Available online at http://scik.org
J. Math. Comput. Sci. 11 (2021), No. 4, 4552-4562
https://doi.org/10.28919/jmcs/5864
ISSN: 1927-5307

STABILITY ANALYSIS OF DELAY INDUCED TUMOR AND IMMUNE SYSTEM INTERACTION MODEL

B. RAVINDRA REDDY*
Department of Mathematics, JNTUH College of Engineering Hyderabad,
Hyderabad-500085, Telangana, India

Abstract: This paper consists of interactions among T-helper cells (resting cells), Cytotoxic-T lymphocytes (hunting cells) and tumor cells with time delay. Stability analysis of equilibrium points and existence of hopf bifurcation is studied. Time delay is utilized as bifurcation parameter. Numerical simulations depict the dynamical performance of the system with different time delay values, which illustrate the phenomenon of long term tumor decline.

Key words: T-helper cells; cytotoxic – T lymphocytes; tumor cells; stability; hopf bifurcation.

Mathematics subject Classification: 37G15, 37N25, 93D05.

1. INTRODUCTION

Cancer is the one of the leading disease in the world. One of the challenge is understanding the advanced dynamics of interactions between tumor and immune system. The cancer result is the abnormal growth of healthy cells which attack closer parts of our body [1]. In recent decades, the disciplines of nonlinear dynamics, cybernetics and stability theory have given priority to study the immunology. Cell mediated immunity involve the cytotoxic T- lymphocytes (CTLs)

---

*Corresponding author
E-mail address: rbollareddy@gmail.com
Received April 15, 2021

production; activate the macrophages and release of cytokines in reaction to an antigen. Many authors have proposed various mathematical models of dispersed cancers, which illustrate the attribute of its cell kinetics [7, 8]. Clinically to understand the mechanism of malignant tumor proliferation & destruction is very complicated. For better understanding of such complicated process, researchers developed various mathematical models [2-6]. Different kinds of approaches have been taken to construct the mathematical models, which are close to the reality [9, 10]. Banerjee and Sarkar [11] developed a different model and proposed that tumor regression is an interaction between tumor cells with immune cells (CTLs). They analyzed the threshold conditions to control malignant tumor growth. Helper T cells (resting T-cells) release the cytokine interleukin -2, which convert the CTLs into hunting cells or natural killer cells. The conversion process of resting T-cells to hunting cytotoxic T-cells is not instantaneous; it will take some period of time observed as delay. This happens due to the identification of tumor cells by T-cells. Incorporating time delay in a mathematical model might cause the periodic solutions at steady state points [12].

In the present paper, tumor- immune system interactions analyze through a system of differential equations. Existence of equilibrium points and its stability is discussed. Condition for Hopf bifurcation is analytically proved.

2. MATHEMATICAL MODEL

The delay differential equations are

$$\begin{aligned}
\frac{dx}{dt} &= r_1 x\left(1-\frac{x}{k_1}\right)-\alpha_1 xy \\
\frac{dy}{dt} &= \beta yz(t-\tau)-d_1 y \qquad (1)\\
\frac{dz}{dt} &= r_2 z\left(1-\frac{z}{k_2}\right)-\beta yz(t-\tau)-d_2 z
\end{aligned}$$

x(t) is tumor cells density, y(t) is Cytotoxic T- lymphocytes the density and z(t) is T- helper cells density. r_1 is intrinsic growth rate of tumor, k_1 is the carrying capacity of tumor cells, α_1 is the destruction of tumor cells by the CTLs, β is the conversion rate of resting cells to CTLs, d_1 is the natural death rate of CTLs, r_2 is the resting cells growth rate, k_2 is the carrying capacity of resting cells are helper cells, d_2 is the natural death rate of resting cells, $\tau > 0$ is the time delay .All the initial conditions are positive.

3. STABILITY ANALYSIS

The feasible equilibrium points of the system (1) are (i) Trivial equilibrium $E_1(0,0,0)$,

(ii) Tumor free equilibrium $E_2(0,\bar{y},\bar{z})$ where $\bar{y} = \frac{1}{\beta}\left(r_2 - \frac{r_2 d_1}{\beta k_2} - d_2 \right), \bar{z} = \frac{d_1}{\beta}$ and (iii) Interior equilibrium $E_3^*(x^*, y^*, z^*)$ where,

$$x^* = \frac{k_1}{r_1}(r_1 - \alpha_1 y^*), y^* = \frac{1}{\beta}\left(r_2 - \frac{r_2 d_1}{\beta k_2} - d_2 \right), z^* = \frac{d_1}{\beta}$$

3.1 Stability Analysis at the tumor free equilibrium $E_2(0,\bar{y},\bar{z})$:

Variation matrix of the system (1) without delay at E_2 is given by

$$J(E_2) = \begin{bmatrix} r_1 - \alpha_1 \bar{y} & 0 & 0 \\ 0 & \beta \bar{z} - d_1 & \beta \bar{y} \\ 0 & -\beta \bar{z} & r_2 - \frac{2 r_2 \bar{z}}{k_2} - \beta \bar{y} - d_2 \end{bmatrix}$$

Characteristic equation

$$(r_1 - \alpha_1 \bar{y} - \lambda)\left((\beta \bar{z} - d_1 - \lambda)((r_2 - \frac{2 r_2 \bar{z}}{k_2} - \beta \bar{y} - d_2 - \lambda) + \beta^2 \bar{y}\,\bar{z}) \right) = 0 \qquad (2)$$

$$\lambda_1 = r_1 - \alpha_1\bar{y}, \quad \lambda^2 + \left(\frac{2r_2}{k_2} - \beta\bar{z} - d_1 + \beta\bar{y} + d_2\right)\lambda + (\beta\bar{z} - d_1)\left(r_2 - \frac{2r_2\bar{z}}{k_2} - \beta\bar{y} - d_2\right) + \beta^2\bar{y}\,\bar{z} = 0$$

$\lambda^2 + p_1\lambda + p_2 = 0$, where $p_1 = \dfrac{2r_2}{k_2} - \beta\bar{z} - d_1 + \beta\bar{y} + d_2 > 0$

$$p_2 = \left((r_2 - \frac{2r_2\bar{z}}{k_2} - \beta\bar{y} - d_2) + \beta^2\bar{y}\,\bar{z}\right)(\beta\,\bar{z} - d_1) > 0$$

E_2 is locally asymptotically stable if $r_1 < \alpha\bar{y}$, i.e $r_1 < \dfrac{r_2\alpha}{\beta}\left(1 - \dfrac{d_1}{\beta k_2} - \dfrac{d_2}{r_2}\right)$

$\dfrac{\beta r_1}{\alpha r_2} + \dfrac{d_1}{\beta k_2} + \dfrac{d_2}{r_2} < 1$ and $\lambda_2 < 0$ & $\lambda_3 < 0$

Basic reproduction number R_0 defined as $R_0 = \dfrac{\beta r_1}{\alpha r_2} + \dfrac{d_1}{\beta k_2} + \dfrac{d_2}{r_2}$

If $R_0 < 1$ the model (1) is locally asymptotically stable at E_2 by Routh- Hurwitz criteria. If $R_0 > 1$ then E_2 is not stable and interior equilibrium exists.

In the presence of delay, characteristic equation of system (1) at E_2 is

$$(r_1 - \alpha_1\bar{y} - \lambda)(\beta\bar{z}e^{-\lambda\tau} - d_1 - \lambda)\left((r_2 - \frac{2r_2\bar{z}}{k_2} - \beta\bar{y} - d_2 - \lambda) + \beta^2\bar{y}\,\bar{z}e^{-\lambda\tau}\right) = 0$$

$$\lambda^2 + \left(\frac{2r_2}{k_2} + d_1 + \beta\bar{y} + d_2 - r_2\right)\lambda + d_1\left(\frac{2r_2\bar{z}}{k_2} + \beta\bar{y} + d_2 - r_2\right)$$
$$+e^{-\lambda\tau}\left(-\beta\bar{z}\lambda + \beta\bar{z}(\frac{2r_2}{k_2} + d_1 + \beta\bar{y} + d_2 - r_2) + \beta^2\bar{y}\,\bar{z}\right) = 0$$

$$\lambda^2 + l_1\lambda + l_2 - e^{-\lambda\tau}(l_3\lambda + l_4) = 0 \qquad (3)$$

$$l_1 = \left(\frac{2r_2}{k_2} + \beta\bar{y} + d_1 + d_2 - r_2\right), l_2 = d_1\left(\frac{2r_2\bar{z}}{k_2} + \beta\bar{y} + d_2 - r_2\right), l_3 = -\beta\bar{z}$$

$$l_4 = \beta\overline{z}(\frac{2r_2}{k_2} + d_1 + \beta\overline{y} + d_2 - r_2) + \beta^2\overline{y}\,\overline{z} \quad .$$

when $\tau > 0$, put $\lambda = i\omega$ in (3)

$$-\omega^2 + l_1 i\omega + l_2 - (\cos\omega\tau - i\sin\omega\tau)(l_3 i\omega + l_4) = 0$$

$$\omega^4 + a_1\omega^2 + a_2 = 0$$

$$a_1 = l_1^2 - 2l_2 - l_3^2 > 0, a_2 = l_2^2 - l_4^2 > 0$$

By Descartes rule there is no positive ω for $\lambda = i\omega$ and $R_0 < 1$

Model (1) is locally asymptotically stable at E_2 when $R_0 < 1$ and unstable if $R_0 > 1$.

3.2 stability analysis at the interior equilibrium E_3:

Variation matrix is

$$J(E^*) = \begin{bmatrix} r_1 - -\frac{2r_1x^*}{k_1} - \alpha_1 y^* & 0 & 0 \\ 0 & \beta z^* e^{-\lambda\tau} - d_1 & \beta y^* \\ 0 & -\beta z^* e^{-\lambda\tau} & r_2 - \frac{2r_2z^*}{k_2} - \beta y^* - d_2 \end{bmatrix}$$

Characteristic equation is

$$(r_1 - \frac{2r_1x^*}{k_1} - \alpha_1 y^* - \lambda)\left((\beta z^* e^{-\lambda\tau} - d_1 - \lambda)(r_2 - \frac{2r_2z^*}{k_2} - \beta y^* - d_2 - \lambda) + \beta^2 y^* z^* e^{-\lambda\tau}\right) = 0$$

$$\begin{aligned}&\lambda^3 + \lambda^2(\alpha_1 y^* + \beta y^* + d_2 + d_1 - c_1 - c_2) + \lambda(d_1(c_1 - \alpha_1 y^*) + (c_2 - \beta y^* - d_2)(d_1 - c_1 + \alpha_1 y^*)) + \\ &(c_1 - \alpha_1 y^*)(c_2 - \beta y^* - d_2)d_1 + e^{-\lambda\tau}(-\beta z^*\lambda^2 + (\beta z^*(c_2 - \beta y^* - d_2) - \beta^2 y^* z^*)\lambda + \\ &(c_1 - \alpha_1 y^*)\beta z^*(c_2 - \beta y^* - d_2) + (c_1 - \alpha_1 y^*)\beta^2 y^* z^* = 0\end{aligned}$$

$$c_1 = r_1 - \frac{2r_1x^*}{k_1}, c_2 = r_2 - \frac{2r_2z^*}{k_2}$$

$$\lambda^3 + m_1\lambda^2 + m_2\lambda + m_3 + e^{-\lambda\tau}(n_1\lambda^2 + n_2\lambda + n_3) = 0 \tag{4}$$

$$m_1 = \alpha_1 y^* + \beta y^* + d_2 + d_1 - c_1 - c_2,\ m_2 = d_1(c_1 - \alpha_1 y^*) + (c_2 - \beta y^* - d_2)(d_1 - c_1 + \alpha_1 y^*)$$
$$m_3 = (c_1 - \alpha_1 y^*)(c_2 - \beta y^* - d_2)d_1,\ n_1 = -\beta z^*, n_2 = \beta z^*(c_2 - \beta y^* - d_2) - \beta^2 y^* z$$
$$n_3 = (c_1 - \alpha_1 y^*)\beta z^*(c_2 - \beta y^* - d_2) + (c_1 - \alpha_1 y^*)\beta^2 y^* z^*$$

Case(i): $when\ \tau < 0$ equation (4) becomes

$$\lambda^3 + m_1\lambda^2 + m_2\lambda + m_3 + (n_1\lambda^2 + n_2\lambda + n_3) = 0$$

$$\lambda^3 + (m_1 + n_1)\lambda^2 + (m_2 + n_2)\lambda + m_3 + n_3 = 0 \tag{5}$$

For the suitable values of $m_1, m_2, m_3, n_1, n_2, n_3$ the Eigen values of (5) has negative real parts if $m_1 + n_1 > 0, m_2 + n_2 > 0, (m_1 + n_1)(m_2 + n_2) - (m_3 + n_3) > 0$

By Routh-Hurwitz criteria interior equilibrium is locally asymptotically stable when $R_0 > 1$

Case(ii): $when\ \tau > 0$

Put $\lambda = i\omega$ in (4)

$$-i\omega^3 - \omega^2 m_1 + m_2 i\omega + m_3 + (\cos\omega\tau - i\sin\omega\tau)(-\omega^2 n_1 + n_2 i\omega + n_3) = 0$$

Separating real and imaginary parts

$$\begin{aligned} &-m_1\omega^2 + (-\omega^2 n_1\cos\omega\tau + n_3\cos\omega\tau) + n_2\omega\sin\omega\tau + m_3 = 0 \\ &-\omega^3 + (\omega^2 n_1 - n_3)\sin\omega\tau + n_2\omega\cos\omega\tau + m_2\omega = 0 \end{aligned} \tag{6}$$

Squaring and adding we get

$$\omega^6 + (m_1^2 - 2m_2 + n_1^2)\omega^4 + (m_2^2 - 2m_1 m_3 + 2n_1 n_3 + n_2^2)\omega^2 + m_3^2 - n_3^2 = 0$$

$$\omega^6 + h_{11}\omega^4 + h_{12}\omega^2 + h_{13} = 0 \tag{7}$$

where $h_{11} = m_1^2 - 2m_2 + n_1^2, h_{12} = m_2^2 - 2m_1 m_3 + 2n_1 n_3 + n_2^2, h_{13} = m_3^2 - n_3^2$

If any one of $h_{12} < 0\ \ or\ \ h_{13} < 0$ there is a unique positive ω_0 satisfies (4). From this equation (4) has pair of purely imaginary roots $\pm i\omega_0$

$$\tau_k = \frac{1}{\omega} arc\ \cos\left[\frac{(m_2 - m_1 n_1)\omega^4 + (m_3 n_1 + m_1 n_3 - m_2 n_2)\omega^2 - m_3 n_3}{(n_1\omega^2 - n_3)^2 + n_2^2\omega^2}\right] \tag{8}$$

Hopf bifurcation in the system for which the transversality condition $\frac{d}{d\tau}(\operatorname{Re}\lambda)_{\tau=\tau_k} > 0$ there exists at least an Eigen value with positive real part for $\tau > \tau_0$

$$sign\left(\frac{d}{d\tau}(\operatorname{Re}\lambda)\right)_{\tau=\tau_0} = sign\left(\operatorname{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1}\right)_{\tau=\tau_0}$$

Consider $\lambda^3 + m_1\lambda^2 + m_2\lambda + m_3 + e^{-\lambda\tau}(n_1\lambda^2 + n_2\lambda + n_3) = 0$

differentiating with respect to τ

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{3\lambda^2 + 2m_1\lambda + m_2}{-\lambda(\lambda^3 + m_1\lambda^2 + m_2\lambda + m_3)} + \frac{2n_1\lambda + n_2}{\lambda(n_1\lambda^2 + n_2\lambda + n_3)} - \frac{\tau}{\lambda}$$

put $\lambda = i\omega_0$

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{-3\omega_0{}^2 + 2m_1 i\omega_0 + m_2}{-i\omega_0(-i\omega_o^3 - m_1\omega_o^2 + m_2 i\omega_0 + m_3)} + \frac{2n_1 i\omega_0 + n_2}{i\omega_0(n_1\omega_o^2 + n_2 i\omega_0 + n_3)} + \frac{\tau}{\omega_0}$$

$$\operatorname{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1} = \operatorname{Re}\left[\frac{-3\omega_0{}^2 + 2m_1 i\omega_0 + m_2}{(-\omega_0^4 + m_2\omega_o^2) + i(m_1\omega_o^3 + m_3\omega_0)} + \frac{2n_1 i\omega_0 + n_2}{(-n_2\omega_0{}^2 + i(-n_1\omega_o^3 + n_3\omega_0)}\right]$$

$$\operatorname{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1} = \mathrm{si}\,g\,\mathrm{n}\left[\operatorname{Re}\left(\frac{u_{11} + iv_{11}}{u_{22} + iv_{22}} + \frac{u_{33} + iv_{33}}{u_{44} + iv_{44}}\right)\right]$$

$$u_{11} = -3\omega_0{}^2 + m_2, v_{11} = 2m_1\omega_0, u_{22} = -\omega_0^4 + m_2\omega_o^2, v_{22} = m_1\omega_o^3 + m_3\omega_0,$$
$$u_{33} = n_2, v_{33} = 2n_1\omega_0, u_{44} = n_2\omega_0{}^2, v_{44} = -n_1\omega_o^3 + n_3\omega_0$$

$$\operatorname{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{u_{11}u_{22} + v_{11}v_{22}}{u_{22}^2 + v_{22}^2} + \frac{u_{33}u_{44} + v_{33}v_{44}}{u_{44}^2 + v_{44}^2}$$
$$= \frac{3\omega_0^6 + (2m_1^2 - m_2)\omega_0^4 + (m_2^2 + 2m_1 m_3 - 3m_2)}{(\omega_0^4 - m_2\omega_0)^2 + (m_1\omega_0^3 + m_3\omega_0)^2} + \frac{(-2n_1^2\omega_0^4 + (2n_1 n_3 - n_2))}{\omega_0^4 n_2^2 + (n_1\omega_0^3 - n_3\omega_0)} > 0$$

Thus the transversality codition exists and the model (1) undergoes a Hopf bifurcation at $\tau = \tau_0$.

3.3 Global stability:

Theorem: The interior equilibrium of the system (1) without delay is globally asymptotically stable in the region of Ω.

Proof: Choose a Lyapunov function

$$w = x - x^* - x^* \ln\left(\frac{x}{x^*}\right) + y - y^* - y^* \ln\left(\frac{y}{y^*}\right) + z - z^* - z^* \ln\left(\frac{z}{z^*}\right)$$

$$\frac{dw}{dt} = \left(\frac{x - x^*}{x}\right)\frac{dx}{dt} + \left(\frac{y - y^*}{y}\right)\frac{dy}{dt} + \left(\frac{z - z^*}{z}\right)\frac{dz}{dt}$$

$$= (x - x^*)\left(r_1 - \frac{r_1 x^*}{k_1} - \alpha_1 y^*\right) + (y - y^*)(\beta z^* - d_1) + (z - z^*)\left(r_2 - \frac{r_2 z^*}{k_2} - \beta y^* - d_2\right)$$

$$= (x - x^*)\left[-\frac{r_1}{k_1}(x - x^*) - \alpha_1 (y - y^*)\right] - \beta (y - y^*)(z - z^*) + (z - z^*)\left[-\frac{r_2}{k_2}(z - z^*) - \beta (y - y^*)\right]$$

$$= -\frac{r_1}{k_1}(x - x^*)^2 - \alpha_1 (y - y^*)(x - x^*) - (y - y^*)(z - z^*) - \frac{r_2}{k_2}(z - z^*)^2 - \beta (y - y^*)(z - z^*)$$

$$= -\frac{r_1}{k_1}(x - x^*)^2 - \frac{\alpha_1}{2}\left((y - y^*)^2 + (x - x^*)^2\right) - \frac{\beta}{2}\left((y - y^*)^2 + (z - z^*)^2\right) - \frac{r_2}{k_2}(z - z^*)^2 < 0$$

Therefore $\frac{dw}{dt} < 0$, system (1) without delay is globally asymptotically stable.

4. NUMERICAL SIMULATIONS

For the set of values $r_1=1.5$; $r_2=2.8$; $\alpha=0.0066$, $k_1=80$, $k_2=100$, $\beta=0.3$, $d_1=0.3$, $d_2=0.1$, $E_3^*(70.006, 26.44, 2)$ $R_0 = 8.1625$

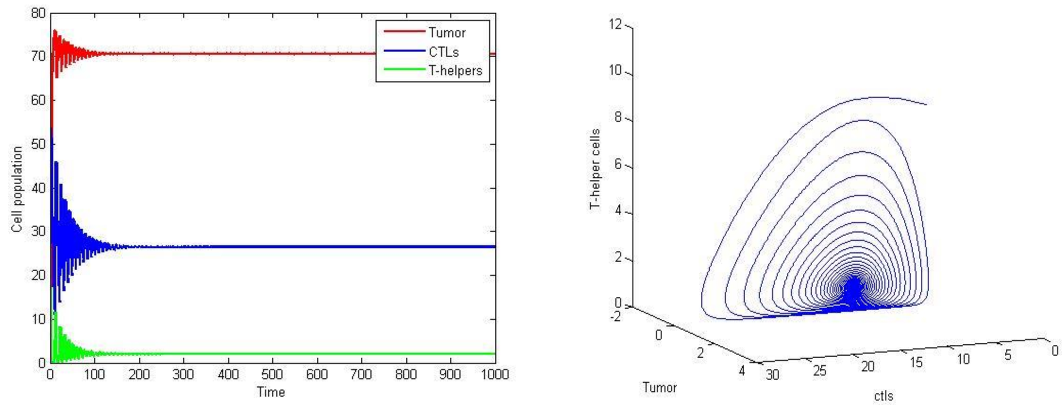

Figure1. Trajectories and phase portrait of the system

For the set of values r_1=2.2; r_2=3.5; α=0.0556; k_1=100; k_2=200; β=0.2; d_1=0.3; d_2=0.1

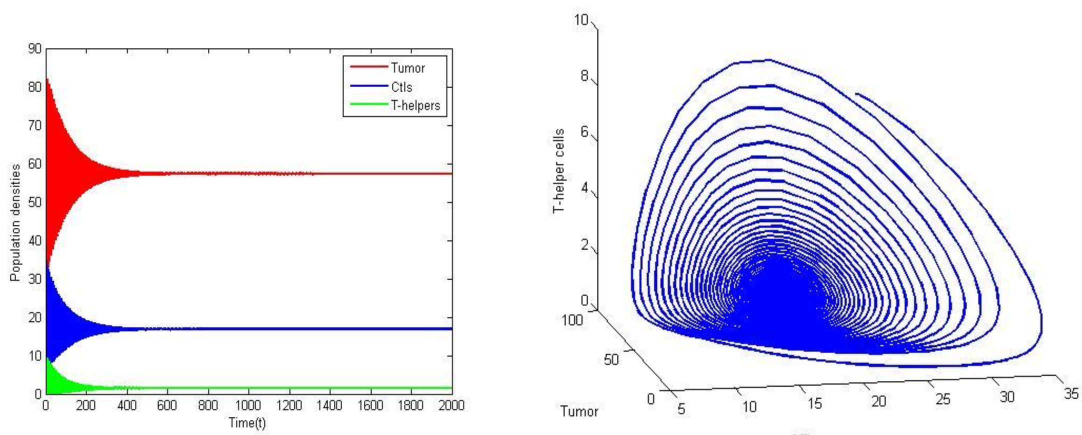

Figure2. Simulations of tumor, Ctls, T-helper cells when $\tau = 0.001$ at E^*

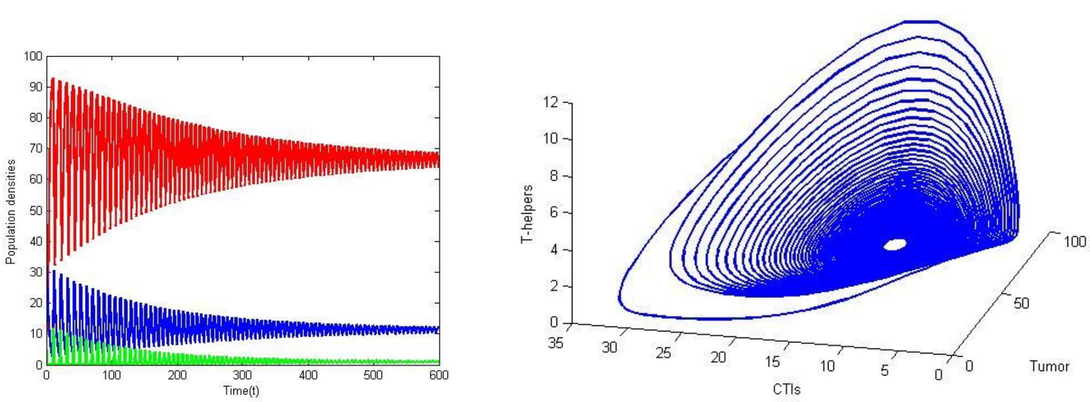

Figure3. For the same set of values when $\tau = \tau_0 = 0.005$ trajectories & phase portrait.

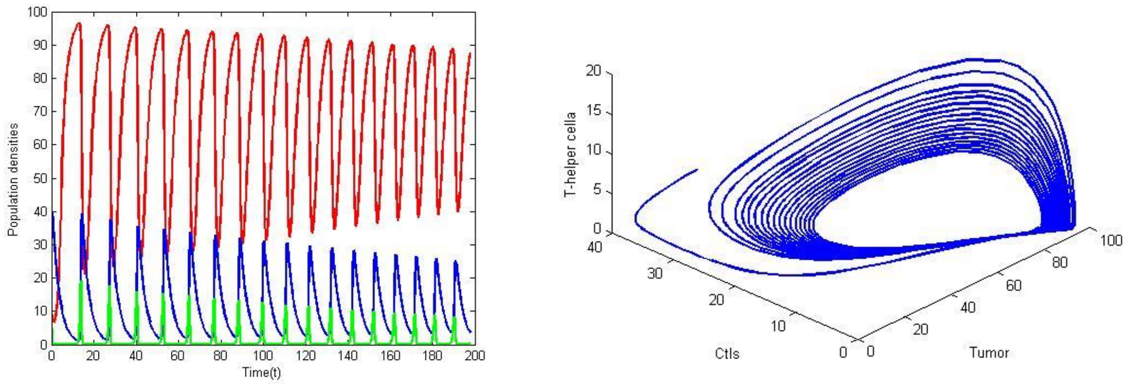

Figure3. For the same set of values when $\tau = 0.009 > \tau_0 = 0.005$ trajectories & phase portrait.

5. CONCLUSION

This paper analyzes the interactions between tumor and immune system through a system of delay differential equations. Existence of possible equilibrium points and its stability is discussed. If $R_0 < 1$ tumor free equilibrium is locally asymptotically stable and if $R_0 > 1$ the interior equilibrium is attained, the local stability and global stability of the interior equilibrium is investigated. The growth of the tumor is influenced by time delay. when $\tau < \tau_0$ system (1) is stable and τ crosses τ_0 then the steady state behaviour of interior equilibrium is changed around E^*. It is observed that, when $\tau > \tau_0$ the unstable oscillations occurred and growth rate of tumor is increased. Activation rate of immune cells depend on the transmission rate also. The admissible time delay for activation of immune cells to attack on tumor cells is to be found. Numerical simulations support the analytical results.

CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

REFERENCES

[1] J.A. Adam, N. Bellomo, A survey of models for tumor-immune system dynamics, Birkhauser, Boston, 1999 .

[2] S. Khajanchi, Uniform persistence and global stability for a brain tumor and immune system interaction, Biophys. Rev. Lett. 12 (2017), 187–208.

[3] S. Banerjee, S. Khajanchi, S. Chaudhuri, A mathematical model to elucidate brain tumor abrogation by immunotherapy with T11 target structure, PLoS ONE. 10 (2015), e0123611.

[4] V. Kuznetsov, I. Makalkin, M. Taylor, A. Perelson, Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis, Bull. Math. Biol. 56 (1994), 295–321.

[5] A. d'Onofrio, Metamodeling tumor–immune system interaction, tumor evasion and immunotherapy, Math. Computer Model. 47 (2008), 614–637.

[6] S. Khajanchi, Modeling the dynamics of glioma-immune surveillance, Chaos Solitons Fractals. 114 (2018), 108–118.

[7] M. Villasana, A. Radunskaya, A delay differential equation model for tumor growth, J. Math. Biol. 47 (2003), 270–294.

[8] C.E. Kelly, S.M. Cox, H.M. Byrne, Macrophage-tumour interactions: In vivo dynamics, Discr. Contin. Dyn. Syst. – B, 4 (2003), 81–98.

[9] N. Kronik, Y. Kogan, M. Elishmereni, K. Halevi-Tobias, S. Vuk-Pavlović, Z. Agur, Predicting Outcomes of Prostate Cancer Immunotherapy by Personalized Mathematical Models, PLoS ONE. 5 (2010), e15482.

[10] Y. Kogan, K. Halevi–Tobias, M. Elishmereni, S. Vuk-Pavlović, Z. Agur, Reconsidering the paradigm of cancer immunotherapy by computationally aided real-time personalization, Cancer Res. 72 (2012), 2218–2227.

[11] Y. Kuang, Delay differential equation with applications in population dynamics, Academic Press, New York, 1993.

[12] M, Sridevi, B. Ravindra Reddy, Hopf bifurcation analysis and stochastic influence of a cancer therapy model, Int. J. Ecol. Econ. Stat. 42 (2021), 13-21.