions of death of malignant cells (θ) when all other parameters are constant.

It is observed that expected number of premalignant cells ; expected number of malignant cells ; variance of premalignant cells; variance of malignant cells, co variance of premalignant and malignant cells are decreasing functions of time (t) when all other parameters are constant.

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