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Effect of Delay of Immune System Response in Cancer Dynamics: Bifurcation and Chaos Analysis

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Abstract— **The mathematical models of cancer dynamics consider interactions between different cells and give a deep understanding the progress of the tumor growth. In most of the cases, the proposed models are formed by assuming that the interactions occur in the exact times, i.e., no delay is incorporated into the models. On the other hand, this assumption may not be valid as the interactions could have possible delays. The purpose of this paper is to determine the effect of delay interactions between tumor cells and immune system cells. By adding delay time to the cancer model, behavior of the new model is analyzed. In this paper, we investigate the stability of equilibria points, Hopf bifurcation and chaotic behavior of the system. The critical value of time delay is computed by an analytical method. Finally, we show that increasing the delay time will lead series of bifurcations to chaos.**

I. INTRODUCTION

The immune system is the primary defense mechanism of the body against cancer cells. When an unknown tissue, organism or tumor cell appears in the body, the immune system tries to diagnose and remove them successfully. Tumor-immune system interactions show more complicated behavior in uncontrolled tumor growth. Therefore, mathematical modeling of tumor growth is a powerful tool in the treatment of cancer. The mathematical modeling of cancer which includes tumor-immune interaction has been studied by many researchers using a variety of models over the past decade [1]–[4].

When tumor cells increase and reach a detectable threshold size, the immune system begins to search and destroy them [5]. The response of the immune system is expressed by two different interacting responses; namely "the cellular" and "the humoral" responses. The cellular response is mediated by T lymphocytes. Humoral response is related to another class of that called B-lymphocytes [5]. The immune system's response begins with the identification of tumor cells. Then tumor cells are caught by macrophages, which exist in the bloodstream and in all tissues in the body. Macrophages absorb tumor cells and destroy them. They also release a series of signal called the cytokine which activates T helper cells (i.e., a subpopulation of T lymphocytes) to coordinate a counter attack against tumor cells. The T helper cells are directly stimulated to interact with the antigens. These helper cells cannot kill tumor cells, but they send emergency biochemical signals to a specific type of T lymphocytes called natural killers (NKs). T helper cells stimulate more T cells, B cells, and NK cells by multiplying and releasing more cytokines. When the number of B cells increases, the T helper cells send signals to initiate the antibody production process. Antibodies circulate in blood and bind to tumor cells. Then tumor cells are swallowed up more rapidly by macrophages or killed by NK cells. Like all T cells, NK cells have also been trained to recognize a particular infected cell or a cancer cell [6], [7]. Fig. 1 shows the process of this activation.

It is interesting to note that this activation process occurs by some time lag. Several reasons cause this time lag such as identification of tumor cells, the process of activation NK cells, etc. A considerable amount of literature has been published on time delays in connection with tumor growth [5]–[9].

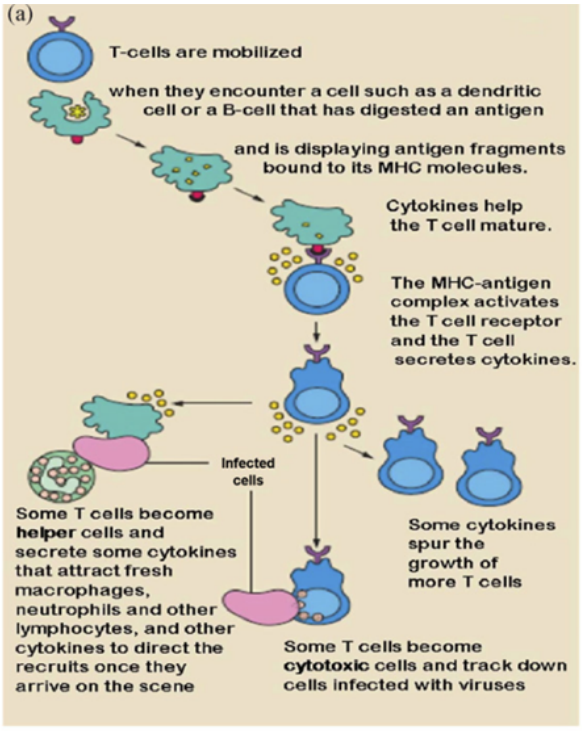

Fig. 1. Mechanism of activation of T cells [7]

It has been established that the time delays in differential equations exhibit complex behaviors, and also lead to limit cycle, loss of stability, bifurcation and chaos. In Ref. [7], [8], the authors investigated the Hopf bifurcation in a delay differential equations (DDEs) model for the immune-tumor

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growth. Some works have studied relative to stability analysis, limit cycle, bifurcation, and chaos in DDEs [10], [11]. In addition, chaotic behavior of different ordinary differential equation (ODE) of the cancer models such as virotherapy and immunotherapy of cancer exist in the literature [12], [13].

In this study, we investigate the effect of delay in immune system response. The mathematical model of a cancer nonlinear dynamics is modified by considering delay terms in the immune system. Then the behavior of the overall dynamics is analyzed in terms of bifurcation and chaos. Through the analytical study and simulations, it is shown that by increasing the delay time, the bifurcation behavior tends to chaotic one.

II. CANCER MODEL

We modified the model of L.G. De Pillis and A. Randunskaya [1] using the time delay in detection of tumor cells. For simplicity of calculation, we assumed that activation process of NK cells is instantaneous and not followed by time delay. The system of DDEs, which describes the cancer model is:

$$\begin{aligned} \dot{N} &= r_2 N(1-b_2 N) - c_4 T N \\ \dot{T} &= r_1 T(1-b_1 T) - c_2 I(t-\tau) T - c_3 T N \\ \dot{I} &= s + \frac{\rho I(t-\tau) T}{\alpha + T} - c_1 I(t-\tau) T - d_1 I \end{aligned} \tag{1}$$

where, $N(t)$ is the population of normal cells at time t, $T(t)$ is the population of tumor cells at time t and $I(t)$ is the population of immune cells at time t. The parameters of the cancer model are given in TABLE I.

In the model proposed in [1], it is assumed that the source of the immune cells is outside the system. Therefore, the resource input is assumed to be constant. Moreover, in the absence of any tumor cells, the cells die off at a per capita rate d_1 due to the person.

The presence of tumor cells stimulates the immune cells with delay when the number of tumor cells reach the threshold value. This competition represent by the positive nonlinear growth term for the immune cells:

$$\frac{\rho I(t-\tau) T}{\alpha + T} \tag{2}$$

where ρ and α are positive constants and T is a positive, increasing, and concave function. Furthermore, the interaction of immune system cells with tumor cells can lead to either the death of tumor cells or the inactivation of the immune cells. This relationship is represented by the following two competing terms:

$$\frac{dI}{dt} = -c_1 I(t-\tau) T \tag{3}$$

$$\frac{dT}{dt} = -c_2 I(t-\tau) T \tag{4}$$

TABLE I
SYSTEM PARAMETERS

Parameter	Description	Unit	Value
b_1	Tumor cell carrying capacity	cell^{-1}	1
b_2	Normal cell carrying capacity	cell^{-1}	1
c_1	Fractional tumor cell kill by immune cells	$\text{cell}^{-1}\text{day}^{-1}$	1
c_2	Fractional immune cell kill by tumor cells	$\text{cell}^{-1}\text{day}^{-1}$	0.5
c_3	Fractional tumor cell kill by normal cells	$\text{cell}^{-1}\text{day}^{-1}$	0.5
c_4	Fractional normal cell kill by tumor cells	$\text{cell}^{-1}\text{day}^{-1}$	1
d_1	Death rate of immune cells	day^{-1}	0.2
r_1	Tumor cell growth rate	day^{-1}	1.5
r_2	Normal cell growth rate	day^{-1}	1
s	Steady source rate for immune cells	cell day^{-1}	0.32
α	Immune threshold rate	cell	0.1
ρ	Immune response rate	day^{-1}	0.1

III. STABILITY ANALYSIS AND HOPF BIFURCATION

First, the system is linearized and the Jacobian matrix is obtained in order to analyze the local behavior at equilibrium points. The Jacobian matrix of the system is as follows:

$$J = \begin{pmatrix} r_2 - 2r_2 b_2 N - c_4 T & -c_4 N & 0 \\ -c_3 T & r_1 - 2r_1 b_1 T - c_2 I - c_3 N & -c_2 T e^{-\lambda\tau)} \\ 0 & \frac{\rho\alpha I}{(\alpha+T)^2} - c_1 I & \frac{\rho T}{\alpha+T} e^{-\lambda\tau} - c_1 T e^{-\lambda\tau} - d_1 \end{pmatrix}$$

The equilibrium points of the system are as follows:

$$\dot{N} = 0 \quad \Rightarrow \quad \begin{cases} N = 0 \\ N = \dfrac{1}{b_2} - \dfrac{c_4}{r_2} T \end{cases} \tag{5}$$

$$\dot{T} = 0 \quad \Rightarrow \quad \begin{cases} T = 0 \\ T = \dfrac{1}{b_1} - \dfrac{c_2}{r_1 b_1} I - \dfrac{c_3}{r_1 b_1} N \end{cases} \tag{6}$$

$$\dot{I} = 0 \quad \Rightarrow \quad \left\{ I = \frac{s(\alpha+T)}{c_1 T(\alpha+T) + d_1(\alpha+T) - \rho T} \right. \tag{7}$$

The equilibrium points are obtained from the solution of the Eqs. (5)-(7) and their local behavior according to their biological relevance are discussed as follows;

The first equilibrium point is $E_1 = [0, 0, s/d_1]$. This equilibrium shows that normal cells and the tumor cells do not exist which is not biologically possible. The eigenvalues of the Jacobian matrix for this point are $\lambda_1 = r_2, \lambda_2 = r_1 - c_2 s/d_1$ and $\lambda_3 = -d_1$, since all parameters are positive, hence this equilibrium point is unstable.

The second equilibrium point is obtained as $E_2 = [1/b_2, 0, s/d_1]$. This equilibrium point means that tumor cell populations is zero and system is in healthy stage. At the tumor-free equilibrium point, the eigenvalues are obtained

as $\lambda_1 = -r_2, \lambda_2 = r_1 - c_2 s/d_1 - c_3/b_2$ and $\lambda_3 = -d_1$. Since λ_1 and λ_3 are negative for stability of this point must be $r_1 < c_2 s/d_1 + c_3/b_2$.

$E_3 = [0, \bar{T}, \bar{I}]$ is the third equilibrium point of the system. This equilibrium is biologically irrelevant because the number of normal cells is zero. According to the selected parameter values given in Table 1, this equilibrium point has the numerical values $E_3 = [0, 0.893737, 0.318789]$.

In the fourth equilibrium point, all the cells exist $E_4 = [N^*, T^*, I^*]$. According to the parameter values in TABLE I $E_4 = [0.170093, 0.829906, 0.340186]$. The eigenvalues of this equilibrium point at $\tau = 0$ are $\lambda_1 = -1.53244, \lambda_2 = -0.72502$ and $\lambda_3 = -0.09815$. Since all eigenvalues are negative, this equilibrium point is stable. However, depending on the variation of the delay component, the stability state will be discussed in the context of the following explanations.

Theorem 1: Consider the characteristic equation $P(\lambda) + Q(\lambda)e^{-\lambda\tau} = 0$ associated to a fixed point, where $P(\lambda)$ and $Q(\lambda)$ are analytic functions in a right half-plane $Re\lambda > -\delta, \delta > 0$ which satisfy the following conditions [14]:

i. $P(\lambda), Q(\lambda)$ have no common imaginary zero,

ii. $\overline{P(-iy)} = P(iy), \overline{Q(-iy)} = Q(iy), y \in \mathbb{R}$ where the bar means conjugate,

iii. $P(0) + Q(0) \neq 0$,

iv. There are at most a finite number of roots of $P(\lambda) + Q(\lambda)e^{-\lambda\tau} = 0$ in the right half-plane if $\tau = 0$,

v. $F(y) = |P(iy)|^2 - |Q(iy)|^2$ with $y \in \mathbb{R}$ has at most a finite number of real zeros.

Under these conditions, the following statements are true:

a. Suppose $F(y) = 0$ has no positive real roots. Then if the associated equilibrium point is stable (unstable) for $\tau = 0$ it remains stable (unstable) for all $\tau = 0$.

b. Suppose $F(y) = 0$ has at least one positive root and that each positive root is simple. As τ increases, stability switches may occur. There exists $\tau^* > 0$ such that $P(\lambda) + Q(\lambda)e^{-\lambda\tau} = 0$ is unstable for all $\tau > \tau^*$. As τ varies from 0 to τ^* at most a finite number of stability switches may occur.

In the case of positive delay, the following characteristic equation is obtained from the linearized system equation around $E_4 = [N^*, T^*, I^*]$. The steps required for the critical τ^* can be found as follows.

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

where $P(\lambda)$ and $Q(\lambda)$ represent the non-delayed portion and the delayed portion of the characteristic equation, respectively, and can be represented by the following polynomial expressions:

$$\begin{aligned} P(\lambda) &= \lambda^3 + p_1\lambda^2 + p_2\lambda + p_3 \\ Q(\lambda) &= q_1\lambda^2 + q_2\lambda + q_3 \end{aligned} \tag{8}$$

where

$$\begin{aligned} p_1 &= d_1 + c_2 I + c_3 N - r_1 - r_2 + b_2 r_2 N + c_4 T + 2 r_1 b_1 T \\ p_2 &= c_2 d_1 I + c_3 d_1 N - d_1 r_1 - d_1 r_2 - c_3 r_2 N - c_2 r_2 I \\ &\quad + 2 b_2 d_1 r_2 N + 2 b_2 c_2 r_2 N I + 2 b_2 c_3 r_2 N^2 + r_1 r_2 \\ &\quad - 2 b_2 r_1 r_2 N + c_4 d_1 T + c_2 c_4 T I - c_4 r_1 T + 2 b_1 d_1 r_1 T \\ &\quad - 2 b_1 r_1 r_2 T + 4 b_1 b_2 r_1 r_2 N T + 2 b_1 c_4 r_1 T^2 \\ p_3 &= d_1 r_1 r_2 - c_2 d_1 r_2 I - c_3 d_1 r_2 N + 2 b_2 c_2 d_1 r_2 N I \\ &\quad + 2 b_2 c_3 d_1 r_2 N^2 - 2 b_2 d_1 r_1 r_2 N + c_2 c_4 d_1 T I - c_4 d_1 r_1 T \\ &\quad - 2 b_1 d_1 r_1 r_2 T + 4 b_1 b_2 d_1 r_1 r_2 N T + 2 b_1 c_4 d_1 r_1 T^2 \\ q_1 &= c_1 T - \frac{\rho T}{\alpha + T} \\ q_2 &= c_1 c_3 N T - c_1 r_1 T - c_1 r_2 T + 2 b_2 c_1 r_2 N T + c_1 c_4 T^2 \\ &\quad + 2 b_1 c_1 r_1 T^2 - \frac{c_2 \rho T I}{\alpha + T} - \frac{c_3 \rho N T}{\alpha + T} + \frac{r_1 \rho T}{\alpha + T} + \frac{r_2 \rho T}{\alpha + T} \\ &\quad - \frac{2 b_2 r_2 \rho T N}{\alpha + T} - \frac{c_4 \rho T^2}{\alpha + T} - \frac{2 b_1 r_1 \rho T^2}{\alpha + T} - \frac{c_2 \rho \alpha T I}{(\alpha + T)^2} \\ q_3 &= 2 b_2 c_1 c_3 r_2 N^2 T - c_1 c_3 r_2 N T + c_1 r_1 r_2 T - 2 b_2 c_1 r_1 r_2 N T \\ &\quad - c_1 c_4 r_1 T^2 - 2 b_1 c_1 r_1 r_2 T^2 + 4 b_1 b_2 c_1 r_1 r_2 N T^2 \\ &\quad + 2 b_1 c_1 c_4 r_1 T^3 - \frac{c_2 r_2 \rho \alpha T I}{(\alpha + T)^2} + \frac{2 b_2 c_2 r_2 \rho \alpha N T I}{(\alpha + T)^2} \\ &\quad + \frac{c_2 c_4 \rho \alpha T^2 I}{(\alpha + T)^2} + \frac{c_2 r_2 \rho T I}{\alpha + T} + \frac{c_3 r_2 \rho T N}{\alpha + T} - \frac{2 b_2 c_2 r_2 \rho N T I}{\alpha + T} \\ &\quad - \frac{2 b_2 c_3 r_2 \rho N^2 T}{\alpha + T} - \frac{r_1 r_2 \rho T}{\alpha + T} + \frac{2 b_2 r_1 r_2 \rho N T}{\alpha + T} - \frac{c_2 c_4 \rho T^2 I}{\alpha + T} \\ &\quad + \frac{c_4 r_1 \rho T^2}{\alpha + T} + \frac{2 b_1 r_1 r_2 \rho T^2}{\alpha + T} - \frac{4 b_1 b_2 r_1 r_2 \rho N T^2}{\alpha + T} \\ &\quad - \frac{2 b_1 c_4 r_1 \rho T^3}{\alpha + T} \end{aligned}$$

As stated [14], periodic behavior depends on pure imaginary eigenvalues, in which the real part does not exist. By writing $\lambda = i\omega$ in Eq. 8, the new form of the system is rewritten as:

$$p_1\omega^2 - p_3 = (q_3 - q_1\omega^2)\cos(\omega\tau) + q_2\omega\sin(\omega\tau) \tag{9}$$

$$\omega^3 - p_2\omega = q_2\omega\cos(\omega\tau) - (q_3 - q_1\omega^2)\sin(\omega\tau) \tag{10}$$

Eq. 11 is obtained by squaring and adding Eq. 9 and Eq. 10:

$$(q_3 - q_1\omega^2)^2 + (q_2\omega)^2 = (p_1\omega^2 - p_3)^2 + (\omega^3 - p_2\omega)^2 \tag{11}$$

Simplification of Eq. 11 gives us:

$$\omega^6 + A_1\omega^4 + A_2\omega^2 + A_3 = 0 \tag{12}$$

where

$$\begin{aligned} A_1 &= p_1^2 - 2p_2 - q_1^2 \\ A_2 &= p_2^2 - q_2^2 - 2p_1p_3 + 2q_1q_3 \\ A_3 &= p_3^2 - q_3^2 \end{aligned}$$

Thus, the positive ω obtained from Eq. 12 shows that the characteristic equation has only one pair of imaginary roots $\pm i\omega$. From Eq. 9 and Eq. 10, the following equaiton can be obtained.

$$\tan(\omega\tau) = \frac{(p_1\omega^2 - p_3)(q_2\omega) - (\omega^3 - p_2\omega)(q_3 - q_1\omega^2)}{(p_1\omega^2 - p_3)(q_3 - q_1\omega^2) + (\omega^3 - p_2\omega)(q_2\omega)} \tag{13}$$

In this case τ_n^* is obtained as follows

$$\tau_n^* = \frac{1}{\omega}\tan^{-1}\frac{(p_1\omega^2 - p_3)(q_2\omega) - (\omega^3 - p_2\omega)(q_3 - q_1\omega^2)}{(p_1\omega^2 - p_3)(q_3 - q_1\omega^2) + (\omega^3 - p_2\omega)(q_2\omega)} \tag{14}$$

For the Hopf-bifurcation in the system, the following condition must be satisfied;

$$\left[\frac{d(Re\lambda)}{d\tau}\right]_{\lambda=i\omega,\tau=\tau^*} > 0$$

This implies that there exists at least one eigenvalue with a positive real part for $\tau > \tau^*$.

IV. NUMERICAL RESULTS

According to the parameters given in TABLE I, the numerical value of the fourth equilibrium point is $E_4 = [0.170093, 0.829906, 0.340186]$. The eigenvalues of this equilibrium point are stable at $\tau = 0$ because $\lambda_1 = -1.53244, \lambda_2 = -0.72502$ and $\lambda_3 = -0.09815$ and all are negative.

From the numerical solution of Eq. 12, we obtain $\omega = 0.29623$. According to Theorem 1, it is known that the stability of the system may change by increasing τ. The critical delay τ^* is calculated $\tau^* = 3.06836$ from the Eq. 14. It can easily be concluded that the system is stable for $\tau < \tau^*$ and the system exhibits an unstable behavior for $\tau > \tau^*$.

According to the expression given in Eq. 14, the value of τ where stability of the system change is $\tau = 3.06836$. This is where Hopf bifurcation is begun. As can be seen in Fig. 2, the system behavior is stable for values $\tau < 3.06836$, after this value bifurcation occurs. Moreover, Fig. 2 shows chaotic behavior starts when the delay component τ reaches approximately 34 days.

Time responses of the cells $N(t), T(t)$ and $I(t)$ are illustrated in the following figures for the initial conditions $x_0 = [1 \quad 0.2 \quad 0.15]$ and different time delays. As shown in Fig. 3, the system is stable for $\tau = 3$ which is less than critical time delay $\tau^* = 3.06836$. As time delay τ increases and reaches critical time delay, stability of the system changes and Hopf-bifurcation occurs. Fig. 4 shows this periodic behavior for $\tau = 5$. Fig. 5 presents chaotic behavior of the system when delay time is $\tau = 45$.

Chaotic behavior and Hopf bifurcation of the system in the phase space are shown in the following figures. Figures 6 to 8 represent chaotic behaviors in different phase planes. Fig. 9 illustrates the Hopf bifurcation. Finally, Fig. 10 shows the chaotic behavior in three dimensional phase plane.

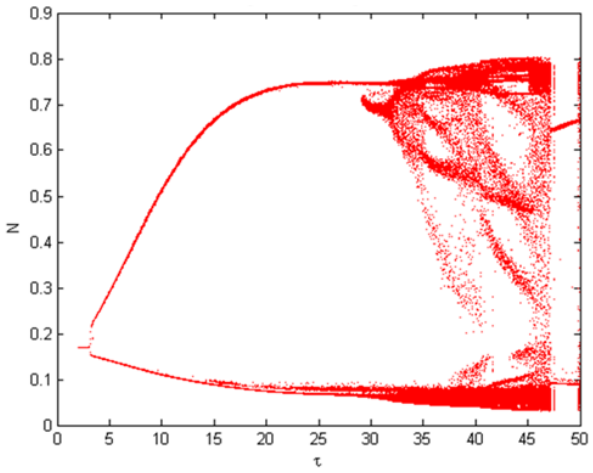

Fig. 2. Bifurcation diagram

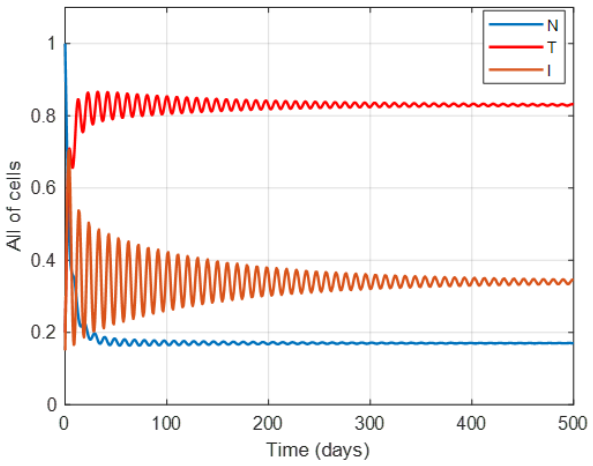

Fig. 3. Time evolution of the cells for delay time $\tau = 3$ and initial condition $x_0 = [1 \quad 0.2 \quad 0.15]$

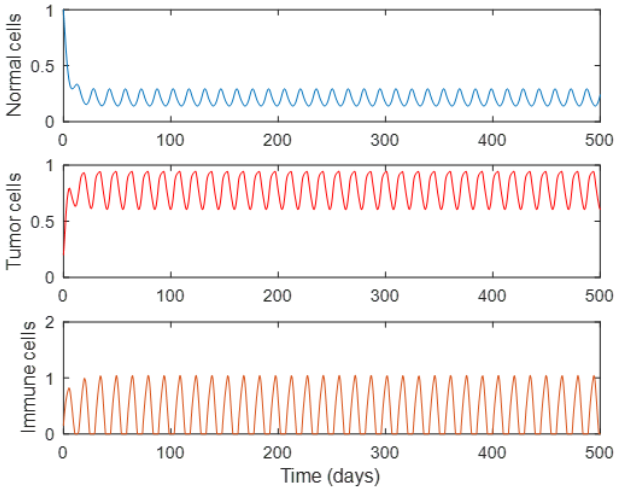

Fig. 4. Time evolution of the cells for time delay $\tau = 5$ and initial condition $x_0 = [1 \quad 0.2 \quad 0.15]$

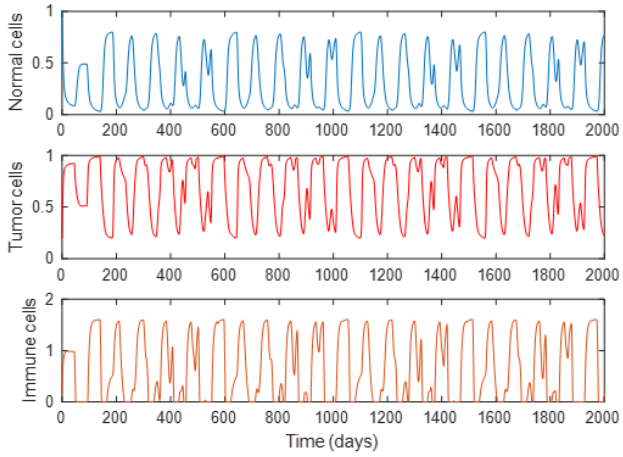

Fig. 5. Time evolution of the cells for time delay $\tau = 45$ and initial condition $x_0 = [1 \quad 0.2 \quad 0.15]$

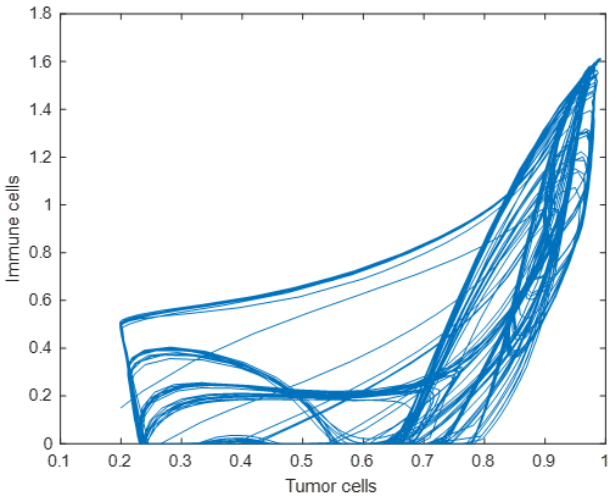

Fig. 8. Chaotic behavior of the system in phase-space

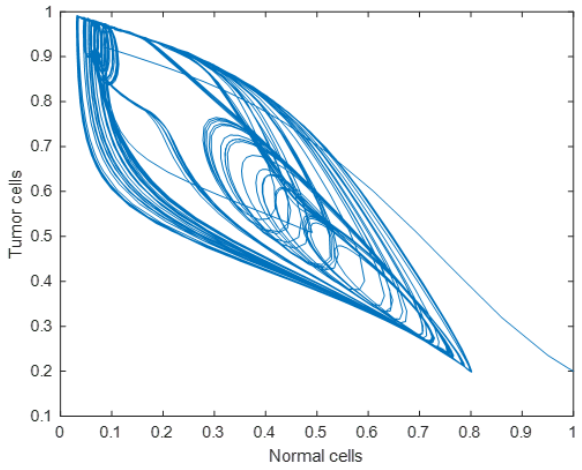

Fig. 6. Chaotic behavior of the system in phase-space

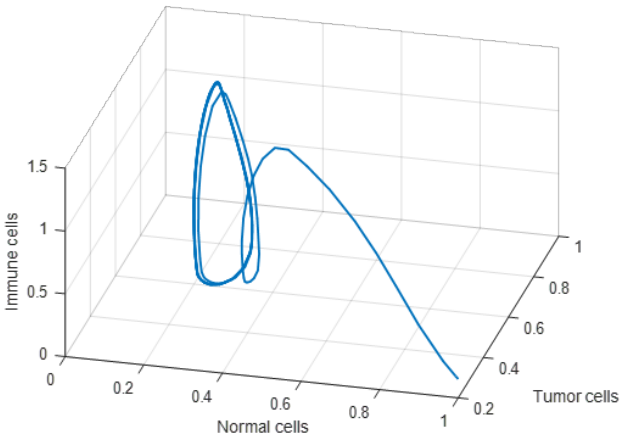

Fig. 9. Hopf bifurcation of the system in phase space

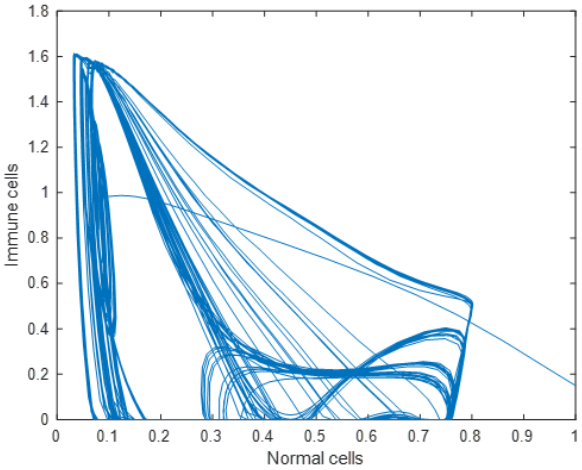

Fig. 7. Chaotic behavior of the system in phase-space

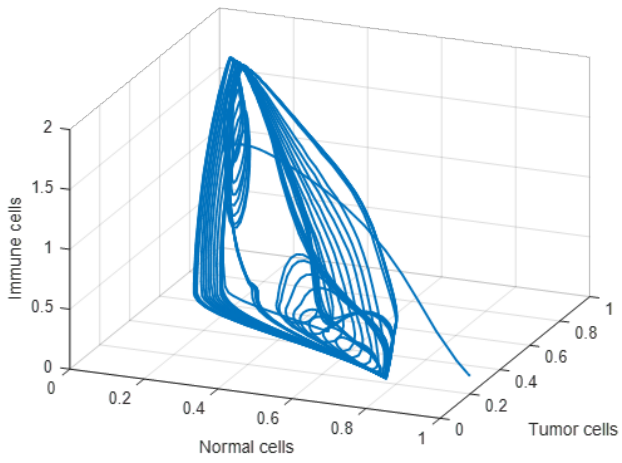

Fig. 10. Chaotic behavior of the system in phase space

V. CONCLUSIONS

The purpose of the current study is to determine the influence of time delay on the dynamical behaviors of the mathematical model of cancer. L.G. De Pillis and A. Randunskaya proposed the mathematical model of cancer in which time delay in detection of tumor cells by immune cells has been neglected. Therefore, it does not provide significant information about the system behavior. In this study, we incorporate time delay into the mathematical model proposed by L.G. De Pillis and A. Randunskaya in [1]. In this new cancer model, the effect of the time delay on cancer dynamics and chaotic behavior was investigated. We have formulated the critical values of time delays for stability changes. Then, the critical time delay of the system is obtained by analytical method which is calculated as $\tau^* = 3.06836$. The results of this study indicate that increasing time delay lead to stability change, Hopf bifurcation and chaos. From the bifurcation diagram, we showed that the system has stable behavior for $\tau < 3.06836$, periodic behavior for $3.06836 < \tau < 35$ and chaotic behavior for approximately $35 < \tau < 47$. The numerical simulations represent the mathematical model for different time delays. In order to develop more realistic models, future studies should focus on time delay in activation NK cells, which we do not consider these effect in the model proposed in this study.

ACKNOWLEDGMENT

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