Applied Mathematics & Information Sciences
An International Journal

http://dx.doi.org/10.18576/amis/140618

Modeling of Tumor-Immune Competitive System with Saturated Incidence

*M. Rajalakshmi and Mini Ghosh**

Division of Mathematics, School of Advanced Sciences, Vellore Institute of Technology, Chennai Campus, Chennai-600 127, India.

Received: 2 Jun. 2020, Revised: 2 Jul. 2020, Accepted: 26 Aug. 2020
Published online: 1 Nov. 2020

Abstract: In this paper, a non-linear mathematical model for tumor-immune system is formulated and analyzed by considering saturated incidence for the interaction between tumor cells and cytotoxic-T lymphocytes (CTLs). It is assumed that both the tumor cells as well as T-helper cells follow logistic growth. In Addition, a time lag exists in the activation of CTLs because of T-helper cells. Existence and stability of different equilibria of the model are discussed in detail. The model is analyzed using the theory of delay differential equations. It was observed that delay played an important role in defining the dynamics of the system. The system exhibited Hopf-bifurcation when the value of time delay crossed a certain threshold. Existence of Hopf-bifurcation and condition for stability switch are discussed in detail. Numerical simulation is performed to support the analytical findings.

Keywords: Cancer; Stability theory; Hopf-bifurcation.

1 Introduction

Cancer is a disease which involves abnormal growth of cells and there are more than 100 types of cancer. It causes cells to divide in a uncontrolled manner and it invades neighboring tissues. It is a complicated disease and its treatment varies depending upon its different stages. Moreover, it has overtaken cardiovascular diseases and become the leading cause of death in rich nations. There are different types of cancer treatment methods, such as radiation therapy, chemotherapy, immunotherapy, targeted therapy, hormone therapy,...etc. Some patients need a combination of these therapies. The proper understanding of the interaction between tumor cells and immune system is most required to predict the success of any therapy. Several research papers have addressed the interaction between tumor cells and immune cells. Currently, it can be cured if detected at an early stage, but treatment procedure of cancer varies from a patient to another, which creates a challenge for modern medicine. The cancer treatment should aim to kill cancer cells with minimum damage to healthy cells [1].

Mathematical modeling of cancer growth and treatment is discussed over time by different researchers [2-7]. In this paper, the authors asserted the importance of both helper cells and CTLs in antitumor-immune response. In [8-9], the authors considered delay-differential equation model to describe the dynamics of tumor-immune interaction. They also considered the discrete delay as the bifurcation parameter and obtained the length of delay which preserves stability. They demonstrated that when the delay crosses a critical value, Hopf-bifurcation occurs. In [10], authors discussed cancer self remission and tumor stability by stochastic approach. Recently Khajanchi and Nieto [11] extended this model by incorporating discrete time lag to the recruitment of cytotoxic-T-lymphocytes or hunting cells because of the interaction with resting cells or T-helper cells. The authors discussed the existence and stability of equilibrium points, existence of Hopf-bifurcation and its direction and stability. In these models authors assumed the interaction between tumor cells and CTLs as simple mass-action type where many researchers have assumed that the removal of tumor cells due to CTLs follows saturation type incidence [12]. In the present study, we formulate our model based on [11] and consider saturation type incidence for the interaction between tumor cells and CTLs. Furthermore, we do not consider the natural death rate of T-helper cells separately because it is already involved in the logistic growth of T-helper cells. This makes our model different from existing models and more realistic.

* Corresponding author e-mail: minighosh@vit.ac.in

The remaining part of this paper is organized as follows: Section 2 describes the proposed mathematical model. Section 3 analyzes the model without delay. Section 4 demonstrates the stability analysis of the non-trivial equilibrium for the model with delay. Section 5 illustrates the Hopf-bifurcation analysis and stability switching phenomena. Section 6 exhibits the numerical simulation results. Section 7 is dedicated to conclusion.

2 The Mathematical Model

Here we formulate a non-linear mathematical model by considering the state variables, i.e. the density of tumor populations $y(t)$, the density of cytotoxic T-lymphocytes (CTLs) or hunting cells $z(t)$ and the density of T-helper cells (THLs) or resting cells $w(t)$ at any time t in a single tumor-site compartment. Basically, we extend the model of Khajanchi and Nieto [11] by considering the saturated type incidence between the tumor cells and CTLs. It is assumed that the malignant tumor cells are eliminated by immune system, namely, cytotoxic T-lymphocytes (CTLs) and T-helper cells (THLs). The T-helper cells are directly unable to kill the tumor cells, but they release some cytokines (a kind of proteins), which activate the hunting cells or CTLs population. CTLs destroy the malignant tumor cells by phagocytosis process. As in [11], we assume that both the tumor cells and T-helper cells follow the logistic growth. As the activation process of CTLs due to T-helper cells is not an instantaneous process, a discrete time delay in the term corresponding to interaction between the CTLs and THLs is incorporated in the proposed model. Furthermore, when cells get transferred from T-helper cells to CTLs, they never come back to the previous stage i.e. T-helper cells. Keeping the above fact in mind we formulate our model as follows:

$$\begin{aligned}
\frac{dy}{dt} &= ry\left(1-\left(\frac{y}{K}\right)\right)-\frac{\alpha yz}{\sigma+z},\\
\frac{dz}{dt} &= \beta_1 z(t-\tau)w(t-\tau)-\delta z,\\
\frac{dw}{dt} &= sw\left(1-\left(\frac{w}{L}\right)\right)-\beta_2 z(t-\tau)w(t-\tau),
\end{aligned} \tag{1}$$

where r and s are the intrinsic growth rate of tumor cells and CTLs respectively, K and L are the carrying capacities of tumor cells and CTLs respectively, the tumor cells are removed by CTLs with saturation at the rates $\frac{\alpha yz}{\sigma+z}$; $\beta_1 z(t-\tau)w(t-\tau)$ is the proliferation rate of CTLs due to conversion of resting stage to hunting stage with a discrete delay τ, δ is the natural death rate of CTLs, $\beta_2 z(t-\tau)w(t-\tau)$ represents the conversion rate of T-helper cells to CTLs with same delay τ. The initial condition for the system (1) are given by $y(\theta) = \phi_1(\theta), z(\theta) = \phi_2(\theta), w(\theta) = \phi_3(\theta)$, $\phi_1(\theta) \geq 0, \phi_2(\theta) \geq 0, \phi_3(\theta) \geq 0$, where $\phi_1(\theta), \phi_2(\theta), \phi_3(\theta) \in \mathscr{C}([-\tau,0], \mathscr{R}^3_+)$, the Banach space of continuous functions mapping the interval $[-\tau,0]$ into $\mathscr{R}^3_+$ where $\mathscr{R}^3_+ = \{(y,z,w) : y,z,w \geq 0\}$.

3 Analysis of the Model without Delay

3.1 Existence of Equilibria

The model system (1) produces six equilibria as follows: (i) trivial equilibrium point $E_1(0,0,0)$, (ii) axial equilibria $E_2(K,0,0)$ and (iii) $E_3(0,0,L)$ (iv) The $y-w$ planner equilibrium point $E_4(K,0,L)$ (v) tumor-free equilibrium point $E_5(0,\bar{z},\bar{w})$ with $\bar{z} = \frac{s}{\beta_2}\left(1-\frac{\bar{w}}{L}\right), \bar{w} = \frac{\delta}{\beta_1}$ which exists only when $L > \frac{\delta}{\beta_1}$ and (vi) $E_6(\hat{y},\hat{z},\hat{w})$ with $\hat{y} = \frac{K}{r}\left(r-\frac{\alpha z}{\sigma+z}\right), \hat{z} = \bar{z}, \hat{w} = \bar{w}$, which exists only when $r\sigma + (\alpha - r)\frac{s}{\beta_1\beta_2 L}(\delta - \beta_1 L) > 0$.

3.2 Stability Analysis

The Jacobian matrix of the system (1) without delay evaluated at $E_1(0,0,0)$ is given by

$$J(E_1) = \begin{pmatrix} r & 0 & 0 \\ 0 & -\delta & 0 \\ 0 & 0 & s \end{pmatrix}.$$

The eigenvalues are $r, -\delta$ and s. As $r,s > 0$, so the equilibrium point E_1 is always unstable.

The Jacobian matrix of the system (1) without delay evaluated at $E_2(K,0,0)$ is given by

$$J(E_2) = \begin{pmatrix} -r & -\frac{\alpha K}{\sigma} & 0 \\ 0 & -\delta & 0 \\ 0 & 0 & s \end{pmatrix}.$$

The eigenvalues are $-r, -\delta$ and s. As $s > 0$, the equilibrium point E_2 is always unstable.

The Jacobian matrix of the system (1) without delay evaluated at $E_3(0,0,L)$ is given by

$$J(E_3) = \begin{pmatrix} r & 0 & 0 \\ 0 & \beta_1 L - \delta & 0 \\ 0 & -\beta_2 L & -s \end{pmatrix}.$$

The eigenvalues are $r, \beta_1 L - \delta$ and $-s$. As $r > 0$, the equilibrium point E_3 is always unstable.

The Jacobian matrix of the system (1) without delay evaluated at $E_4(K,0,L)$ is given by

$$J(E_4) = \begin{pmatrix} -r & -\frac{\alpha K}{\sigma} & 0 \\ 0 & \beta_1 L - \delta & 0 \\ 0 & -\beta_2 L & -s \end{pmatrix}.$$

The eigenvalues are $-r, \beta_1 L - \delta$ and $-s$. The equilibrium point E_4 is stable if $L < \frac{\delta}{\beta_1}$. It is easy to observe that in this case the equilibria E_5 and E_6 do not exist.

The Jacobian matrix of the system (1) without delay evaluated at $E_5(0,\bar{z},\bar{w})$ is given by

$$J(E_5)=\begin{pmatrix} r-\frac{\alpha\bar{z}}{(\sigma+\bar{z})} & 0 & 0 \\ 0 & 0 & \beta_1\bar{z} \\ 0 & -\beta_2\bar{w} & -\frac{\bar{w}s}{L} \end{pmatrix},$$

An eigenvalue is $r-\frac{\alpha\bar{z}}{(\sigma+\bar{z})}$ and other two eigenvalues are the roots of the following quadratic equation:

$$\lambda^2+\left(\frac{s\delta}{\beta_1 L}\right)\lambda+s\delta\left(1-\frac{\delta}{\beta_1 L}\right)=0.$$

The coffcients of λ and the constant term are positive as $L>\frac{\delta}{\beta_1}$, so both the roots will have negative real parts. The first eigenvalue is negative provided $r<\frac{\alpha\bar{z}}{(\sigma+\bar{z})}$ i.e. $r\sigma+(\alpha-r)\frac{s}{\beta_1\beta_2 L}(\delta-\beta_1 L)<0$. In this case, the interior equilibrium point E_6 does not exist. Hence, the equilibrium point E_5 is locally asymptotically stable according to the above-mentioned condition.

The Jacobian matrix of the system (1) without delay evaluated at $E_6(\hat{y},\hat{z},\hat{w})$ is given by

$$J(E_6)=\begin{pmatrix} -\frac{r\hat{y}}{K} & \frac{\alpha\sigma\hat{y}}{(\sigma+\hat{z})^2} & 0 \\ 0 & 0 & \beta_1\hat{z} \\ 0 & -\beta_2\hat{w} & -\frac{s\hat{w}}{L} \end{pmatrix},$$

An eigenvalue is $-\frac{r\hat{y}}{K}$ and other two eigenvalues are the roots of the following quadratic equation:

$$\lambda^2+\left(\frac{s\delta}{\beta_1 L}\right)\lambda+s\delta\left(1-\frac{\delta}{\beta_1 L}\right)=0.$$

The coefficients of λ and the constant term are positive as $L>\frac{\delta}{\beta_1}$, so both the roots of above quadratic equation will have negative real parts. Hence the equilibrium point E_6 is locally asymptotically stable whenever it exists.

4 Analysis of the Model with Delay

The equilibria of the model with delay are the same as those without delay. In addition, it is found that the existence of interior equilibrium point E_6 implies the instability of E_4 and E_5. Moreover, the equilibria E_1, E_2 and E_3 are always unstable. Thus, we will concentrate on the stability of only interior equilibrium point E_6 in presence of delay. Stability of the equilibrium point is defined by computing the roots of the following characteristic equation evaluated at the corresponding equilibrium point

$$det(A+Be^{-\lambda t}-\lambda I)=0, \tag{2}$$

where I is the identity matrix of order 3 and

$$A=\begin{pmatrix} r\left(1-\frac{2y}{K}\right)-\frac{\alpha z}{\sigma+z} & \frac{\alpha\sigma y}{(\sigma+z)^2} & 0 \\ 0 & -\delta & 0 \\ 0 & 0 & s(1-\frac{2w}{L}) \end{pmatrix},$$

$$B=\begin{pmatrix} 0 & 0 & 0 \\ 0 & \beta_1 w & \beta_1 z \\ 0 & -\beta_2 w & -\beta_2 z \end{pmatrix}.$$

The characteristic polynomial evaluated at $E_6(\hat{y},\hat{z},\hat{w})$ is given by

$$\left(\lambda+\frac{r\hat{y}}{K}\right)\left[\left\{\lambda^2+\lambda P_1+P_2\right\}+e^{-\lambda\tau}\left\{\lambda R_1+R_2\right\}\right]=0,$$

where

$$P_1=\delta-s+\frac{2s\delta}{\beta_1 L},\ P_2=\frac{2s\delta^2}{\beta_1 L}-s\delta,$$

$$R_1=-\delta+s-\frac{s\delta}{\beta_1 L},\ R_2=2s\delta-\frac{3s\delta^2}{\beta_1 L}.$$

One root of the aforementioned characteristic polynomial is $\frac{r\hat{y}}{K}$ and remaining are the roots of following transcendental equation:

$$P(\lambda)+e^{-\lambda\tau}Q(\lambda)=0, \tag{3}$$

where

$$P(\lambda)=\left\{\lambda^2+\lambda P_1+P_2\right\},\ Q(\lambda)=\left\{\lambda R_1+R_2\right\}=0.$$

When $\tau=0$, we get $\left[\lambda^2+\lambda\left(P_1+R_1\right)+\left(P_2+R_2\right)\right]=0$. As previously mentioned, this equilibrium point E_6 is locally asymptotically stable in absence of delay as both P_1+R_1 and P_2+R_2 are positive. When $\tau\neq 0$, $\lambda=i\omega$. Substituting $\lambda=i\omega$ in the equation (3) and equating the real and imaginary parts we get the following two equations:

$$-\omega^2+P_2=\cos\omega\tau\left[-R_2\right]-\sin\omega\tau\left[\omega R_1\right] \tag{4}$$

$$\omega P_1=\cos\omega\tau\left[-\omega R_1\right]+\sin\omega\tau\left[R_2\right] \tag{5}$$

Now squaring and adding equations (4) and (5), we get the following biquadratic equation:

$$\omega^4+P_2^2-2P_2\omega^2+\omega^2P_1^2-R_2^2-\omega^2R_1^2=0 \tag{6}$$

Assuming $\omega^2=u$ we have

$$F(u)=u^2+ud_1+d_2=0, \tag{7}$$

where

$$d_1=\left[P_1^2-2P_2-R_1^2\right],\ d_2=\left[P_2^2-R_2^2\right]. \tag{8}$$

Theorem 1 *If the coefficients d_1,d_2 in $F(u)$ satisfy the conditions of Routh-Hurwitz criterion (i.e. $d_1>0$ and $d_2>0$), then the interior equilibrium point $E_6(\hat{y},\hat{z},\hat{w})$ if it exists is asymptotically stable for all delay $\tau>0$ provided it is stable in absence of delay.*

Theorem 2 *If the coefficients d_1,d_2 in $F(u)$ satisfy Routh-Hurwitz criterion (i.e. $d_1>0$ and $d_2>0$), and the interior equilibrium point $E_6(\hat{y},\hat{z},\hat{w})$ is unstable at $\tau=0$, it will remain unstable for all $\tau\geq 0$.*

This theorem is inapplicable to our model as the equilibrium point E_6 if it exists is locally asymptotically stable in absence of delay.

If $F(u)=0$ has a positive root, we have the following result.

Theorem 3 *The endemic equilibrium point E_6 of the system (1) is conditionally stable if and only if all the roots of the characteristic equation (3) have negative real parts at $\tau = 0$ and there exist some positive values of the delay τ such that the characteristic equation (3) has a pair of purely imaginary roots $\pm i\omega_0$ (say). The system will undergo a stability change for an infinite number of values of τ say τ_n^*, where*

$$\tau_n^* = \tau = \frac{1}{\omega_0} cos^{-1}\left[\frac{R_2(\omega_0^2 - P_2) - \omega_0^2 P_1 R_1}{R_2^2 + \omega_0^2 R_1^2}\right] + \frac{2n\pi}{\omega_0}, \quad n = 0, 1, 2, \ldots \tag{9}$$

5 Analysis of Hopf-bifurcation

Now, we shall investigate the Hopf bifurcation of the model system (1), for which we need to verify the transversality condition $\frac{d(Re\lambda)}{d\tau}|_{\tau=\tau_0} > 0$ i.e. $\frac{d\xi}{d\tau}|_{\xi=0} > 0$ for $\lambda(\tau) = \xi(\tau) + i\omega(\tau)$. This will designate that there exists at least one eigenvalue with nonnegative real part for $\tau > \tau_s$. Moreover, the conditions for Hopf bifurcation are necessary to prove the existence of periodic solutions. First, we are interested in purely complex roots $\lambda = i\omega_0$ of (3). Equation (3) implies that $|P(i\omega_0)| = |Q(i\omega_0)|$ and this defines the possible set of values of ω_0. Now, we aim to observe the direction of motion of λ as τ is varied, for which we find,

$$\Omega = sign\left[\frac{d(Re\lambda)}{d\tau}\right]|\tau = \tau_n = sign\left[\frac{d(Re\lambda)}{d\tau}\right]^{-1}|\tau = \tau_n.$$

On differentiating (3) with respect to τ, we get

$$\left[(2\lambda + P_1) - R_1 e^{-\lambda\tau} - \tau e^{-\lambda\tau}(R_1\lambda + R_2)\right]\left(\frac{d\lambda}{d\tau}\right)$$

$$-\lambda e^{-\lambda\tau}(R_1\lambda + R_2) = 0$$

which leads to

$$\left(\frac{d\lambda}{dt}\right)^{-1} = \frac{e^{\lambda\tau}(2\lambda + P_1)}{\lambda(R_1\lambda + R_2)} + \frac{R_1}{\lambda(R_1\lambda + R_2)} - \frac{\tau}{\lambda}.$$

Since $\lambda(\tau_0) = i\omega_0$ is a simple root of the characteristic equation(3), we can evaluate the expressions involved in the above derivative at $\tau = \tau_0$ as follows:

$$\begin{aligned}\{(2\lambda + P_1)e^{\lambda\tau}\}|_{\tau=\tau_0} &= \eta_1 + i\eta_2\\ \{\lambda(R_1\lambda + R_2)\}|_{\tau=\tau_0} &= \eta_3 + i\eta_4\\ R_1|_{\tau=\tau_0} &= \eta_5\end{aligned} \tag{10}$$

where

$$\eta_1 = P_1\cos\omega_0\tau_0 - 2\omega_0\sin\omega_0\tau_0,$$
$$\eta_2 = 2\omega_0\cos\omega_0\tau_0 + P_1\sin\omega_0\tau_0,$$
$$\eta_3 = -\omega_0^2 R_1, \eta_4 = \omega_0 R_2, \eta_5 = R_1.$$

Now

$$\left(\frac{d\lambda}{d\tau}\right)^{-1}_{\tau=\tau_0} = \left(\frac{dRe\lambda(\tau_0)}{d\tau}\right) = \frac{\eta_1\eta_3 + \eta_2\eta_4 + \eta_3\eta_5}{\eta_3^2 + \eta_4^2}$$

Using the equations in (4) and (5), we can rewrite above expression as follows:

$$\begin{aligned}\left(\frac{d\lambda}{d\tau}\right)^{-1}|_{\tau=\tau_0} &= \frac{\omega_0^2\left[2\omega_0^2 + (P_1^2 - 2P_2R_1^2\right]}{\eta_3^2 + \eta_4^2}\\ &= \frac{\omega_0^2}{\eta_3^2 + \eta_4^2}(2u + d_1)|_{u=\omega_0^2}\\ &= \frac{\omega_0^2}{\eta_3^2 + \eta_4^2}F'(u)|_{u=\omega_0^2}\end{aligned}$$

Therefore

$$\begin{aligned}sign\left[\left(\frac{d}{d\tau}Re\lambda(\tau_0)\right)\right] &= sign\left[\left(\frac{d}{d\tau}Re\lambda(\tau_0)\right)^{-1}\right]\\ &= sign\left[\frac{\omega_0^2}{\eta_3^2 + \eta_4^2}F'(u)|_{u=\omega_0^2}\right].\end{aligned}$$

As $\eta_3^2 + \eta_4^2 > 0$, $\omega_0^2 > 0$ and $F'(u)|_{u=\omega_0^2} \neq 0$, the $sign\left[\left(\frac{d}{d\tau}Re\lambda(\tau_0)\right)\right]$ will be determined by the $sign\left[F'(u)|_{u=\omega_0^2}\right]$.

We already have $Re(\lambda(\tau)) = \xi(\tau)$ and $\xi(\tau_0) = 0$. Thus if $sign\left[F'(u)|_{u=\omega_0^2}\right] < 0$, then there exists a $\zeta > 0$ such that $\xi(\tau)$ is decreasing in $(\tau_0 - \zeta, \tau_0)$ and $\xi(\tau) = 0$ at $\tau = \tau_0$. Hence for all $\tau \in (\tau_0 - \zeta, \tau_0)$, $\xi(\tau) > 0$, which contradicts the fact that roots of the characteristic equation (3) have negative real parts for all $\tau \in [0, \tau_0]$ and $\tau = \tau_0$ is the minimum value of delay τ for which (3) will have purely imaginary roots. Hence $sign\left[F'(u)|_{u=\omega_0^2}\right] > 0$ which shows that there exists at least one $\lambda(\tau)$ with $\xi(\tau) > 0$ for $\tau > \tau_0$.

5.1 Switching phenomena

Now, we study the conditions for stability switches using the results of Cooke and van den Driessche [13] for a scalar delay differential equation

$$\sum_{k=0} a_k \frac{dk}{dt^\kappa}x(t) + \sum_{k=0} b_k \frac{dk}{dt^\kappa}x(t-\tau) = 0.a_n \neq 0.n \geq m$$

The characteristic equation corresponding to system (1) is

$$\begin{aligned}&P(\lambda) + e^{-\lambda\tau}Q(\lambda) = \left[\lambda^2 + \lambda P_1 + P_2\right]\\ &+e^{-\lambda\tau}[\lambda R_1 + R_2] = 0,\end{aligned}$$

where

$$P_1 = \delta - s + \frac{2s\delta}{\beta_1 L},\ P_2 = \frac{2s\delta^2}{\beta_1 L} - s\delta,$$

$$R_1 = -\delta + s - \frac{s\delta}{\beta_1 L},\ R_2 = 2s\delta - \frac{3s\delta^2}{\beta_1 L}.$$

We can adopt numerous methods to investigate the characteristic equation has a root λ with nonnegative real part. Geometric arguments can be utilized to determine the stability of a given fixed point [14], where the argument principle is utilized to count the number of zeros of $\phi(\lambda)$ on the right hand side of the imaginary plane. In our case, we use the results by Cooke and van den Driessche [13], which satisfy the following conditions:

1.P(λ) and $Q(\lambda)$ have no common root and both are analytic function with $Re(\lambda)$,
2.$\overline{P(-iy)} = P(iy)\overline{Q(-iy)} = Q(iy),\ \forall y$
3.$P(0)+Q(0) = P_2 + R_2 \neq 0$
4.$\limsup_{|\lambda|\to+\infty}\left|\frac{Q(\lambda)}{P(\lambda)}\right| = 0 < 1$
5.$\phi(y) = |P(iy)|^2 - |Q(iy)|^2$
i.e, $\phi(y) = y^4 + \phi_1 y^2 + \phi_2 = 0$, where

$$\begin{aligned}\phi_1 &= \left[P_1^2 - 2P_2 - R_1^2\right],\\ \phi_2 &= \left[P_2^2 - R_2^2\right]\\ &= -3(s\delta)^2\left(1-\frac{\delta}{\beta_1 L}\right)\left[\left(1-\frac{5\delta}{3\beta_1 L}\right)\right].\end{aligned}$$

For $P_2^2 - R_2^2 < 0$ we need the condition $L > \frac{5\delta}{3\beta_1}$. Under this condition ϕ_2 is negative, so $\phi(y)$ must have at least one nonnegative root. Therefore, using the result of [15], we conclude that at most finite number of stability switching is possible for the model system (1) when $L > \frac{5\delta}{3\beta_1}$.

6 Numercial Simulations

Here, we first simulate our model system (1) without delay for the following set of parameters:

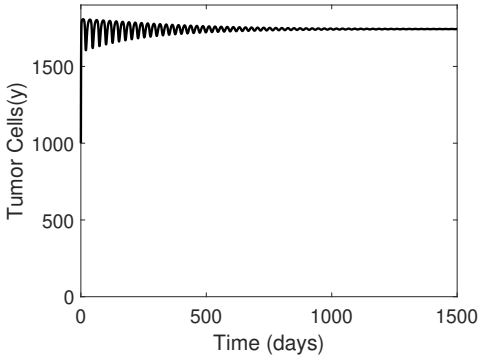
$$r = 1.8097, \alpha = 2, \sigma = 100, \beta_2 = 0.05, \beta_1 = 0.1,$$

$$s = 0.2, K = 1818, \delta = 0.35, L = 100.$$

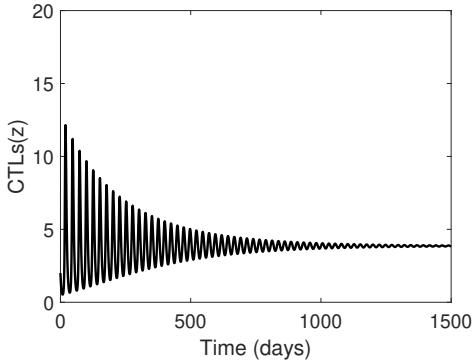
The units of all the parameters mentioned above are in per day. For this set of parameter the system (1) has unique interior equilibrium point as $(1444.6, 3.9, 3.5)$ which is locally asymptotically stable. The results of this simulation are demonstrated in Figure 1. Then we simulate our model system (1) with delay using MATLAB function dde23. Here, we observe that this interior equilibrium point is locally asymptotically stable as long as delay is less than 0.053 and model system exhibits periodic oscillations once this delay τ crosses this value. Hence this value is the threshold τ_0. Here we present our simulation results for two different values of delay e.g. (i) $\tau = 0.03 < \tau_0$ and (ii) $\tau = 0.055 > \tau_0$. So for $\tau < \tau_0$, our system exhibits stable interior equilibrium point. This fact is demonstrated in Figure 2. The Hopf-bifurcating periodic behaviour of the system (1) is demonstrated in Figure 3 where $\tau = 0.055 > \tau_0$. The Hopf-bifurcating periodic solution occurs when τ crosses τ_0 from left to right i.e. when $\tau > \tau_0$. This indicates that the Hopf-bifurcation is supercritical. Accordingly, in the absence of any therapy, system may exhibits Hopf-bifurcating periodic oscillations. This corresponds to long-run tumor relapse. This phenomenon is also reported clinically and is known as Jeff's phenomenon [17]. Next we change $\alpha = 10$ and try to see the impact of the parameter β_2 which corresponds to the conversion rate of T-helper cells to CTLs. Change in these parameters does not change the threshold τ_0 as they are not directly involved in the expression for τ_0. It is observed that the small change in the parameter β_2 causes large change in the period of the Hopf-bifurcating periodic solution of the tumor cells. And in this case, it will be very difficult to predict the success of any therapy to control the growth of tumor cells. Here Figure 4 demonstrates this fact, where β_2 changes from 0.05 to 0.04 and all other parameters and the value of the delay τ are kept fixed. It also indicates that the period of the oscillation increases with the decrease in this parameter β_2. This result is different from the available results, e.g. in [11] it was shown that increase in β_2 causes increase in the magnitude of oscillations. This difference happens primarily because of our assumption of saturation type incidence between tumor cells and CTLs. Thus the inhibition rate β_2 of T-helper cells is a key parameter which plays an important role in defining the relapse period of tumor.

7 Conclusion

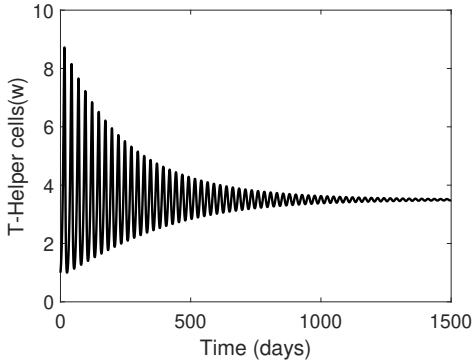
The present paper investigated a non-linear model for tumor-immune system by assuming the interaction between tumor cells and CTLs to be of saturated type by incorporating a time delay. The model was analyzed using the theory of delay differential equation. The non-trivial equilibrium point was locally stable without delay. There existed a critical value of delay below which this non-trivial equilibrium was stable. When the delay(τ) crossed a threshold value, Hopf-bifurcation occured and periodic solution appeared. The analysis of Hopf-bifurcation and stability switches were demonstrated using numerical simulation. The impact of the parameter β_2 corresponding to inhibition rate of T-helper cells were also demonstrated using numerical simulation. Moreover, the amplitude of the periodic oscillations increased with the decrease in the parameter β_2. In this situation, success of any therapy is highly unpredictable. As immune system varies person to another, health professionals should aim to have a proper estimate of the delay τ and the parameter β_2 for an individual patient to predict the dynamics of tumor-immune system and to develop a treatment policy.



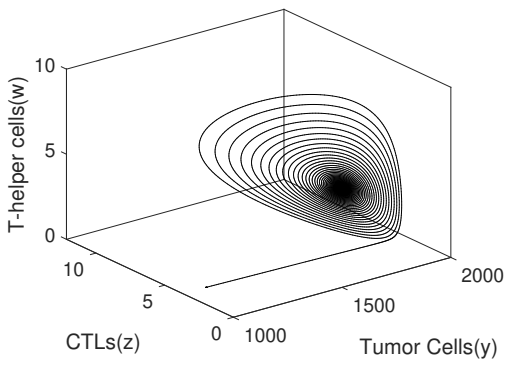
(a) Variation of Tumor cells with time.



(b) Variation of CTLs with time.

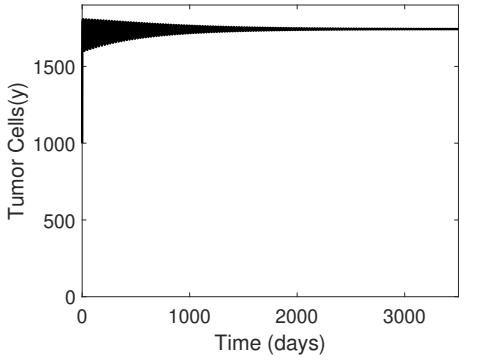


(c) Variation of T-helper cells with time.

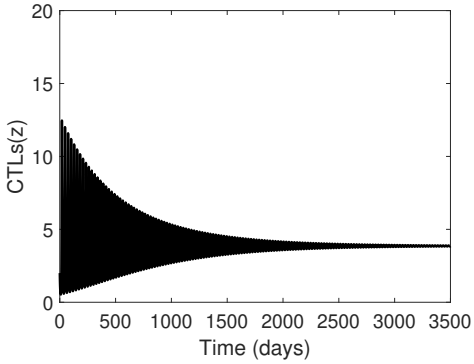


(d) 3-d plot.

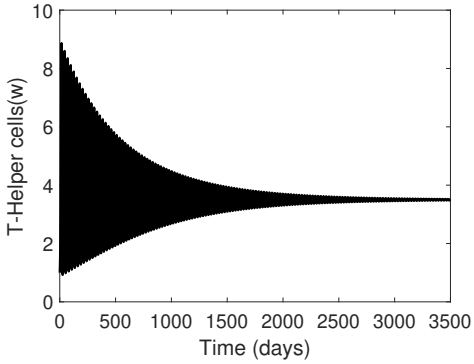
Fig. 1: Variation of state variables with time when delay $\tau = 0$.



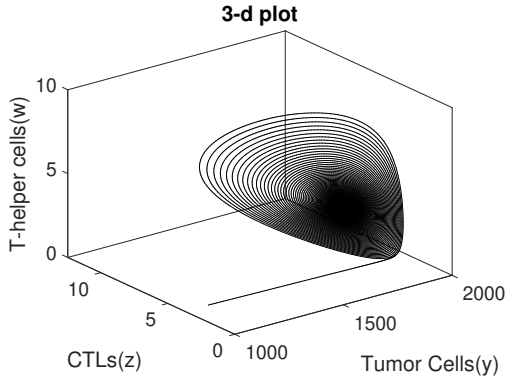
(a) Variation of Tumor cells with time.



(b) Variation of CTLs with time.

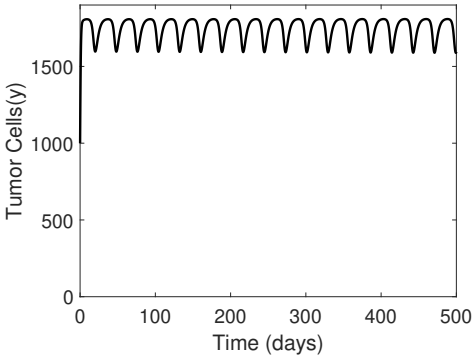


(c) Variation of T-helper cells with time.

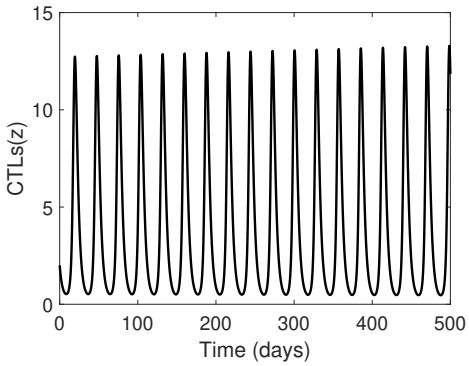


(d) 3-d plot.

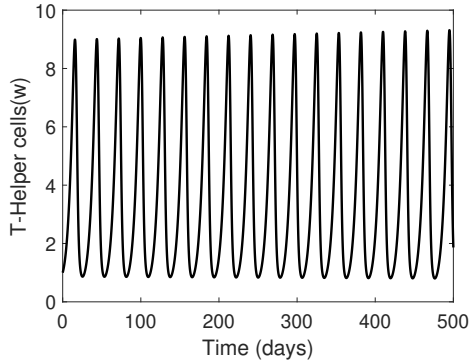
Fig. 2: Variation of state variables with time when delay $\tau = 0.03$.



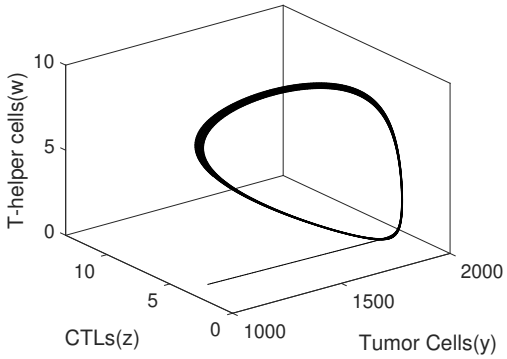
(a) Variation of Tumor cells with time.



(b) Variation of CTLs with time.

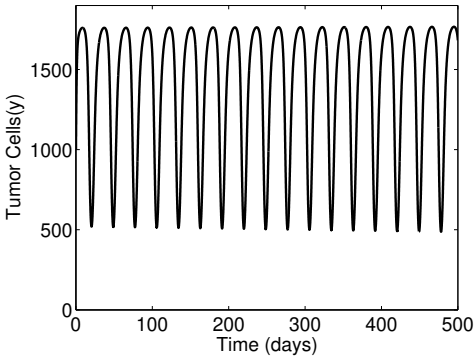


(c) Variation of T-helper cells with time.

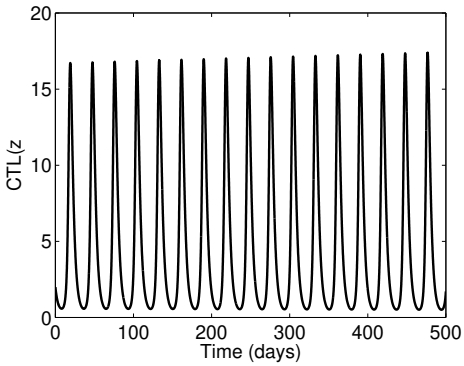


(d) 3-d plot.

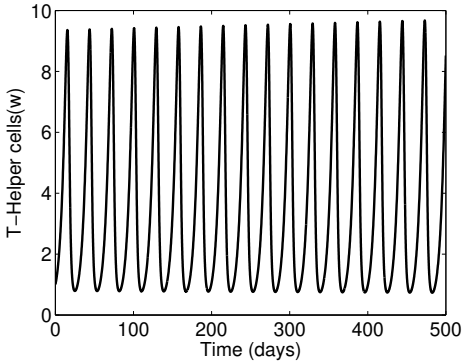
Fig. 3: Variation of state variables with time when delay $\tau = 0.055$.



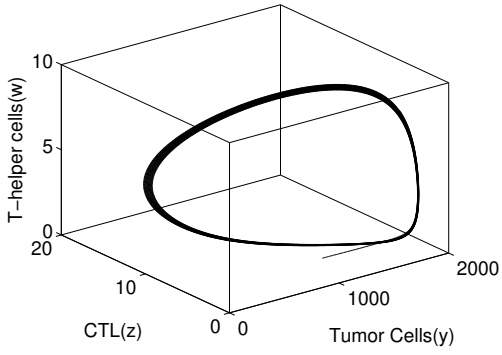
(a) Variation of Tumor cells with time.



(b) Variation of CTLs with time.



(c) Variation of T-helper cells with time.



(d) 3-d plot.

Fig. 4: Variation of state variables with time when delay $\tau = 0.055$ and $\beta_2 = 0.04$.

Acknowledgement

The authors are grateful to the editor and the anonymous referees for their valuable comments and suggestions which improved the original manuscript.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

[1] F. A. Rihan, D. H. Abdelrahman, F. Al-Maskari, F. Ibrahim, and M. A. Abdeen. Delay differential model for tumour-immune response with chemoimmunotherapy and optimal control. *Computational and Mathematical Methods in Medicine* **2014**, Article ID 982978 (2014).

[2] N. Bellomo, N. K. Li, and P. K. Maini. On the foundations of cancer modelling: selected topics, speculations, and perspectives. *Mathematical Models and Methods in Applied Sciences*, **18(4)**, 593-646 (2008).

[3] M. A. J. Chaplain. *Modelling aspects of cancer growth: insight from mathematical and numerical analysis and computational simulation*, in Multiscale Problems in the Life Sciences. Lecture Notes in Mathematics, vol. 1940. Capasso V., Lachowicz M. (eds), Ed. Springer, Berlin, Heidelberg, 147-200 (2008).

[4] J. D. Nagy. The ecology and evolutionary biology of cancer: a review of mathematical models of necrosis and tumor cell diversity. *Mathematical Biosciences and Engineering*, **2(2)**, 381-418 (2005).

[5] R. Yafia. Dynamics analysis and limit cycle in a delayed model for tumor growth with quiescence. *Nonlinear Analysis: Modelling and Control*, **11(1)**, 95-110 (2006).

[6] R. Yafia. A study of differential equation modeling malignant tumor cells in competition with immune system. *International Journal of Biomathematics*, **4(2)**, 185-206 (2011).

[7] Eladdadi, Amina, Lisette de Pillis, and Peter Kim. Modelling tumour-immune dynamics, disease progression and treatment. *Letters in Biomathematics*, **5(Sup1)**, S1-S5 (2018).

[8] S. Banerjee and R. R. Sarkar. Delay-induced model for tumor-immune interaction and control of malignant tumor growth. *Biosystems*, **91(1)**, 268-288 (2008).

[9] S. Khajanchi and S. Banerjee. Stability and bifurcation analysis of delay induced tumor immune interaction model. *Applied Mathematics and Computation*, **248**, 652-671 (2014).

[10] R. R. Sarkar and S. Banerjee. Cancer self remission and tumor stability- a stochastic approach. *Math. Biosci.*, **196**, 65-81 (2005).

[11] S. Khajanchi and J. J. Nieto. Mathematical modeling of tumor-immune competitive system, considering the role of time delay. *Applied Mathematics and Computation*, bf 340, 180-205 (2019).

[12] C. Macnamara and R. Eftimie. Memory versus effector immune responses in oncolytic virotherapies. *Journal of Theoretical Biology*, **377**, 1-9 (2015).

[13] K. L. Cooke and P. van den Driessche. On zeros of some trancendental equations. *Funkcialaj Ekvacioj*, **29**, 77-90 (1986).

[14] J. Mahaffy. A test for stability of linear differential equations. *Quart. Appl. Math.*, **40**, 193-202 (1982).

[15] Y. Kuang. *Delay Differential Equation with Applications in Population Dynamics*, Academic Press, New York, (1993).

[16] B. D. Hassard, D. Kazarinof and Y. Wan. *Theory and Applications of Hopf Bifurcation*, Cambridge University Press, Cambridge, (1981).

[17] R. H. Thomlinson. Measurement and management of carcinoma of the breast. *Clin Radiol.*, **33(5)**, 481-493 (1982).

M. Rajalakshmi received her Master of Science (M.Sc.) in Mathematics from the Mother Teresa Women's University, Kodaikanal and Master of Philosophy (M.Phil.) in Mathematics from Seethalakshmi Achi College for Women, Pallathur; Tamil Nadu, India. Currently she is pursuing her Doctor of Philosophy (Ph.D.) in Mathematics at School of Advanced Sciences, Vellore Institute of Technology, Chennai Campus, India. Her research interests are: Mathematical modeling of Cancer and Non-linear dynamics.

Mini Ghosh is a Professor at the School of Advanced Sciences, Vellore Institute of Technology, Chennai Campus, India. She received her Ph.D in Mathematics from the IIT, Kanpur, India in 2002. After her doctoral degree she was a Post Doctoral Research Fellow at the Department of Mathematics, University of Trento, Italy from 2002-2004, and Institute of Information and Mathematical Sciences, Massey University, New Zealand from 2004-2006. Currently she is actively involved in many research problems, and specializes in the areas of Mathematical modelling of epidemiological/ecological systems.