International Journal of Multidisciplinary and Current Research ISSN: 2321-3124
Research Article Available at: http://ijmcr.com

Four Stage Stochastic Modeling of Cancer cells under Oncolytic Virotherapy

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Received 16 March 2022, Accepted 15 April 2022, Available online 18 April 2022, **Vol.10 (March/April 2022 issue)**

Abstract

In this study, a stochastic model is created for assessing the direct effect of viral concoction on the cancer cells . The first order statistical measures of the cells were estimated for the four stages of cancer derived from the difference differential equations. This estimation model might assist in the development of a new treatment time for oncolytic virotherapy.

Keywords: *Stochastic model, Oncolytic virotherapy, Poisson process, First order statistical measures*

1. Introduction

Malignant growth is a sort of sickness where cells outgrow control, partition and attack different tissues. In an individual without malignant growth, cell division is taken care of. In many tissues, solid cells partition in a controlled way and duplicate themselves to make new sound cells. With malignant growth, this ordinary cell division runs wild. Cells change their temperament since transformations have happened in their qualities. All the daughter cells of disease cells are additionally malignant.

Oncolytic Virotherapy is one of the promising treatments in the recent years which are affordable by all. In this study we have used this treatment for analyzing the growth of the cancer cells using a Stochastic Model. Here we have explored the study for the four stages of cancer namely Initial stage, Promoted stage, Tumor stage and the Metastatic stage. In each stage the growth rate of the cancer cells was studied under the presence of the viral infusion.

2. Assumptions of the stochastic model

The following assumptions are considered to develop the stochastic model. Let us suppose that the trials considered without overlapping be statistically independent. Let $\Delta\tau$ be an infinitesimal interval of time.

At time τ, suppose that there are 'n' normal cells in the initial stage, 'm' premalignant cells in the Promoted stage, 'k' malignant cells in the tumor cells and 'l'malignant cells in the metastatic stage. Let $\alpha_1$be the growth rate of the cancer cells from the normal stage to the initial stage.

Let β_1 be the growth rate of the cancer cells from the initial stage to the promoted stage, γ_1 be the growth rate of the cancer cells from the promoted stage to the tumor stage and δ_1 be the growth rate of the cancer cells from the tumor stage to the metastatic stage. Let $\lambda_1, \varepsilon_1, \mu_1, \theta_1$ be the death rate of the cells in the initial, promoted, tumor, metastatic stages respectively.

Assume that all of the above occurrences are governed by the Poisson Process.

3. Analysis of the model

Let $\{P(\tau), \tau \geq 0\}, \{Q(\tau), \tau \geq 0\}\{R(\tau), \tau \geq 0\}$ $\{S(\tau), \tau \geq 0\}$be the individual stochastic processes of the cancer cells in each stage such that $P\{P(\tau) = \mathrm{n}\} = P_{\mathrm{n}}(\tau)$, $P\{Q(\tau) = \mathrm{m}\} = P_{\mathrm{m}}(\tau)$, $P\{R(\tau) = \mathrm{k}\} = P_{\mathrm{k}}(\tau)$ and $P\{S(\tau) = \mathrm{l}\} = P_{\mathrm{l}}(\tau)$ and the joint process will be $P\{P(\tau), Q(\tau), R(\tau), S(\tau) = (\mathrm{n}, \mathrm{m}, \mathrm{k}, \mathrm{l})\} = p_{\mathrm{n,m,k,l}}(\tau)$.

In the presence of viral injection, the possibility of no transformation of normal cells to premalignant cells from the initial stage to promoted stage, Pre – malignant cells to malignant cells from promoted stage to tumor stage, Malignant cells to death cells from tumor stage to metastatic stage, no death of normal, premalignant, malignant cells at the time τ be

$$1 - [n(\alpha_1 + \lambda_1 + \alpha_{11}) + m(\beta_1 + \varepsilon_1 + \beta_{11}) + k(\gamma_1 + \mu_1 + \gamma_{11}) + l(\delta_1 + \theta_1)]\Delta\tau + O(\Delta\tau)$$

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DOI: https://doi.org/10.14741/ijmcr/v.10.2.7

The difference differential equation of the model is

$$P'_{n,m,k,l}(\tau) = -[n(\alpha_{11}+\alpha_1+\lambda_1)+m(\beta_{11}+\beta_1+\varepsilon_1)+k(\gamma_{11}+\gamma_1+\mu_1)+l(\delta_1+\theta_1)]P_{n,m,k,l}(\tau) + (n-1)\alpha_{11}P_{n-1,m,k,l}(\tau)+(n+1)\lambda_1 P_{n+1,m,k,l}(\tau)+(n+1)\beta_1 P_{n+1,m-1,k,l}(\tau)+ (m-1)\beta_{11}P_{n,m-1,k,l}(\tau)+(m+1)\varepsilon_1 P_{n,m+1,k,l}(\tau)+(m+1)\gamma_1 P_{n,m+1,k-1,l}(\tau)+ (k-1)\gamma_{11}P_{n,m,k-1,l}(\tau)+(k+1)\mu_1 P_{n,m,k+1,l}(\tau)+(k+1)\delta_1 P_{n,m,k+1,l-1}(\tau)+(l+1)\theta_1 P_{n,m,k,l+1}(\tau) \quad (1)$$

Let $p(x,y,z,w,\tau)$ be the joint probability generating function of $p_{\mathrm{n,m,k,l}}(\tau)$.

$$p(\mathrm{x,y,z,w},\tau) = \sum_{l=0}^{\infty}\sum_{k=0}^{\infty}\sum_{m=0}^{\infty}\sum_{n=0}^{\infty} x^n y^m z^k w^l\, p_{n,m,k,l}(\tau) \quad (2)$$

$$\frac{\partial}{\partial\tau}p(x,y,z,w,\tau) = \sum_{l=0}^{\infty}\sum_{k=0}^{\infty}\sum_{m=0}^{\infty}\sum_{n=0}^{\infty} x^n y^m z^k w^l \begin{Bmatrix} -\begin{bmatrix} n(\alpha_{11}+\alpha_1+\lambda_1)+m(\beta_{11}+\beta_1+\varepsilon_1)+k(\gamma_{11}+\gamma_1+\mu_1) \\ +l(\delta_1+\theta_1) \end{bmatrix} P_{n,m,k,l}(\tau) + \\ (n-1)\alpha_{11}P_{n-1,m,k,l}(\tau)+(n+1)\lambda_1 P_{n+1,m,k,l}(\tau)+(n+1)\beta_1 P_{n+1,m-1,k,l}(\tau)+ \\ (m-1)\beta_{11}P_{n,m-1,k,l}(\tau)+(m+1)\varepsilon_1 P_{n,m+1,k,l}(\tau)+(m+1)\gamma_1 P_{n,m+1,k-1,l}(\tau)+ \\ (k-1)\gamma_{11}P_{n,m,k-1,l}(\tau)+(k+1)\mu_1 P_{n,m,k+1,l}(\tau)+(k+1)\delta_1 P_{n,m,k+1,l-1}(\tau)+ \\ (l+1)\theta_1 P_{n,m,k,l+1}(\tau) \end{Bmatrix} \quad (3)$$

Remodifying the terms, we get

$$\frac{\partial}{\partial\tau}p(x,y,z,w,\tau) = [-(\alpha_{11}+\alpha_1+\lambda_1)x+\alpha_{11}x^2+\lambda_1+\beta_{11}xy]\frac{\partial}{\partial x}p(x,y,z,w,\tau)+ [-(\beta_{11}+\beta_1+\varepsilon_1)y+\gamma_{11}y^2+\varepsilon_1+\beta_1 yz]\frac{\partial}{\partial y}p(x,y,z,w,\tau)+ [-(\gamma_{11}+\gamma_1+\mu_1)z+\mu_1+\delta_1 zw]\frac{\partial}{\partial z}p(x,y,z,w,\tau)+ [-(\delta_1+\theta_1)w+\theta_1 w^2]\frac{\partial}{\partial w}p(x,y,z,w,\tau) \quad (4)$$

To find the moments of the first order, let $x=e^a, y=e^b, z=e^c, w=e^d$ and $Q(a,b,c,d,\tau)$ be the joint cumulant generating function of $p_{n,m,k,l}(\tau)$.

$$\frac{\partial}{\partial\tau}Q(a,b,c,d,\tau) = [-(\alpha_{11}+\alpha_1+\lambda_1)+\alpha_{11}e^a+\lambda_1 e^{-a}+\beta_{11}e^b]\frac{\partial Q}{\partial a}+ [-(\beta_{11}+\beta_1+\varepsilon_1)+\gamma_{11}e^b+\varepsilon_1 e^{-b}+\beta_1 e^c]\frac{\partial Q}{\partial b}+ [-(\gamma_{11}+\gamma_1+\mu_1)+\mu_1 e^{-c}+\delta_1 e^d]\frac{\partial Q}{\partial c}+ [-(\delta_1+\theta_1)+\theta_1 e^d]\frac{\partial Q}{\partial d} \quad (5)$$

Let $S_{u,v,w,r}(\tau)$ denotes the moments of the tumor cells in each stage at timeτ.

Equating the coefficients of a's, b's, c's and d's. We get

$$\frac{\partial}{\partial\tau}S_{1,0,0,0}(\tau) = (\alpha_{11}-\alpha_1-\lambda_1)S_{1,0,0,0}(\tau) \quad (6)$$

$$\frac{\partial}{\partial\tau}S_{0,1,0,0}(\tau) = \alpha_1 S_{1,0,0,0}(\tau)-(\beta_{11}-\beta_1-\varepsilon_1)S_{0,1,0,0}(\tau) \quad (7)$$

$$\frac{\partial}{\partial\tau}S_{0,0,1,0}(\tau) = \beta_1 S_{0,1,0,0}(\tau)+(\gamma_{11}-\gamma_1-\mu_1)S_{0,0,1,0}(\tau) \quad (8)$$

$$\frac{\partial}{\partial\tau}S_{0,0,0,1}(\tau) = \mu_1 S_{0,0,1,0}(\tau)+(\delta_1-\theta_1)S_{0,0,0,1}(\tau) \quad (9)$$

Solving the above equations, we get

Average growth of cancer cells from the normal stage to initial stage at 'τ':

$$S_{1,0,0,0}(\tau) = N_0 e^{(\alpha_{11}-\alpha_1-\lambda_1)(\tau)}$$

Average growth of cancer cells from the initial stage to promoted stage at 'τ':

$$S_{0,1,0,0}(\tau) = \frac{\alpha_1 N_0\left[e^{(\alpha_{11}-\alpha_1-\lambda_1)(\tau)}-e^{(\beta_{11}-\beta_1-\varepsilon_1)(\tau)}\right]}{\alpha_{11}-\alpha_1-\lambda_1-\beta_{11}+\beta_1+\varepsilon_1}+M_0 e^{(\beta_{11}-\beta_1-\varepsilon_1)(\tau)}$$

Average growth of cancer cells from promoted stage to tumor stage at 'τ':

$$S_{0,0,1,0}(\tau)=\frac{\alpha_1\beta_1 e^{(\gamma_{11}-\gamma_1-\mu_1)(\tau)}N_0}{\alpha_{11}-\alpha_1-\lambda_1-\beta_{11}+\beta_1+\varepsilon_1}\left\{\frac{e^{(\alpha_{11}-\alpha_1-\lambda_1-\gamma_{11}+\gamma_1+\mu_1)(\tau)}}{\alpha_{11}-\alpha_1-\lambda_1-\gamma_{11}+\gamma_1+\mu_1}-\frac{e^{(\beta_{11}-\beta_1-\varepsilon_1-\gamma_{11}+\gamma_1+\mu_1)(\tau)}}{\beta_{11}-\beta_1-\varepsilon_1-\gamma_{11}+\gamma_1+\mu_1}\right\}+\frac{\beta_1 M_0 e^{(\beta_{11}-\beta_1-\varepsilon_1)(\tau)}}{\beta_{11}-\beta_1-\varepsilon_1-\gamma_{11}+\gamma_1+\mu_1}+\frac{\beta_1 e^{(\gamma_{11}-\gamma_1-\mu_1)(\tau)}}{\beta_{11}-\beta_1-\varepsilon_1-\gamma_{11}+\gamma_1+\mu_1}$$

Average number of cancer cells from tumor stage to metastatic stage at time 'τ':

$$S_{0,0,0,1}(\tau)=\frac{\mu_1\beta_1 e^{(\delta_1-\theta_1)(\tau)}N_0}{\alpha_{11}-\alpha_1-\lambda_1-\beta_{11}+\beta_1+\varepsilon_1}\left\{\frac{e^{(\alpha_{11}-\alpha_1-\lambda_1-\delta_1+\theta_1)(\tau)}}{\alpha_{11}-\alpha_1-\lambda_1-\delta_1+\theta_1}-\frac{e^{(\beta_{11}-\beta_1-\varepsilon_1-\delta_1+\theta_1)(\tau)}}{\beta_{11}-\beta_1-\varepsilon_1-\delta_1+\theta_1}\right\}+\frac{\mu_1 M_0 e^{(\beta_{11}-\beta_1-\varepsilon_1)(\tau)}}{\beta_{11}-\beta_1-\varepsilon_1-\delta_1+\theta_1}+\frac{\mu_1 K_0 e^{(\gamma_{11}-\gamma_1-\mu_1)(\tau)}}{\gamma_{11}-\gamma_1-\mu_1-\delta_1+\theta_1}+\frac{\mu_1 e^{(\delta_1-\theta_1)(\tau)}}{\gamma_{11}-\gamma_1-\mu_1-\delta_1+\theta_1}$$

4. Illustration

The values established here are taken arbitrarily under specific uncertainties and it tends to be altered. The impact of the moments depends correspondingly. For the particular values of the parameters and varying the normal cells under virotheraphy, the analysis has been done and given below.

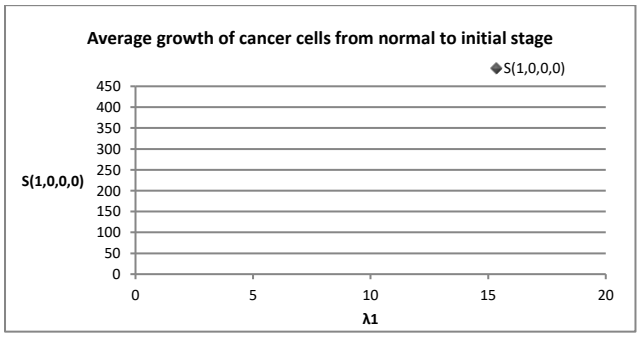

Figure 1

Considering the fixed values for all the parameters and varying only the values of one parameter, it is observed that under the continuous implication of Oncolytic Virotheraphy, the increase in the death of cancer cells from the normal to initial stage results in the constant maintenance of the cancer cells from the normal to initial stage.

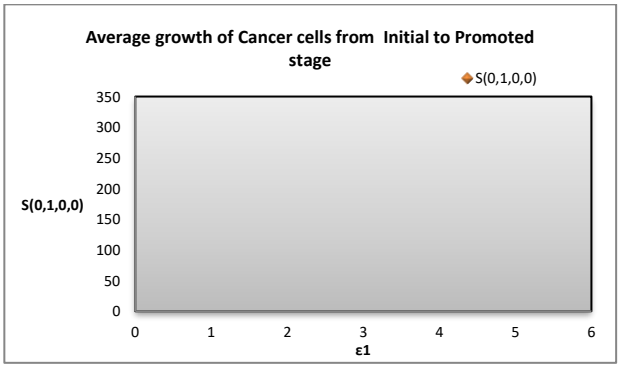

Figure 2

The second figure represents the variation of the growth of the malformed cells which is decreasing from the initial to Promoted stage keeping all the other parameters fixed and increasing the death rate of cancer cells under continuous monitoring of Oncolytic Virotherapy.

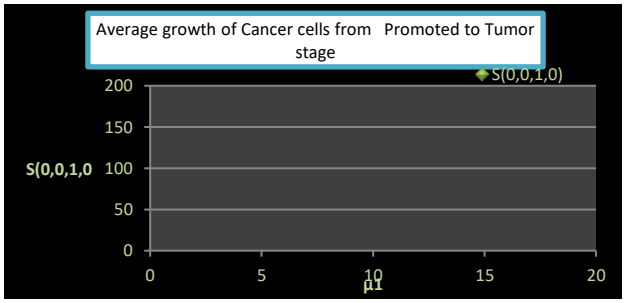

Figure 3

The third figure represents the variation of the growth of the abnormal cells remains stable from the Promoted to Tumor stage keeping all the other parameters fixed and increasing the death rate of cancer cells under continuous screening of Oncolytic Virotherapy.

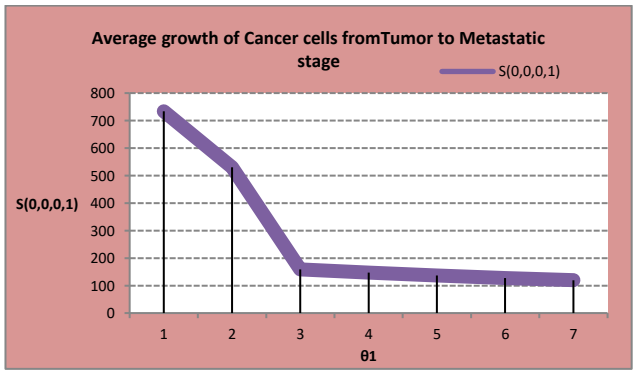

Figure 4

The fourth figure corresponds to the deviation of the growth of the malformed cells which is decreasing from the Tumor to Metastatic stage keeping all the other parameters fixed and increasing the death rate of cancer

cells under uninterrupted examining of Oncolytic Virotherapy.

Conclusion

It is observed that, under the uninterrupted screening of Oncolytic Virotherapy, the growth rate of the cancer cells either remains stable or declines while transforming from one stage to another stage. Hence in the upcoming era of cancer treatments, this therapy would be an affordable and emerging one. In the future study, the amalgamation of other therapy treatments can be made with this virotherapy to make better cure.

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