International Journal of Applied Mathematics
& Statistical Sciences (IJAMSS)
ISSN(P): 2319-3972; ISSN(E): 2319-3980
Vol. 5, Issue 6, Oct - Nov 2016; 43-52

International Academy of Science,
Engineering and Technology
Connecting Researchers; Nurturing Innovations

STABILITY ANALYSIS OF CRITICAL POINTS TO CONTROL GROWTH OF TUMOR IN AN IMMUNE-TUMOR-NORMAL CELL-DRUG MODEL

RANU PAUL

Department of Mathematics, Pandu College, Guwahati, Assam

ABSTRACT

In this paper we attempted to present a policy to control an immune cell-tumor cell-normal cell-drug model proposed by Pillis ET all. The drug administered to the patient in the form of chemotherapy is assumed to be time dependent and follows a definite rule. It is also assumed that the drug kills all types of cells. In this paper we assumed that the drug administration follows either of the three different mathematical laws viz. (1) Logistic law, (2) Exponential law and (3) Oscillatory law. Stability analyses of the tumor free critical points are done to find a range for the amount of drug to be administered to the patient.

KEYWORDS: Control an Immune Cell-Tumor Cell-Normal Cell-Drug Model

INTRODUCTION

The growth of cancerous tumor is a very complex phenomenon that includes many biological interactions. Till date many authors has proposed many tumor cell growth models and has suggested various control policies including treatment such as surgery, radiotherapy, drug therapy (Chemotherapy) [3],[4],[5],[6],[7],[8],[9],[10],[11],[13],[14]. In 2000, Pillis et all proposed a tumor growth model that involves immune cells, tumor cells and normal cells [12]. In the model proposed by Pillis et all, the immune cells and the tumor cells compete in a predator prey fashion whereas the normal cells and the tumor cells compete for available resources. The drug administered is assumed to kill all types of cells with different kill rates. In [2], the authors studied an almost similar model with the difference that the normal cells were not considered to interfere in the tumor growth model, with the drug administration following any of the three laws namely the logistic law, the exponential law and the oscillatory law. In this paper we have considered the tumor model suggested by Pillis et all [12], in which we have assumed that the tumor cells has no effect on the growth of normal cells as the number of tumor cells are negligible as compared to that of normal cells and so the normal cells does not need to compete with the tumor cells for the available resources whereas the normal cells effects the growth of tumor cells. This is possible as because we have considered the model for small sized tumor. We have assumed the drug administration in terms of chemotherapy follows one of the three basic mathematical laws viz. the logistic law, the exponential law and the oscillatory law.

Main Study

The model proposed by Pillis ET all in [12] is

$$\frac{dI}{dt} = s + \frac{\rho IT}{\sigma + T} - c_1 IT - d_1 I - a_1(1 - e^{-V})I$$

$$\frac{dT}{dt} = r_1 T(1 - b_1 T) - c_2 IT - c_3 TN - a_2(1 - e^{-V})T$$

$$\frac{dN}{dt} = r_2 N(1 - N) - c_4 TN - a_3(1 - e^{-V})N$$

$$\frac{dV}{dt} = f(V)$$

Where, $I(t)$,$T(t)$, $N(t)$ and $V(t)$ denotes the number of immune cells, tumor cells, normal cells and the amount of drug administered at time t respectively. The units of cells are normalized by taking the carrying capacity of normal cells to be one.

Here, s = the constant number of immune cells present in the body.

σ = Steepness coefficients.

ρ = Recruitment rate of immune cells stimulated by the presence of tumor cells

$d1$= Natural death rate of immune cells.

r_1= Intrinsic tumor growth rate.

$1/b_1$ = Tumor population carrying capacity.

a_1, a_2 and a_3 are the kill rates of immune cells, tumor cells and normal cells respectively due to drug administration.

In the above model we have considered a small sized tumor so that the number of tumor cells is negligible as compared to that of normal cells. So the tumor cells has no significant effect on the growth of normal cells. Thus we can choose the value of the parameter c_4 to be zero.

As studied by the authors in [2], we also assumed three different drug administration model as given below:

The drug equation as per logistic growth is as follows:

$$\frac{dV}{dt} = \alpha_3 V(1 - \beta_3 V) \quad (1)$$

The drug equation as per exponential growth is as follows:

$$\frac{dV}{dt} = \alpha_3 e^{-\beta_3 V} - \gamma_3 \quad (2)$$

The drug equation as per oscillatory growth is as follows:

$$\frac{dV}{dt} = \alpha_3 Sin(\beta_3 V) \quad (3)$$

Where α_3 = intrinsic rate of drug application, $1/\beta_3$ = maximum drug carrying capacity, α_3 = a constant rate of reduction of drug.

Since the main objective of drug administration is to make the tumor size zero so we have considered the tumor free equilibrium points and analyzed their stability.

Logistic Drug Administration Model

$\frac{dV}{dt} = 0 \Rightarrow V = 0 \; or \; V = {}^{1}/_{\beta_3}$

When, $V = 0$, $\frac{dT}{dt} = 0$ gives $T = 0$ or $T = \frac{r_1 - c_2 I - c_3 N}{b_1 r_1}$

When, $V = 0$, $T = 0$, $\frac{dN}{dt} = 0$ gives $N = 0$ or $N = 1$

But $N = 0$ is the dead case and so it is discounted.

So when, $V = 0$, $T = 0$, $N = 1$, $\frac{dI}{dt} = 0$ gives $I = {}^{s}/_{d_1} = I_0(say)$

Thus a tumor free equilibrium point is $A(I_0, 0,1,0)$, which is also drug free.

Again for $V = {}^{1}/_{\beta_3}$, $\frac{dT}{dt} = 0$ gives $T = 0$ or $T = \frac{r_1 - c_2 I - c_3 N - a_2(1 - e^{-{}^{1}/_{\beta_3}})}{b_1 r_1}$

For $V = {}^{1}/_{\beta_3}$, $T = 0$, $\frac{dN}{dt} = 0$ gives $N = 0$ or $N = 1 - \frac{a_3(1 - e^{-{}^{1}/_{\beta_3}})}{r_2} = N_1(say)$

When, $V = {}^{1}/_{\beta_3}$, $T = 0$, $N = N_1$ then $\frac{dI}{dt} = 0$ gives $I = \frac{s}{d_1 + a_1(1 - e^{-{}^{1}/_{\beta_3}})} = I_1(say)$

Thus another tumor free equilibrium point is $B(I_1, 0, N_1, {}^{1}/_{\beta_3})$.

The Jacobian matrix of the tumor growth model for the logistic drug administration at the equilibrium point A is,

$$J_A^L = \begin{pmatrix} -d_1 & \frac{\rho I_0}{\sigma} - c_1 I_0 & 0 & -a_1 I_0 \\ 0 & r_1 - c_2 I_0 - c_3 & 0 & 0 \\ 0 & 0 & -r_2 & -a_3 \\ 0 & 0 & 0 & \alpha_3 \end{pmatrix}$$

The eigen values of J_A^L are:

$\lambda_1 = -d_1$, $\lambda_2 = r_1 - c_2 I_0 - c_3$, $\lambda_3 = -r_2$ and $\lambda_4 = \alpha_3$.

The equilibrium point A is stable only when $\lambda_1, \lambda_2, \lambda_3 \; and \; \lambda_4$ are all less than zero. But $\lambda_4 = \alpha_3 < 0$ is not possible because negative drug administration is not a realistic case Thus there does not exist any tumor free drug free stable equilibrium point i.e. the tumor size can not be diminished to zero without drug administration and this is a very realistic case.

The Jacobian matrix of the tumor growth model for the logistic drug administration at the equilibrium point B is,

$$J_B^L = \begin{pmatrix} -d_1 - a_1(1 - e^{-{}^{1}/_{\beta_3}}) & \frac{\rho I_1}{\sigma} - c_1 I_1 & 0 & -a_1 e^{-{}^{1}/_{\beta_3}} I_1 \\ 0 & r_1 - c_2 I_1 - c_3 N_1 - a_2(1 - e^{-{}^{1}/_{\beta_3}}) & 0 & 0 \\ 0 & 0 & (1 - 2N_1) r_2 - a_3(1 - e^{-{}^{1}/_{\beta_3}}) & -a_3 e^{-{}^{1}/_{\beta_3}} N_1 \\ 0 & 0 & 0 & -\alpha_3 \end{pmatrix}$$

The eigen values of J_B^L are:

$\lambda_1 = -d_1 - a_1(1 - e^{-{}^{1}/_{\beta_3}})$,

$\lambda_2 = r_1 - c_2 I_1 - c_3 N_1 - a_2(1 - e^{-1/\beta_3})$,

$\lambda_3 = (1 - 2N_1)r_2 - a_3(1 - e^{-1/\beta_3})$

and $\lambda_4 = -\alpha_3$.

Since $\lambda_4 = -\alpha_3 < 0$ is obvious so for B to be stable, we must have, $\lambda_1 < 0$, $\lambda_2 < 0$ and $\lambda_3 < 0$.

$\lambda_1 < 0$ gives $\frac{1}{\beta_3} > Log(\frac{a_1}{a_1+d_1})$, which holds for any β_3 because $\frac{a_1}{a_1+d_1} < 1 => \frac{1}{Log(\frac{a_1}{a_1+d_1})} < 0$ but $\frac{1}{\beta_3} > 0$ ($\frac{1}{\beta_3}$ represents the maximum amount of drug administration and so it is positive).

$\lambda_3 < 0$ gives $\beta_3 > \frac{1}{Log(\frac{a_3}{a_3-r_2})}$. But this happens only when$a_3 - r_2 > 0$.

Again $\lambda_2 < 0$ gives $\beta_3 < \frac{1}{Log(\frac{n}{n-m})}$, where $m = r_1 - c_3 - \frac{c_2 s}{d_1}$ and $n = -\frac{c_2 a_3}{r_2} + a_2$

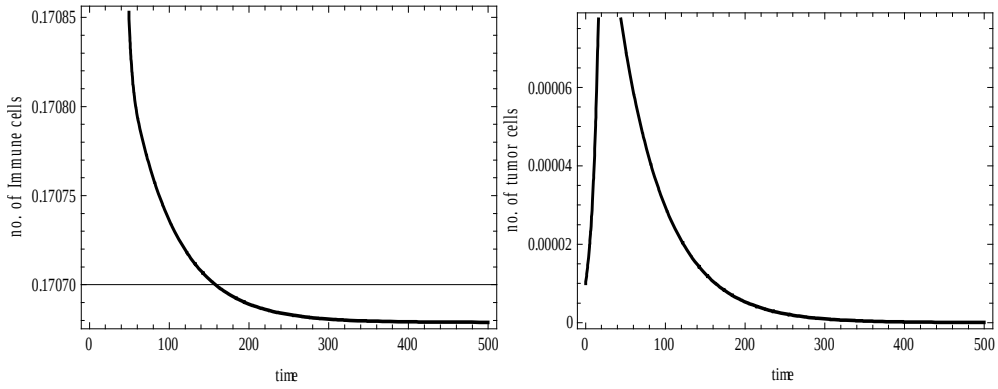
Thus for the tumor free equilibrium point B to be stable, we must restrict the maximum amount of drug administration $\frac{1}{\beta_3}$ by the rule

$\frac{1}{Log(\frac{a_3}{a_3-r_2})} < \beta_3 < \frac{1}{Log(\frac{n}{n-m})}$ if $a_3 - r_2 > 0$

And

$0 < \beta_3 < \frac{1}{Log(\frac{n}{n-m})}$ if $a_3 - r_2 \leq 0$

The following are the plots of number of immune cells, tumor cells and normal cells Vs. time respectively for the parameter values within the restricted range for the stability of the equilibrium point B. The plots clearly shows the stability of the equilibrium point B. The parameter values we chose to plot the graphs are $s = 0.05$, $\rho = 1$, $\sigma = 0.3$, $c_1 = 0.2$, $d_1 = 0.2$, $a_1 = 0.2$, $r_1 = 0.4$, $b_1 = 1.5$, $c_2 = 0.3$, $c_3 = 0.2$, $a_2 = 0.5$, $r_2 = 0.35$, $c_4 = 0$, $a_3 = 0.25$, $\alpha_3 = 0.5$, $\beta_3 = 1.6$ and the initial points are taken as $I(0) = {}^{s}/_{d_1}$, $T(0) = 10^{-5}$, $N(0) = 0.9$, $V(0) = 10^{-5}$.



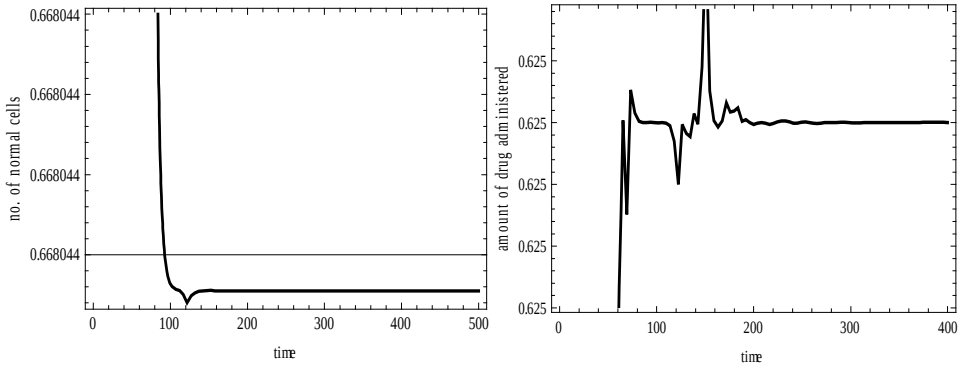


Figure 1

Exponential Drug Administration Model

$\frac{dV}{dt} = 0 \Rightarrow V = {}^{1}/_{\beta_3} Log\left(\frac{\alpha_3}{\gamma_3}\right) = V'(say)$

For $V = V'$, $\frac{dT}{dt} = 0$ gives $T = 0$ or $T = \frac{r_1 - c_2 I - c_3 N - a_2(1-e^{-V'})}{b_1 r_1}$

For $V = V'$, $T = 0$, $\frac{dN}{dt} = 0$ gives $N = 0$ or $N = 1 - \frac{a_3(1-e^{-V'})}{r_2} = N'(say)$

$N = 0$ is the dead case and so it is discounted.

When, $V = V'$, $T = 0$, $N = N'$ then $\frac{dI}{dt} = 0$ gives $I = \frac{s}{d_1 + a_1(1-e^{-V'})} = I'(say)$

Thus the only tumor free equilibrium point is $P(I', 0, N', V')$.

The Jacobian matrix of the tumor growth model for the logistic drug administration at the equilibrium point P is,

$$J_P^L = \begin{pmatrix} -d_1 - a_1(1-e^{-V'}) & \frac{\rho I'}{\sigma} - c_1 I' & 0 & -a_1 e^{-V'} I' \\ 0 & r_1 - c_2 I' - c_3 N' - a_2(1-e^{-V'}) & 0 & 0 \\ 0 & 0 & (1-2N')r_2 - a_3(1-e^{-V'}) & -a_3 e^{-V'} N' \\ 0 & 0 & 0 & -\alpha_3 \beta_3 e^{-\beta_3 V'} \end{pmatrix}$$

The eigen values of J_P^L are:

$\lambda_1 = -d_1 - a_1(1-e^{-V'})$,

$\lambda_2 = r_1 - c_2 I' - c_3 N' - a_2(1-e^{-V'})$,

$\lambda_3 = (1-2N_1)r_2 - a_3(1-e^{-V'})$ and $\lambda_4 = -\alpha_3 \beta_3 e^{-\beta_3 V'}$.

Since $\lambda_4 = -\alpha_3 \beta_3 e^{-\beta_3 V'} < 0$ always holds so for P to be stable we need only $\lambda_1 < 0$, $\lambda_2 < 0$ and $\lambda_3 < 0$

$\lambda_1 < 0$ Gives $\beta_3 < \frac{Log(\frac{\alpha_3}{\gamma_3})}{Log(\frac{a_1}{a_1 + d_1})}$ (i)

$\lambda_3 < 0$ Gives $\beta_3 > \frac{Log(\frac{\alpha_3}{\gamma_3})}{Log(\frac{a_3}{a_3 - r_2})}$, this holds only when $a_3 - r_2 > 0$ (ii)

Again $\lambda_2 < 0$ Gives $\beta_3 < \frac{Log(\frac{\alpha_3}{\gamma_3})}{Log(\frac{n}{n-m})}$, where $m = r_1 - c_3 - \frac{c_2 s}{d_1}$ and $n = -\frac{c_2 a_3}{r_2} + a_2$ (iii)

Thus for the tumor free equilibrium point P to be stable, we must restrict the maximum amount of drug administration $\frac{1}{\beta_3}$ by the rule

$$\frac{Log\left(\frac{\alpha_3}{\gamma_3}\right)}{Log\left(\frac{a_3}{a_3-r_2}\right)} < \beta_3 < Minimum\{\frac{Log\left(\frac{\alpha_3}{\gamma_3}\right)}{Log\left(\frac{a_1}{a_1+d_1}\right)}, \frac{Log\left(\frac{\alpha_3}{\gamma_3}\right)}{Log\left(\frac{n}{n-m}\right)}\} \; if \; a_3 - r_2 > 0$$

And

$$0 < \beta_3 < Minimum\{\frac{Log\left(\frac{\alpha_3}{\gamma_3}\right)}{Log\left(\frac{a_1}{a_1+d_1}\right)}, \frac{Log\left(\frac{\alpha_3}{\gamma_3}\right)}{Log\left(\frac{n}{n-m}\right)}\} \; if \; a_3 - r_2 \leq 0$$

The following are the plots of number of immune cells, tumor cells and normal cells Vs. time respectively for the parameter values within the restricted range for the stability of the equilibrium point P. The plot clearly shows the stability of the equilibrium point$P$. The parameter values we chose to plot the graphs are $s = 0.05$, $\rho = 1$, $\sigma = 0.3$, $c_1 = 0.2$, $d_1 = 0.2$, $a_1 = 0.2$, $r_1 = 0.4$, $b_1 = 1.5$, $c_2 = 0.3$, $c_3 = 0.2$, $a_2 = 0.5$, $r_2 = 0.35$, $c_4 = 0$, $a_3 = 0.25$, $\alpha_3 = 0.5$, $\gamma_3 = 0.05$, $\beta_3 = 3$ and the initial points are taken as $I(0) = {}^{S}/_{d_1}$, $T(0) = 10^{-5}$, $N(0) = 0.9$, $V(0) = 10^{-5}$.

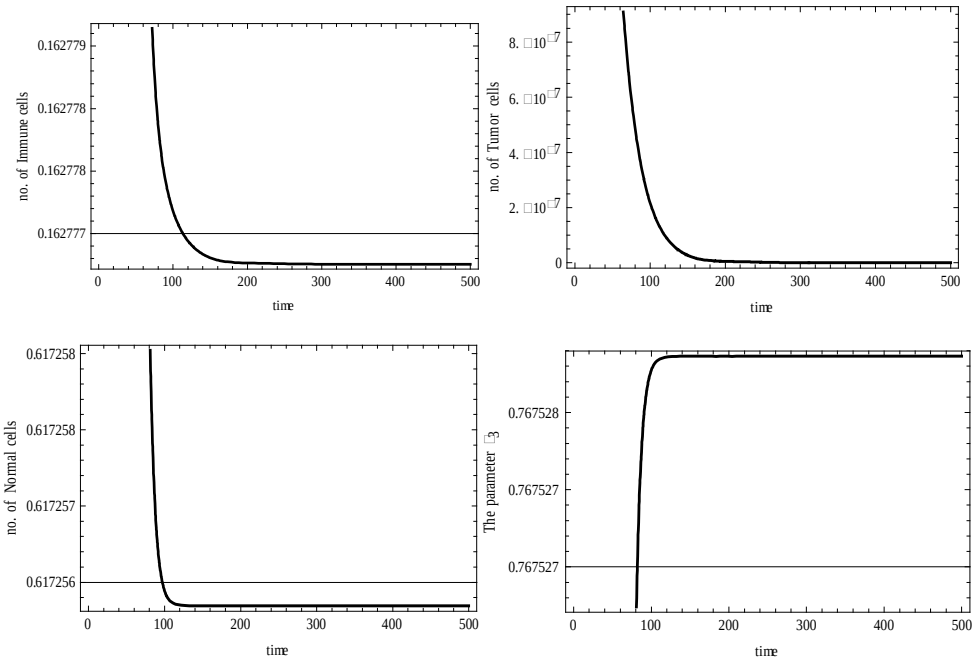


Figure 2

Oscillatory Drug Administration Model

$\frac{dV}{dt} = 0 \Rightarrow V = {}^{k\pi}/_{\beta_3} = V^*(say), where \; k \; is \; a \; positive \; integer$

For$V = V^*$, $\frac{dT}{dt} = 0$ gives $T = 0$ or $T = \frac{r_1 - c_2 I - c_3 N - a_2(1-e^{-V^*})}{b_1 r_1}$

For$V = V^*$, $T = 0$, $\frac{dN}{dt} = 0$ gives $N = 0$ or $N = 1 - \frac{a_3(1-e^{-V^*})}{r_2} = N^*(say)$

As $N = 0$ is the dead case and so it is not feasible and discounted.

When, $V = V^*, T = 0, N = N^*$ then $\frac{dI}{dt} = 0$ gives $I = \frac{s}{d_1 + a_1(1-e^{-V^*})} = I^*(say)$

Thus the only tumor free equilibrium point for this model is$Q(I^*, 0, N^*, V^*)$.

The Jacobian matrix of the tumor growth model for the logistic drug administration at the equilibrium point Q is,

$$J_Q^L = \begin{pmatrix} -d_1 - a_1(1-e^{-V^*}) & \frac{\rho I^*}{\sigma} - c_1 I^* & 0 & -a_1 e^{-V^*} I^* \\ 0 & r_1 - c_2 I^* - c_3 N^* - a_2(1-e^{-V^*}) & 0 & 0 \\ 0 & 0 & (1-2N^*)r_2 - a_3(1-e^{-V^*}) & -a_3 e^{-V^*} N^* \\ 0 & 0 & 0 & -\alpha_3\beta_3 Cos(\beta_3 V^*) \end{pmatrix}$$

The Eigen values of J_Q^L are:

$\lambda_1 = -d_1 - a_1(1-e^{-V^*})$,

$\lambda_2 = r_1 - c_2 I^* - c_3 N^* - a_2(1-e^{-V^*})$,

$\lambda_3 = (1-2N^*)r_2 - a_3(1-e^{-V^*})$ and$\lambda_4 = -\alpha_3\beta_3 Cos(\beta_3 V^*)$.

For Q to be stable$\lambda_1 < 0$, $\lambda_2 < 0$, $\lambda_3 < 0$ and $\lambda_4 < 0$ must be satisfied.

$\lambda_4 < 0 \Rightarrow Cos(\beta_3 V^*) < 0 \Rightarrow Cos(k\pi) < 0 \Rightarrow k\ is\ odd$

$\lambda_1 < 0$ gives $\frac{1}{\beta_3} > \frac{Log(\frac{a_1}{a_1+d_1})}{k\pi}$, which holds for any β_3 because $\frac{a_1}{a_1+d_1} < 1 \Rightarrow \frac{1}{Log(\frac{a_1}{a_1+d_1})} < 0$ but $\frac{1}{\beta_3} > 0$.

$\lambda_3 < 0$ gives $\beta_3 > \frac{k\pi}{Log(\frac{a_3}{a_3-r_2})}$, this holds only when $a_3 - r_2 > 0$ (b)

Again $\lambda_2 < 0$ gives $\beta_3 < \frac{k\pi}{Log(\frac{n}{n-m})}$, where $m = r_1 - c_3 - \frac{c_2 s}{d_1}$ and $n = -\frac{c_2 a_3}{r_2} + a_2$ (c)

Thus for the tumor free equilibrium point Q to be stable, we must restrict the maximum amount of drug administration $\frac{1}{\beta_3}$ by the rule

$$\frac{k\pi}{Log\left(\frac{a_3}{a_3-r_2}\right)} < \beta_3 < \frac{k\pi}{Log\left(\frac{n}{n-m}\right)}\ if\ a_3 - r_2 > 0$$

And

$$0 < \beta_3 < \frac{k\pi}{Log(\frac{n}{n-m})}\ if\ a_3 - r_2 \leq 0$$

Here k is an odd positive integer. Since we are interested in minimum drug administration so that the normal cells gets less effected, so we chose$k = 1$. Then $V^* = {}^{\pi}/_{\beta_3}$ and the relation between the parameters become

$$\frac{\pi}{Log\left(\frac{a_3}{a_3-r_2}\right)} < \beta_3 < \frac{\pi}{Log\left(\frac{n}{n-m}\right)}\ if\ a_3 - r_2 > 0$$

And

$$0 < \beta_3 < \frac{\pi}{Log(\frac{n}{n-m})} \; if \; a_3 - r_2 \leq 0$$

The following are the plots of number of immune cells, tumor cells and normal cells vs. time respectively for the parameter values within the restricted range for the stability of the equilibrium point$Q$. The plot clearly shows the stability of the equilibrium point$Q$. The parameter values we chose to plot the graphs are $s = 0.05$, $\rho = 1$, $\sigma = 0.3$, $c_1 = 0.2$, $d_1 = 0.2$, $a_1 = 0.2$, $r_1 = 0.4$, $b_1 = 1.5$, $c_2 = 0.3$, $c_3 = 0.2$, $a_2 = 0.5$, $r_2 = 0.35$, $c_4 = 0$, $a_3 = 0.25$, $\alpha_3 = 0.5$, $\beta_3 = 4.5$ and the initial points are taken as $I(0) = {}^{S}/_{d_1}$, $T(0) = 10^{-5}$, $N(0) = 0.9$, $V(0) = 10^{-5}$.

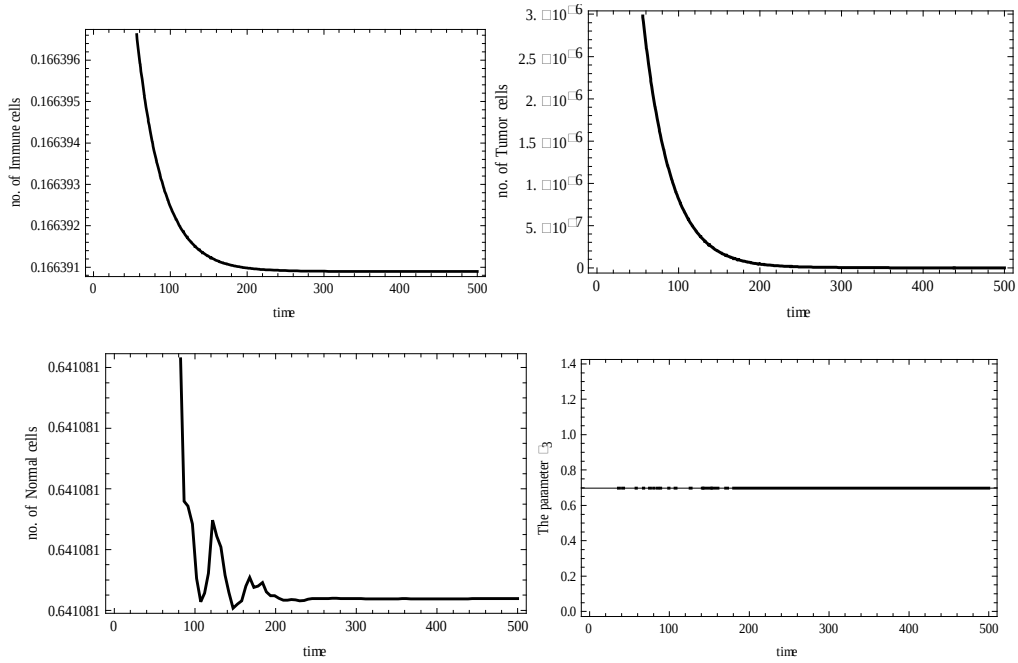


Figure 3

CONCLUSIONS

The stability of all the tumor free equilibrium points of the immune-tumor-normal cell model subjected to the three different drug administration laws are analyzed. It is found that for all the three models there does not exist any stable tumor free drug free equilibrium point whereas there exists tumor free stable equilibrium points satisfying certain conditions for the maximum drug dose.

REFERENCES

1. Devi, and A. Ghosh, On the stability of Immune-Tumor (I−T) model with the effect of drug administration, Int. Journal of Pure and Applied Mathematics, 79 (2012), no. 4, 547-560.
2. Devi and A. Ghosh, Some Control Policies for Control of Cancer, Nonlinear Analysis and Differential Equations, Vol. 4, 2016, no. 1, 27 – 41, HIKARI Ltd.
3. M. Eisen, Mathematical Models in Cell Biology and Cancer Chemotherapy, Springer-Verlag, Berlin, 1979. http://dx.doi.org/10.1007/978-3-642-93126-0
4. D. Kirschner, and J. Panetta, Modeling immunotherapy of the tumor immune interaction, Journal of Mathematical Biology, 37 (1998), no. 3, 235-252.

5. J.A. Adam, The dynamics growth-factor-modified immune response to cancer growth: One dimensional models, Mathematical and Computer Modeling, 17 (1993), no. 3, 83-106.
6. J.M. Murrey, Optimal control for a cancer chemotherapy problem with general growth and loss functions, Mathematical Biosciences, An International Journal, 98 (1990), no. 2, 273-287.
7. M. Owen, and J. Sherratt, Modeling the macrophage invasion of tumors: Effects on growth and composition, Mathematical Medicine and Biology - A Journal of the IMA, 15 (1998), no. 2, 165-185.
8. Federico Frascoli, Peter S. Kim, Barry D. Hughes, Kerry A. Landman, A dynamical model of tumor immunotherapy, Mathematical Biosciences, 253 (2014), 50-62.
9. G. B. West, J. H. Brown & B. J. Enquis, A general model for ontogenetic growth, Letters to Nature, 628-631.
10. G.W. Swan, Optimal control applications in the chemotherapy of multiple myeloma, Mathematical Medicine and Biology - A Journal of the IMA, 2 (1985), no. 3, 139-160.
11. G.W. Swan, Optimal control analysis of a cancer chemotherapy problem, Mathematical Medicine and Biology - A Journal of the IMA, 4 (1987), no. 2, 171-184.
12. L. G. De Pillis and A. Radunskaya, A mathematical tumor model with immune resistance and drug therapy: an optimal control approach, Journal of Theoretical Medicine, 3(2001), 79-100
13. A. Schrefler, G. Sciumè, M. Ferrari, P. Decuzzi, W. G. Gray, On Computational Modeling in Tumor Growth, Archives of Computational Methods in Engineering, 20 (2013), 327-352
14. Tosin A, Initial/boundary-value problems of tumor growth within a host tissue, Journal of Mathematical Biology, 66 (2013), 163-202.