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Drug Administered Cancer Model Under one Term Delay

Aditya Ghosh[1,*], Anuradha Devi[1,+]

[1] Department of Mathematics, Royal Group of Institutions, Betkuchi, Guwahati, Assam-781035, INDIA

[*] *ghosh.aditya.iitg08@gmail.com,*

[+] *devianuradha09@gmail.com*

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Abstract

A mathematical model is presented here that describes the growth of tumor cells and intrinsic behavior of it in the presence of immune cells. In this model we have also considered another drug variable which has the effect on both the cells. Hence it is a model for cancer that contains immune, tumor and drug. The model is highly nonlinear in nature. The effect of growth of normal cell is not considered. Constant number of immune cells is assumed to be present in the system. In this model we have considered a delay term in the growth of tumor which makes the model more realistic. We also assume that drug kills both immune cells and tumor cells simultaneously in different rate. Stability of both immune and tumor cells with and without delay has been analyzed under equilibrium condition analytically as well as numerically. It is found that the stability of the model depends on both tumor cells as well as on the delay.

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

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

1. Introduction

Cancer is a disease which is complex in nature. Mathematical modeling of cancer involves many process and therefore mathematical modeling of cancer has have been a topic of continuous and extensive research. The fundamental theory of cancer research involves in looking into the growth of cancer causing tumor cells, growth of stimulant immune cells and their interaction. An extensive study of the growth of tumor and immune cells can be observed in [1], [3], [6], [8], [12].

Naturally the growth of tumor shows delay. Hence the growth of tumor is remodeled under effect of delay. This behavior of tumor growth under one term delay has been described in [5]. Also the growth of tumor under two term delay has been considered in [3]. Both these models are two variable models where the drug is not considered.

Mathematical modeling of cancer under drug has been another important topic of research which can be seen in [2], [6], [10], [11], [14], [15], [16], [17].

In this paper the following have been considered

(i) Tumor growth undergoes a one term delay.
(ii) Drug is considered to be of Logistic form.
(iii) Both tumor and Immune cells are negatively affected by drug.

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 tumor cells at time t. Immune and tumor cells together behave as a predator-pray model of interacting species [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 d_1. Hence the growth of immune cells can be modelled as

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

where
s =The constant immune cells present in the body.
σ=stepness coefficients.
r=recruitement rate of immune cells
Furthermore, the interaction of immune cells and tumor cells can result in either the death of tumor cells or the deactivation of immune cells, resulting in the two competition terms

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

and

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

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

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

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

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

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

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 rate for immune cells and β_2 be the kill rate for tumor cell $\beta_1 \neq \beta_2$.
- The rate of drug administered at time t assume to follow logistic growth model ([19]). Thus Immune-Tumor-Drug model equation under one term delay can be described as:

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

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

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

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
$\beta_{3=}$ Carrying capacity of drug.
α_3= Drug administrated constant.

3. Stability Analysis

3.1 Immune-Tumor Model with One Term Delay

3.1.1 Equilibrium Points: Immune-Tumor-Drug under delay model is a model with delay τ has both $T(t)$as well as $T(t-\tau)$ in its rate equation. So considering growth to be zero

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

Leads to equilibrium points

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

and

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

Putting $T(t) = 0$ we get either $v(t) = 0$ or $v(t) = \frac{1}{\beta_3}$ (3.4)

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

When $T(t-\tau) = \frac{a - c_2 I(t) - \beta_2 v(t)}{ab}$, then as tumor growth with delay does not affect the equilibrium of immune and drug. The equilibrium points for the growth of immune and drug can be considered as a two variable model given by

$$\frac{dI}{dt} = s + \frac{rI(t)T(t)}{\sigma + T(t)} - c_1 I(t)T(t) - d_1 I(t) - \beta_1 I(t)v(t) \quad (3.5)$$

$$\frac{dv}{dt} = \alpha_3 v(t)\left(1 - \beta_3 v(t)\right) \quad (3.6)$$

Now drug equilibrium are $v(t) = 0$ or $v(t) = \frac{1}{\beta_3}$ [from (3.4)]

When $(t) = 0$, $\dot{I} = 0$ implies $I(t) = \frac{s}{A}$ where $A = c_1 T^* + d_1 - \frac{rT^*}{\sigma + T^*}$

When $(t) = \frac{1}{\beta_3}$, $\dot{I} = 0$ implies $I(t) = \frac{s}{B}$ where $B = c_1 T^* + d_1 - \frac{rT^*}{\sigma + T^*} + \frac{\beta_1}{\beta_3}$

Hence the equilibrium points are

- Drug free Immune equilibrium $\left(\frac{s}{A}, 0\right)$
- Drug existing immune equilibrium $\left(\frac{s}{B}, \frac{1}{\beta_3}\right)$

3.1.2 Stability Analysis for Drug free Immune equilibrium $\left(\frac{s}{A}, 0\right)$: Linearizing around $\left(\frac{s}{A}, 0\right)$ give a linear system of equation

$$\begin{pmatrix} \dot{I} \\ \dot{v} \end{pmatrix} = \begin{pmatrix} \frac{rT^*}{\sigma + T^*} - c_1 T^* - d_1 & -\beta_1 \frac{s}{A} \\ 0 & \alpha_3 \end{pmatrix} \begin{pmatrix} I - \frac{s}{A} \\ v \end{pmatrix} \quad (3.7)$$

With eigenvalues:

$$\lambda_1 = \frac{rT^*}{\sigma + T^*} - c_1 T^* - d_1 \quad (3.8)$$

$$\lambda_2 = \alpha_3 \quad (3.9)$$

The model will be stable if

$$\lambda_1 < 0 \quad (3.10)$$

$$\lambda_2 < 0 \quad (3.11)$$

Which means

$$\frac{rT^*}{\sigma + T^*} - c_1 T^* - d_1 < 0 \quad (3.12)$$

$$\alpha_3 < 0 \quad (3.13)$$

All the eigen values depends on the parameters. This means that if $\lambda_1 < 0$ and $\lambda_2 < 0$, then the system will be stable else the system will be unstable. But the condition of stability of the model given in (3.13) is contradictory as the system parameters are always positive. Hence the mathematical model considered here is not stable around $\left(\frac{s}{A}, 0\right)$

3.1.3 Stability Analysis for Drug existing immune equilibrium $\left(\frac{s}{B}, \frac{1}{\beta_3}\right)$: linearizing the system around $\left(\frac{s}{B}, \frac{1}{\beta_3}\right)$ we get

$$\begin{pmatrix} \dot{I} \\ \dot{v} \end{pmatrix} = \begin{pmatrix} \frac{rT^*}{\sigma + T^*} - c_1 T^* - d_1 - \frac{\beta_1}{\beta_3} & -\beta_1 \frac{s}{B} \\ 0 & -\alpha_3 \end{pmatrix} \begin{pmatrix} I - \frac{s}{B} \\ v - \frac{1}{\beta_3} \end{pmatrix} \quad (3.14)$$

Leads to the eigen values

$$\lambda_1 = \frac{rT^*}{\sigma + T^*} - c_1 T^* - d_1 - \frac{\beta_1}{\beta_3} \quad (3.15)$$

$$\lambda_2 = -\alpha_3 \quad (3.16)$$

The model will be stable if

$$\lambda_1 < 0 \quad (3.17)$$
$$\lambda_2 < 0 \quad (3.18)$$

Which means

$$\frac{rT^*}{\sigma + T^*} - c_1 T^* - d_1 - \frac{\beta_1}{\beta_3} < 0 \quad (3.19)$$
$$-\alpha_3 < 0 \quad (3.20)$$

All the eigen values depends on the parameters. This means that if $\lambda_1 < 0$ and $\lambda_2 < 0$, then the system will be stable else the system will be unstable. As λ_2 is always negative so the system will be depending on λ_1.

4. Analysis and Conclusion

Here the model considered is described in (2.7), (2.8), (2.9). The analysis of the model for the equilibrium point $T(t) = 0$ has already been published in [3]. As there is no delay of tumor cell considered in the Immune growth and the drug rate equation, the three variable model is reduced to a two variable model.

In the case of Drug free Immune equilibrium$\left(\frac{s}{A}, 0\right)$, we observed that (3.12) and (3.13) describe the condition for stability. But the condition (3.13) is not realistic; hence the model is not stable. Fig-1. Fig-2 describes that for satisfying the condition (3.12) the immune growth is stable and immune growth is unstable for violating (3.12) which is given in Fig-3. So the immune cell growth stability depends on the condition (3.13) but drug administered seems to show instability. So the system is unstable for the case of $\left(\frac{s}{A}, 0\right)$.

In the case of drug existing immune equilibrium$\left(\frac{s}{B}, \frac{1}{\beta_3}\right)$, (3.19) and (3.20) gives the condition for stability. Fig-4 shows the stability of drug for the condition (3.20). Fig-5 shows the stability of immune for satisfying the condition (3.19) whether Fig-6 shows the instability of immune for violating the condition (3.19).

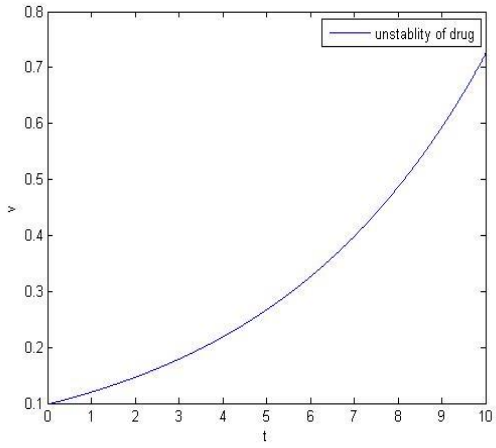

Figure 1. Instability of drug for $\left(\frac{S}{A}, 0\right)$

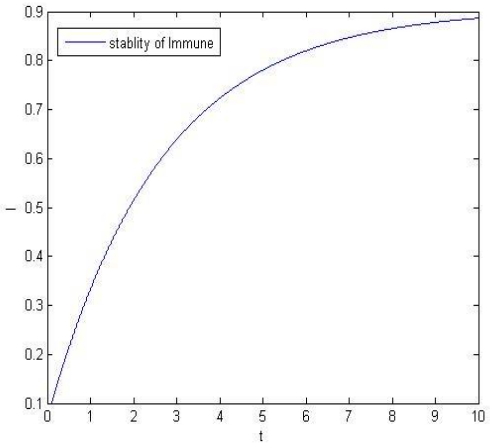

Figure 2. Stability of Immune for $\left(\frac{S}{A}, 0\right)$

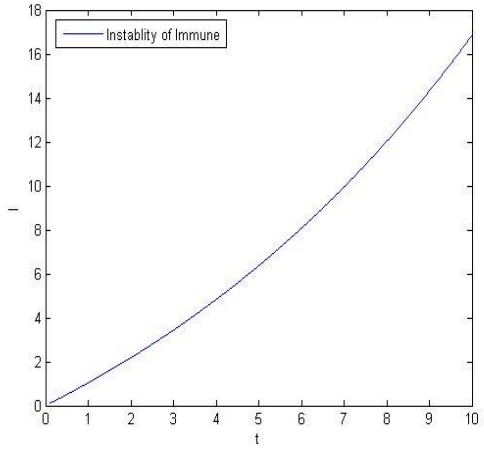

Figure 3. Instability of Immune for $\left(\frac{S}{A}, 0\right)$

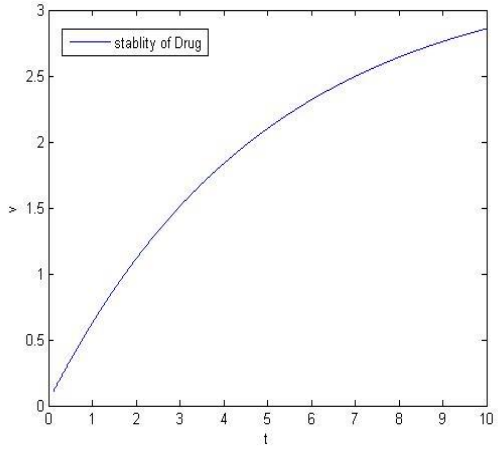

Figure 4. Stability of drug for $\left(\frac{s}{B}, \frac{1}{\beta_3}\right)$

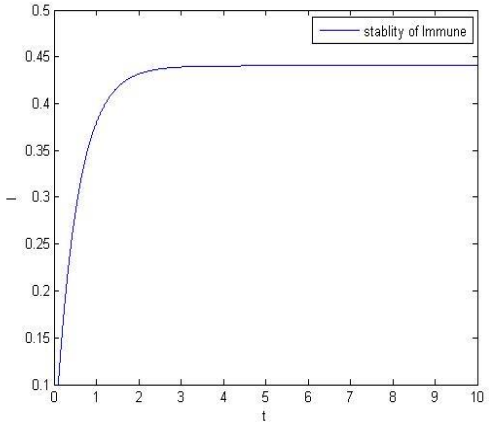

Figure 5. Stability of immune for $\left(\frac{s}{B}, \frac{1}{\beta_3}\right)$

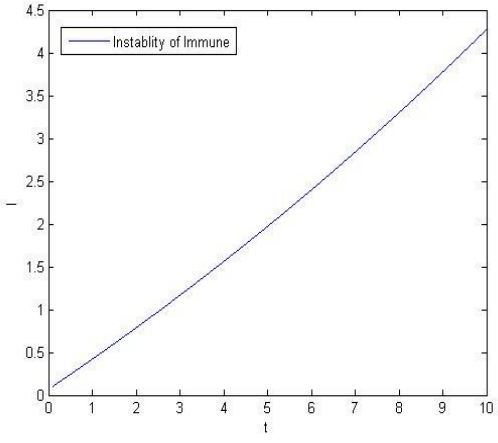

Figure 6. Instability of immune for $\left(\frac{s}{B}, \frac{1}{\beta_3}\right)$

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