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ORIGINAL PAPER

A Detailed Study on a Tumor Model with Delayed Growth of Pro-Tumor Macrophages

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Abstract
This paper investigates a tumor-macrophages interaction model with a discrete-time delay in the growth of pro-tumor M2 macrophages. The steady-state analysis of the governing model is performed around the tumor dominant steady-state and the interior steady-state. It is found that the tumor dominant steady-state is locally asymptotically stable under certain conditions, and the stability of the interior steady-state is affected by the discrete-time delay; as a result, the unstable system experiences a Hopf bifurcation and gets stabilized. Furthermore, the transversality conditions for the existence of Hopf bifurcations are derived. Several graphical representations in two and three-dimensional postures are given to examine the validity of the results provided in the current study.

Keywords Tumor-macrophages interaction · Discrete-time delay · Steady-state analysis · Hopf bifurcation · Numerical resolution

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Introduction

Nowadays, mathematical models have been widely used in epidemiology to address the complexity of population dynamics [1, 2], viral-disease dynamics [3–8], and tumor-immune dynamics [9, 10], etc. The mathematical models involved a system of differential equations with ordinary or fractional derivatives and delay differential equations. In this study, a tumor-immune macrophages model has been investigated using discrete-time delay in terms of the growth of pro-tumor macrophages. Tumor cells evolve due to the uncontrolled growth of abnormal cells. During the progression of tumor cells, several immune cells are responsible for their different actions. Over the past few decades, researchers have been approached by mathematical modeling using various models [11–15] to understand tumor-immune dynamics better. Kirschner and Panetta [11] illustrated a mathematical model which describes the dynamics of a growing tumor in the presence of immune effector cells and IL-2. The authors also explored the effects of adoptive cellular immunotherapy on their model. Kolev et al. [12] investigated a model of integro-differential bilinear equations that describes the early-stage competition between single-cell cancer and the immune system. In [13], the authors analyzed a mathematical model of the immune system and abnormal cells, including healthy and unhealthy diet patterns. They observed that the immune system could inhibit and eliminate abnormal cells through three stages: the response stage, the interaction stage, and the recovery stage. The authors of [14] developed a spatio-temporal mathematical model to explain cancer dormancy in a moving boundary problem. A study carried out by Galindo et al. [15] demonstrated the chaotic behavior of a three-dimensional cancer model. Letellier et al. [16] analyzed a tumor growth model based on [17], where the author investigated the chaotic dynamics of the considered model that is relevant to the realistic scenario. Song et al. [18] proposed a mathematical tumor-immune interaction model to explore the action of natural killer cells and CD8+ T cells in tumor suppression.

Recent studies [19, 20] proved that macrophages' role in tumor evolution and progression is crucial. There are two types of macrophages with different tumor responses: M1 macrophages are called anti-tumor macrophages, and M2 macrophages are called pro-tumor macrophages. Several works [21–24] have been relevant to tumor-macrophages interactions. Through a modeling approach, Owen et al. [20] investigated the role of chemotaxis and chemokine production as well as the efficacy of macrophages as vehicles for drug delivery to hypoxic tumor sites. A mathematical model has been proposed in [21] to compare the responses of avascular tumor spheroids to two modes of action: either the macrophages deliver an enzyme that activates an externally applied prodrug (bystander model), or they deliver cytotoxic factors directly (local model). den Breems and Eftimie [22] described interactions between tumor cells, M1 and M2 macrophages, and Th1 and Th2 cells by analyzing a mathematical model and investigating the role of the re-polarization between M1 and M2 macrophages on tumor growth. In [23], the author discussed the activity of tumor-associated macrophages, which can support the development of a potential anti-cancer therapy. Byrne et al. [24] studied tumor-macrophages interactions in vivo and described the role of macrophages in eliminating tumor cells. In 2020, Shu et al. [19] developed a tumor-macrophages interaction model, which suggests that the activation of M1 and M2 macrophages and the transition between M1 and M2 macrophages are responsible for reducing tumor growth.

Many authors have used delay differential models to describe the tumor-immune dynamics. Several research works [25–28] found that time delay plays a crucial role in the tumor growth model. The authors used the time delay term in growing and stimulating cells, cellular

interactions, cell progression, differentiation of cell populations, and activation of cell populations. Dong et al. [25] discussed a time-delayed tumor-immune model with two discrete-time delays: the immune activation delay for effector cells and the activation delay for helper T cells (HTCs). Their study revealed that the immune activation delay for HTCs can induce heteroclinic cycles to connect the tumor-free and immune-control equilibriums. In [26], the authors investigated a delayed mathematical tumor model and showed that the model exhibits periodic oscillations and chaotic behavior, which indicate long-term tumor relapse. Dehingia et al. [27] analyzed a time-delayed mathematical cancer model, showing the system undergoes different states: stable state, Hopf bifurcations, periodic oscillations, and unstable states concerning the system's parameters. In [28], the authors investigated the chaotic behavior of a discrete-time delay cancer model and described the system's stability. Following the above studies, a time-delayed tumor-macrophage interaction model, based on Shu et al. [19], is investigated in the present study.

The rest of the paper is assembled as follows: In Sect. 2, the considered model is formulated. The steady-state analysis and the analysis of Hopf bifurcation of the considered model are investigated in Sect. 3 and Sect. 4, respectively. The analytical findings of the study have been verified numerically in Sect. 5. Finally, a concluding remark has been made in Sect. 6.

The model

Shu et al. [19] already discussed the model formulation and the model's behavior without time delay. We introduce the discrete-time delay in activating pro-tumor M2 macrophages as the time required to develop molecules in the M2 macrophages. Hence, our considered model takes the form

$$\begin{aligned}
\frac{dT}{dt} &= aT(1-bT) - fTM_1 + gTM_2,\\
\frac{dM_1}{dt} &= e_1TM_1 - d_1M_1 - r_1M_1 + r_2M_2,\\
\frac{dM_2}{dt} &= e_2T(t-\theta)M_2(t-\theta) - d_2M_2 + r_1M_1 - r_2M_2,
\end{aligned} \tag{1}$$

where T, M_1, and M_2 are the population of tumor cells, anti-tumor M1 macrophages, and pro-tumor M2 macrophages at any time $t > 0$, respectively. Here, θ is the discrete-time delay factor added due to the growth delay of pro-tumor macrophages M2. The initial conditions are $T(0) = M_1(0) = M_2(0) = 10^6$ cells.

By considering $(x, y, z) = \left[\frac{T}{T(0)}, \frac{M_1}{M_1(0)}, \frac{M_2}{M_2(0)}\right]$, $\tau = e_1T(0)t$, and new dimensionless parameter set as

$$\begin{aligned}
\alpha = \frac{a}{e_1T(0)}, \beta = bT(0), \delta = \frac{f}{e_1}, \eta = \frac{g}{e_1}, \mu_1 = \frac{d_1}{e_1T(0)}, \mu_2\\
= \frac{d_2}{e_1T(0)}, \gamma_1 = \frac{r_1}{e_1T(0)}, \gamma_2 = \frac{r_2}{e_1T(0)}, \xi = \frac{e_2}{e_1},
\end{aligned}$$

we get the following non-dimensional form of the model (1) after replacing τ by t,

$$\begin{aligned}
\frac{dx}{dt} &= \alpha x(1-\beta x) - \delta xy + \eta xz,\\
\frac{dy}{dt} &= xy - \mu_1 y - \gamma_1 y + \gamma_2 z,
\end{aligned} \tag{2}$$

$$\frac{dz}{dt} = \xi x(t-\theta)z(t-\theta) - \mu_2 z + \gamma_1 y - \gamma_2 z,$$

where x, y, and z are the population of tumor cells, anti-tumor M1 macrophages, and pro-tumor M2 macrophages at any time $t > 0$, respectively. The corresponding initial conditions are $x(\omega) = \psi_1(\omega)$, $y(\omega) = \psi_2(\omega)$, and $z(\omega) = \psi_3(\omega)$ such that $\omega \in [-\theta, 0]$ and $\psi = (\psi_1(\omega), \psi_2(\omega), \psi_3(\omega)) \in C_+$ where C is the Banach space of continuous functions $\psi : [-\theta, 0] \to R^3$ and $C_+ = \{\psi = (\psi_1, \psi_2, \psi_3) \in C : \psi_j(\omega) \geq 0 \text{ for all } \omega \in [-\theta, 0] \text{ and } j = 1, 2, 3\}$.

Steady-State Analysis

The steady-states of the system (2) with delay $\theta \neq 0$ are the same as the steady-states of the system (2) without delay $\theta = 0$. Steady-states of the system (2) have been reported in [19] as

i. Trivial steady-state: $E_0(0, 0, 0)$,
ii. Tumor dominant steady-state: $E_1\left(\frac{1}{\beta}, 0, 0\right)$, and
iii. Interior or co-axial steady-state: $E^*(x^*, y^*, z^*)$,

where

$$y^* = \frac{\alpha(1-\beta x^*)\gamma_2}{\delta\gamma_2 + \eta(x^* - \mu_1 - \gamma_1)},$$
$$z^* = \frac{\alpha(1-\beta x^*)(\mu_1 + \gamma_1 - x^*)}{\delta\gamma_2 + \eta(x^* - \mu_1 - \gamma_1)},$$

and x^* will be the positive root of the following quadratic equation

$$\xi x^2 - (\xi\mu_1 + \xi\gamma_1 + \mu_2 + \gamma_2)x + (\mu_1\mu_2 + \mu_1\gamma_2 + \mu_2\gamma_1) = 0. \tag{3}$$

Clearly, E^* exists only if $y^* > 0$, $z^* > 0$, and $\mu_1 + \gamma_1 - \frac{\delta\gamma_2}{\eta} < x^* < \mu_1 + \gamma_1 < \frac{1}{\beta}$.

The local stability analysis around the steady-states of the system (2) without delay ($\theta = 0$) has been reported in Shu et al. [19] as shown in Table 1.

Table 1 The steady-states of the system and conditions for their stability

Steady-state	Nature of the stability	Stability conditions
E_0	always unstable	
E_1	locally asymptotically stable	$\xi < \left(\frac{\gamma_1\gamma_2\beta}{1-(\mu_1+\gamma_1)\beta} + \mu_2 + \gamma_2\right)\beta$ and $\frac{1}{\beta} - \mu_1 - \gamma_1 < 0$
E^*	locally asymptotically stable	$x^* < \frac{1}{\beta}$ and $\left(\alpha\beta x^* + \frac{\gamma_2 z^*}{y^*} + \frac{\gamma_1 y^*}{z^*}\right)\left[\alpha\beta x^*\left(\frac{\gamma_2 z^*}{y^*} + \frac{\gamma_1 y^*}{z^*}\right) + x^*\left(\delta y^* - \xi\eta z^*\right)\right] - \alpha x^*(1-\beta x^*)\left(\xi\frac{\gamma_2 z^*}{y^*} + \frac{\gamma_1 y^*}{z^*}\right) > 0$

Now, we will discuss the effect of delay on the stability of the system (2). It is evident that if E^* exists, then E_1 is unstable. So, we will investigate the stability of only the interior steady-state E^* in the presence of the time delay factor. Accordingly, we compute the characteristic equation corresponding to the steady-state E^* as follows

$$\det\left(\lambda I - P - Qe^{-\lambda\theta}\right) = 0, \tag{4}$$

where I is the identity matrix of order 3 and

$$P = \begin{bmatrix} \alpha - 2\alpha\beta x^* - \delta y^* + \eta z^* & -\delta x^* & \eta x^* \\ y^* & x^* - \mu_1 - \gamma_1 & \gamma_2 \\ 0 & \gamma_1 & -\mu_2 - \gamma_2 \end{bmatrix},$$

$$Q = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ \xi z^* & 0 & \xi x^* \end{bmatrix}.$$

Since (x^*, y^*, z^*) satisfy the system (2), hence we get the relation $\alpha\beta x^* + \delta y^* = \alpha + \eta z^*$ and $x^* - \mu_1 - \gamma_1 = -\frac{\gamma_2 z^*}{y^*}$. Hence, the corresponding characteristic Eq. (4) becomes

$$\lambda^3 + p_1\lambda^2 + p_2\lambda + p_3 + e^{-\lambda\theta}\{\lambda^2 q_1 + q_2\lambda + q_3\} = 0, \tag{5}$$

where

$$\begin{aligned}
p_1 &= \alpha\beta x^* + \mu_2 + \gamma_2 + \frac{\gamma_2 z^*}{y^*}, \\
p_2 &= \alpha\beta x^*\left(\mu_2 + \gamma_2 + \frac{\gamma_2 z^*}{y^*}\right) + (\mu_2 + \gamma_2)\frac{\gamma_2 z^*}{y^*} + \delta y^* x^* - \gamma_1\gamma_2, \\
p_3 &= (\mu_2 + \gamma_2)\left(\frac{\gamma_2 z^*}{y^*}\alpha\beta x^* + \delta x^* y^*\right) - \alpha\beta\gamma_1\gamma_2 x^* - \gamma_1\eta x^* y^*, \\
q_1 &= -\xi x^*, \\
q_2 &= -\xi x^*\left(\frac{\gamma_2 z^*}{y^*} + \alpha\beta x^* + \eta z^*\right), \\
q_3 &= -\xi x^*\left(\tfrac{\gamma_2 z^*}{y^*}\alpha\beta x^* + \delta x^* y^* + z^*\left(\tfrac{\gamma_2 z^*}{y^*}\eta - \delta\gamma_2\right)\right).
\end{aligned}$$

Now, setting $\lambda = i\phi$ in (5) (where ϕ is positive) and separating real and imaginary parts results in

$$\phi^3 - p_2\phi = q_2\phi\cos(\phi\theta) - \left(q_3 - q_1\phi^2\right)\sin(\phi\theta), \tag{6}$$

$$p_1\phi^2 - p_3 = \left(q_3 - q_1\phi^2\right)\cos(\phi\theta) + q_2\phi\sin(\phi\theta). \tag{7}$$

By squaring and adding both sides of the above Eqs. (6) and (7), we get

$$\left(\phi^3 - p_2\phi\right)^2 + \left(p_1\phi^2 - p_3\right)^2 = \left(q_3 - q_1\phi^2\right)^2 + q_2^2\phi^2. \tag{8}$$

Equation (8) can be re-written as

$$\phi^6 + \Pi_1\phi^4 + \Pi_2\phi^2 + \Pi_3 = 0, \tag{9}$$

where

$$\Pi_1 = p_1^2 - 2p_2 - q_1^2,$$
$$\Pi_2 = p_2^2 - q_2^2 - 2p_1p_3 + 2q_1q_3,$$
$$\Pi_3 = p_3^2 - q_3^2 = (p_3 + q_3)(p_3 - q_3).$$

It is easy to observe that Eq. (9) has a unique positive root (say ϕ_0) if $\Pi_3 = p_3^2 - q_3^2 = (p_3 + q_3)(p_3 - q_3) < 0$. Hence, the characteristic Eq. (5) has a pair of purely imaginary roots of the form $\pm i\phi_0$.

Eliminating $\cos(\phi\theta)$ from Eqs. (6) and (7), we get

$$\sin(\phi\theta) = \frac{(q_1\phi^2 - q_3)(\phi^3 - p_2\phi) + q_2\phi(p_1\phi^2 - p_3)}{(q_3 - q_1\phi^2)^2 + q_2^2\phi^2}.$$

Then, θ_c is given by $\theta_c = \frac{1}{\phi_0}\arcsin\left[\frac{(q_1{\phi_0}^2 - q_3)({\phi_0}^3 - p_2\phi_0) + (q_2\phi_0)(p_1{\phi_0}^2 - p_3)}{(q_3 - q_1{\phi_0}^2)^2 + q_2^2{\phi_0}^2}\right] + \frac{2c\pi}{\phi_0}$, $c = 0, 1, \ldots$

Analysis of Hopf Bifurcation

To establish the condition of Hopf bifurcation of the system (2), we must prove the transversality condition

$$\frac{d(\mathrm{Re}\lambda)}{d\theta}|_{\theta=\theta_c} > 0,$$

which indicates that there exists at least one eigenvalue with a positive real part for $\theta > \theta_c$. Basically, we are interested in purely complex roots $\lambda = i\phi_0$ of Eq. (5) as it implies $|P(i\phi_0)| = |Q(i\phi_0)|$ and this defines the possible values of ϕ_0. Also, we aim to observe the direction of motion of λ when θ_c is varied. For this purpose, we need to find

$$\Omega = \mathrm{sign}\left[\frac{d(\mathrm{Re}\lambda)}{d\theta_c}\right]_{\lambda=i\phi_0} = \mathrm{sign}\left[\mathrm{Re}\left(\frac{d\lambda}{d\theta_c}\right)^{-1}\right]_{\lambda=i\phi_0}. \tag{10}$$

On differentiating (5) with respect to θ, we find

$$\left[\left(3\lambda^2 + 2p_1\lambda + p_2\right) + e^{-\lambda\theta_c}\left(2q_1\lambda + q_2\right) - \theta e^{-\lambda\theta_c}\left(q_1\lambda^2 + q_2\lambda + q_3\right)\right]\frac{d\lambda}{d\theta_c}$$
$$= \lambda e^{-\lambda\theta_c}\left(q_1\lambda^2 + q_2\lambda + q_3\right),$$

which leads to $\Omega = \mathrm{sign}\left[\mathrm{Re}\left(\frac{2\lambda^3 + p_1\lambda^2 - p_3}{-\lambda^2(\lambda^3 + p_1\lambda^2 + p_2\lambda + p_3)} + \frac{q_1\lambda^2 - q_3}{\lambda^2(q_1\lambda^2 + q_2\lambda + q_3)} - \frac{\theta_c}{\lambda}\right)\right]_{\lambda=i\phi_0}$.

By inserting $\lambda = i\phi_0$ into the above expressions, we get $\Omega = \frac{1}{\phi_0^2}\mathrm{sign}\left[\frac{2\phi_0^6 + \phi_0^4(p_1^2 - 2p_2 - q_1^2) + (q_3^2 - p_3^2)}{q_2^2\phi_0^2 + (q_3 - q_1\phi_0^2)^2}\right]$.

This, if $p_1^2 - 2p_2 - q_1^2 > 0$ and $q_3^2 - p_3^2 > 0$, then the transversality conditions

$$\frac{d(\mathrm{Re}\lambda)}{d\theta}|_{\theta=\theta_c} > 0,$$

holds. Hence, the system undergoes a Hopf bifurcation at time delay $\theta = \theta_c$. Moreover, the stability of the system may change from unstable to stable or stable to unstable via a Hopf bifurcation.

Numerical Resolution

In this section, we will present some numerical simulations of the system (2), which will help to understand the analytical results in a better way. The MATLAB solver DDE-23 is formally used for numerical simulations of the model. We choose a parameter set as $\alpha = 0.565$, $\beta = 0.002$, $\delta = 2$, $\eta = 0.1$, $\mu_1 = 0.2$, $\mu_2 = 0.2$, $\xi = 1.05$, $\gamma_1 = 0.05$, and $\gamma_2 = 0.04$ that have been taken from [19]. We will vary the time delay ($\theta \neq 0$) to observe its effect on the system (2). For the above parameter set, there exist three biologically feasible steady-states $E_0 = (0, 0, 0)$, $E_1 = (500, 0, 0)$, and $E^* = (0.194, 0.304, 0.422)$. It is found that the steady-states E_0 and E_1 are unstable. To investigate the effects of time delay on the system, we vary the value of θ. The stability of the system around E^* for different values of discrete-time delay θ is shown below.

Figure 1 indicates that for time delay, $\theta = 0.0325$; all the three cells co-exist. As there is a small-time lag in the growth process of pro-tumor M2 macrophages, which indicates that the fast proliferation of tumor cells and hence the anti-tumor M1 macrophages cannot stabilize the tumor cells' growth. It suggests that the system is not stable around the interior steady-state E^*.

Figure 2 shows that for time delay, $\theta = 0.1$; all the three cells co-exist and due to the increase of time delay in the growth process of pro-tumor M2 macrophages, the proliferation of tumor cells is also negatively affected. Hence, the anti-tumor M1 macrophages can compete with tumor cells, and the system shows periodic oscillations, which indicates that the system has limit cycle solutions around the interior steady-state E^*.

Figure 3 demonstrates that for time delay, $\theta = 0.205$; all the three cells co-exist and compete. At this value of time delay, the system undergoes a Hopf bifurcation, and the system switches its stability from unstable to stable position around the interior steady state E^*.

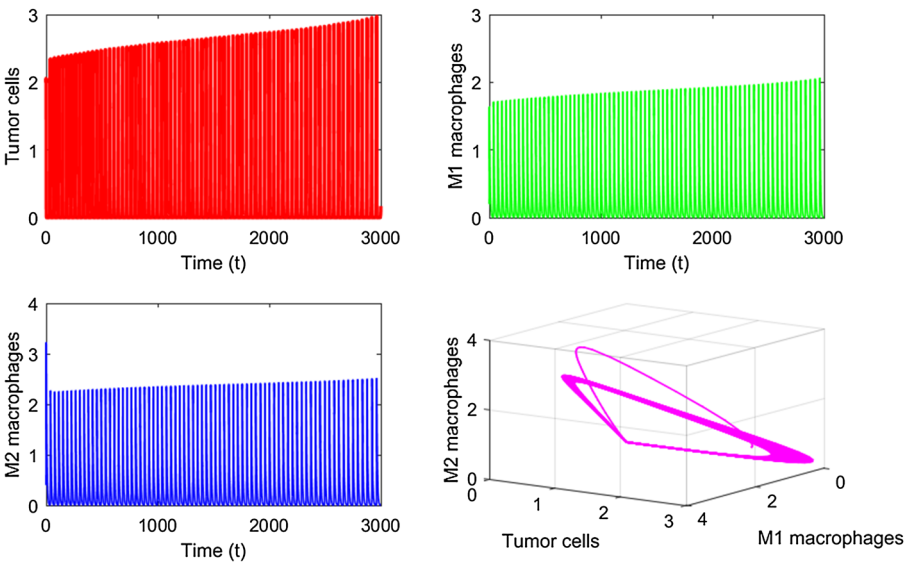

Fig. 1 Time series evolution curve and 3D plot of the system for the initial values (2, 0.2, 0.4) with time delay $\theta = 0.0325$

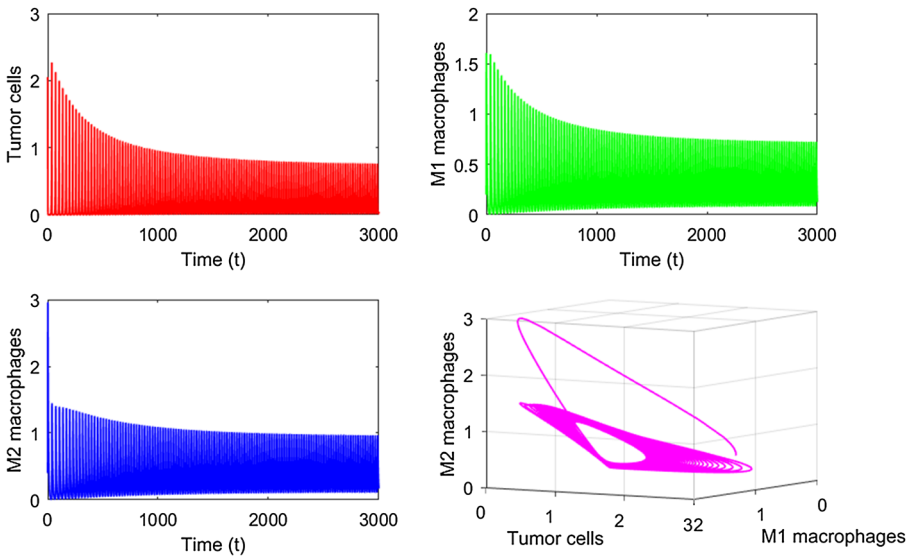

Fig. 2 Time series evolution curve and 3D plot of the system for the initial values (2, 0.2, 0.4) with time delay $\theta = 0.1$

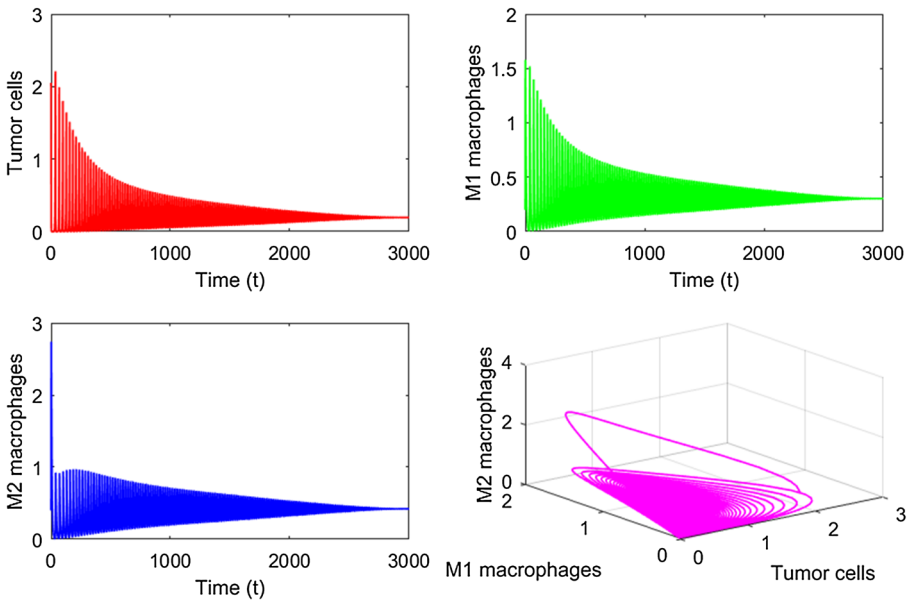

Fig. 3 Time series evolution curve and 3D plot of the system for the initial values (2, 0.2, 0.4) with time delay $\theta = 0.205$

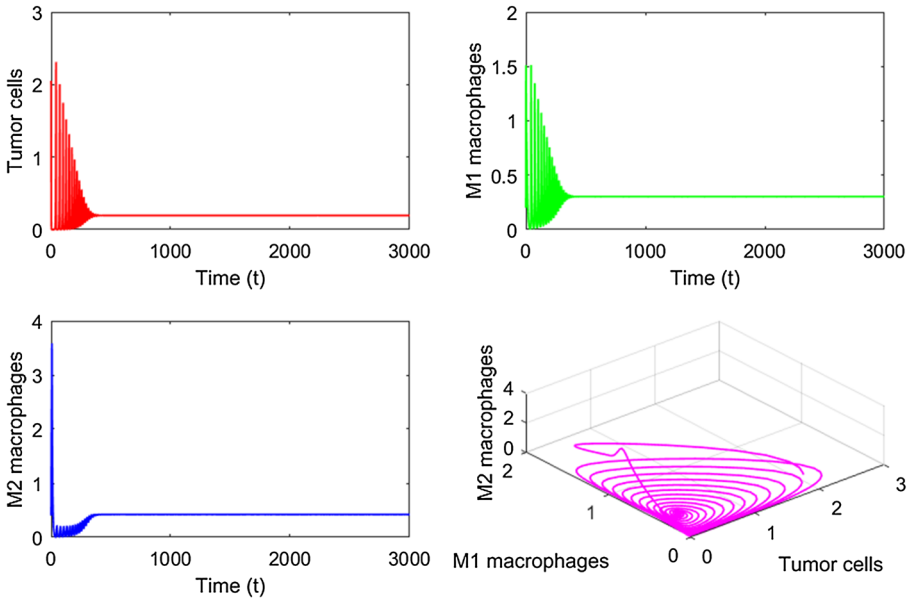

Fig. 4 Time series evolution curve and 3D plot of the system for the initial values (2, 0.2, 0.4) with time delay $\theta = 5$

Figure 4 indicates that for time delay $\theta = 5$, all the three cells co-exist, and due to significant delay in the growth of pro-tumor M2 macrophages, anti-tumor M2 macrophages can suppress the tumor growth, and the system gets stabilized around E^*.

Conclusion

This study presented a modified delay differential model that describes the tumor-macrophages interaction. The steady-state analysis demonstrated that the time delay in the growth of M2 macrophages, which is a pro-tumor stage, changes the system's stability around the interior steady-state. Because of the slight delay in developing pro-tumor M2 macrophages, the anti-tumor M1 macrophages cannot control the growth of fast proliferating tumor cells; as a result, the system undergoes an unstable state. This suggest that the pro-tumor macrophages help in proliferation of tumor cells. However, by increasing the value of time delay in the growth of pro-tumor M2 macrophages, the system changes its stability from limit cycle solutions to stable nature via a Hopf bifurcation, which suggests that an increase in the time delay in the growth of pro-tumor M2 macrophages also negatively affects the growth of tumor cells and the anti-tumor M1 macrophages able to suppress tumor growth. In this paper, we have found a new result: the considered delay factor in the growth of pro-tumor macrophages changes the systems' stability from unstable to stable via a Hopf bifurcation. Therefore, this new finding suggests that using the specified drugs such that the growth of pro-tumor M2 macrophages is slowed down can be a successful treatment for cancer management, which can be studied in the future. However, a clinical investigation is also needed to claim this new finding. Furthermore, in this study, we have not discussed the length of

discrete-time delay and direction and stability of Hopf bifurcation; this will be carried out in our future research.

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Data Availability Enquiries about data availability should be directed to the authors.

Declarations

Conflict of interest The authors declare no conflict of interest.

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