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ON THE STABILITY OF IMMUNE-TUMOR(I-T) MODEL WITH THE EFFECT OF DRUG ADMINISTRATION

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Abstract: A mathematical model is presented that describes growth of the tumor cells and intrinsic behaviour of it in the presence of immune cells. Two models considered here are:

- Immune-Tumor growth model(I-T Model)
- Immune-Tumor-Drug Model(I-T-D Model)

Both I-T and I-T-D models are highly non-linear in nature. The effect of growth of these cells on normal cells have not been considered. In presence of both cells the model behave as a competing model. Constant number of immune cells are assumed to be present in the system. In the absence of tumor cells, the immune cells will not be stimulated to grow and these leads to a natural death of immune cells. Immune-Tumor-Drug(I-T-D) is a modified version of Immune-Tumor(I-T) model which incorporate the effect of drug administered assuming that drug kills both tumor and immune cells at different rates.

Stability of both models have been analyzed under various equilibrium conditions.

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1. Introduction

The growth of tumor cell for cancer is very complex in nature as it involves many biological factor. Cancer is caused due to unnatural growth of malignant cells which forms tumor. The malignant cells that causes tumor also effects the normal and immune cell of human body till treatments are started. To understand the behaviour of complex tumor growth, mathematical modelling of cancer 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 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 behaviour of tumor cells([11]). Here two very simple model described in ([16]) have been considered with modification.

2.1. Model Equation

2.1.1. Immune-Tumor Model(I-T)

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 preditor-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 activation of immune cells, resulting in the two competition terms

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

and

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

Hence the model equation equation for immune-tumor(I-T) cell growth may be represented as:

$$\frac{dI(t)}{dt} = s + \frac{rI(t)T(t)}{\sigma + T(t)} - c_1 I(t)T(t) - d_1 I(t) \tag{2.4}$$

$$\frac{dT(t)}{dt} = aT(t)(1 - bT(t)) - c_2 I(t)T(t) \tag{2.5}$$

where:
s=constant immune cell,
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=Kill rate tumor cell.

2.1.2. Immune-Tumor-Drug Model(I-T-D)

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 β_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 exponential decay model([17]). Thus Immune-Tumor-Drug model equation is described as:

$$\frac{dI(t)}{dt} = s + \frac{rI(t)T(t)}{\sigma + T(t)} - c_1 I(t)T(t) - d_1 I(t) - \beta_1 v(t) \tag{2.6}$$

$$\frac{dT(t)}{dt} = aT(t)(1 - bT(t)) - c_2 I(t)T(t) - \beta_2 T(t)v(t) \tag{2.7}$$

$$\frac{dv(t)}{dt} = \alpha_3 v(1 - \beta_3 v) \tag{2.8}$$

3. Stability Analysis

3.1. Immune-Tumor Model(I-T)

Immune-Tumor model is a drug free model.

The equilibrium points are:

- Tumor free equilibrium $(\frac{s}{d_1}, 0)$.
- Co existing immune-tumor equilibrium (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

$$\begin{pmatrix} \dot{I} \\ \dot{T} \end{pmatrix} = \begin{pmatrix} -d_1 & \frac{rs}{d_1\sigma} - \frac{c_1 s}{d_1} \\ 0 & a - \frac{c_2 s}{\sigma} \end{pmatrix} \begin{pmatrix} I - \frac{s}{d_1} \\ T \end{pmatrix} \tag{3.1}$$

with eigenvalues:

$$\lambda_1 = -d_1, \tag{3.2}$$

$$\lambda_2 = a - \frac{c_2 s}{d_1} \tag{3.3}$$

The the model will be stable if:

$$a < \frac{c_2 s}{d_1} \tag{3.4}$$

This is an implication that if $a > \frac{c_2 s}{d_1}$, then the system will be unstable, means no amount of drug will be able to completely iradicate the tumor.

3.1.2. Stability Analysis for Co-Existing Immune-Tumor Model

Linearizing around the point (I^*, T^*), where

$$I^* = \frac{a}{c_2}[1 - \frac{b}{a}(p - \frac{H}{p} - b)] \tag{3.5}$$

$$T^* = \frac{1}{b}(p - \frac{H}{p} - b) \tag{3.6}$$

where $p \neq 0$ is given by

$$p = \frac{1}{2}(-G + \sqrt{G^2 + 4H^3})^{\frac{1}{3}} \tag{3.7}$$

$$and \tag{3.8}$$

$$H = a_0 a_1 - a_1^2 \tag{3.9}$$

$$G = a_0^2 a_3 - 3a_0 a_1 a_2 + 2a_1^3 \tag{3.10}$$

where a_0, a_1, a_2, a_3 are constants involving system parameters and

$$a_0 = c_1 ab \tag{3.11}$$

$$a_1 = \frac{1}{3}(c_1 ab\sigma - rab - c_1 a + d_1 ab) \tag{3.12}$$

$$a_2 = \frac{1}{3}(c_2 s + ra - c_1\sigma - d_1 a + d_1 ab\sigma) \tag{3.13}$$

$$a_3 = c_2 s\sigma - ad_1\sigma \tag{3.14}$$

Eigenvalues corresponding to this equilibrium points are:

$$\lambda_1 = \frac{(A + D) + \sqrt{(A - D)^2 + 4BC}}{2} \tag{3.15}$$

$$\lambda_2 = \frac{(A + D) - \sqrt{(A - D)^2 + 4BC}}{2} \tag{3.16}$$

Here:

$$A = (\frac{rT^*}{\sigma + T} - c_1 T^* - d_1) \tag{3.17}$$

$$B = (\frac{\sigma r I^*}{(\sigma + T^*)^2} - c_1 I^*) \tag{3.18}$$

$$C = -c_2 T^* \tag{3.19}$$

$$D = a - 2abT^* - c_2 I^* \tag{3.20}$$

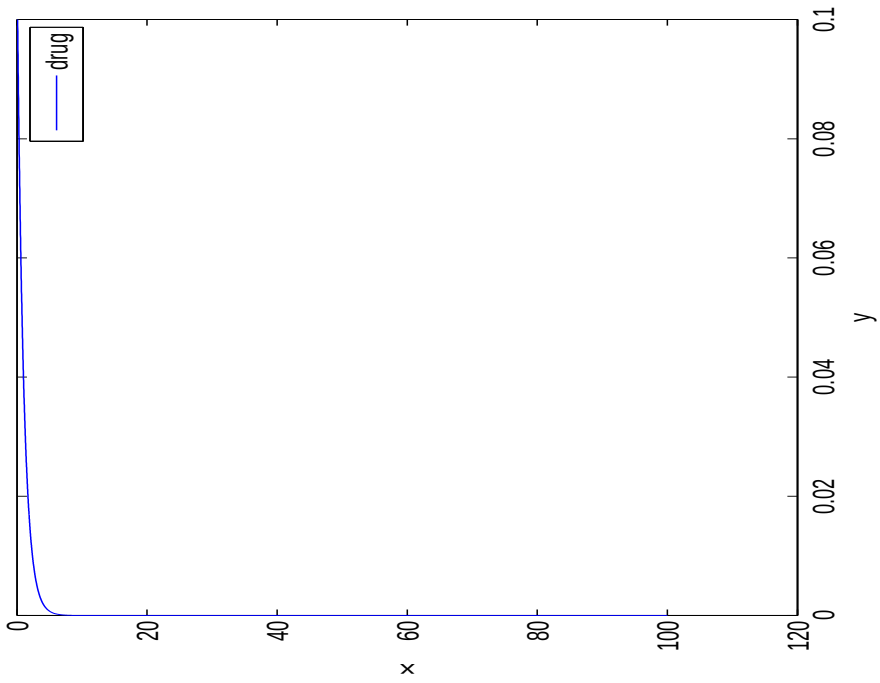

Figure 1: Drug administered for $\nu_3 = 0.3, \beta_3 = 0.2, v(0) = 0.1$

This I-T model will stable around the co-existing equilibrium point (I^*, T^*), if both eigenvalues

$$\lambda_1 < 0 \tag{3.21}$$

$$\lambda_2 < 0 \tag{3.22}$$

So, the required for stability is found to be,

$$AD < BC \tag{3.23}$$

3.2. Immune-Tumor-Drug Model [I-T-D]

The equilibrium points for this model are:

- Tumor free equilibria.

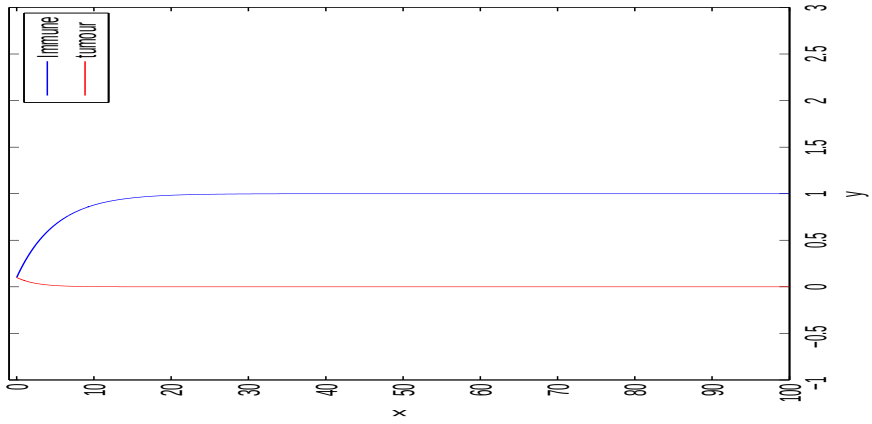

Figure 2: I-T model satisfying stability condition for $a = 0.2, c_1 = c_2 = 1, d_1 = s = r = 0.2, \sigma = 0.3, I(0) = 0.1, T(0) = 0.1$

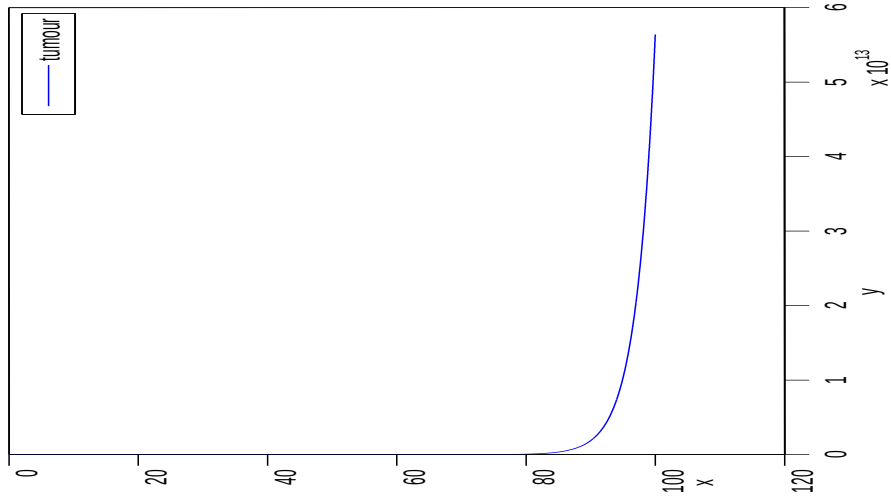

Figure 3: I-T model violating the stability condition for $a = 1, c_1 = c_2 = 1, d_1 = s = r = 0.2, \sigma = 0.3, I(0) = 0.1, T(0) = 0.1$

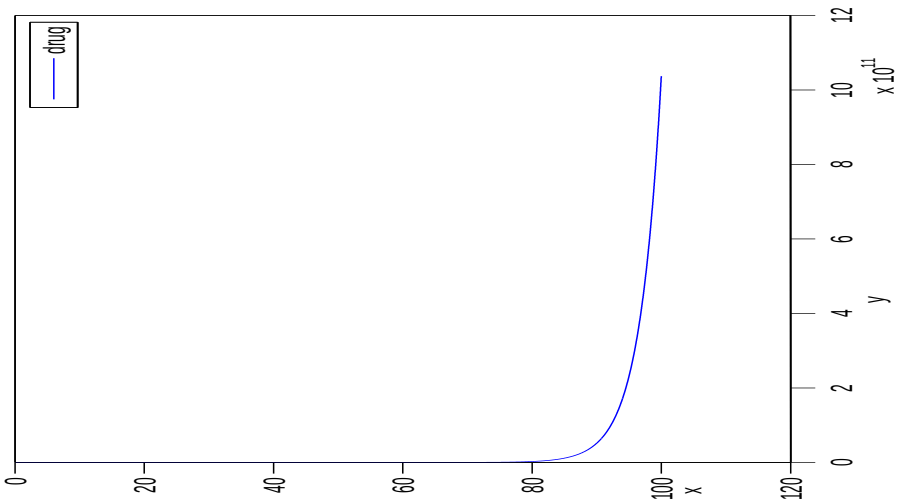

Figure 4: I-T-D model(Drug) is violating the stability condition for $\alpha_3 = 0.3, v(0) = 0.1$

- Drug free equilibrium point is $(\frac{s}{d_1}, 0, 0)$
- With drug administration $(\frac{s}{d_1+\frac{\beta_1}{\beta_3}}, 0, \frac{1}{\beta_3})$

- Co-existing Immune-Tumor equilibria.
  - Drug free equilibria $(I^*, T^*, 0)$ [same as Immune-Tumor model].

3.2.1. Stability Analysis for Tumor Free, Drug Free Equilibria

Linearizing the I-T-D model around $(\frac{s}{d_1}, 0, 0)$ a linearize system of equations have been describes as:

$$\begin{pmatrix} \dot{I} \\ \dot{T} \\ \dot{v} \end{pmatrix} = \begin{pmatrix} -d_1 & \frac{rs}{d_1\sigma} - \frac{c_1 s}{d_1} & -\frac{\beta_1 s}{d_1} \\ 0 & a - \frac{c_2 s}{d_1} & 0 \\ 0 & 0 & \alpha_3 \end{pmatrix} \begin{pmatrix} I - \frac{s}{d_1} \\ T \\ v \end{pmatrix} \tag{3.24}$$

Eigenvalues are:

$$\lambda_1 = -d_1 \tag{3.25}$$

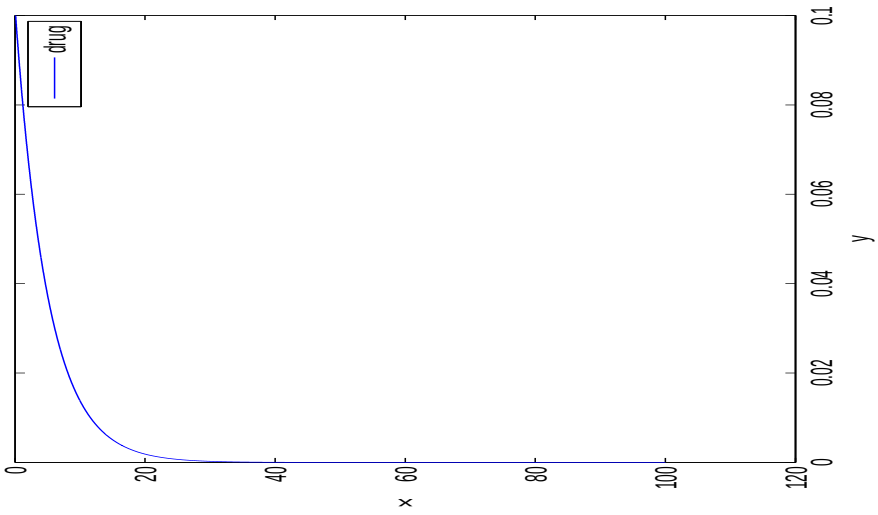

Figure 5: I-T-D model(Drug) figure is stable for $\alpha_3 = -0.2, v(0) = 0.1$

$$\lambda_2 = a - \frac{c_2 s}{d_1} \tag{3.26}$$

$$\lambda_3 = \alpha_3 \tag{3.27}$$

$$\tag{3.28}$$

Hence the model will be stable if:

$$a < \frac{c_2 s}{d_1} \tag{3.29}$$

and

$$\alpha_3 < 0 \tag{3.30}$$

As the parameter α_3 always positive, hence the system around $(\frac{s}{d_1}, 0, 0)$ is not stable.

3.2.2. I-T-D Model for Tumor Free Drug Administered Equilibrium

Linearize system around $(\frac{s}{d_1 + \frac{\beta_1}{\beta_3}}, 0, \frac{1}{\beta_3})$ give rise

$$\lambda_1 = -(d_1 + \frac{\beta_1}{\beta_3}) \tag{3.31}$$

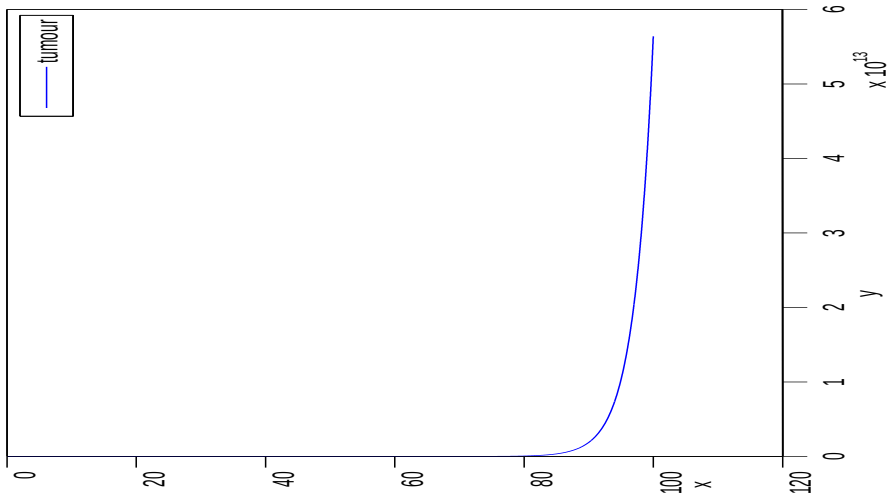

Figure 6: I-T-D model(Tumor) is violating the stability condition for $a = 1, c_2 = 1, s = 0.2, d_1 = 0.3, T(0) = 0.1$

$$\lambda_2 = a - c_2 \frac{s}{d_1 + \frac{\beta_1}{\beta_3}} - \frac{\beta_2}{\beta_3} \tag{3.32}$$

$$\lambda_3 = -\alpha_3 \tag{3.33}$$

$$\tag{3.34}$$

Hence the condition for stability will be:

$$a < c_2 \frac{s}{d_1 + \frac{\beta_1}{\beta_3}} + \frac{\beta_2}{\beta_3}$$

3.2.3. I-T-D Model for Co-Existing Immune Tumor Drug Free Equilibrium

The stability of this model bahaves exactly similar way as in case of co-existing I-T model. So the condition for stability will be same as (3.4).

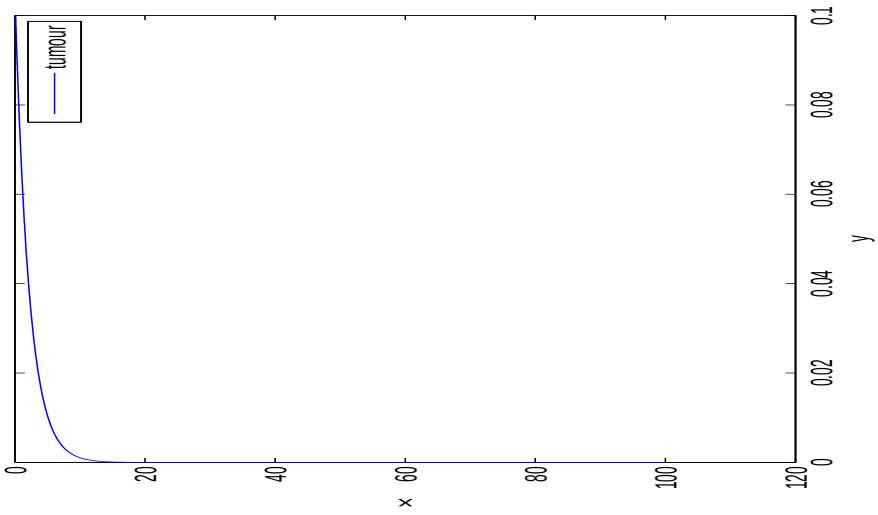

Figure 7: I-T-D model(Tumor) stable for $a = 0.2, c_2 = 1, s = 0.2, d_1 = 0.3, T(0) = 0.1$

4. Analysis and Conclusion

The initial number of immune cells and tumor cells assumed to be 0.1. As the conditions for stability depends on the system parameters, both I-T and I-T-D models are simulated under different stability conditions.

The condition for stability for I-T model around tumor free equilibrium is given by (3.4). Considering the parameters value given in figure 2 shows that the I-T model is stable.

Changing the parameters figure 3 shows instability for tumor growth as the stability condition is being violated.

I-T-D model has also been simulated under same initial conditions and system parameters are chosen considering the conditions for stability (3.29) and (3.30). Figure 4 shows instability where as figure 5 shows for drug administration. Considering the tumor cell growth, figure 6 shows instability where as figure 7 shows stable tumor growth for $(\frac{s}{d_1}, 0, 0)$. The immune cell growth for $(\frac{s}{d_1+\frac{\beta_1}{\beta_3}}, 0, \frac{1}{\beta_3})$ is verified in figure 8, which shows stability.

In any dynamical system, the system behaviour depends on the point of

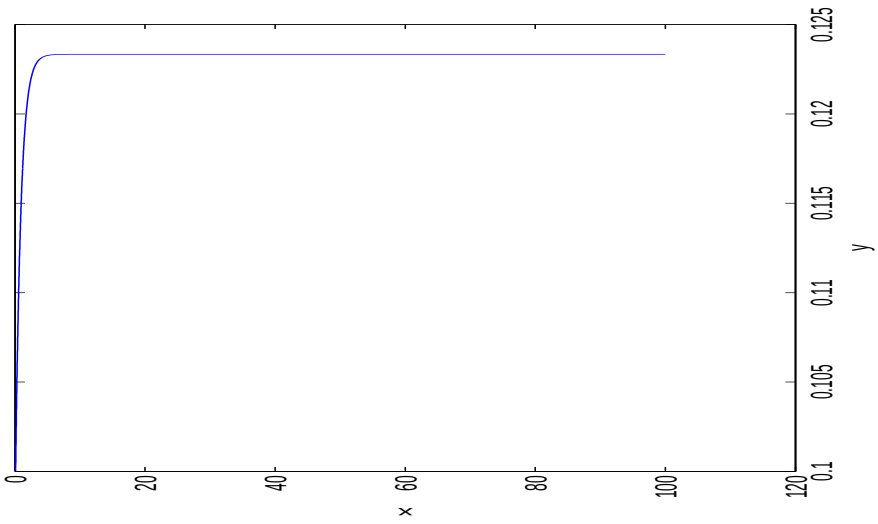

Figure 8: I-T-D model(Immune) stable for $r = 0.2, \beta_1 = 0.3, \beta_2 = 0.2, \beta_3 = 0.3, a = 1, c_1 = 1, s = 0.2, d_1 = 0.2, I(0) = 0.1$

equilibrium. The behaviour of a non-linear system around the equilibrium point is an important aspect of stability analysis. In this paper, both I-T and I-T-D models with different parameters and under same initial conditions are analyzed and observed an insight to the system behaviour.

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.

[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).