Wasit Journal for Pure Science

Journal Homepage: https://wjps.uowasit.edu.iq/index.php/wjps/index
e-ISSN: 2790-5241 p-ISSN: 2790-5233

Explicit Representations of Solutions and Parameter Estimations Problems of Time Delay Tumor Cells Model

Ibrahim Makki Khalil[1]*, Jehan Mohammed Khudhir[2]

[1]Mathematics Department, Science College, Basrah University, IRAQ,

[2]Mathematics Department, Science College, Basrah University, IRAQ,

*Corresponding Author: Ibrahim Makki Khalil

DOI: https://doi.org/ 10.31185/wjps.314
Received 10 January 2024; Accepted 03 March 2024; Available online 30 March 2024

ABSTRACT: This paper considers ordinary differentials of cancerous tumor cells model with time delay that illustrates and represents the interactions of the tumor cells with effector cells include immune response of natural, dendritic and cytotoxic cells. The time delay is incorporated here into the model to justify the time required to stimulate the effector cells. This also help to study the behavior of the system without using all kinds of treatments. The stability of the model will be studied that confirms a free tumor steady state and displays two equilibrium points. The numerical simulations show that growing of the tumor cells reduces and the effector cells increase after few days for different values of time delay up to $\tau > 3$, even without considering the treatment strategies in the model. In addition, an efficient numerical technique is presented to show how we can first represent the periodic solution of the tumor nonlinear equation and then effectively estimate the unknown parameters of the model.

Keywords: Tumor cells, time delay differential equations, steady states of ODEs.

1. INTRODUCTION

Cancer is the most dangerous tumors and difficult to reach in early stages which can cause death if it effects certain parts of the human body. Fighting cancer and stopping the tumor to grow becomes important for public health. For that, extensive researches are trying to understand the mechanism of tumor growth of cancer and to study the results of changing some biological elements on the system. Many developments in cancer therapies have been discovered and developed such as chemotherapy, immunotherapy, and radiotherapy, surgeries, however, some unclear information about how tumor cells of cancer are created, growing, and destroyed still need to be intensively studied.

Over the past few decades, several developed techniques and experimental approaches have been practically discovered and applied to understand how much the interactions of tumor cells with the immune system does control the dynamics of the tumor growth [5,9]. These have also helped to inform that how the immunotherapy specifically increases the ability of the human body to fight cancerous tumors by improving the efficiency of the immune system by different ways.

Mathematical modeling is one of the promising approaches which identify cancer growth and propagation, and the interactions between tumor cells and immunity cells [17,19,8]. It plays a role to describe the dynamics of these interactions that helps then for biological parameter estimations, satisfying the stability analysis of the model, and tumor dynamics prediction [1,12,13,18,21,22,23]. The tumors growth has been also controlled by dynamics of the practical components of the immune system, the natural killer cells and cytotoxic cells, which are working to fight and destroy the cancerous tumor cells.

The immunity system is working like weapons to attack any foreign cells in human body. This system is activated and it takes time to response before destroying the abnormal cells. To study the realistic nature of the mathematical cancer models, time delays are incorporated to force the systems to depend on the present state and the past state in some equivalent terms of the system. Therefore, we can understand and explain the effects of the immunity on tumor growth by including the delays [6,14,19]. However, because of the delays the system may lose its stability and have some bifurcations and oscillatory behaviors [3,4,15,20]. In [4,7], Bi and Xiao and Ghosh et al. studied the dynamics of tumor growth with concluding two different values of time delays incorporated into the immune response terms and found out their effectiveness on growing the tumor cells. Khajanchi et al. and Khajanchi studied in details the chaotic dynamics of

tumor-immune interaction model and the effects of time delay on the model, see [10,11] for more details. The best values of the time delay that confirms the system's stability and Hopf-bifurcation's direction have been also analytically estimated.

In this study, we consider a mathematical model that illustrating the interactions between the tumor cells and the effector cells. Then, the model, originally proposed by Pranav Unni and Padmanabhan Seshaiyer [24], considers four differential equations. Incorporating time delays is into the immune cells could affect dynamical behaviors of the tumor growth and the stability of the system in some sense. However, existence of exact formula of solutions for this model was not often confirmed and therefore it is required to use numerical methods to solve it. Parameter estimation techniques are also required to optimally estimate parameters for a given extrapolated dataset. The objective of this paper is to adopt the tumor cells differential model with time delay and analyze the optimal values of the unknown parameters explicitly and then evaluate dynamics of all the variables of the system.

This paper will be outlined as follows. In Section 2, we describe the model with incorporating time delay into some terms of the system. The existence of solutions and stability conditions of the delay tumor cells model are discussed in details in section 3. In Section 4, numerical simulations for different values of delays will be considered by figures. Section 5 includes the application of parameterized representation method for the nonlinear tumor cells equation for estimation parameters and the initial value of tumor. Then, the conclusion will be given in Sections 6.

2. TUMOR GROWTH MODEL

Let us consider the tumor growth model proposed by Pranav Unni et al. [24]. The model describes the dynamics of tumor-immune system interactions represented by four ordinary differential equations (ODEs). We will incorporate one value of time-delay τ into some terms of the dendritic equation which could help to understand the fast response of the immune system to be effective after recognizing and then fighting the strange cells. The model with time delay is in the following form:

$$
\begin{aligned}
\frac{\mathrm{dT}}{\mathrm{dt}} &= \mathrm{aT}(1-\mathrm{bT}) - (\mathrm{c_1N} - \mathrm{jD} + \mathrm{kL})\mathrm{T} - \mathrm{K_T z}(\mathrm{M_z})\mathrm{T} \\
\frac{\mathrm{dN}}{\mathrm{dt}} &= \mathrm{s_1} + \frac{g_1 NT^2}{h_1 + T^2} - (c_2 T - d_1 D)N - K_N z(M_z)N - qN \\
\frac{dD}{dt} &= s_2 - (f_1 L(t-\tau) + d_2 N(t-\tau) - d_3 T(t-\tau))D(t-\tau) - K_D z(M_z)D - gD \\
\frac{dL}{dt} &= f_2 DT - hLT - uNL^2 + r_1 NT + \frac{p_1 LI}{g_1 + I} - K_L z(M_z)L - iL + v_L(t) \\
\frac{dM}{dt} &= v_M(t) - d_4 M \\
\frac{dI}{dt} &= v_I(t) - d_5 I
\end{aligned}
\tag{1}
$$

The main cell populations of this model are the tumor cells $T(t)$, the natural killer cells $N(t)$, the dendritic cells $D(t)$ and the cytotoxic cells $L(t)$. The interactions rates between these cells are introduced in the model's parameters. The dynamics of their interactions with the chemotherapy $M(t)$ and the immunotherapy $I(t)$ treatments and their concentration in the blood stream has also been considered in the model.

In the first equation of system (1), a is the growth rate of the tumor cells per day and b is the maximum carrying capacity of tumor cells in the absence of the immunity and drugs. The interactions of tumor cells with natural killer cells, dendritic cells and cytotoxic cells can kill the tumor cells and stop their activation, and these are represented by the terms $-c_1\,NT$, jDT and $-kLT$.

The second equation includes the rate of change of immune cells with respect to time denoted by c_1, and $\mathrm{s_1}$ is the source rate of the immune cells. The second term is dominated by tumor cells through the term $\frac{g_1 NT^2}{h_1+T^2}$ where the rate when the immune cells grow and h_1 is the changing rate of immune response. The third term includes $-c_2 NT$ which represents the kill rate c_2 of immune cells to the tumor cells because of their interaction, while $\mathrm{d_1}$ in the term $-d_1 DN$ represents the die rate of the immune cells per day. The last two equations of system (1) describe the dynamics of the active concentrations of chemotherapy and immunotherapy drugs in the blood stream which could be filtered from the body over time and these are represented by $d_4 M$ and $d_5 I$, respectively, for more details about the rest of parameters see [24]. We will consider the system as assumed in [24] where it supposed that the system could practically and analytically work without the recruitment terms for cytotoxic cells and natural killer cells. Moreover, removing the regulation, suppression and activation of cytotoxic cells, not influencing of drugs and vaccine interventions and without considering

the corresponding death rates, means $r_1 = g_1 = h_1 = p_I = g_I = u = K_T = K_N = K_D = K_L = d_4 = d_5 = 0$ have also been considered for studying this system.

3. POSITIVE INVARIANCE AND BOUNDEDNESS

Let us investigate the ultimate bound and positively invariant set of the equations of system (1) but without considering chemotherapy and immunotherapy drug, starting by:

$$\frac{dT}{dt} = aT(1-bT) - (c_1N - jD + kL)T \le aT(1-bT)$$

Integration the both sides leads to

$$T(t) \le \frac{1}{b + T(0)e^{-at}} \Rightarrow \limsup_{t\to\infty}(T(t)) \le \frac{1}{b}$$

Moreover,

$$\frac{dN}{dt} = s_1 + \frac{g_1 N T^2}{h_1 + T^2} - (c_2 T - d_1 D)N - qN \le s_1 - qN$$

Then, as the above process, we have

$$N(t) = \frac{s_1}{q} + N(0)e^{-qt} \Rightarrow \lim_{t\to\infty}\sup(N(t)) \le \frac{s_1}{q}$$

and similarly, we find

$$\frac{dD}{dt} = s_2 - (f_1 L(t-\tau) + d_2 N(t-\tau) - d_3 T(t-\tau))D(t-\tau) - gD \le s_2 - gD$$

Therefore, we get

$$D(t) \le \frac{s_2}{g} + D(0)e^{-gt} \Rightarrow \limsup_{t\to\infty}(D(t)) \le \frac{s_2}{g}$$

From the last equation, we also have:

$$\frac{dL}{dt} = f_2 DT - hLT - uNL^2 + r_1 NT - iL \le iL$$

$$L(t) \le ce^{it} \Rightarrow \limsup_{t\to\infty}(L(t)) \le 0$$

with initial condition $T(t) > 0, M(t) > 0, D(t) > 0$ and $L(t) > 0$ such that

$$\Delta = \{(T(t), N(t), D(t), L(t)) \in \mathbb{R}^4 : 0 \le T(t) \le \frac{1}{b}, 0 \le N(t) \le \frac{s_1}{q}, 0 \le D(t) \le \frac{s_2}{g}, L(t) = 0\}$$

Hence, the boundedness of solutions of system (1) is proved.

System (1) without time delay was discussed and proved by Pranav Unni and Padmanabhan Seshaiyer [22]. Inducing the time delay does not affect the existence conditions for equilibria of the system and we have the same two equilibrium points, $E(T^*, N^*, D^*, L^*)$, satisfy that $\frac{dT^*}{dt} = \frac{dN^*}{dt} = \frac{dD^*}{dt} = \frac{dL^*}{dt} = 0$. The types of steady states show that free tumor steady state have the form $E_1 = (0, N^*, D_1^*, 0)$ and $E_2 = (0, N^*, D_2^*, 0)$ in which the tumor cell and cytotoxic cell populations have died off, while the natural killer cells and dendritic cells have survived, where

$$N^* = \frac{s_1}{q - d_1 D^*} \tag{2}$$

$$D_{1,2}^* = \frac{(d_1 s_2 + d_2 s_1 + qg) \pm \sqrt{(d_1 s_2 + d_2 s_1 + qg)^2 - 4gqs_2}}{2gd_1} \tag{3}$$

which satisfy the conditions

$$q - d_1 D^* > 0 \quad \text{and} \quad d_1 s_2 + d_2 s_1 + qg \ge 2\sqrt{gqs_2} \tag{4}$$

Biologically, the stability of this equilibrium is because the number of tumor cells T will remain at 0, and other two cell populations increase.

We are interested in studying the nature of stability of the free tumor equilibrium. The local stability at each of the equilibrium points can be checking by using the Jacobian matrix for system (1):

$$J = J_0 + e^{-\lambda\tau} J_{(\tau_1)}$$

Evaluating the matrix at the free tumor equilibrium point gives

$$J_E = \begin{pmatrix} a-(c_1N^* + jD^*) & 0 & 0 & 0 \\ -c_2 & d_1D^* - q & d_1N^* & 0 \\ d_3e^{-\lambda\tau}D^* & -d_2e^{-\lambda\tau}D^* & -(d_2e^{-\lambda\tau}N^* + g) & -f_1e^{-\lambda\tau}D^* \\ f_2D^* + r_1N^* & 0 & 0 & -i \end{pmatrix}$$

To find the eigen values λ of the matrix J_E we use the characteristic polynomial:

$$\det(J_E - \lambda I) = 0$$

Then

$$\det\begin{pmatrix} a-(c_1N^* + jD^*) - \lambda & 0 & 0 & 0 \\ -c_2 & d_1D^* - q - \lambda & d_1N^* & 0 \\ d_3e^{-\lambda\tau}D^* & -d_2e^{-\lambda\tau}D^* & -(d_2e^{-\lambda\tau}N^* + g) - \lambda & -f_1e^{-\lambda\tau}D^* \\ f_2D^* + r_1N^* & 0 & 0 & -i - \lambda \end{pmatrix}$$

which yields

$$(a-(c_1N^* + jD^*) - \lambda)(-i - \lambda)det(A - \lambda I) = 0 \quad (5)$$

where matrix A is given by

$$A = \begin{pmatrix} d_1D^* - q & d_1N^* \\ -d_2e^{-\lambda\tau}D^* & -(d_2e^{-\lambda\tau}N^* + g) \end{pmatrix}$$

Then, the trace and determinant for matrix A are computed as:

$$tr(A) = (d_1D^* - q) - (d_2e^{-\lambda\tau}N^* + g) \quad (6)$$

$$det(A) = d_1d_2e^{-\lambda\tau}N^*D^* - (d_1D^* - q)(d_2e^{-\lambda\tau}N^* + g) \quad (7)$$

Hence, we have two values of eigenvalues:

$$\lambda_1 = a-(c_1N^* + jD^*) \quad \text{and} \quad \lambda_2 = -i$$

We notice that λ_3 . λ_4 are the roots of the equation:

$$\lambda^2 - \lambda[(d_1D^* - q) - (d_2e^{-\lambda\tau}N^* + g)] + d_1d_2e^{-\lambda\tau}N^*D^* - (d_1D^* - q)(d_2e^{-\lambda\tau}N^* + g) = 0$$

This can be rewritten as

$$\lambda^2 - tr(A)\lambda + \det(A) = 0$$

Because $tr(A)$ and $\det(A)$ includes $e^{-\lambda\tau}$ then let $\tau = 0$. Therefore, using (5) in equations (6) and (7) with assuming $\tau = 0$, we can conclude that

$$tr(A) < 0 \quad \text{and} \quad \det(A) > 0$$

we get that equation (5) has eigenvalues λ_3 and λ_4 with negative real parts. To ensure the stability of the free tumor equilibrium, λ_1 is required that $a < c_1N^* + jD^*$. Hence, the eigenvalues λ_1, λ_2, λ_3 and λ_4 are negatives, leads to have that E_1 and E_2 are locally stable when $\tau = 0$.

Now, if τ is chosen arbitrarily and as $\lambda_1 = a - (c_1N^* + jD^*)$ and $\lambda_2 = -i$ are roots of equation (5), we only need to consider

$$\lambda^2 - \lambda[(d_1D^* - q) - (d_2e^{-\lambda\tau}N^* + g)] + d_1d_2e^{-\lambda\tau}N^*D^* - (d_1D^* - q)(d_2e^{-\lambda\tau}N^* + g) = 0 \quad (8)$$

which is equivalent to

$$\lambda^2 - \lambda[(d_1D^* - q) - (d_2e^{-\lambda\tau}N^* + g)] = -d_1d_2e^{-\lambda\tau}N^*D^* + (d_1D^* - q)(d_2e^{-\lambda\tau}N^* + g)$$

Let us separate the real and the imaginary parts and suppose that $\lambda = wi$ is a root of equation (8), then we get:

$$-w^2 - wi(d_1D^* - q) + wi(d_2cos(w\tau)N^* + g) + wd_2sin(w\tau)N^* = -d_1d_2(cos(w\tau) - isin(w\tau))N^*D^* + (d_1D^* - q)(d_2(cos(w\tau) - isin(w\tau))N^* + g)$$

Hence, we have the equations:

$$\begin{aligned} -w^2 + wd_2sin(w\tau)N^* &= [-d_1d_2cos(w\tau)N^*D^* + (d_1D^* - q)(d_2cos(w\tau)N^* + g)] \\ w[-(d_1D^* - q) + (d_2cos(w\tau)N^* + g)] &= [d_1d_2D^* - (d_1D^* - q)d_2]sin(w\tau)N^* \end{aligned} \quad (9)$$

Taking squares of both equations in (9) implies that:

$$w^4 + w^2 d_2^2 \sin^2(w\tau)N^{*2} - 2wd_2 \sin(w\tau)N^* = [-d_1 d_2 \cos(w\tau)N^* D^* + (d_1 D^* - q)(d_2 \cos(w\tau)N^* + g)]^2 \quad (10)$$

$$w^2 - \frac{[d_1 d_2 D^* - (d_1 D^* - q)d_2]^2 \sin^2(w\tau)N^{*2}}{[-(d_1 D^* - q) + (d_2 \cos(w\tau)N^* + g)]^2} = 0$$

Then,

$$w^4 + w^2[1 - \frac{[d_1 d_2 D^* - (d_1 D^* - q)d_2]^2}{[-(d_1 D^* - q) + (d_2 \cos(w\tau)N^* + g)]^2}]\sin^2(w\tau)N^{*2} - 2wd_2 \sin(w\tau)N^* =$$

$$[-d_1 d_2 \cos(w\tau)N^* D^* + (d_1 D^* - q)(d_2 \cos(w\tau)N^* + g)]^2$$

This equation can be rewritten in the following form:

$$w^4 + \alpha_1 w^2 + \alpha_2 w + \alpha_3 = 0 \quad (11)$$

Where

$$\alpha_1 = [1 - \frac{[d_1 d_2 D^* - (d_1 D^* - q)d_2]^2}{[-(d_1 D^* - q) + (d_2 \cos(w\tau)N^* + g)]^2}]\sin^2(w\tau)N^{*2}$$

$$\alpha_2 = -2d_2 \sin(w\tau)N^*$$

$$\alpha_3 = -[d_1 d_2 \cos(w\tau)N^* D^* - (d_1 D^* - q)(d_2 \cos(w\tau)N^* + g)]^2$$

The equation (11) will have positive roots if

$$\alpha_1 = [1 - \frac{[d_1 d_2 D^* - (d_1 D^* - q)d_2]^2}{[-(d_1 D^* - q) + (d_2 \cos(w\tau)N^* + g)]^2}]\sin^2(w\tau)N^{*2} > 0 \quad (12)$$

And

$$\alpha_3 = -[d_1 d_2 \cos(w\tau)N^* D^* - (d_1 D^* - q)(d_2 \cos(w\tau)N^* + g)]^2 < 0$$

We can solve the equations of (9) using the cross-multiplication method to have:

$$[w^2 + (d_1 D^* - q)g][d_1 d_2 D^* - (d_1 D^* - q)d_2]\sin(w\tau)N^* - (g - (d_1 D^* - q)d_2)w\sin(w\tau)N^* =$$

$$w(g - (d_1 D^* - q))(d_1 d_2 D^* - (d_1 D^* - q)d_2)\cos(w\tau)N^* + [w^2 + (d_1 D^* - q)g]w\cos(w\tau)N^*$$

Then, we get

$$\tan(w\tau) = \frac{K_1 + K_2}{K_3 - K_4} \quad (13)$$

Where

$$K_1 = w(g - (d_1 D^* - q))(d_1 d_2 D^* - (d_1 D^* - q)d_2)$$

$$K_2 = [w^2 + (d_1 D^* - q)g]w$$

$$K_3 = [w^2 + (d_1 D^* - q)g][d_1 d_2 D^* - (d_1 D^* - q)d_2]$$

$$K_4 = (g - (d_1 D^* - q)d_2)w$$

Suppose we have a non-negative root w_0 of equation (11) which reflect that equation (9) has an imaginary root in the form $w_0 i$. Then from equation (13) the time τ_k corresponding to w_0 is as follows:

$$\tau_k = \frac{1}{w_0} arctan\left(\frac{K_1^* + K_2^*}{K_3^* - K_4^*}\right) + \frac{2k\pi}{w_0}; \qquad k = 0,1,2,\ldots \quad (14)$$

such that

$$K_1^* = w_0(g - (d_1 D^* - q))(d_1 d_2 D^* - (d_1 D^* - q)d_2)$$

$$K_2^* = [w_0^2 + (d_1 D^* - q)g]w_0$$

$$K_3^* = [w_0^2 + (d_1 D^* - q)g][d_1 d_2 D^* - (d_1 D^* - q)d_2]$$

$$K_4^* = (g - (d_1 D^* - q)d_2)w_0$$

Therefore, the equilibrium points E_1 and E_2 are locally asymptotically stable but the conditions (12) for $\tau_k = 0$ should be satisfied. This shows also the equilibrium points E_1 and E_2 remain stable for $\tau_k < \tau_0$. This suggest that for $\tau_k > \tau_0$ the equilibrium points E_1 and E_2 are unstable means it is impossible to have stability for positive values of τ. This then implies that if the interactions at the time delay crosse their given critical interactions values, the tumor cells can propagate faster and the system may lose its stability at both E_1 and E_2.

From (12) we get $\alpha_3 < 0$ for both positive and negative values of w, however, $\alpha_2 < 0$, and α_1 depends on the term in the bracket which should be positive:

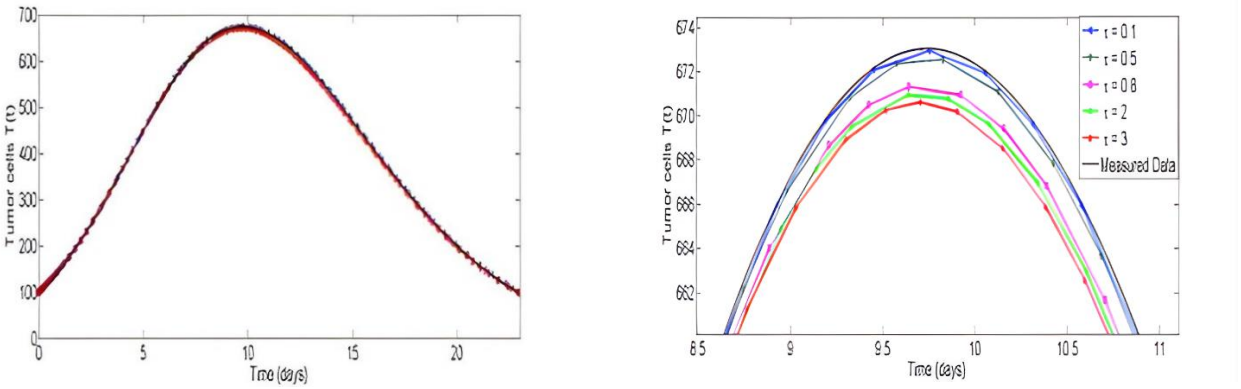
$$\frac{[d_1 d_2 D^* - (d_1 D^* - q)d_2]^2}{[-(d_1 D^* - q) + (d_2 cos(w\tau)N^* + g)]^2} < 1$$

which is not possibly happened in some cases.
Hence, there is no imaginary root $\lambda = wi; w > 0$ in equation (8). This implies that the roots of equation (11) are not crossing the imaginary axis. Thus, all roots of equation (8) have negative parts. Then, the equilibrium points are locally asymptotically stable.

4. NUMERICAL SIMULATION

This section will consider and solve system (1) by the numerical simulations method of Runge-Kutta. Assume that the step size h, such that $t_T - t_0 = h_T$. In the current simulations, we vary the delay τ, and fix the parameters of system (1)[24]:

- $a = 0.431\ day^{-1}$(tumor growth rate),
- $b = 2.17 * 10^{-4}\ cells^{-1}$(tumor growth carrying capacity),
- $c_1 = 3.5 * 10^{-6}\ cells^{-1}$(natural-tumor cells kill rate),
- $c_2 = 1.0 * 10^{-7}\ cells^{-1} day^{-1}$(natural cells inactivation rate by tumor cells),
- $d_1 = 1.0 * 10^{-6} cells^{-1}$(rate of dendritic cell priming NK cells),
- $d_2 = 4.0 * 10^{-6} cells^{-1}$(natural cells dendritic cells kill rate),
- $d_3 = 1.0 * 10^{-4}$(rate of tumor cells priming dendritic cells),
- $q = 4.12 * 10^{-2} day^{-1}$(death rate of natural cells),
- $f_1 = 10^{-8}\ cells^{-1}$(cytotoxic-dendritic cells kill rate),
- $f_2 = 0.01\ cells^{-1}$(cytotoxic-tumor cells kill rate),
- $g = 2.4 * 10^{-2} cells^{-1}$(death rate of dendritic cells),
- $h = 3.42 * 10^{-10}\ cells^{-1} day^{-1}$(cytotoxic inactivation rate by tumor cells),
- $i = 2.0 * 10^{-2} day^{-1}$(death rate of cytotoxic cells) ,
- $j = 1.0 * 10^{-7} cells^{-1}$(dendritic-tumor cells kill rate),
- $k = 1.0 * 10^{-7} cells^{-1}$(cytotoxic-tumor cells kill rate),
- $s_1 = 1.3 * 10^{4} cells^{-1}$(source of natural cells),
- $s_2 = 4.8 * 10^{2} cells^{-1}$(source of dendritic cells).



(i)

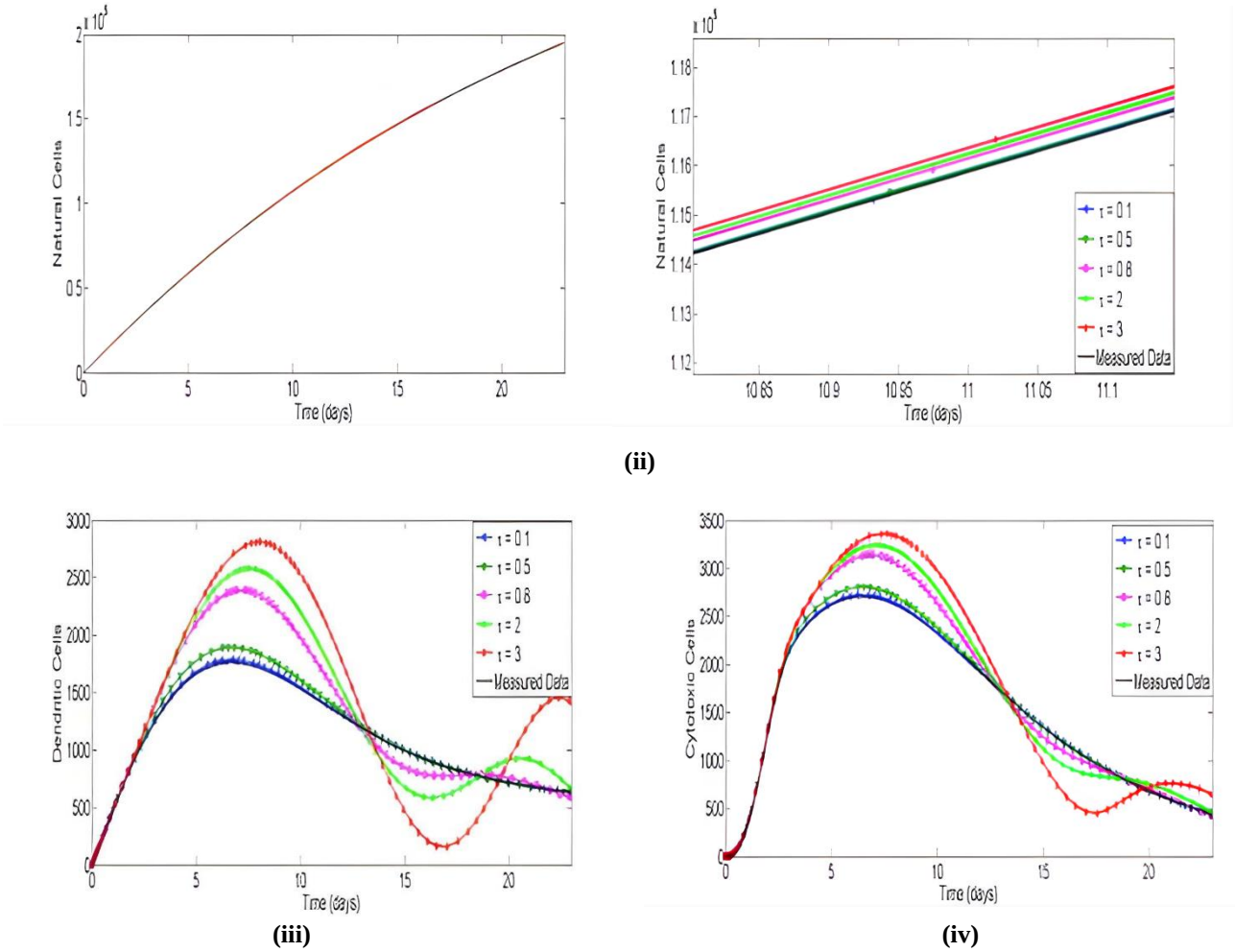


FIGURE 1. Dynamics (i) Tumor Cells, (ii) Natural Cells, (iii) Dendritic Cells and (iv) cytotoxic cells for $\tau = 0.1, 0.5, 0.8, 2, 3$ comparing with their dynamics without delay which is showed in the black curves. Figure (i) shows the periodic solutions of the tumor growth in the period of time [0,22.915]. The oscillation behaviors of the delay tumor growth are clearly decreased with increasing τ as shown in the right panel.

The system is solved to predict the evolution of the tumor cells and the effector (natural killer, dendritic and cytotoxic) cells throughout 22.915 days. Figure 1 shows the numerical simulations of system (1) over time in the absence of chemotherapy and immunotherapy drugs. We note that, the effector cells population grow up significantly with different values of τ, while the tumor cells population decreases and is totally reduced after 10 days, then reached the initial value. The presence of delay helps the immune system to keep the tumor growth under its curve of measured tumor values. In the same time, Figure (1) shows in (i)-(iv) that natural killer cells, dendritic cells and cytotoxic cells are growing faster from the beginning of the time which means the tumor cells faced strong immunity in the body before spreading and then the tumor cells become weak and no way to grow and will stay in low ranges.

Figure 1 shows the impact of time delays when we use the parameter values as listed above and $\tau = 0.1, 0.5, 0.8, 2, 3$. We notice that the effector cells population grows up significantly, while the tumor cells population decreases and is totally eradicated after 20 days and goes to the starting value and satisfying the periodicity. In the meantime, the natural cells population, showed in (ii), becomes higher their measured data (without delay), for all values of τ. Therefore, the evolution of the delay system without immunotherapy and chemotherapy) reflects best results for treatment of tumors, decreasing the curve of infections and the recovery grows faster with high dosage of immunity in past time which can reach the higher results for specific range values for τ in the stability region of the system.

5. PARAMETER ESTIMATION

Selecting appropriate real parameter values is an important issue, especially in biological systems, since, for example, in this study they determine the dynamics of the tumor and the effector cells. Changing values of at least one parameter can show different behaviors for the solutions of the equations. Many studies found appropriate biological parameter values by minimizing an error function of least squares to fit data points. We can make a best guess from appropriate range for the parameters by analyzing the biological meaning of systems' parameters. The description of rates of the tumor growth is defined in terms of many principal parameters as determined in the previous section.
In this section, we assume that some parameters in system (1) are unknown and focus on estimating these parameters based on given experimental data of tumor growth using the parameter estimation methods. In this work, we will study the reliability of the delay tumor model to estimate parameters optimally.

First, the method in [2] is applied to represent the periodic solution of the first equation of system (1) that is a solution of adaptive observer design of the first nonlinear equation as follow:

$$\frac{dT}{dt} = F(y,t)T + \Psi(y,t)\theta + \Phi(y,N,M,H,\vartheta,t) \tag{15}$$

$$y = C^T T(t)$$

Here y is the measured tumor cells, parameters $c_1, q, f_2, g, i, s_1, s_2$ are assumed to be known, other parameters may vary but should start with initial random values and thus are considered unknown, $C = col(1,0,0,\dots,0) \in \mathbb{R}^n$. Given that T(·) is T -periodic. Denoting $\Psi(y,t) = \left(y(t)\,,\ -y^2(t)\right)$, $\Phi(y,N,M,H,\vartheta,t) = (c_1 N - jD + kL)T$ and the vector of combined parameters represented as $\theta = (a\,, ab)$, $\vartheta = (c_1, q, f_2, g, i, s_1, s_2)$, we can rewrite the tumor cell equation of system (1) in the form of equation (15) with:

$$p(t,y(t)) = \begin{pmatrix} F(y,t) & \Psi(y,t) \\ 0 & 0 \end{pmatrix} = \begin{pmatrix} 0 & y(t) & -y^2(t) \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \tag{16}$$

Thus, we have:

$$\dot{\chi} = \begin{pmatrix} \dot{T} \\ \dot{\theta}_1 \\ \dot{\theta}_2 \end{pmatrix} = p(t,y)\chi + \begin{pmatrix} \Phi([y],[N],[M],[H],\vartheta,t \\ 0 \\ 0 \end{pmatrix} \tag{17}$$

and the output is: $y(t) = \tilde{C}^T \chi(t)$

The solution of other equations will be evaluated by using any numerical methods since we have another nonlinear equation which is the fourth equation of system (1).
We define the representation of the periodic solution $\hat{\chi}$ by using the following Auxiliary observer form

$$\dot{\hat{\chi}} = \begin{pmatrix} \dot{T} \\ \dot{\theta}_1 \\ \dot{\theta}_2 \end{pmatrix} = p(t,y)\hat{\chi} + \begin{pmatrix} \Phi([y],[N],[M],[H],\vartheta,t \\ 0 \\ 0 \end{pmatrix} - R^{-1}\tilde{C}\left(\tilde{C}^T\hat{\chi} - y\right) \tag{18}$$

$$\dot{R} = -\alpha R - P(t,y(t))^T R - RP(t,y(t)) + \tilde{C}\tilde{C}^T$$

$$\hat{\chi}(t_0) \in \mathbb{R}^{n+m} \quad , \quad R(t_0) \in \mathbb{R}^{(n+m)\times(n+m)} \quad , \quad \tilde{C} = col(1,0,0,\dots,0) \in \mathbb{R}^{n+m}$$

The integral parametrization of periodic solutions of system (18) is starting by the periodic solution the observer's state $\hat{\chi}$ proved in [2] and is defined for (18) as:

$$\hat{y}(t,\vartheta) = \tilde{C}^T\hat{\chi} = \tilde{C}^T B(t,t_0)\hat{\chi}(t_0) + \int_{t_0}^{t} B(t,\tilde{t})\left(R^{-1}(\tilde{t})\tilde{C}y(t) + \begin{pmatrix} \Phi(y(\tilde{t}),N(\tilde{t}),M(\tilde{t}),H(\tilde{t}),\vartheta,\tilde{t}) \\ 0 \end{pmatrix}\right)d\tilde{t}$$

where

$$\hat{\chi}(t_0) = (I_{n+m} - B(t_0+t_T,t_0))^{-1}\int_{t_0}^{t_0+t_T} B(t_0+t_T,\tilde{t})\left(R^{-1}(\tilde{t})\tilde{C}y(t) + \begin{pmatrix} \Phi(y(\tilde{t}),N(\tilde{t}),M(\tilde{t}),H(\tilde{t}),\vartheta,\tilde{t}) \\ 0 \end{pmatrix}\right)d\tilde{t} \tag{19}$$

Moreover, $R(t)$ is defined for a positive-definite symmetric matrix $R(t_0)$ and a real positive parameter α, given by:

$$R(t) = e^{\alpha(t_0-t)}B_P(t_0,t)^T R(t_0)B_P(t_0,t) + \int_{t_0}^{t} e^{\alpha(\tilde{t}-t)}B_P(\tilde{t},t)^T\tilde{C}\tilde{C}^T R(t_0)B_P(\tilde{t},t)d\tilde{t} \tag{20}$$

where $B(t,t_0)$ and $B_P(t,t_0)$ are fundamental solution (3×3)-matrices computed by the improved Euler method over $t \in [0,22.915]$ starting with the initial rows (1,0,0), (0,1,0) and (0,0,1) for the linear systems $\dot{\hat{\chi}} = \left(P(t,y(t)) -\right.$

$R^{-1}\tilde{C}\tilde{C}^T)\hat{\chi}$, $\dot{R} = -\alpha R - P\big(t, y(t)\big)^T R - R\,P(t, y(t)) + \tilde{C}\tilde{C}^T$,and $\dot{\chi} = \mathrm{P(t,y)}\chi$, respectively. To compute the matrices values of $R(t)$ in (20), we set $\alpha = 2$ and $R(t_0)$ was chosen to be a unique solution of which is called Sylvester equation (see Lemma 3 in [2]).

The algorithm starts by evaluating equations of the delay differential model separately. Solving the second, third and fourth equations of system (1) requires to employ the measured data of tumor growth and use Euler method for numerical simulation. Then, the periodic solutions of dynamics of tumor growth are represented and corresponded in equation (18) with employing the simulated data of the effector cells. Next, we make a guess for values $\hat{\vartheta}$ of the unknown parameters ϑ used as initial values to start the estimation process. Then, we apply an expression that is the sum of the squared errors between the predicted values $T\big(t, \hat{\vartheta}\big)$ and the measured data $T(t, \vartheta)$ as follows:

$$E\,(t\,,\hat{\vartheta}) = \min_{\hat{\lambda}} \sum_{i=1}^{n} \Big(T\,(t\,,\vartheta) - T\,(t\,,\hat{\vartheta})\Big)^2 \tag{21}$$

Here, the period of oscillations is $t_T = 22.915$, and hence the integration interval is chosen as $[t_0, t_0 + t_T] = [0, 22.915]$. Moreover, the numerical evaluation of integrals and solutions of all differential equations is performed with the step size of 0.001.

The parameterized representation in (19) is used in combination with a direct search algorithm called Nelder-Mead [15] which attempts here to find minimum value for least square function and only evaluate the function without needing any derivatives. Nelder-Mead algorithm is an unconstrained nonlinear optimization algorithm working as minimization algorithm searches for the local minimum and then to recover the values of parameters ϑ. If the error $E\big(t, \hat{\vartheta}\big)$ is within a very small tolerance TOL, the algorithm stops and accepts the values of $\hat{\vartheta}$ as optimal values. Otherwise, the last values of parameters are used as new values to start the algorithm's steps and need to solve the system for the updated values of parameters $\hat{\vartheta}$.

The relative error between the numerical evaluation of the representation (19) for the estimated values of parameters and the measured data $y(t)$ (computed by Runge-Kutta with step size 0.001) for the final estimated parameter values is defined as follow

$$E\,(t\,) = \frac{\hat{y}\,(t\,,\hat{\vartheta}) - y\,(t\,,\vartheta)}{\big\|y\,(t\,,\vartheta)\big\|_{\infty,[t_0,t_0+\infty]}} \quad ; \quad \big\|y\,(t\,,\vartheta)\big\|_{\infty} = \max\{y\,(t_i\,,\vartheta)\}_{i=1}^{n}$$

and shown in Figure (5). The values of the parameters ϑ and θ are recovered by using the parameterized representation in combination with the Nelder-Mead algorithm. Results are provided in Table 1 and Table 2 for parameters.

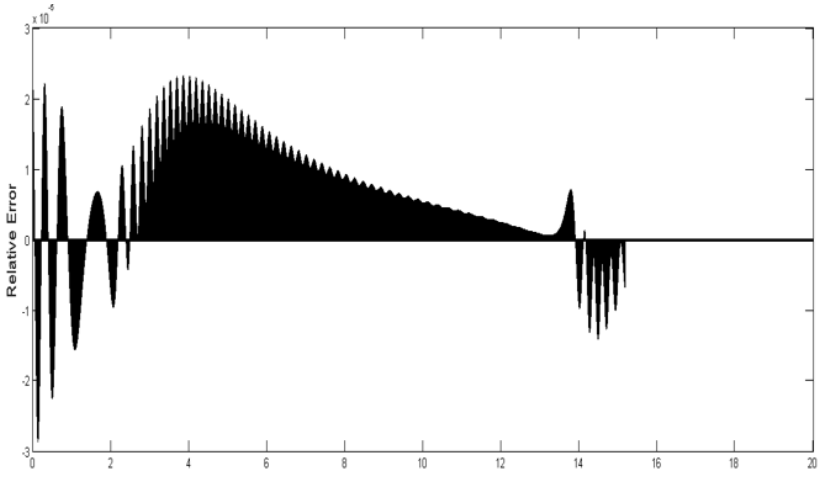


FIGURE 2. Relative error $e(t) = \frac{y(t) - F(t,\hat{\theta})}{\|y\|_{\infty,[t_0,t_0+\infty]}}$ as a function of t.

Table 1. First row and second row show the true and estimated values of ϑ, respectively.
vector $\vartheta = (c_1, e, f_2, g, i, s_1, s_2)$

c_1	q	f_2	g	i	s_1	s_2
$3.50 * 10^{-6}$	$4.12 * 10^{-2}$	0.01	$2.4 * 10^{-2}$	0.0200	$1.3 * 10^{4}$	$4.8 * 10^{2}$
$2.89 * 10^{-5}$	$4.55 * 10^{-2}$	0.0098	$2.56 * 10^{-2}$	0.0234	$1.299 * 10^{4}$	$4.803 * 10^{2}$

Table 2. First row and second row show the true and estimated values of a and b and the initial value T_0, respetively .

vector $\boldsymbol{\theta} = (\boldsymbol{a}, \boldsymbol{ab})$

a	b	T_0
0.43100	$2.17 * 10^{-4}$	1
0.43236	$1.993 * 10^{-4}$	0.99998

It is clear that the estimated values are close enough to the real values of parameters. The computational advantage of the method we used is offering scalability and reduction of dimensionality of the parameterized problem of $n + m$ to $n + m - 2$, where $m = 9$ is the number of unknown parameters $a, b, c_1, q, f_2, g, i, s_1, s_2$, due to incorporating linearly parameterized part of θ_1 and θ_2 of the model in to internal variables of the representations in (18). These internal variable T were uniquely determined with parameters $\vartheta = (c_1, q, f_2, g, i, s_1, s_2)$ that enter the model nonlinearly and become as a part of the representation. Then the values of the representation are computed for the variables T, θ_1 and θ_2, and it is finally employing the solutions for estimating ϑ and T_0. The results of Table 1 and 2 show very accurate estimation for the parameters. Nelder-Mead algorithm was working in 7-dimension with 8 vertices for estimating ϑ which took 1200 iterations and spent approximately 280 minutes.

6. CONCLUSION

In this study, we considered the model for dynamic growth of tumor cells and the behavior of their general interactions with the effector cells. Incorporating the time delay into the system showed more reality for positive and convenient decreasing results of growing the tumor in somewhere in the body and increase the immunity even without considering the treatment in the model. This experiment was computationally studied to show the influence of the dynamics of the cell populations at the real values of parameters with various values of delay τ. This showed that for a period of time we get important results about decreasing the tumor growth. This required first to ensure the stability of the model and we proved that it has a tumor-free steady state in both its equilibrium points. Another part of the study is the application of a parameter estimation algorithm to predict the unknown parameters accurately for a measured set of data of tumor growth. We employed the representation of the periodic solution of the nonlinear equation technique in [2] to, therefore, estimate the unknown parameters of the model. To estimate the parameters, it was required to employ the data of the representation with the measured data to compute the least square error.
This work can be extended to consider the model with incorporating different time delays to study the interactions for different behavior of delays specifically in the immunity. This also could be applied with incorporating the drug terms in the system and using machine learning algorithms to study changing behaviors of the tumor growth which could help to develop the therapy treatment at least.

REFERENCES

[1] A. Matzavinos, M. A. J. Chaplain, and V. A. Kuznetsov, “Mathematical modelling of the spatio-temporal response of cytotoxic T-lymphocytes to a solid tumor,” *Mathematical Medicine and Biology*, vol. 21, no. 1, pp. 1–34, 2004.

[2] Al-Ameri, Jehan MK. *Explicit Representations of Periodic Solutions of Nonlinearly Parameterized Ordinary Differential Equations And Their Applications To Inverse Problems*. Diss. University of Leicester, 2018.

[3] Banerjee, Sandip, and Ram Rup Sarkar. "Delay-induced model for tumor–immune interaction and control of malignant tumor growth." *Biosystems* 91.1 (2008): 268-288.

[4] Bi, P., Xiao, H.: Bifurcations of tumor-immune competition systems with delay.Abstr.Appl.Anal. 2014,723159 (2014).

[5] C. R. Parish, “Cancer immunotherapy: the past, the present and the future,” *Immunology and Cell Biology*, vol.81, no. 2, pp. 106–113, 2003.

[6] Galach, M.: Dynamics of the tumor-immune system competition—the effect of time delay. Int. J. Appl. Math. Comput. Sci. 13, 395–406 (2003).

[7] Ghosh, D., Khajanchi, S., Mangiarotti, S., Denis, F., Dana, S.K., Letellier, C.: How tumor growth can be influenced by delayed interactions between cancer cells and the microenvironment? Biosystems 158, 17–30 (2017).

[8] Hashim, Mohammed S., and Ali A. Yassin. "Feature Selection Using a Hybrid Approach Depends on Filter and Wrapper Methods for Accurate Breast Cancer Diagnosis." *J. Basrah Res.(Sci.)* 49, no. 1 (2023): 45-56.

[9] J. N. Blattman and P. D. Greenberg, "Cancer immunotherapy: a treatment for the masses," *Science*, vol. 305, no.5681, pp. 200–205, 2004.

[10] Khajanchi, S., Perc, M., Ghosh, D.: The influence of time delay in a chaotic cancer model. Chaos, Interdiscip. J.Nonlinear Sci. 28(10), 103101, 2018.

[11] Khajanchi, S.: Chaotic dynamics of a delayed tumor-immune interaction model. Int. J. Biomath. 13(2), 2050009(2020).

[12] L. G. de Pillis and A. Radunskaya, "A mathematical model of immune response to tumor invasion," in *Computational Fluid and Solid Mechanics*, pp. 1661–1668, Elsevier Science, Amsterdam, Netherlands, 2003.

[13] L. G. de Pillis, W. Gu, and A. E. Radunskaya, "Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations," *Journal of 9eoretical Biology*, vol. 238, no. 4, pp. 841–862, 2006.

[14] Li, Y., Li, D.: Long time behavior of a tumor-immune system competition model perturbed by environmental noise. Adv. Differ. Equ. 2017, 58, 2017.

[15] Liu, D., Ruan, S., Zhu, D.: Stable periodic oscillations in a two-stage cancer model of tumor and immune system interactions. Math. Biosci. Eng. 9, 347–368, 2012.

[16] Nelder, J. A. and Mead, R. (1965). A simplex method for function minimization. The computer journal, 7(4):308–313.

[17] P. Veeresha, D. G. Prakasha, and H. M. Baskonus, "New numerical surfaces to the mathematical model of cancer chemotherapy effect in Caputo fractional derivatives," *Chaos: An Interdisciplinary Journal of Nonlinear Science*, vol. 29, no.1, Article ID 013119, 2019.

[18] P. Bonnotte, A. Palladini, F. Pappalardo, and S. Motta, "Predictive models in tumor immunology," *Selected Topicsin Cancer Modeling*, E. Angelis, M. A. J. Chaplain, and N. Bellomo, Eds., Springer Science Business Media, LLC, Berlin, Germany, 2008.

[19] Quinonez, J., Dasu, N., Qureshi, M.: A mathematical investigation on tumor-immune dynamics: the impact of vaccines on the immune response. J. Cancer Sci. Ther. 9(10), 675–682, 2017.

[20] Rihan, F.A., Safan, M., Abdeen, M.A., Rahman, D.A.: Qualitative and computational analysis of a mathematical model for tumor-immune interactions. J. Appl. Math. 2012, 475720, 2012.

[21] S. Wilson and D. Levy, "A mathematical model of the enhancement of tumor vaccine efficacy by immunotherapy," *Bulletin of Mathematical Biology*, vol. 74, no. 7, pp. 1485–1500, 2012.

[22] Shakir, Sahab K., Arwa HM AL-Saeed, and Ali A. Abdulwahid. "Estimation of Some Hematological Parameters, Liver Enzymes and Iron Mineral in Adult of Celiac Disease Patients." *Basrah Journal of Science* 39.3 (2021): 484-495.

[23] T. Trisilowati, S. McCue, and D. Mallet, "Numerical solution of an optimal control model of dendritic cell treatment of a growing tumour," *ANZIAM Journal*, vol. 54, pp. 664 680, 2013.