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On the stability of immune-tumor model with one term delay in tumor $(I - T_D)$

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ABSTRACT

A mathematical model is presented that describes the growth of the tumor cells with delay T_D and intrinsic behavior of it in the presence of immune cells I.The immune-tumor model is modified with inclusion of one term delay factor. The behavior and stability of $I - T_D$ model have been analyzed. It is found that stability of the model depends on both intrinsic growth of tumor cells as well as on the delay. The stability of both immune and tumor cells with delay has been analyzed under equilibrium condition and the conditions for stability of both immune and tumor cells under delay are found.

Keywords: Mathematical model; Tumor cell; Immune cell; Drug; Eigenvalue; Stability; Delay.

1. Introduction

The growth of tumor cell for cancer is very complex in nature as it involves many biological factors. Cancer is caused due to unnatural growth of malignant cells which form tumor. The malignant cells that cause tumor also affect the normal and immune cells of human body till treatments are started. Again growth of tumor has been seen to follow a delay process, due to many reasons such as tumor cells taking time to release toxin, due to the length of interphase or due to late reaction of immune system. To understand the behavior of complex tumor growth, mathematical modelling of cancer with one term delay have been of great interest. Many useful works have been done on models including tumor cells and immune cells (see [1],[7] ,[10]), between tumor and normal cells (see [3] and [4],[6]), and between tumor and control using chemotherapy alone (see [2],[3],[4],[8],[9],[12],[13],[14],[15]). The works related to delay work is discussed in many articles(see [18],[19],[20],[21],[22]).

The mathematical model includes the growth of immune cells, tumor cells and also the use of drug administrated to control growth of these cells.

2. Model Description

There exists numerous mathematical model to study the behavior of tumor cells . In this paper two very simple models described in ([16]) have been considered with introduction of delay term in tumor growth.In the paper ([16]) authors described two mathematical models namely

1. Immune-Tumor and Normal cell growth model
2. Immune-Tumor-Normal cell growth model with addition of control variable(drug administration)

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No delay term were considered by authors. This paper concentrate only on Immune and tumor cells, their intrinsic growth and interaction between them. The delay term is used to make the model more realistic as in most of the cases cancer is diagonised after a period of time of growth of tumor.

2.1 *Model Equation*

2.1.1 *Immune-Tumor Model with delay($I - T_D$) in Tumor growth*

Let $I(t)$ denote the number of immune cell at time t, $T(t)$ denote the tumor cells at time t. Immune cell $I(t))$ and tumor cell $T(t)$ behaves as a predator-pray model of ineracting spacis([17]). In the absence of any tumor the immune cell will die out at a rate d_1 and presence of tumor cells stimulates the immune cell which may be represented as non-linear growth of immune cells as follows:

$$\frac{rI(t)T(t)}{\sigma + T(t)} \tag{2.1}$$

where r and σ are positive constants. This type of response term as of the same form as the terms used in the respective models of ([7]) and ([5]). 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

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

and

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

Also the growth of tumor cell has been effected by a delay term

$$1 - bT(t - \tau) \tag{2.4}$$

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

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

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

Here, equation (2.6) represents equation of tumor growth with one term delay. Where:

s	=	constant immune cell already present in human body,
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 one term delay($I - T_D$)*

Immune-Tumor delay model is a model which has $T(t)$ as well as $T(t - \tau)$. here, if we consider equation

$$aT(t)(1 - bT(t - \tau)) - c_2 I(t)T(t) = 0 \tag{3.1}$$

we will get two equilibrium points

$$T(t) = 0 \tag{3.2}$$

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

Now, for the value $T(t) = 0$ we get $I(t) = \frac{s}{d_1}$. Hence, the equilibrium point will be $(\frac{s}{d_1}, 0)$ For $T(t-\tau) = \frac{a-c_2 I}{ab}$ we will not get any corresponding $I(t)$.

3.1.1 *Stability analysis for tumor free equilibria* $(\frac{s}{d_1}, 0)$

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

$$\begin{pmatrix} \dot{I} \\ \dot{T} \end{pmatrix} = \begin{pmatrix} -d_1 & \frac{rs}{d_1\sigma} - \frac{c_1 s}{d_1} \\ 0 & a(1 - bT(t-\tau)) - \frac{c_2 s}{d_1} \end{pmatrix} \begin{pmatrix} I - \frac{s}{d_1} \\ T \end{pmatrix} \tag{3.4}$$

with eigenvalues :

$$\lambda_1 = -d_1, \tag{3.5}$$

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

The the model will be stable if :

$$a(1 - bT(t-\tau)) < \frac{c_2 s}{d_1} \tag{3.7}$$

This is an implication that if $a(1 - bT(t-\tau)) > \frac{c_2 s}{d_1}$, then the system will be unstable, means no amount of drug will be able to completely irradiate the tumor.

3.1.2 *Stability analysis for co-existing immune-tumor delay($I - T_D$) model*

Now, if we consider the equilibrium point $T(t-\tau) = \frac{a-c_2 I}{ab}$, for this point the equation 2.5 will not be affected. Now, if we consider the equation 2.5, we can write the equation as follows:

$$\frac{dI(t)}{dt} = s + I(\frac{rT(t)}{\sigma + T(t)} - c_1 T(t) - d_1) \tag{3.8}$$

This model will be stable if

$$(\frac{rT(t)}{\sigma + T(t)} - c_1 T(t) - d_1) < 0 \tag{3.9}$$

now, if we consider the equation 2.6, we can write the equation in the following form:

$$\frac{dT(t)}{dt} = RT(t)(1 - \frac{T(t-\tau)}{K}) \tag{3.10}$$

where

$$R = a - c_2 I \tag{3.11}$$

$$K = \frac{a - c_2 I}{ab} \tag{3.12}$$

Now according to analysis of Hutchinson equation we can conclude

- If $0 \leq R\tau < \frac{\pi}{2}$, then the equilibrium $T(t-\tau) = \frac{a-c_2 I}{ab}$ will be asymptotically stable.
- If $R\tau > \frac{\pi}{2}$, then the equilibrium $T(t-\tau) = \frac{a-c_2 I}{ab}$ will be unstable.

4. Analysis and Conclusion

The initial tumor and immune cells are taken to be 0.1. Here the condition of stability of $I-T_D$ model depends on cell growth, i.e, the tumor cell growth and tumor cell growth with delay. The condition for stability are given in equation $(3.7), (3.9)$. The tumor model leads to Hutchinson equation which has some conclusion which has been proved earlier and is mentioned in ([20]) .

The models have simulated under same initial condition for both equilibrium points. In Figure1 and Figure2, the stability of $I-T_D$ model without delay are analyzed and observed that the condition of stability are established. Similarly in Figure3, Figure4, and Figure5 describes the model behavior with delay term under the condition of stability. In this case also the condition for stability are established. As the model described in this paper is completely different from the model description of ([16]), the result found here cannot compare with ([16]). This is due to the reason that the goal of ([16]) is to find an optimal control policy for tumor model with immune resistance, whereas this paper emphasis only on the model bahaviour of Immune-Tumor model under the delay.

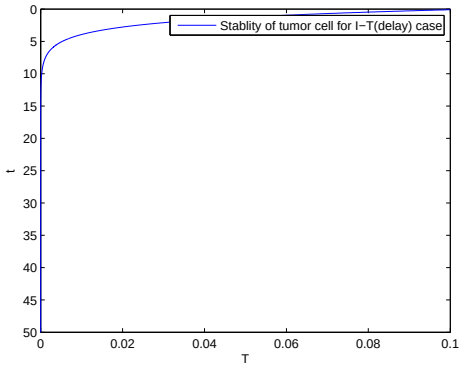

Figure 1: $I-T_D$ model tumor stability $a=1, b=0.2, c_2=1, s=0.2, T(t-\tau)=3.0, d_1=0.2$

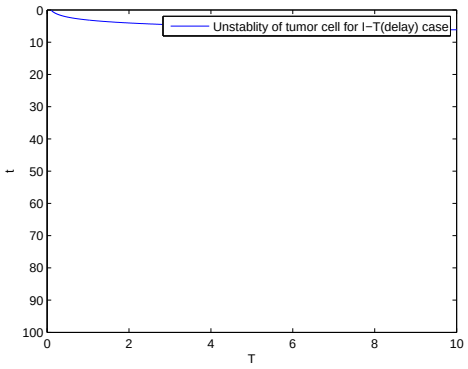

Figure 2: $I-T_D$ model violating stability condition for $a=1, b=0.2, c_2=0.2, s=0.2, T(t-\tau)=0.2, d_1=0.2$

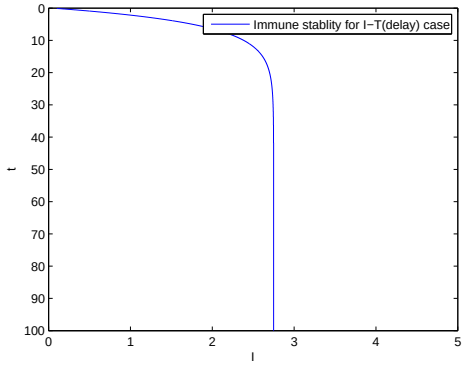

Figure 3: $I-T_D$ model satisfying the stability condition for $a=1, c_1=c_2=1, d_1=s=r=0.2$

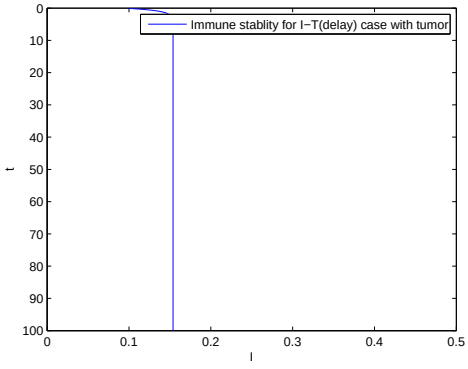

Figure 4: $I-T_D$ model is stable for $s=r=d_1=\sigma=0.2, T(t)=1.0$

References

[1] Adam J. A., The dynamics growth-factor-modified immune response to cancer growth: One- dimensional models, *Mathematical and Computer modelling* **17**(1993), 83-106.

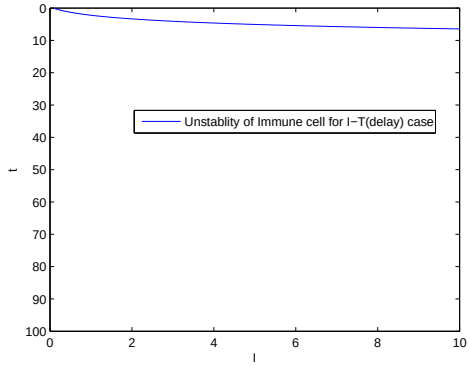

Figure 5: $I - T_D$ model unstable for $r = 2, s = d_1 = \sigma = 0.2, T(t) = 1.0$

[2] Adam J. A, Panetta, J., A simple mathematical model and alternative paradigm for certain chemotherapeutic regimens, *Mathematical and Computer modelling* **22(8)**(1995), 49-60.

[3] Dibrov, B.F.,Zhabotinsky, A. M.,Neyfakh, Y.A.,Orlova, M.P. and Churikova, L.I., Mathematical model of cancer chemotherapy. Periodic scheduled of phase-specific cytotoxic-agent administration increasing the selectivity of therapy. *Mathematical Biosciences, An international journal* **73**(1)(1985), 1-31.

[4] Eisen, M., *Mathematical models in cell biology and cancer chemotherapy*, Springer- Verlag, Berlin(1979).

[5] Kirschner, D. and Panetta, J., Modelling immunotherapy of the tumor immune intaraction, *Journal of Mathematical biology* **37**(3)(1998), 235-252.

[6] Knolle, H., *Cell kinetic modelling and the chemotherapy of Cancer*, Springer-Verlag, Berlin(1988).

[7] Kuznetsov, V., Makalkon, I.,Taylor, M. and Perelson, A.: Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis, *Bull. of Math. Bio.* **56**(2)(1994), 295-321.

[8] Martin, R.B., Fisher, M.E.,Minchin, R.F.and Teo, K.L., A mathematical model of cancer cheotherapy with an optimal selection of parameters, *Mathematical Biosciences, An international Journal* **99**(2)(1990), 205-230.

[9] Murrey, J.M., Optimal control for a cancer chemotherapy problem with general growth and loss functions, *Mathematical Biosciences, An international Journal*, **98**(2)(1990), 273-287.

[10] Owen, M. and Sherratt, J., Modelling the macrophase invasion of tumors: Effects on growth and composition, *IMA Journal of Mathematics Applied in Medicine and Biology*, **15**(1998), 165-185.

[11] Prehn, R., Stimulatory effects of immune-reactions upon the growths of untransplanted tumors, *Cancer Research* **54**(4)(1994), 908-914.

[12] Shochat, E., Hart, D. and Agur, Z., Using computer simulations for evaluating the efficacy of breast cancer chemotherapy protocols, *Mathematical Models and Methods in Applied Sciences* **9**(4)(1999), 599-615.

[13] Coldman, A. J. and Goldie, J.H., A stochastic model for the origin and treatments of tumor containing drug-resistant cells*Bulletin of Mathematical Biology* **48**(3-4)(1986), 279-292. Simulation in Cancer research (Durham, N. C., 1986)

[14] Swan, G. W., Optimal control applications in the chemotherapy of multiple myelona, *IMA Journal of Mathematics Applied in Medicine and Biology*, **2**(3)(1985), 139-160.

[15] Swan, G. W. Optimal control analysis of cancer chemotherapy problem, *IMA Journal of Mathematics Applied in Medicine and Biology*, **4**(2)(1987), 171-184.

[16] L. G. de Pillis and A. Radunskaya., A Mathematical Tumor Model with Immune Resistance and Drug Therapy: an optimal Control Approach,*Journal of Theoritical Medicine, vol 3*(2000), 79-100.

[17] Kapoor J.N., Mathematical Modelling, *New Age International Publishers* **ISBN : 81- 224-0006-x**(1998).

[18] Bodnar M.: The nonnegetivity of solutions of delay differential equations,*Appl. Math. Let.,vol. 13, No. 6* (2000), 91-95.

[19] Forys U., On the Mikhailov criterian and stability of delay differential equations,*Prep. Warsaw University*(2001) , No. RW 01-14(97)

[20] Gopalsamy K., Stability and Ossilations in Delay Differential Equations of Population Dynamics(1992)

[21] Hale J., Theory of Functional Differential Equations.,*New York, Springer*

[22] Murray J.D., Mathematical Biology.,*Berlin: Springer*