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Effect of Delay in Immune-Tumor Model under Drug Administration

Anuradha Devi and Aditya Ghosh

Abstract

A mathematical Model is presented here which describes the growth of tumor cells with one term delay and it's intrinsic behaviour in the presence of immune cell. Here in this model we have also considered the effect of drug administered and assumed that drug kills both immune and tumor cells. The stability of immune cells and tumor cells with the effect of drug and delay is analyzed under equilibrium conditions.

AMS Subject Classification: 92B05, 90-08, 65L07, 65L06

Key Words: Mathematical model, Tumor cell, Immune cell, Drug, Stability, Delay

1 INTRODUCTION

The growth of tumor and cancer is a topic of interest in mathematical modeling. The complex behaviour of growth of tumor cell and it's effect on normal cell and immune cell already have been researched in [1], [9], [12]; between tumor and normal cells in [3], [6], [8]. Naturaly the growth of tumor shows delay, hence the growth needs to be remodeled under the effect of delay to get an appropriate and perfect mathematical model. The behavior of tumor with one term delay has already discussed in [5]. Again the behavior of tumor model under drug like chemotherapy is another important aspect of mathematical modeling of cancer which is extensively discussed in [2], [3], [6], [10], [11], [14], [15], [16], [17]. In the paper we have considered with three variable model with tumor (T), immune (I), under drug administration (v). The model also have been considered under delay in tumor growth.

2 MODEL DESCRIPTION

A Immune-Tumor Model with the effect of drug administration described in [4] has been considered and modified by introducing delay in one term for tumor growth. A

mathematical model of Immune-Tumor under delay in one term has been already introduced in [5].

2. 1. Model Equation

2. 1. 1. Immune-Tumor-Drug Model with delay in Tumor growth

Let I (t) denote the number of immune cell at time t that kill tumor cells, T (t) denote the tumorcells at time t. Immune and tumor cells together behaves as a predator-pray model of interactingspecies [19]. Immune cells in human body have a constant source and also get stimulated and recruited by the presence of tumor cells. Immune cells shows natural death at a rate $d1$. Hence thegrowth of immune cells can be modelled as

$$\frac{dI}{dt} = s + \frac{rI(t)T\,(t)}{\sigma + T\,(t)} - d_1 I(t) \quad (2.1)$$

where

s =The constant immune cells present in the body.

σ=stepness coefficients.

r=recruitement rate of immune cells stimulatedby

Furthermore, the interaction of immune cells andtumor cells can result in either the death of tumorcells or the deactivation of immune cells, resultingin the two competition terms

$$\frac{dI}{dt} = -c_1 I(t)T(t) \quad (2.2)$$

and

$$\frac{dT}{dt} = -c_2 I(t)T(t) \quad (2.3)$$

The tumor cells follows a logistic growth $aT\,(t)\,(1 - bT(t))$ undergo a delay. So the growth of tumor ismodified by

$$aT(t-\tau)\big(1 - bT(t-\tau)\big) \quad (2.4)$$

Hence, the model equation for immune-tumor cell growth with one term delay may be represented as

$$\frac{dI}{dt} = s + \frac{rI(t)T\,(t)}{\sigma + T\,(t)} - c_1 I(t)T(t) - d_1 I(t) \quad (2.5)$$

$$\frac{dT}{dt} = aT(t)\big(1 - bT(t-\tau)\big) - c_2 I(t)T(t) \quad (2.6)$$

Here, equation (2. 6) represents equation of tumor growth with one term delay. In the Immune Tumor model described above, the effect of drug is added to formulate a new mathematical model. Let v (t) is the amount of drug administered at time t. Assumptions taken are

Drug kills both immune and tumor cells

The kill rate of immune cells and tumor cells by drug are different. Let $\beta_1$be the kill ratefor immune cells and $\beta_2$be the kill rate for tumor cell$\beta_1 \neq \beta_2$.

The rate of drug administered at time *t*assume to follow exponential decay model ([19]). ThusImmune-Tumor-Drug model equation under one term delay can be described as:

$$\frac{dI}{dt} = s + \frac{rI(t)T\,(t)}{\sigma + T\,(t)} - c_1 I(t)T(t) - d_1 I(t) - \beta_1\, I(t)v\,(t) \quad (2.7)$$

$$\frac{dT}{dt} = aT(t)\big(1 - bT(t-\tau)\big) - c_2 I(t)T(t) - \beta_2 T(t)v(t) \quad (2.8)$$

$$\frac{dv}{dt} = \alpha_3 v(t)\big(1 - \beta_3 v(t)\big) \quad (2.9)$$

where

c_1=Tumour deactivation rate of effectors.

d_1=Natural death rate of immune cells.

a=intrinsic tumor growth rate

$\frac{1}{b}$=tumour population carrying capacity

c_2=death rate of tumor cell

τ=delay term

3 STABILITY ANALYSIS

3. 1 Immune-Tumor Model with two term delay

3. 1. 1 Equilibrium points

Immune-Tumor-Drug under delay model is a model with delay τhas$T(t)$as well as $T\,(t-\tau)$ in

$$aT(t)\big(1 - bT(t-\tau)\big) - c_2 I(t)T(t) - \beta_2 T(t)v(t) = 0 \quad (3.1)$$

Leads to equilibrium points

$$T(t) = 0 \quad (3.2)$$

and

$$T(t-\tau) = \frac{a - c_2 I(t) - \beta_2 v\,(t)}{ab} \quad (3.3)$$

Putting$T(t) = 0$ we geteither $v(t) = 0$ or $v(t) = \frac{1}{\beta_3}$

When $v(t) = 0$, then $I(t) = \frac{s}{d_1}$

And

For $v(t) = \frac{1}{\beta_3}$, then $I(t) = \frac{s}{d_1 + \frac{\beta_1}{\beta_3}}$

Hence here the equilibrium points are

Tumor free drug free equilibrium $\left(\frac{s}{d_1}, 0, 0\right)$

Tumor free drug equilibrium $\left(\frac{s}{d_1+\frac{\beta_1}{\beta_3}}, 0, \frac{1}{\beta_3}\right)$

3. 1. 2 Stability Analysis for Tumor free drug free equilibrium $\left(\frac{s}{d_1}, 0, 0\right)$

Linearizing around$\left(\frac{s}{d_1}, 0, 0\right)$ give a linear system of equation

$$\begin{pmatrix} \dot{I} \\ \dot{T} \\ \dot{v} \end{pmatrix} = \begin{pmatrix} -d_1 & \frac{rs}{d_1\sigma} - \frac{c_1 s}{d_1} & -\frac{\beta_1 s}{d_1} \\ 0 & a\left(1 - bT(t-\tau)\right) - \frac{c_2 s}{d_1} & 0 \\ 0 & 0 & \alpha_3\,(1 - 2\beta_3) \end{pmatrix} \begin{pmatrix} I - \frac{s}{d_1} \\ T \\ v \end{pmatrix} \quad (3.4)$$

With eigenvalues:

$$\lambda_1 = -d_1 \quad (3.5)$$

$$\lambda_2 = a\left(1 - bT(t-\tau)\right) - \frac{c_2 s}{d_1} \quad (3.6)$$

$$\lambda_3 = \alpha_3(1 - 2\beta_3) \quad (3.7)$$

The model will be stable if

$$\lambda_1 < 0 \quad (3.8)$$

$$\lambda_2 < 0 \quad (3.9)$$

$$\lambda_3 < 0 \quad (3.10)$$

Which means

$$a\left(1 - bT(t-\tau)\right) - \frac{c_2 s}{d_1} < 0 \quad (3.11)$$

$$\beta_3 > \frac{1}{2} \quad (3.12)$$

All the eigen values depends on the parameters. This means that if $\lambda_2 < 0$and $\lambda_3 < 0$, then the system will be stable else the system will be unstable. As λ_1 is always negative so the system will be depending on $\lambda_2$and λ_3. $\lambda_3$is negative when $\frac{1}{\beta_3}$ is the maximum capacity of drug administrated is less than 2.

3. 1. 3 Stability Analysis for Tumor free drug equilibrium $\left(\frac{s}{d_1+\frac{\beta_1}{\beta_3}}, 0, \frac{1}{\beta_3}\right)$

Linearizing the system around $\left(\frac{s}{d_1+\frac{\beta_1}{\beta_3}}, 0, \frac{1}{\beta_3}\right)$we get

$$\begin{pmatrix} \dot{I} \\ \dot{T} \\ \dot{v} \end{pmatrix} = \begin{pmatrix} -\frac{\beta_1}{\beta_3} - d_1 & \frac{rs}{\sigma\left(\frac{\beta_1}{\beta_3} + d_1\right)} - \frac{c_1 s}{\frac{\beta_1}{\beta_3} + d_1} & -\frac{\beta_1 s}{\frac{\beta_1}{\beta_3} + d_1} \\ 0 & a\big(1 - bT(t-\tau)\big) - \frac{c_2 s}{\frac{\beta_1}{\beta_3} + d_1} & 0 \\ 0 & 0 & \alpha_3\,(1 - 2\beta_3) \end{pmatrix} \begin{pmatrix} I - \frac{s}{\frac{\beta_1}{\beta_3} + d_1} \\ T \\ v - \frac{1}{\beta_3} \end{pmatrix} \quad (3.13)$$

Leads to the eigen values

$$\lambda_1 = -\frac{\beta_1}{\beta_3} - d_1 \quad (3.14)$$

$$\lambda_2 = a\big(1 - bT(t-\tau)\big) - \frac{c_2 s}{\frac{\beta_1}{\beta_3} + d_1} \quad (3.15)$$

$$\lambda_3 = \alpha_3(1 - 2\beta_3) \quad (3.16)$$

The model will be stable if

$$\lambda_1 < 0 \quad (3.17)$$

$$\lambda_2 < 0 \quad (3.18)$$

$$\lambda_3 < 0 \quad (3.19)$$

Which means

$$a\big(1 - bT(t-\tau)\big) - \frac{c_2 s}{\frac{\beta_1}{\beta_3} + d_1} < 0 \quad (3.20)$$

$$\beta_3 > \frac{1}{2} \quad (3.21)$$

All the eigen values depends on the parameters. This means that if $\lambda_2 < 0$and $\lambda_3 < 0$, then the system will be stable else the system will be unstable. As λ_1 is always negative so the system will be depending on $\lambda_2$and λ_3. $\lambda_3$is negative when $\frac{1}{\beta_3}$ is the maximum capacity of drug administrated is less than 2.

4 ANALYSIS AND CONCLUSION

Numerical solution of the mathematical model representing Immune-Tumor-Drug Model described by (2. 7), (2. 8), (2. 9) have been derived. The model have been analyzed under the condition of stability given in (3. 11), (3. 12) for tumor free drug free equilibrium point and in (3. 20), (3. 21) for tumor free-drug administered equilibrium point. The system parameters are chosen in such a way that the condition of stability either satisfied or not satisfied.

Fig-1 and Fig-2 justifies the stability condition for Immune-Tumor growth under tumor free drug free equilibrium point $\left(\frac{s}{d_1}, 0, 0\right)$. Fig-3 shows stable drug administration for both equilibrium points. Fig-4 shows instability of tumor growth

when the conditions of stability are violated under $\left(\frac{s}{d_1}, 0, 0\right)$considering the equilibrium point$\left(\frac{s}{d_1+\frac{\beta_1}{\beta_3}}, 0, \frac{1}{\beta_3}\right)$, Fig-5 and Fig-6 justifies the stable tumor and immune growth. The violation of stability condition leads to the unstable tumor growth under $\left(\frac{s}{d_1+\frac{\beta_1}{\beta_3}}, 0, \frac{1}{\beta_3}\right)$ shown in Fig-7. Fig-8 gives drug instability under both equilibrium points.

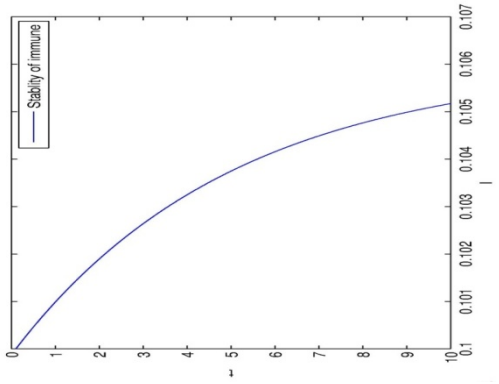

Fig-1: Stability of Immune for $\left(\frac{s}{d_1}, 0, 0\right)$

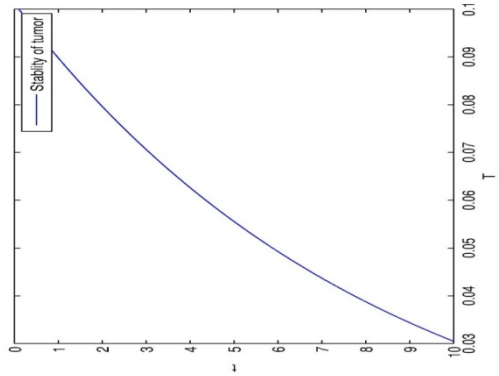

Fig-2: Stability of Tumor for $\left(\frac{s}{d_1}, 0, 0\right)$

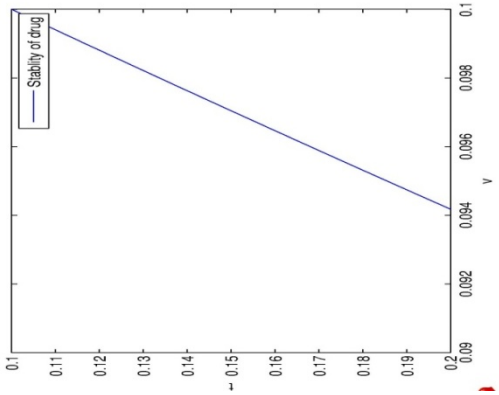

Fig-3: Stability of drug for $\left(\frac{s}{d_1}, 0, 0\right)$and $\left(\frac{s}{d_1+\frac{\beta_1}{\beta_3}}, 0, \frac{1}{\beta_3}\right)$

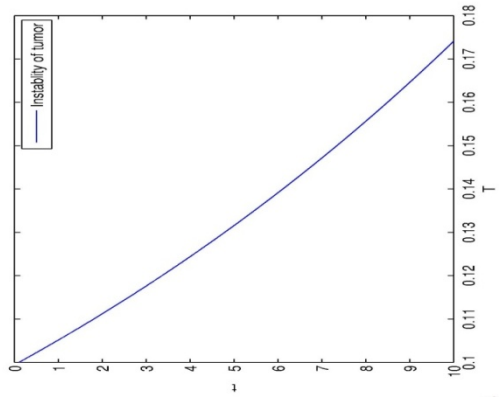

Fig-4: Unstable tumor growth for $\left(\frac{s}{d_1}, 0, 0\right)$

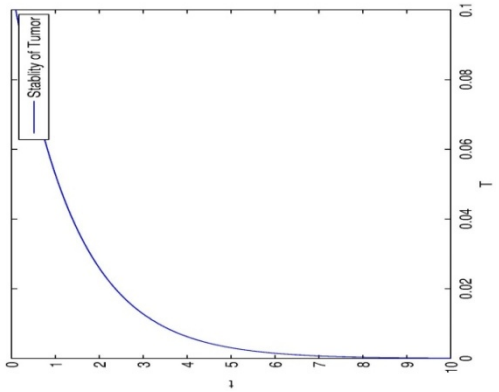

Fig-5: Stability of Tumor for $\left(\frac{s}{d_1+\frac{\beta_1}{\beta_3}}, 0, \frac{1}{\beta_3}\right)$

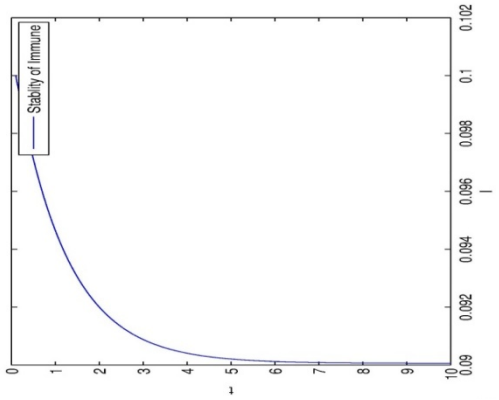

Fig-6: Stability of Immune for $\left(\frac{s}{d_1+\frac{\beta_1}{\beta_3}}, 0, \frac{1}{\beta_3}\right)$

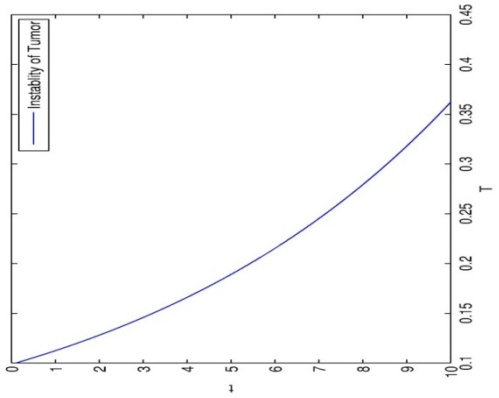

Fig-7: Unstable tumor growth for $\left(\frac{s}{d_1+\frac{\beta_1}{\beta_3}}, 0, \frac{1}{\beta_3}\right)$

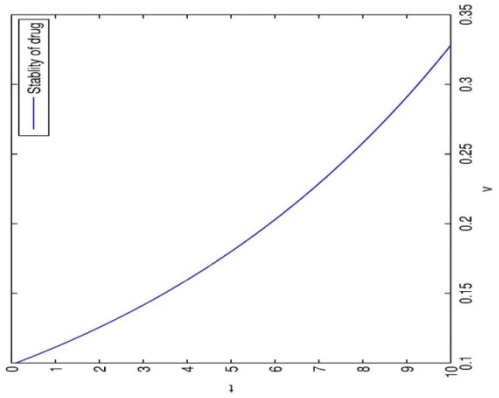

Fig-8: Drug instability for $\left(\frac{s}{d_1}, 0, 0\right)$and $\left(\frac{s}{d_1+\frac{\beta_1}{\beta_3}}, 0, \frac{1}{\beta_3}\right)$

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