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Stability and Hopf Bifurcation Analysis of Tumors with Immature and Mature Lymphocytes

M.Sridevi[1], R.Srilatha[2], T. Vidyanath[3], Karuna BNR[4], Lakshmi Appidi[5]

[1]Department of Mathematics, Koneru Lakshmaiah Education Foundation Hyderabad-500043, Telangana, India, Email: mandapatisridevi@gmail.com

[2]Department of Mathematics, VNR Vignana Jyothi Institute of Engineering and Technology Hyderabad-500090, Telangana, INDIA; Email: srilatha_r@vnrvjiet.in

[3]Department of Mathematics, CMR College of Engineering & Technology, Hyderabad-501401, Telangana, INDIA; Email: vidyanath.t @gmail.com

[4]Department of Mathematics, Koneru Lakshmaiah Education Foundation, Hyderabad-500043, Telangana, INDIA; Email: karunakrao@gmail.com

[5]Department of Mathematics, CMR Technical Campus, Hyderabad-501401, Telangana, INDIA. lakshmiappidi25@gmail.com

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Abstract:

The competition between immune system and tumor is highly intricate. Our aim is to develop a simple authentic mathematical model to understand the crucial factors that influence the outcomes of anti -tumor response. We are focusing on the concept that lymphocytes progress through two developing stages immature and mature lymphocytes. We formulated a new model for anti-tumor immune responses and have examined it characteristics. Steady states are found under specific conditions. Using Routh-Hurwitz criteria, local asymptotical stability of equilibria is investigated. Hopf bifurcation is analysed with a time delay as a bifurcation parameter. The length of the delay is derived to maintain stability. Analytical findings demonstrate the impact of delay on destabilizing the system and generating the periodic oscillations. The system undergoes different phases where the rate of mature lymphocytes influx progresses through many stages. This includes uncontrolled tumor growth initially, then reaching a stable state with considerable tumor presence, followed by periodic oscillations. Further progressing to a stable state with minimal tumor and ultimately attaining a stable state free of tumors. Analytical work is illustrated by numerical simulations.

Keywords: Tumor-Immune system, Delay, Stability, Routh Hurwitz criteria, Hopf bifurcation Analysis.

1. Introduction

In accord with the reports of World Health Organization every year millions of population suffer with cancer and mortality rate is creating panic throughout the world. Cancer is an abnormal growth of cells and uncontrolled cell division. It is just like wound that never heals. The immune system strives against tumor cells prevailing in the body and destroys them. The interaction of the immune system in presence of tumor is categorized into two different response processes viz., humoral response and cellular response [1]. Humoral response is related to the B-lymphocytes and the cellular response conveyed by T lymphocytes. The law of growth of cancer and the reaction of the

immune system in the presence of the tumor is still unknown to many researchers. In any case, research has shown that once tumor cells are recognized the immune system can eliminate them. Macrophages, perhaps found in every tissue of the body, absorb tumor cells to propagate them into the blood [2]. Macrophages discharge cytokines that triggers the T-helper cells and these cells multiply & discharge other cytokines resulting in more T-cells and B-cells. These T-helper cells instead of killing the tumor cells, sends a biochemical signal to the T-Lymphocytes (Natural killers) and initiates the production of antibodies as the B-cells raise. Antibodies diffused in the blood are connected to cancer cells and destroy them.

Researchers adopted mathematical modelling techniques in the field of Oncology to treat cancer. Many significant contributions were made to understand and analyze the tumor immune dynamics [3-5]. Kuznetsov et al. [6] define a mathematical model for two cell populations' tumor cells and effector cells. They predicted bounds for the threshold which showed that the disease attenuates with periodic aggravations developing in 3-4 months for the lower bound and an uncontrollable tumor growth for the upper bound. Liu et.al [7] refined a scientific model with tumor cells evoking a resistant retaliation suggested by Rescigno and DeLisi [8] to examine immune system and tumor interactions. Ruan and Liu [7] considered reasonable assumptions in their model by taking into the two stages development in lymphocytes viz., Immature and mature lymphocytes. In the second phase lymphocytes (mature) are more effectual to kill the tumor cells. Several mathematical concepts materialized later to understand the dynamics of immune response to the tumor [19-22]. Pang.et.al [9] proposed a model which included different states in tumor growth such as Immune escape of tumor, dormant stage etc.

In this study we proposed a simple mathematical model to understand the mechanism of tumor cells and anti-immune response of lymphocytes to eradicate tumor cells. Discrete time delay is incorporated in the recruitment term of the mature lymphocytes. We formulated the model in section2, stability analysis of the equilibrium points is discussed in section 3, Conditions for Hopf bifurcation are established in Section 4, numerical simulations and conclusions are discussed in section 5 and section 6 respectively.

2. Mathematical Model

Immune system plays a vital role to protect the human body from tumor cells. Many mathematical models were proposed to find the interactions between tumor and immune system. We observed that each model describes the mechanism of tumor and its reduction in the body. Lymphocytes play a crucial part in the immune system that deactivates the tumor cells. In this paper, tumor cells, immature lymphocytes and mature lymphocytes are represented by $T(t_k)$, $L_1(t_k)$ and $L_2(t_k)$.

$$\frac{dL_1}{dt_k} = S - P_1 L_1 + \frac{\beta_1 L_2(t_k - \tau) T(t_k - \tau)}{g + T(t_k - \tau)}$$

$$\frac{dL_2}{dt_k} = P_1 L_1 - \mu L_2 \qquad (1)$$

$$\frac{dT}{dt_k} = P_2 T - \beta_2 T L_2$$

The rate of change in immature T-lymphocytes population is represented in the first equation. S is the production rate of the immature T-lymphocytes. Matured T-lymphocytes are procured from the immature T-lymphocytes, the rate of transformation from immature lymphocytes to young lymphocytes is denoted by P_1. As the young T-lymphocytes are a part of the inherent immune system, they appear in the human body even under tumor cells absentia.

In presence of a tumor, immature T-lymphocytes are augmented by the stimulation of tumor cells [13, 14, 15]. The term $\frac{\beta_1 L_2(t_k-\tau)T(t_k-\tau)}{g+T(t_k-\tau)}$ describes the response of the anti-tumor immunity, where β_1 rate of maximum recruitment, g is saturation constant and τ is time delay. The strength of mature T-lymphocytes is characterized by the second equation. The mature T-lymphocytes make the tumor cells inactive when interacting with them. The rate of inactivation in mature T- lymphocytes is μ. There is an exponential growth of tumor cells in the absentia of immune response denoted in tumor cells growth model [10]. The growth rate of tumor cell is denoted by P_2. Mature T-lymphocytes can only kill the tumor cells [11, 12]. $\beta_2 TL_2$ is the tumor cells and mature T-lymphocytes interaction term, where β_2 represents inhibition factor of tumor cells with mature T-Lymphocytes.

To facilitate discussion on model (1), we take the following substitution $S = P_0 L_0$ and use the non-dimensional variables and parameters as

$$\left(x_1, x_2, x_3\right) = \left(\frac{\beta_2}{\beta_1}(L_1 - \frac{P_0}{P_1}L_0), \frac{L_2\beta_2}{P_1}, \frac{T}{g}\right) \text{with} \, t_k = \frac{1}{p_1}t$$

The corresponding standardized system is

$$\begin{aligned} \frac{dx_1}{dt} &= -x_1 + \frac{x_2(t-\tau)x_3(t-\tau)}{1+x_3(t-\tau)} \\ \frac{dx_2}{dt} &= b_1 x_1 - b_2 x_2 + b_3 \\ \frac{dx_3}{dt} &= cx_3 - x_2 x_3 \end{aligned} \qquad (2)$$

with initial condition $x_1(\theta) = \phi_1, x_2(\theta) = \phi_2, x_3(\theta) = \phi_3$ (2.1)

with $\phi_j \geq 0 \ \forall \ j = 1,2,3$ for $\theta \in [-\tau, 0]$, where $X(t) = X\left[t; X(0)\right], \forall t > 0 \ \& \ b_3 - b_2 c > 0$.

Lemma 1. The solution $\left(x_1(t), x_2(t), x_3(t)\right)$ of model (2) are non-negative subjected to positive initial conditions $\left(\phi(\text{j}), \ j = 1,2,3\right)$ on $\left[0, +\infty\right)$.

Proof. System (2) is expressed as

$$\dot{X} = \begin{pmatrix} \dot{x}_1(t) \\ \dot{x}_2(t) \\ \dot{x}_3(t) \end{pmatrix} = \begin{pmatrix} -x_1 + \dfrac{x_2(t-\tau)x_3(t-\tau)}{1+x_3(t-\tau)} \\ b_1x_1 - b_2x_2 + b_3 \\ cx_3 - x_2x_3 \end{pmatrix} = \begin{pmatrix} \nu_1(X) \\ \nu_2(X) \\ \nu_3(X) \end{pmatrix} = \nu(X) \qquad (3)$$

Where $\nu : R_+^3 \to R^3$ is the function defined $\forall\ \nu \in C^\infty(R_+^3)$ in the positive octant R_+^3. The R.H.S of system (3) be locally Lipschitz with bounded derivatives thus satisfies

$\nu_i(X)_{x_i(t)},\ X \in R_+^3 = \nu_i(0) \geq 0\ \forall\ i = 1,2,3.$

In relation to the lemma by Yang et.al [16], all the solutions of system (2) with the positive initial values, $X(t) = X\left[t; X(0)\right], \varphi_i(t) \in R_+^3, \forall t > 0$, i.e., they remain non negative throughout the region R_+^3, $\forall t > 0$.

3. Existence of Equilibria

The system has two equilibrium points. Tumor free equilibrium point $E_0\left(0, \dfrac{b_3}{b_2}, 0\right)$ and tumor present equilibrium point where $x_1^* = \dfrac{b_2c - b_3}{b_1}$, $x_2^* = c$ and $x_3^* = \dfrac{b_2c - b_3}{b_1c + b_3 - b_2c}$

Tumor free equilibrium E_0 exists always and tumor present equilibrium E^* exists for $b_2c - b_3 > 0$

Lemma 2. In the absence of delay $(\tau = 0)$, the system (2) is locally asymptotically stable around the tumor free state E_0 when $b_2c < b_3$, or else it is unstable.

Proof. The Jacobian matrix is $J(E_0) = \begin{bmatrix} -1 & 0 & \dfrac{b_3}{b_2} \\ b_1 & -b_2 & 0 \\ 0 & 0 & c - \dfrac{b_3}{b_2} \end{bmatrix}$

And the characteristic equation is $(-1-\lambda)(-b_2-\lambda)(c - \dfrac{b_3}{b_2} - \lambda) = 0$

$\lambda_1 = -1, \lambda_2 = -b_2, \lambda_3 = \dfrac{-(b_3 - b_2c)}{b_2}$ where λ_3 exists if $\dfrac{b_2c}{b_3} < 1$

The tumor free equilibrium point is locally asymptotic stable for $\dfrac{b_2c}{b_3} < 1$,

and otherwise unstable.

The characteristic equation shows that the Eigen values are negative, hence the system is locally asymptotic stable whenever $\frac{b_2 c}{b_3} < 1$.

Lemma 3. The necessary and sufficient conditions for local asymptotic stability of equation (2) around the tumor present equilibrium state $E_1(x_1^*, x_2^*, x_3^*)$.

Proof. Jacobian matrix $J(E^*) = \begin{bmatrix} -1 & \frac{x_3^*}{1+x_3^*} e^{-\lambda\tau} & \frac{x_2^*}{(1+x_3^*)^2} e^{-\lambda\tau} \\ b_1 & -b_2 & 0 \\ 0 & -x_3^* & c - x_2^* \end{bmatrix}$

And the characteristic equation is

$$\lambda^3 + \lambda^2(-1 - b_2 + c - x_2^*) - \lambda(-b_2(c - x_2^*) - (c - x_2^*) + b_2 - b_1 \frac{x_3^*}{1+x_3^*} e^{-\lambda\tau})$$

$$+ b_2(c - x_2^*) - e^{-\lambda\tau}(b_1 \frac{x_3^*}{1+x_3^*} + b_1 \frac{x_2^* x_3^*}{(1+x_3^*)^2}) = 0$$

$$\lambda^3 + \lambda^2(b_2 - c + x_2^* + 1) + \lambda(-b_2(c - x_2^*) - (c - x_2^*) + b_2 - b_1 \frac{x_3^*}{1+x_3^*} e^{-\lambda\tau})$$

$$- b_2(c - x_2^*) + e^{-\lambda\tau}(b_1 \frac{x_3^*}{1+x_3^*} + b_1 \frac{x_2^* x_3^*}{(1+x_3^*)^2}) = 0 \quad (4)$$

When $\tau = 0$ we have

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$$

$$a_1 = b_2 - c + x_2^* + 1,\ a_2 = b_2 x_2^* + x_2^* - c - b_2 c + b_2 - b_1 \frac{x_3^*}{1+x_3^*}$$

$$a_3 = b_1 \frac{x_2^*}{1+x_3^*} - b_2 c + b_2 x_2^* + b_1 \frac{x_2^* x_3^*}{(1+x_3^*)^2}$$

Which implies a_1, a_2, a_3 are all positive and by Routh–Hurwitz criterion the system becomes locally asymptotic stable.

For $\tau > 0$, the characteristic equation is

$$\lambda^3 + \lambda^2(b_2 - c + x_2^* + 1) + \lambda(b_2 + x_2^* - b_2 c + b_2 x_2^* - c) + b_2(c - x_2^*) +$$

$$e^{-\lambda\tau}(b_1 \frac{x_3^*}{1+x_3^*}\lambda + \frac{b_1(c - x_2^*)}{1+x_3^*} + \frac{b_1 x_2^* x_3^*}{(1+x_3^*)^2}) = 0 \quad (5)$$

$$\lambda^3 + a_{11}\lambda^2 + a_{12}\lambda + a_{13} + e^{-\lambda\tau}(a_{14}\lambda + a_{15}) = 0 \quad (6)$$

$a_{11} = (b_2 - c + x_2^* + 1),\ a_{12} = b_2 + x_2^* - b_2 c + b_2 x_2^* - c,\ \ a_{13} = b_2(c - x_2^*)$

$a_{14} = \frac{b_1 x_3^*}{1 + x_3^*}, a_{15} = \frac{b_1(c - x_2^*)}{1 + x_3^*} + \frac{b_1 x_2^* x_3^*}{(1 + x_3^*)^2}$

when $\tau > 0$ there exists a positive τ_0 such that the roots of equation (6) are $\lambda = \pm i\omega, \omega > 0$

Put $\lambda = i\omega$ in equation (6), we get

$-i\omega^3 - a_{11}\omega^2 + a_{12} i\omega + a_{13} + (\cos\omega\tau - i\sin\omega\tau)(a_{14} i\omega + a_{15}) = 0$

Separating real and imaginary parts

$a_{15}\cos\omega_0\tau + a_{14}\omega_0 \sin\omega_0\tau = a_{11}{\omega_0}^2 - a_{13}$

$a_{14}\omega_0 \cos\omega_0\tau - a_{15}\sin\omega_0\tau = {\omega_0}^3 + a_{12}\omega_0 \qquad (7)$

$\left(a_{11}\omega^2 - a_{13}\right)^2 + \left(\omega^3 + a_{12}\omega\right)^2 = {a_{15}}^2 + {a_{14}}^2\omega^2$

$\omega^6 + c_1\omega^4 + c_2\omega^2 + c_3 = 0 \qquad (8)$

$c_1 = 2a_{12} + a_{11}^2,\ c_2 = a_{12}^2 - 2a_{11}a_{13} - {a_{14}}^2, c_3 = a_{13}^2 - {a_{15}}^2$

In equation (8), $f(\omega)$ is written in the form $H(\omega^2)$

Let $z = \omega^2$

$M(z) = z^3 + c_1 z^2 + c_2 z + c_3 \qquad (9)$

If c_1, c_2, c_3 are positive then there is no positive root of (9)

$\frac{dM}{dz} = 3z^2 + 2c_1 z + c_2 = 0$

$z = \frac{-c_1 \pm \sqrt{c_1^2 - 3c_2}}{3}$

If $c_2 > 0$ then $\sqrt{c_1^2 - 3c_2} < c_2$, either z_1 *or* z_2 are not positive. (9) has no positive roots and $M(0) = c_3 > 0$. It shows that (9) has no positive roots. Thus, no ω holds in order that $i\omega$ become an eigen value of (9). Hence all the latent roots possess negative real parts for $\tau > 0$.

For $c_2 < 0,$ we have $\sqrt{c_1^2 - 3c_2} > c_2$ and (9) has positive root ω_0. That is a couple of purely imaginary roots exist for equation (8). Let $\lambda(\tau) = \xi(\tau) + i\omega(\tau)$ is a latent root of (6) so that $\xi(\tau_0) = 0$ and $\omega(\tau_0) = \omega_0$.

From (7)

$$\tau_k = \frac{1}{\omega_0}\left(\cos^{-1}\left(\frac{a_{14}\omega^4 + a_{11}a_{15}\omega^2 + a_{12}a_{14}\omega - a_{13}a_{15}}{a_{15}^2 + a_{14}^2\omega^2}\right) + 2n\pi\right) \quad n = 0,1,2...$$

4. Hopf Bifurcation Analysis

If $\tau < \tau_0$ then E^* is stable, when the transversality constraint $\left.\frac{d\,\mathrm{Re}(\lambda)}{dt}\right|_{\tau=\tau_0}$ holds and for $\tau > \tau_0$ atleast one eigen value with positive real part exists.

To justify this

$$sign\left(\left.\frac{d\,\mathrm{Re}(\lambda)}{d\tau}\right)\right|_{\tau=\tau_0} = sign\left(\left.\mathrm{Re}\left[\frac{d\lambda}{d\tau}\right]^{-1}\right)\right|_{\tau=\tau_0}$$

Considering (6), we have

$$\lambda^3 + a_{11}\lambda^2 + a_{12}\lambda + a_{13} + e^{-\lambda\tau}(a_{14}\lambda + a_{15}) = 0$$

Differentiating with respect to τ

$$\frac{d\lambda}{d\tau} = \frac{\lambda e^{-\lambda\tau}(a_{14}\lambda + a_{15})}{3\lambda^2 + 2a_{11}\lambda + a_{12} + a_{14}e^{-\lambda\tau} - \tau(a_{14}\lambda + a_{15})e^{-\lambda\tau}}$$

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{3\lambda^2 + 2a_{11}\lambda + a_{12}}{\lambda e^{-\lambda\tau}(a_{14}\lambda + a_{15})} + \frac{a_{14}}{\lambda(a_{14}\lambda + a_{15})} - \frac{\tau}{\lambda}$$

Put $\lambda = i\omega$

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

$u_{11} = a_{12} - 3\omega^2, v_{11} = 2a_{11}\omega, u_{22} = a_{12}\omega^2 - \omega^4, v_{22} = a_{11}\omega^2 - a_{13}\omega$

$u_{33} = a_{14}, v_{33} = 0, u_{44} = -a_{14}\omega^2, v_{44} = a_{15}$

$$\mathrm{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1} = \mathrm{Re}\left[\frac{v_1v_2 + u_1u_2}{v_2^2 + u_2^2} + \frac{v_3v_4 + u_3u_4}{v_4^2 + u_4^2}\right]$$

Under the condition $v_1v_2 + u_1u_2 > 0$ and $v_3v_4 + u_3u_4 > 0$

$$\left.\frac{d\,\mathrm{Re}(\lambda)}{d\tau}\right|_{\lambda=i\omega_0} > 0$$

Thus the transversality constraint holds and Hopf bifurcation occurs.

Length of Delay Estimation:

For preserving the stability of the limit cycle from bifurcating periodic orbits an estimation for the maximum length of delay is investigated. The delay system (2) for the domain of all real valued

continuous function on $[-\tau,+\infty]$ satisfying the initial conditions (2.1) on $[-\tau,0]$ is considered. The linearized model about the tumor present equilibrium state $E_1(x_1^*, x_2^*, x_3^*)$ is given by

$$\dot{x}_1 = -x_1 + \frac{x_3^*}{1+x_3^*}x_2(t-\tau) + \frac{x_2^*}{1+x_3^*}x_3(t-\tau)$$
$$\dot{x}_2 = b_1x_1 - b_2x_2$$
$$\dot{x}_3 = cx_3 - x_2x_3^* - x_2^*x_3 \tag{10}$$

Taking Laplace transformation on both sides of (10), we get

$$\left.\begin{aligned}(s+1)L_{x_1}(s) &= \frac{x_3^*}{1+x_3^*}e^{-s\tau}L_{x_2}(s) + \frac{x_3^*}{1+x_3^*}e^{-s\tau}U_{x_2}(s) + \frac{x_2^*}{1+x_3^*}e^{-s\tau}L_{x_3}(s) + \frac{x_2^*}{1+x_3^*}e^{-s\tau}U_{x_3}(s) + \bar{x}_1(0)\\ (s+b_2)L_{x_2}(s) &= b_1L_{x_1}(s) + \bar{x}_2(0)\\ (s-c+\bar{x}_3+\bar{x}_2)L_{x_3}(s) &= \bar{x}_3(0)\end{aligned}\right\} \tag{11}$$

Where

$U_{x_2}(s) = \int_{-\tau}^{0} e^{-st}x_2(t)dt$, $U_{x_3}(s) = \int_{-\tau}^{0} e^{-st}x_3(t)dt$ and $L_{x_1}(s), L_{x_2}(s), L_{x_3}(s)$ are respectively the

Laplace Transforms of $x_1(t)$, $x_2(t)$ and $x_3(t)$.

From the theory by Freedman et. al. [10] and the classical Nyquist criterion, conditions for the interior equilibrium E^* to be locally asymptotically stable are given by

$$\operatorname{Re} H(i\zeta_0) = 0 \tag{12}$$

and $$\operatorname{Im} H(i\zeta_0) > 0 \tag{13}$$

Here $H(s) = s^3 + a_{11}s^2 + a_{12}s + a_{13} + e^{-s\tau}(a_{14}s + a_{15})$ and $\zeta_0 > 0$ is a root of (12) which is sufficiently small.

From (12) and (13) we get,

$$a_{15}\cos\zeta_0\tau + a_{14}\zeta_0\sin\zeta_0\tau = a_{11}\zeta_0^{\,2} - a_{13}, \tag{14}$$

$$a_{14}\zeta_0\cos\zeta_0\tau - a_{15}\sin\zeta_0\tau = \zeta_0^{\,3} + a_{12}\zeta_0 \tag{15}$$

$$\text{i.e.,}\left(1+b_2-c\right)\zeta_0^2 = \left(b_2c - b_2x_2^*\right) + \left[\frac{b_1c - b_1x_2^*}{\left(1+x_3^*\right)} - \frac{b_1x_2^*x_3^*}{\left(1+x_3^*\right)^2}\right]\cos\zeta_0\tau + \left(\frac{b_1x_3^*}{\left(1+x_3^*\right)}\right)\zeta_0\sin\zeta_0\tau - x_2^*\zeta_0^2 \tag{16}$$

From the inequalities $|\cos(\zeta_0\tau)| \le 1$ and $|\sin(\zeta_0\tau)| \le 1$, we have

$$\left(1+b_2-c\right)\zeta_0^2 \le \left|\left(b_2c-b_2x_2^*\right)\right| + \left|\left(\frac{b_1c-b_1x_2^*}{\left(1+x_3^*\right)} - \frac{b_1x_2^*x_3^*}{\left(1+x_3^*\right)^2}\right)\right| + \left|\left(\frac{b_1x_3^*}{\left(1+x_3^*\right)}\right)\right|\zeta_0 - \left|x_2^*\right|\zeta_0^2 \qquad (17)$$

From (16), we get

$$\zeta_+ \le \frac{\left|\left(\frac{b_1x_3^*}{\left(1+x_3^*\right)}\right)\right| + \sqrt{\left(\frac{b_1x_3^*}{\left(1+x_3^*\right)}\right)^2 + 4\left(\left\{\left|1+b_2-c\right|-\left|x_2^*\right|\right\}\left(\frac{b_1c-b_1x_2^*}{\left(1+x_3^*\right)} - \frac{b_1x_2^*x_3^*}{\left(1+x_3^*\right)^2} + \left(b_2c-b_2x_2^*\right)\right)\right)}}{2\left\{\left|\left(1+b_2-c\right)-\left|x_2^*\right|\right|\right\}}$$

Thus, $\zeta_0 \le \zeta_+$.

From the equation (15)

$$\zeta_0^2 < \left(b_2 + x_2^* - b_2c + b_2x_2^* - c\right) + \frac{b_1x_3^*}{1+x_3^*}\cos(\zeta_0\tau) - \frac{\left(\frac{b_1c-b_1x_2^*}{1+x_3^*} + \frac{b_1x_2^*x_3^*}{(1+x_3^*)^2}\right)\sin(\zeta_0\tau)}{\zeta_0} \qquad (18)$$

Using (15) in (18)

$$\left\{\frac{b_1c-b_1x_2^*}{1+x_3^*} + \frac{b_1x_2^*x_3^*}{(1+x_3^*)^2} - \left(1+b_2-c\right)\frac{b_1x_3^*}{1+x_3^*}\right\}\left[\cos(\zeta_0\tau)-1\right] + \left\{\frac{b_1x_3^*}{1+x_3^*}\zeta_0 - \left(\frac{\frac{b_1c-b_1x_2^*}{1+x_3^*} + \frac{b_1x_2^*x_3^*}{(1+x_3^*)^2}}{\zeta_0}\right)\right\}\sin(\zeta_0\tau)$$

$$< \left(1+b_2-c\right)\left(b_2 + x_2^* - b_2c + b_2x_2^* - c\right) - \left(b_2c-b_2x_2^*\right) + \left(1+b_2-c\right)\frac{b_1x_3^*}{1+x_3^*} - \left(\frac{b_1c-b_1x_2^*}{1+x_3^*} + \frac{b_1x_2^*x_3^*}{(1+x_3^*)^2}\right) + x_2^*\zeta_0^2$$

Considering the inequality $\zeta_0^2 < \left(b_2x_2^* + x_2^* - b_2c + b_2 - c - \frac{b_1x_3^*}{1+x_3^*}\right)$ when $\tau = 0$, the above equation takes the form

$$\left\{\frac{b_1c-b_1x_2^*}{1+x_3^*} + \frac{b_1x_2^*x_3^*}{(1+x_3^*)^2} - \left(1+b_2-c\right)\frac{b_1x_3^*}{1+x_3^*}\right\}\left[\cos(\zeta_0\tau)-1\right] + \left\{\frac{b_1x_3^*}{1+x_3^*}\zeta_0 - \left(\frac{\frac{b_1c-b_1x_2^*}{1+x_3^*} + \frac{b_1x_2^*x_3^*}{(1+x_3^*)^2}}{\zeta_0}\right)\right\}\sin(\zeta_0\tau)$$

$$< \left(1+b_2-c+x_2^*\right)\left(b_2 + x_2^* - b_2c + b_2x_2^* - c - \frac{b_1x_3^*}{1+x_3^*}\right) - \left\{\left(b_2c-b_2x_2^*\right) + \frac{b_1x_2^*x_3^*}{(1+x_3^*)^2} + \frac{b_1c-b_1x_2^*}{1+x_3^*}\right\} \qquad (19)$$

Using the bounds the first & second terms on the L.H.S of (18) are written respectively as

$$\left\{\frac{b_1c-b_1x_2^*}{1+x_3^*} + \frac{b_1x_2^*x_3^*}{(1+x_3^*)^2} - \left(1+b_2-c\right)\frac{b_1x_3^*}{1+x_3^*}\right\}\left[\cos(\zeta_0\tau)-1\right]$$

$$= 2\left\{\frac{b_1c - b_1x_2^*}{1+x_3^*} + \frac{b_1x_2^*x_3^*}{(1+x_3^*)^2} - (1+b_2-c)\frac{b_1x_3^*}{1+x_3^*}\right\}\left(\sin^2\left(\frac{\zeta_0\tau}{2}\right)\right)$$

$$\leq \frac{1}{2}\zeta_0^2\left|\left\{\frac{b_1c - b_1x_2^*}{1+x_3^*} + \frac{b_1x_2^*x_3^*}{(1+x_3^*)^2} - (1+b_2-c)\frac{b_1x_3^*}{1+x_3^*}\right\}\right|\tau^2$$

And

$$\left\{\frac{b_1x_3^*}{1+x_3^*}\zeta_0 - \left(\frac{\frac{b_1c - b_1x_2^*}{1+x_3^*} + \frac{b_1x_2^*x_3^*}{(1+x_3^*)^2}}{\zeta_0}\right)\right\}\sin(\zeta_0\tau) \leq \left\{\left|\frac{b_1x_3^*}{1+x_3^*}\right|\zeta_+^2 + \left|\frac{b_1c - b_1x_2^*}{1+x_3^*} + \frac{b_1x_2^*x_3^*}{(1+x_3^*)^2}\right|\right\}\tau$$

Hence from equation (18)

$$\psi_1\tau^2 + \psi_2\tau \leq \psi_3 \tag{20}$$

Here,

$$\psi_1 = \frac{1}{2}\zeta_0^2\left|\left\{\frac{b_1c - b_1x_2^*}{1+x_3^*} + \frac{b_1x_2^*x_3^*}{(1+x_3^*)^2} - (1+b_2-c)\frac{b_1x_3^*}{1+x_3^*}\right\}\right|$$

$$\psi_2 = \left\{\left|\frac{b_1x_3^*}{1+x_3^*}\right|\zeta_+^2 + \left|\frac{b_1c - b_1x_2^*}{1+x_3^*} + \frac{b_1x_2^*x_3^*}{(1+x_3^*)^2}\right|\right\}$$

$$\psi_3 = (1+b_2-c+x_2^*)\left(b_2 + x_2^* - b_2c + b_2x_2^* - c - \frac{b_1x_3^*}{1+x_3^*}\right) - \left\{(b_2c - b_2x_2^*) + \frac{b_1x_2^*x_3^*}{(1+x_3^*)^2} + \frac{b_1c - b_1x_2^*}{1+x_3^*}\right\}$$

Thus, when

$\tau_+ = \frac{1}{2\psi_1}\left[-\psi_2 + \sqrt{\psi_2^2 + 4\psi_1\psi_3}\right]$, for $0 \leq \tau \leq \tau_+$ the Nyquist criterion is proved to be successful and the time lag with maximum length for the stability around the equilibrium E^* is preserved.

5. Numerical Simulations

To validate our discussion, numerical simulations are performed using MATLAB software. The delay differential equation model (2) demonstrated that the system displays oscillations. We have chosen suitable parameters to give a meaningful biological scenario of the system (2). We observe that the parameters c and delay τ play a crucial role to destabilizing the steady states. To generate oscillations, parameter c values greater than the b_1, b_2 and b_3 and $b_2c > b_3$. The effect of time delay on steady state point at different values of delay is discussed.

For the set of values b_1=0.4; b_2=0.65; b_3=3.5; c=6.5 tumor present equilibrium $E^*(2.787, 7.278, 0.6068)$ is locally asymptotically stable when $\tau < \tau_0$.

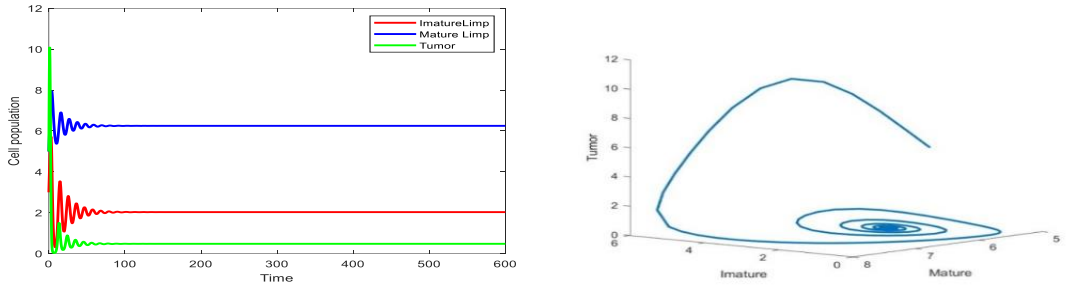

Fig1. Stable variations of the lymphocytes and tumor cell populations against time when $\tau = 0.1253 < \tau_0$ and Phase space trajectories at $\tau = 0.1253 < \tau_0$

Setting the parameters $b_1 = 0.4;\ b_2 = 0.65; b_3 = 3.25;\ c = 7.5;$ the graphs below represent variations in immature, mature lymphocytes and tumor cells. Observations indicate that bifurcation point attained at $\tau = \tau_0 = 0.5153$. There is a balance among the lymphocytes and tumor cells. Periodic oscillations arise at tumor present equilibrium.

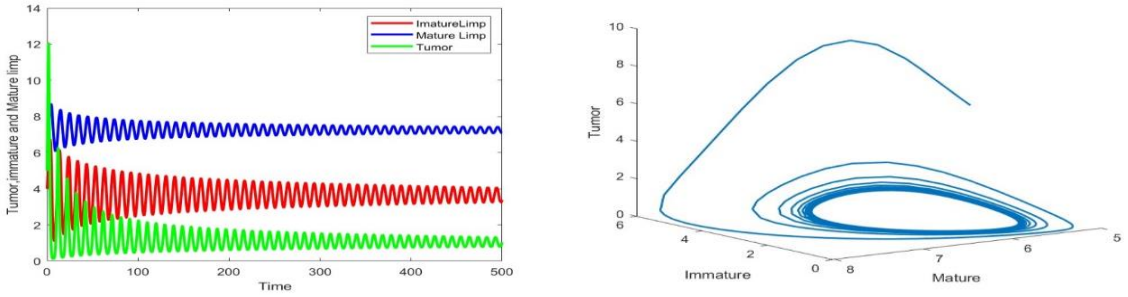

Figure2. Oscillations of the tumor and lymphocytes at the critical value $\tau = 0.5153 = \tau_0$ and Phase space trajectories

For the same set of parametric values as above, for $\tau > \tau_0$, system is unstable at the tumor present equilibrium point. As delay increases then there is a rapid growth in the tumor cell population which effects the immune system of the body which may sometimes become fatal.

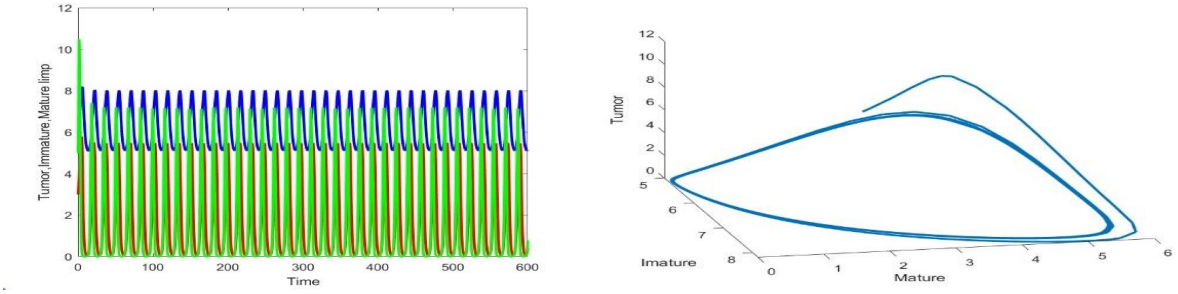

Figure3. Unstable Oscillations of the tumor and lymphocytes and Phase space trajectories at $\tau = 0.9923 > \tau_0$

From the Figures 1, 2 and 3, we observe that when delay value is below the critical value τ_0, E^* is locally asymptotically stable. At the critical value stability switches and periodic oscillations occurred and whenever the delay value is greater than the critical value then unstable oscillations occur.

For the another set of values $b_1 = 0.65;\ b_2 = 1.05; b_3 = 3.25;\ c = 5.75;$

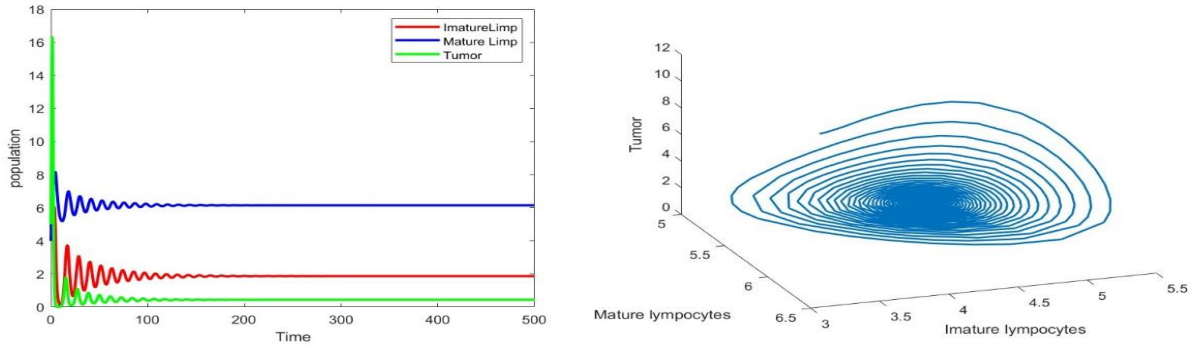

Figure4. Stable variations and phase portrait of the lymphocytes and tumor cell populations with delay $\tau = 0.3275$

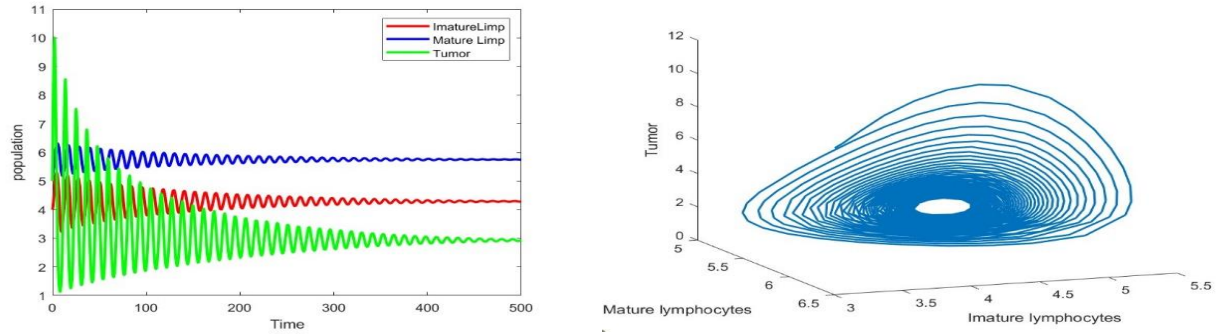

Figure5. Deterministic trajectories and phase portrait of the lymphocytes and tumor cell populations with delay $\tau = 0.3725$

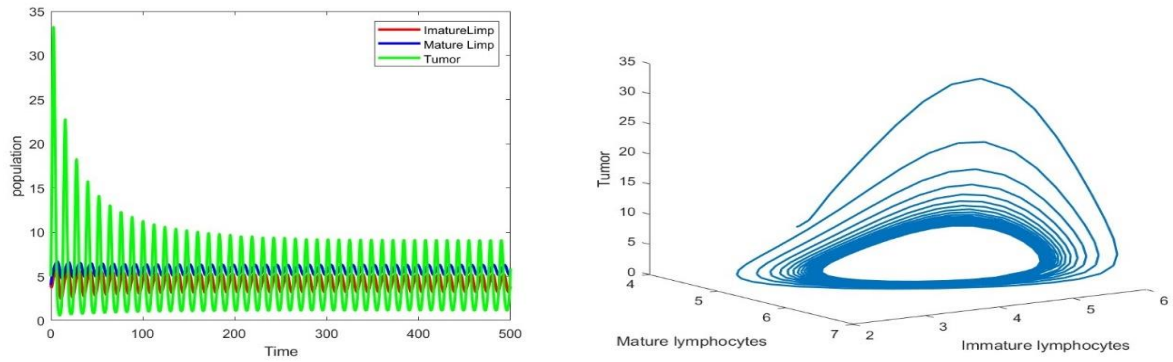

Figure6. Unstable variations and phase portrait of the lymphocytes and tumor cell populations with delay $\tau = 0.4325$

The variations in the stability of the system with time delay can be visualized in the figures 4, 5 and 6. We observed that the rate of attaining stability from $\tau < 0.3752$. In this model delay term describes there is lag to emission of tumor by mature lymphocytes. If delay increases tumor population increases and system is unstable. Through the time delay causes transient oscillations in all parameters, equilibrium point reaches the stability. Delay causes the variations in lymphocytes populations when tumor is in early stage, as the time delay increase there is unstability in cell populations.

6. Conclusions

In this article, we developed a mathematical model to find the delay effect on immune system and tumor interactions. We derived the positive solutions of the system and existence of equilibrium points is discussed. Tumor present equilibrium exists when $b_2 c - b_3 > 0$ and it is locally asymptotically stable by Routh-Hurwitz criteria when $\tau < \tau_0$. When τ crosses τ_0 periodic oscillations occur. Tumor free equilibrium is locally asymptotic stable for $\frac{b_2 c}{b_3} < 1$ and unstable otherwise. When mature T-lymphocytes population is inactivated by the tumor cell population, the immune system becomes weak and tumor cells grow rapidly leading to unstable state. Further we conclude that small changes in delay affect the behaviour of the immune system and also its response towards tumor. The criteria for estimating delay in preserving the stability have been established. Numerical simulations strengthen our analytical findings.

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