A mathematical approach with delay kernel for the role of the immune response time delay in periodic therapy of the tumors

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Abstract

We consider the model of interaction between the immune system and tumor cells including a memory function that reflect the influence of the past states, to simulate the time needed by the latter to develop a chemical and cell mediated response to the presence of the tumor. The memory function is called delay kernel. The results are compared with those from other papers, concluding that the memory function introduces new instabilities in the system leading to an uncontrollable growth of the tumor. If the coefficient of the memory function is used as a bifurcation parameter, it is found that Hopf bifurcation occurs for kernel. The direction and stability of the bifurcating periodic solutions are determined. Some numerical simulations for justifying the theoretical analysis are also given.

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1 Introduction

As everyone knows, cancer is one of the most fearsome illness. It was declared the disease of 20th century. Many efforts were made to cure it, but to do this, first of all it is needed to understand its physiopathological mechanisms. It was discovered that the human body is not completely helpless against this disease and it fights against cancer using its best and powerful weapon, namely immune system.

In what follows, we will not make a general overview of the immune system, but we will mention briefly some of its components and aspects of the dynamics which appear in our model. The cell who performs directly the tumor elimination is T-lymphocyte, which is activated by b-lymphocytes through the cytokines \[3,11\]. It is not of less importance to mention the immunodepression, a phenomenon that appears in the tumor region, when the tumor increases its size, and leads to the deactivation of the lymphocytes.

In the effort of modeling this process an important role plays the time delay. It is obvious for everyone that the biological process do not take place instantaneously and an amount of time is needed for, in our case, the interaction between immune system and the tumor \[2,4\]. During the years, some models, concerning tumor dynamics have been develop \[6,7,12\] and some of them includes time delay \[1,10,13\].

In what follows we propose a model of the interaction tumor-immune system using delay kernel.

Let \(x(t)\) and \(y(t)\) denote respectively the number of malignant and lymphocyte cells, for \(t \in \mathbb{R}\). The rate of malignant cells \((\dot{x}(t))\) is given by \[12\]:

\[
\dot{x}(t) = a_1 x(t) - a_2 x(t)y(t).
\] (1)

We assume that the growth rate is proportional to \(x(t)\) and the decrease rate is proportional to the frequency of interaction with lymphocytes. The coefficients are \(a_1\) and \(a_2\), respectively, where \(a_1\) is tissue dependent.

On the other hand, the growth rate of lymphocytes \((\dot{y}(t))\) is described by \[12\]:

\[
\dot{y}(t) = b_1 x(t)y(t) - b_2 x(t) - b_3 y(t) + b_4.
\] (2)

It is proportional to the interaction with malignant cells and also to the flux per unit time of lymphocytes to the place of interaction. These effects are represented by the first and fourth terms in the right-hand side of equation (2). The mortality of the lymphocytes is proportional with \(y(t)\) (natural
death) and also \(x(t)\), which express the immunodepression phenomenon. The term \(b_1x(t)y(t)\) is important for this study. It means the interaction between the two populations, \(x(t)\) and \(y(t)\) with a frequency \(b_1\) of recognition of malignant cells by the immune system. We consider the effect of influence of the past for this chemical signal mediated interaction which introduces the memory functions \(\rho_1\) and \(\rho_2\), which are nonnegative bounded functions defined on \([0, \infty)\) and

\[
\int_0^\infty k_i(s)ds = 1, \quad \int_0^\infty sk_i(s)ds < \infty, \ i = 1, 2.
\]

The evolution equations (1), (2) become now

\[
\dot{x}(t) = a_1x(t) - a_2x(t)y(t)
\]

\[
\dot{y}(t) = b_1(\int_0^\infty k_1(s)x(t-s)ds)(\int_0^\infty k_2(s)y(t-s)ds) - b_2x(t) - b_3y(t) + b_4. \tag{3}
\]

The memory functions are called delay kernels. The delay becomes a discrete one when the delay kernel is a delta function at a certain time. Usually, we employ the following form

\[
k_i(s) = \frac{1}{p!}q_i^{p+1}s^pe^{-qs}, \quad i = 1, 2,
\]

for the memory function. When \(p = 0\) and \(p = 1\), the memory functions are called "weak" and "strong" kernel, respectively.

For \(k_i(s) = \delta(s - \tau_i), i = 1, 2, \tau_1 \geq 0, \tau_2 \geq 0\) equation (4) is given by

\[
\dot{x}(t) = a_1x(t) - a_2x(t)y(t)
\]

\[
\dot{y}(t) = b_1x(t-\tau_1)y(t-\tau_2) - b_2x(t) - b_3y(t) + b_4. \tag{4}
\]

The model (4) with \(\tau_1 = \tau_2 = \tau\), is the model from [4] which has been studied using only numerical simulations.

In this paper, we analyze the model (4) with the following initial values

\[
x_1(\theta) = \varphi_1(\theta), \quad x_2(\theta) = \varphi_2(\theta), \quad \theta \in (-\infty, 0]
\]
and \( \varphi_1, \varphi_1 \) as differentiable functions.

The paper is organized as follows. In section 2, we discuss the local stability for the equilibrium states of system (4), for different forms of the delay kernels. We investigate the existence of the Hopf bifurcation with respect of the parameters of the delay kernels. In section 3, the direction of the Hopf bifurcation is analyzed by normal form theory and the center manifold theorem. Numerical simulations in order to justify the theoretical results are illustrated in section 4. Finally, some conclusions are made.

2 Local stability and existence of the Hopf bifurcation

We consider model (4) with parameters \( a_1, a_2, b_1, b_2, b_3, b_4 \) assumed positives numbers and \( \frac{b_2}{b_1} < \frac{b_3}{b_2} < \frac{a_1}{a_2} \). The equilibrium states of system (4) are the points \( L_0 = (x_0, y_0) \) and \( L_1 = (0, \frac{b_4}{b_3}) \), where

\[
x_0 = \frac{b_3 a_1 - b_4 a_2}{a_1 b_1 - a_2 b_2}, \quad y_0 = \frac{a_1}{a_2}.
\]

We analyzed the local stability in the equilibrium state \( L_0 \). We consider the following translation

\[
x_1(t) = x(t) - x_0, \quad x_2(t) = y(t) - y_0.
\]

With respect to (5), the system (4) can be expressed as

\[
\begin{align*}
\dot{x}_1(t) &= -a_2 x_0 x_2(t) - a_2 x_1(t) x_2(t) \\
\dot{x}_2(t) &= -b_2 x_1(t) - b_3 x_2(t) + b_1 x_0 \int_0^\infty k_2(s)x_2(t-s)ds + b_1 y_0 \int_0^\infty k_1(s)x_1(t-s)ds \\
&\quad + b_1 \left( \int_0^\infty k_1(s)x_1(t-s)ds \right) \left( \int_0^\infty k_2(s)x_2(t-s)ds \right).
\end{align*}
\]

The system (6) has 0=(0,0) as equilibrium state.

To investigate the local stability of equilibrium state of the system (8), we linearize system (6). The linearized system of (6) is

\[
\dot{U}(t) = AU(t) + B_1 U_1(t) + B_2 U_2(t),
\]
where
\[ A = \begin{pmatrix} 0 & -a_2x_0 \\ -b_2 & -b_3 \end{pmatrix}, \quad B_1 = \begin{pmatrix} 0 & 0 \\ b_1y_0 & 0 \end{pmatrix}, \quad B_2 = \begin{pmatrix} 0 & 0 \\ 0 & b_1x_0 \end{pmatrix} \] (8)

with
\[ U(t) = (u_1(t), u_2(t))^T, \quad U_i(t) = \left( \int_0^\infty k_i(s)u_1(t-s)ds, \int_0^\infty k_i(s)u_2(t-s)ds \right)^T, \quad i = 1, 2. \]

The characteristic equation corresponding to system (7) is \( \Delta(\lambda)=0 \), where
\[ \Delta(\lambda) = \text{det}(\lambda I - A - \left( \int_0^\infty k_1(s)e^{-\lambda s}ds \right)B_1 - \left( \int_0^\infty k_2(s)e^{-\lambda s}ds \right)B_2). \] (9)

From (8) and (9), we have:
\[ \Delta(\lambda) = \lambda^2 + b_3\lambda - a_2b_2x_0 + a_1b_1x_0 \int_0^\infty k_1(s)e^{-\lambda s}ds - \lambda b_1x_0 \int_0^\infty k_2(s)e^{-\lambda s}ds. \] (10)

The equilibrium state \( L_0 \) is locally asymptotically stable if and only if the eigenvalues of \( \Delta(\lambda) = 0 \) have negative real parts.

Because of the presence of two delay kernels \( k_1 \) and \( k_2 \) in the equation \( \Delta(\lambda) = 0 \), the analysis of the sign of real parts of eigenvalues is complicated and a direct approach cannot be considered.

We analyze the eigenvalues for the equation \( \Delta(\lambda) = 0 \) if the delay kernels \( k_1 \) and \( k_2 \) are delta functions or \( k_1 \) is delta function and \( k_2 \) is weak function.

Using results from [3], we obtain:

**Proposition 2.1.** If
\[ k_1(s) = \delta(s - \tau_1), \quad k_2(s) = \delta(s - \tau_2), \quad \tau_1 \geq 0, \tau_2 \geq 0 \] (11)

then

(i) function (10) is given by
\[ \Delta(\lambda, \tau_1, \tau_2) = \lambda^2 + b_3\lambda - a_2b_2x_0 + a_1b_1x_0e^{-\lambda \tau_1} - \lambda b_1x_0e^{-\lambda \tau_2}; \] (12)
(ii) if \( \tau_1 = 0, \tau_2 = 0 \) then the equilibrium state \( L_0 \) of system (4) is locally asymptotically stable;

(iii) if

\[
0 \leq \tau_1 + \tau_2 < \frac{b_3 + b_1 x_0}{a_1 b_1 x_0},
\]

then the equilibrium state \( L_0 \) of the system (4) is asymptotically stable.

Next, we study the existence of Hopf bifurcation of system (4) with \( k_1 \) and \( k_2 \) given by (11), by choosing one of the delays as a bifurcation parameter, e.g. take \( \tau_1 \) as the bifurcation parameter. First, we would like to know when \( \Delta(\lambda, \tau_1, \tau_2) = 0 \), where \( \Delta(\lambda, \tau_1, \tau_2) \) given by (12) has purely imaginary roots \( \lambda = \pm i \omega_0 (\omega_0 > 0) \) at \( \tau_1 = \tau_{10} \). Note that

\[
\begin{align*}
\omega_0^2 + a_2 b_2 x_0 - a_1 b_1 x_0 \cos(\tau_{10} \omega_0) + b_1 x_0 \omega_0 \sin(\tau_{2} \omega_0) &= 0, \\
b_3 \omega_0 - a_1 b_1 x_0 \sin(\tau_{10} \omega_0) - b_1 x_0 \omega_0 \cos(\tau_{2} \omega_0) &= 0,
\end{align*}
\]

which implies that

\[
\sin((\tau_{10} - \tau_{2}) \omega_0) = g(\omega_0),
\]

where

\[
g(\omega) = \frac{\omega^4 - (b_1^2 x_0^2 - b_3^2 - 2a_2 b_2 x_0) \omega^2 + (a_2^2 b_2^2 - a_1^2 b_1^2) x_0^2}{2 a_1 b_1^2 x_0^2 \omega^2}.
\]

From (14), \( g'(\omega) > 0 \). So \( g(\omega) \) is strictly monotonically increasing on \([0, \infty)\), with \( \lim_{\omega \to 0} g(\omega) = -\infty \) and \( \lim_{\omega \to \infty} g(\omega) = \infty \). Clearly, if \( \tau_{10} > \tau_2 \) then \( g(\omega) \) intersects \( \sin((\tau_{10} - \tau_{2}) \omega) \) only in a point. Hence \( \lambda = i \omega_0 \) is a simple root of equation \( \Delta(\lambda, \tau_1, \tau_2) = 0 \). Differentiating \( \Delta(\lambda, \tau_1, \tau_2) \) implicitly with respect to \( \tau_1 \), we obtain

\[
Re\left[ \frac{d\lambda}{d\tau_1} \right]_{\lambda = i \omega_0, \tau_1 = \tau_{10}} = -\frac{a_1^2 b_1^2 x_0^2 + a_1 b_1^2 x_0^2 \tau_{2} \omega_0^2 \cos((\tau_{10} - \tau_{2}) \omega_0) + a_1 b_1 x_0^2 (\omega_0^2 + a_2 b_2 x_0) \cos(\tau_{10} \omega_0)}{l_1^2 + l_2^2},
\]

where

\[
l_1 = b_3 - a_1 b_1 x_0 \tau_{10} \cos(\tau_{10} \omega_0) - b_1 x_0 \cos(\tau_{2} \omega_0) + b_1 x_0 \tau_{2} \omega_0 \sin(\tau_{2} \omega_0),
\]

\[
l_2 = 2 \omega_0 - a_1 b_1 x_0 \tau_{10} \sin(\tau_{10} \omega_0) + b_1 x_0 \sin(\tau_{2} \omega_0) + b_1 x_0 \tau_{2} \omega_0 \cos(\tau_{2} \omega_0).
\]

From the above analysis and the standard Hopf bifurcation theory, we have the following result:
Proposition 2.2. If \( k_1(s) = \delta(s-\tau_1), \ k_2(s) = \delta(s-\tau_2) \) and there is \( \tau_1 = \tau_{10} \) for given \( \tau_2 > 0, \ \tau_{10} > \tau_2 \) so that equations (13) hold and
\[
Re\left(\frac{d\lambda}{d\tau_1}\right)_{\lambda=i\omega_0, \tau_1=\tau_{10}} \neq 0,
\]
then a Hopf bifurcation occurs at \( L_0 \) as \( \tau_1 \) passes through \( \tau_{10} \).

For given \( \tau_2 > 0, \) a solution for (13) is the pair \((\tau_{10}, \omega_{10})\), where
\[
\tau_{10} = \frac{k\pi}{\omega_{10}} + \tau_2, \ k = 1, 2, \ldots
\]
and \( \omega_{10} \) is a positive root of the equation
\[
x^4 - (b_1^2 x_0^2 - b_3^2 - 2a_2b_2 x_0)x^2 + (a_2^2 b_2^2 - a_1^2 b_1^2)x_0^2 = 0.
\]

Proposition 2.3. If
\[
k_1(s) = \delta(s-\tau_1), \ k_2(s) = q_2 e^{-q_2 x}, \ \tau_1 \geq 0, \ q_2 > 0
\]
then
(i) function (10) is given by
\[
\Delta(\lambda, \tau_1, q_2) = \lambda^3 + p_2 \lambda^2 + p_1 \lambda + p_0 + (r_1 \lambda + r_0) e^{-\lambda \tau_1},
\]
where
\[
p_2 = q_2 + b_3, \ p_1 = q_2 b_3 - a_2 b_2 x_0 - b_1 x_0 q_2, \\
p_0 = -q_2 a_2 b_2 x_0, \ r_1 = a_1 b_1 x_0, \ r_0 = a_1 b_1 x_0 q_2;
\]
(ii) if \( \tau_1 = 0 \) and
\[
4(a_1 b_1 - a_2 b_2)^2 < a_2 b_3 (b_1 b_4 - a_2 b_3)
\]
then for \( q_2 \in (0, q_{21}) \cup (q_{22}, \infty) \) the equilibrium state \( L_0 \) is locally asymptotic stable, where \( q_{21}, q_{22} \) are the solutions of the equation
\[
(b_3 - b_1 x_0) x^2 + b_3 (b_3 - b_1 x_0) x + b_3 (a_1 b_1 - a_2 b_2) x_0 = 0.
\]

Next, we study the existence of Hopf bifurcation for system (3) with \( \rho_1 \) and \( \rho_2 \) given by (15), by choosing the delay \( \tau_1 \) as the bifurcation parameter. First, we would like to know when \( \Delta(\lambda, \tau_1, q_2) = 0 \), where \( \Delta(\lambda, \tau_1, q_2) \) is given
by (16), has purely imaginary roots \( \lambda = \pm i \omega_{01} (\omega_{01} > 0) \) at \( \tau_1 = \tau_{11} \). Note that
\[
\begin{align*}
  p_0 - p_2 \omega_{01}^2 + r_0 \cos(\omega_{01} \tau_{11}) + r_1 \sin(\omega_{01} \tau_{11}) &= 0 \\
  - \omega_{01}^3 + p_1 \omega_{01} + r_1 \omega_{01} \cos(\omega_{01} \tau_{11}) - r_0 \sin(\omega_{01} \tau_{11}) &= 0,
\end{align*}
\]
which implies that
\[
\omega_{01}^6 + (p_2^2 - 2p_1) \omega_{01}^4 + (p_1^2 - 2p_0 p_2 + r_1^2) \omega_{01}^2 + p_0^2 - r_0^2 = 0. 
\]
From (17), \( p_0^2 < r_0^2 \) and from (19) \( \lambda = i \omega_{01} \) is a simple root of the equation \( \Delta(\lambda, \tau_1, q_2) = 0 \). From (18) we obtain:
\[
\tau_{11} = \frac{1}{\omega_{01}} \arctan \left( \frac{r_1 \omega_{01}(p_2 \omega_{01}^2 - p_0) + r_0 (p_1 \omega_{01} - \omega_{01}^3)}{p_1 \omega_{01}(\omega_{01} - p_1 \omega_{01}) + r_0 (p_0 - p_2 \omega_{01})} \right).
\]
Differentiating \( \Delta(\lambda, \tau_1, q_2) = 0 \) implicitly with respect to \( \tau_1 \), we obtain
\[
\text{Re} \left( \frac{d\lambda}{d\tau_1} \right)_{\lambda = i \omega_{01}, \tau_1 = \tau_{11}} = \frac{\omega_{01}(r_1 \omega_{01} l_1 - l_2 r_0)}{m_1^2 + m_2^2},
\]
where
\[
\begin{align*}
  m_1 &= (p_1 - 3 \omega_{01}^2) \cos(\omega_{01} \tau_{11}) - 2 p_2 \omega_{01} \sin(\omega_{01} \tau_{11}) + r_1 - r_0 \tau_{11} \\
  m_2 &= 2 p_2 \omega_{01} \cos(\omega_{01} \tau_{11}) + (p_1 - 3 \omega_{01}^2) \sin(\omega_{01} \tau_{11}) - r_1 \tau_{11} - r_1 \tau_{11} \omega_{01}.
\end{align*}
\]

**Proposition 2.4.** If \( k_1(s) = \delta(s - \tau_1) \), \( k_2(s) = q_2 e^{-q_2 s} \) and \( \tau_1 = \tau_{11} \) then
\[
\text{Re} \left( \frac{d\lambda}{d\tau_1} \right)_{\lambda = i \omega_{01}, \tau_1 = \tau_{11}} \neq 0
\]
and a Hopf bifurcation occurs at \( L_0 \) as \( \tau_1 \) passes through \( \tau_{11} \).

### 3 Direction and stability of the Hopf bifurcation for \( k_1(s) = \delta(s - \tau_1) \), \( k_2(s) = \delta(s - \tau_2) \)

In what follows, we will study the direction and stability in two cases: in the first case the both kernels are delta function and in the second case the kernel \( k_1 \) is delta function and the kernel \( k_2 \) is weak function.

**3.1. The case** \( k_1(s) = \delta(s - \tau_1) \), \( k_2(s) = \delta(s - \tau_2) \), \( \tau_1 \geq 0, \tau_2 \geq 0 \).
In Proposition 2.1 and 2.2, we obtained some conditions which guarantee
that system (4) undergoes Hopf bifurcation at $\tau = \tau_{10}$. In this section,
we study the direction, the stability and the period of bifurcating periodic
solutions. The method that we used is based on the normal form theory and
the center manifold theorem introduced by [2].
From the previous section, we know that if $\tau = \tau_{10}$, then all the roots of
$\Delta(\lambda, \tau_{10}, \tau_2) = 0$, other than $\pm i\omega_0$ have negative real parts and any root
of the form $\lambda(\tau_1) = \alpha(\tau_1) + i\omega(\tau_1)$ satisfies $\alpha(\tau_{10}) = 0$, $\omega(\tau_{10}) = \omega_0$ and
$\frac{d\alpha(\tau_{10})}{d\tau_1} \neq 0$. For notational convenience let $\tau_1 = \tau_{10} + \mu, \mu \in \mathbb{R}$. Then $\mu = 0$
is the Hopf bifurcation value for (4). Without loss of generality, assume that
$\tau_{10} > \tau_2$ and define the space of $C^1$ functions as $C^1 = C^1([-\tau_{10}, 0], \mathbb{C}^2)$.
Suppose that for given $a_1, a_2, b_1, b_2, b_3, b_4, \tau_2$, there is a $\tau_{10} > 0$ at which (4)
exhibits a Hopf bifurcation. In $\tau_1 = \tau_{10} + \mu, \mu \in \mathbb{R}$, we regard $\mu$ as the
bifurcation parameter. For $\phi \in C^1$, we define

$$A(\mu)\phi = \begin{cases} \frac{d\phi(\theta)}{d\theta}, & \theta \in [-\tau_{10}, 0) \\ 0, & \theta \in [-\tau_{10}, 0] \end{cases}$$

and

$$R(\mu)\phi = \begin{cases} (0, 0)^T, & \theta \in [-\tau_{10}, 0) \\ (-a_2\phi_1(0)\phi_2(0), b_1\phi_1(-\tau_{10})\phi_2(-\tau_2))^T, & \theta = 0 \end{cases},$$

where

$$\eta(\theta, \mu) = \begin{cases} A, & \theta = 0 \\ B_1\delta(\theta + \tau_2), & \theta \in [-\tau_2, 0) \\ -B_2\delta(\theta + \tau_{10}), & \theta \in [-\tau_{10}, -\tau_2) \end{cases}$$

and $A, B_1, B_2$ are given by (8).
Then, we can rewrite (4) in the following vector form

$$\dot{U}_t = A(\mu)U_t + RU_t,$$

where

$$U = (u_1, u_2)^T, \quad U_t = U(t + \theta), \quad \theta \in [-\tau_{10}, 0].$$

For $\psi \in C^1([0, \tau_{10}], \mathbb{C}^2)$, the adjoint operator $A^*$ of $A$ is defined as

9
\[ A^* \psi(s) = \begin{cases} 
-\frac{d\psi(s)}{ds}, & s \in (0, \tau_{10}] \\
\int_{-\tau_{10}}^{0} d\eta T(t, 0) \psi(-t), & s = 0 
\end{cases} \]

For \( \phi \in C([-\tau_{10}, 0], \mathbb{C}^2) \) and \( \psi \in C([0, \tau_{10}], \mathbb{C}^2) \) we define the bilinear form

\[ <\phi, \psi> = \psi^T(0)\phi(0) - \int_{-\tau_{10}}^{0} \int_{\xi=0}^{\theta} \psi^T(\xi - \theta)d\eta(\theta)\phi(\xi)d\xi, \quad (20) \]

where \( \eta(\theta) = \eta(\theta, 0) \).

**Proposition 3.1.** (i) The eigenvector of \( A(0) \) corresponding to eigenvalue \( \lambda_1 = i\omega_0 \) is given by

\[ h(\theta) = (v_1, v_2)^T e^{\lambda_1 \theta}, \quad \theta \in [-\tau_{10}, 0], \]

where

\[ v_1 = 1, \quad v_2 = \frac{a_2 b_2 - a_1 b_1 e^{\lambda_2 \tau_{10}}}{a_2 (b_3 + \lambda_1 - b_1 x_0 e^{\lambda_2 \tau_{10}})} \]

and \( \lambda_2 = \overline{\lambda_1} \);

(ii) The eigenvector of \( A^* \) corresponding to eigenvalue \( \lambda_2 \) is

\[ h^*(s) = (w_1, w_2)^T e^{\lambda_1 s}, \quad s \in [0, \infty) \]

where

\[ w_1 = \frac{f_1}{\eta}, \quad w_2 = \frac{1}{\eta}, \quad f_1 = \frac{a_2 b_2 - a_1 b_1 e^{\lambda_1 \tau_{10}}}{a_2 \lambda_1} \]

\[ \eta = (f_1 + b_1 y_0 \tau_{10} e^{\lambda_1 \tau_{10}}) + \overline{v_2}(1 + \tau_2 b_2 x_0 e^{\lambda_1 \tau_{12}}); \]

(iii) With respect of (20), we have:

\[ <h^*, h> = 1, \quad <h^*, \overline{h}> = <\overline{h}, h> = 0, \quad <\overline{h^*}, \overline{h}> = 1. \]
Using the approach of [2], [9] we next compute the coordinates of the center manifold $\Omega_0$ at $\mu = 0$. Let $X_t = X(t+\theta), \theta \in [-\tau_{10}, 0)$ be the solution of system (3) when $\mu = 0$.

Define 
\[
z(t) = \langle h^*, X_t \rangle \quad w(t, \theta) = X_t - 2\text{Re}(z(t)h(\theta)).
\]

On the center manifold $\Omega_0$, we have 
\[
w(t, \theta) = w(z(t), \bar{z}(t), \theta) = w_{20}(\theta)\frac{\bar{z}^2}{2} + w_{11}(\theta)\bar{z} + w_{02}(\theta)\frac{\bar{z}^2}{2} + \cdots
\]

where $z$ and $\bar{z}$ are the local coordinates of the center manifold $\Omega_0$ in the direction of $h$ and $h^*$, respectively.

For the solution $u_t \in \Omega_0$, we have:
\[
\hat{z}(t) = \lambda_1 z(t) + g(z(t), \bar{z}(t)),
\]

where 
\[
g(z, \bar{z}) = g_{20}\frac{z^2}{2} + g_{11}z\bar{z} + g_{21}\frac{\bar{z}^2}{2} + g_{02}\frac{z^2}{2}
\]

**Proposition 3.2.** For the system (4), the coefficients $g_{20}, g_{11}, g_{02}, g_{21}$ and the functions $w_{20}(\theta), w_{11}(\theta), w_{02}(\theta)$ are given by
\[
\begin{align*}
g_{20} &= w_1f_{120} + w_2f_{220}, \quad g_{11} = w_1f_{111} + w_2f_{211}, \\
g_{02} &= w_1f_{102} + w_2f_{202}, \quad g_{21} = w_1f_{121} + w_2f_{221},
\end{align*}
\]

where
\[
\begin{align*}
f_{120} &= -2a_2v_1v_2, \quad f_{111} = -2a_2\text{Re}(v_1\bar{v}_2), \quad f_{102} = \overline{f}_{120}, \\
f_{220} &= 2b_1v_1v_2e^{\lambda_2(\tau_{10}+\tau_2)}, \quad f_{211} = 2b_1\text{Re}(v_1\bar{v}_2e^{\lambda_1\tau_2+\lambda_2\tau_{10}}), \quad f_{202} = \overline{f}_{220}, \\
f_{121} &= -a_2(2v_1w_{211}(0) + \overline{v}_1w_{220}(0) + 2v_2w_{111}(0) + \overline{v}_1w_{120}(0)) \\
f_{221} &= b_1(2v_1e^{\lambda_2\tau_{10}}w_{211}(-\tau_2) + \overline{v}_1e^{\lambda_1\tau_0}w_{220}(-\tau_2) + 2v_2e^{\lambda_2\tau_2}w_{111}(-\tau_{10}) + \overline{v}_2e^{\lambda_1+\tau_2}w_{120}(\tau_{10}))
\end{align*}
\]

and
\[
\begin{align*}
w_{20}(\theta) &= (w_{120}(\theta), w_{220}(\theta))^T, \quad w_{11}(\theta) = (w_{111}(\theta), w_{211}(\theta))^T,
\end{align*}
\]
\[ w_{20}(\theta) = -\frac{g_{20}}{\lambda_1}h(0)e^{\lambda_1\theta} - \frac{g_{20}}{3\lambda_1}h(0)e^{2\lambda_1\theta} + E_1e^{2\lambda_1\theta} \]

\[ w_{11}(\theta) = \frac{g_{11}}{\lambda_1}h(0)e^{\lambda_1\theta} - \frac{g_{11}}{\lambda_1}h(0)e^{2\lambda_1\theta} + E_2, \]

and

\[ E_1 = (E_{11}, E_{12})^T, \quad E_2 = (E_{21}, E_{22})^T, \]

where

\[ E_{11} = \frac{(2\lambda_1 + b_3 - b_1x_0e^{\lambda_1\tau_1})f_{120} - a_2x_0f_{220}}{2\lambda_1(-2\lambda_1 - b_3 + b_1x_0e^{2\lambda_1\tau_1}) + a_2x_0(-b_2 + b_1y_0e^{2\lambda_1\tau_1})} \]

\[ E_{12} = \frac{2\lambda_1E_{11} + f_{120}}{a_2x_0}, \quad E_{21} = \frac{(b_1x_0 - b_3)E_{22} + f_{211}}{b_1y_0 - b_2}, \quad E_{22} = -\frac{f_{111}}{a_2x_0}. \]

Based on the above analysis and calculation, we can see that each \( g_{ij} \) in (21) is determined by the parameters and delays in system (3). Thus, we can explicitly compute the following quantities:

\[ C_{10}(0) = \frac{i}{2\omega_0}(g_{20}g_{11} - 2|g_{11}|^2 - \frac{1}{3}|g_{21}|^2) + \frac{g_{21}}{2} \]

\[ \mu_{20} = -\frac{Re C_{10}(0)}{Re \lambda'(0)} \]

\[ T_{20} = -\frac{Im C_{10}(0) + \mu_{20}Im \lambda'(0)}{\omega_0} \]

\[ \beta_{20} = 2Re(C_{10}(0)). \]

In summary, this leads to the following result:

**Theorem 3.1.** In formulas (22), \( \mu_{20} \) determines the directions of the Hopf bifurcations: if \( \mu_{20} > 0(\mu_{20} < 0) \) the Hopf bifurcation is supercritical (subcritical) and the bifurcating periodic solutions exist for \( \tau_1 > \tau_{10}(< \tau_{10}) \); \( \beta_{20} \) determines the stability of the bifurcation periodic solutions: the solutions are orbitally stable (unstable) if \( \beta_{20} < 0(> 0) \) and \( T_{20} \) determines the periodic solutions: the period increases (decreases) if \( T_{20} > 0(< 0) \).

In (22) \( Re(\lambda'(0)) \) and \( Im(\lambda'(0)) \) are given by

\[ Re(\lambda'(0)) = Re\left(\frac{d\lambda}{d\tau_1}\right)_{\lambda = i\omega_0, \tau = \tau_{10}} \]

\[ Im(\lambda'(0)) = Im\left(\frac{d\lambda}{d\tau_1}\right)_{\lambda = i\omega_0, \tau = \tau_{10}} \]
where
\[
\frac{d\lambda}{d\tau_1} = \frac{a_1b_1x_0\lambda e^{-\lambda\tau_1}}{b_3 + 2\lambda - a_1b_1x_0\tau_1 e^{-\lambda\tau_1} - b_1x_0(1 - \lambda\tau_2)e^{-\lambda\tau_2}}.
\]

3.2. The case \( k_1(s) = \delta(s - \tau_1), k_2(s) = q_2 e^{-q_2 s}, \tau_1 \geq 0, q_2 > 0. \)

For \( k_1(s) = \delta(s - \tau_1), k_2(s) = q_2 e^{-q_2 s}, \tau_1 \geq 0, q_2 > 0, \) system (6) is given by:

\[
\begin{align*}
\dot{x}_1(t) &= -a_2x_0x_2(t) - a_2x_1(t)x_2(t), \\
\dot{x}_2(t) &= -b_2x_1(t) - b_3x_2(t) + b_1x_0x_3(t) + b_1y_0x_2(t - \tau_1) + b_1x_3(t)x_2(t - \tau_1), \\
\dot{x}_3(t) &= q_2(x_2(t) - x_3(t)).
\end{align*}
\]

(23)

We linearize system (23) and obtain:

\[
\dot{V}(t) = A_1 V(t) + C_1 V(t - \tau_1),
\]

where

\[
A_1 = \begin{pmatrix}
0 & -a_2x_0 & 0 \\
-b_2 & -b_3 & b_1x_0 \\
0 & q_2 & -q_2
\end{pmatrix},
\]

\[
C_1 = \begin{pmatrix}
0 & 0 & 0 \\
0 & b_1y_0 & 0 \\
0 & 0 & 0
\end{pmatrix},
\]

with \( V(t) = (u_1(t), u_2(t), u_3(t))^T. \)

The characteristic equation of system (23) is given by \( \Delta(\lambda, \tau_1, q_2) = 0, \)

where \( \Delta(\lambda, \tau_1, q_2) \) is function (16). We consider \( \tau_1 = \tau_{11} + \mu, \mu \in \mathbb{R} \) and \( C^1 = C^1([-\tau_{11}, 0], \mathbb{C}^2). \) We regard \( \mu \) as the bifurcation parameter. Then, for \( \phi \in C^1, \) we define

\[
A_1(\mu)\phi = \begin{cases}
\frac{d\phi(\theta)}{d\theta}, & \theta \in [-\tau_{11}, 0) \\
0 - \int_{-\tau_{11}}^0 d\eta(t, \mu)\phi(t), & \theta = 0
\end{cases}
\]

and

13
\( R_1(\mu)\phi = \begin{cases} 
(0,0,0)^T, & \theta \in [-\tau_{11}, 0), \\
(-a_2 \phi_1(0) \phi_2(0), b_1 \phi_3(0) \phi_2(-\tau_{11}), 0)^T, & \theta = 0
\end{cases} \),

where

\[ \eta(\theta, \mu) = \begin{cases} 
A, & \theta = 0 \\
C_1 \delta(\theta + \tau_{11}), & \theta \in [-\tau_{11}, 0).
\end{cases} \]

Then, we can rewrite (23) in the following vector form

\[ \dot{U}_t = A_1(\mu)U_t + R_1 U_t, \]

where

\[ U_t = U(t + \theta), \quad \theta \in [-\tau_{11}, 0]. \]

For \( \psi \in C^1([0, \tau_{11}], \mathbb{C}^2) \), the adjoint operator \( A_1^* \) of \( A_1 \) is defined as

\[ A_1^* \psi(s) = \begin{cases} 
-\frac{d \psi(s)}{ds}, & s \in (0, \tau_{11}] \\
\int_{-\tau_{11}}^0 d\eta^T(t, 0)\psi(-t), & s = 0.
\end{cases} \]

For \( \phi \in C([\tau_{11}, 0], \mathbb{C}^2) \) and \( \psi \in C([0, \tau_{11}], \mathbb{C}^2) \) we define the bilinear form

\[ < \phi, \psi > = \overline{\psi}^T(0)\phi(0) - \int_0^0 \int_{-\tau_{11}}^\theta \overline{\psi}^T(\xi - \theta) d\eta(\theta) \phi(\xi) d\xi, \quad (24) \]

where \( \eta(\theta) = \eta(\theta, 0) \).

**Proposition 3.3.** (i) The eigenvector of \( A_1(0) \) corresponding to eigenvalue \( \lambda_1 = i\omega_{01} \) is given by

\[ h(\theta) = (v_1, v_2, v_3)^T e^{\lambda_1 \theta}, \quad \theta \in [-\tau_{11}, 0], \]

where

\[ v_1 = (\lambda_1 + q_2)(\lambda_1 + b_3 - b_1 y_0 e^{\lambda_2 \tau_{11}}) - q_2 b_1 x_0, \quad v_2 = -b_2(\lambda_1 + q_2), \quad v_3 = -b_2 q_2 \]

and \( \lambda_2 = \overline{\lambda_1} \);
(ii) The eigenvector of $A^*_1$ corresponding to eigenvalue $\lambda_2$ is

$$h^*(s) = (w_1, w_2, w_3)^T e^{\lambda_1 s}, \quad s \in [0, \infty)$$

where

$$w_1 = \frac{f_1}{\eta}, w_2 = \frac{1}{\eta}, w_3 = \frac{f_3}{\eta}, f_1 = -\frac{b_2}{\lambda_2}, f_3 = \frac{b_1 x_0}{\lambda_2 + q_2}$$

$$\eta = f_1 \overline{v}_1 + f_2 \left(1 - \frac{b_1 y_0}{\lambda_2^2} \left(1 - e^{\lambda_1 \tau_{11}} - \lambda_2 \tau_{11} b_2 e^{\lambda_1 \tau_{11}}\right)\right) + f_3 \overline{v}_3;$$

(iii) With respect to (24), we have:

$$<h^*, h> = 1, \quad <h^*, \overline{h}>=<\overline{h}, h> = 0, \quad <\overline{h}, \overline{h}>= 1.$$ 

Using the approach of [2], [9] we next compute the coordinates of the center manifold $\Omega_0$ at $\mu = 0$. Let $X_t = X(t + \theta), \theta \in [-\tau_{11}, 0)$ be the solution of system (3) when $\mu = 0$. Define

$$z(t) = <h^*, X_t> \quad w(t, \theta) = X_t - 2 Re(z(t)h(\theta)).$$

On the center manifold $\Omega_0$, we have

$$w(t, \theta) = w(z(t), \overline{z}(t), \theta) = w_{20}(\theta) \frac{\overline{z}^2}{2} + w_{11}(\theta) z \overline{z} + w_{02}(\theta) \frac{\overline{z}^2}{2} + \cdots$$

where $z$ and $\overline{z}$ are the local coordinates of the center manifold $\Omega_0$ in the direction of $h$ and $h^*$, respectively.

For the solution $X_t \in \Omega_0$, we have:

$$\dot{z}(t) = \lambda_1 z(t) + g(z(t), \overline{z}(t)),$$

where

$$g(z, \overline{z}) = g_{20} \frac{\overline{z}^2}{2} + g_{11} z \overline{z} + g_{21} \overline{z}^2 + g_{21} \frac{z^2 \overline{z}}{2}$$

Proposition 3.4. For the system (23), the coefficients $g_{20}, g_{11}, g_{02}, g_{21}$ and the functions $w_{20}(\theta), w_{11}(\theta), w_{02}(\theta)$ are given by

$$g_{20} = \overline{w}_1 f_{120} + \overline{w}_2 f_{220} + \overline{w}_3 f_{320}, \quad g_{11} = \overline{w}_1 f_{111} + \overline{w}_2 f_{211} + \overline{w}_3 f_{311},$$

$$g_{02} = \overline{w}_1 f_{102} + \overline{w}_2 f_{202} + \overline{w}_3 f_{302}, \quad g_{21} = \overline{w}_1 f_{121} + \overline{w}_2 f_{221} + \overline{w}_3 f_{321}.$$

(25)
where
\[
\begin{align*}
f_{120} &= -2a_2 v_1 v_2, \quad f_{111} = -2a_2 \text{Re}(v_1 v_2), \quad f_{102} = \overline{f}_{120}, \\
f_{220} &= 2b_1 v_2 v_3 e^{\lambda_2 \tau_{11}}, \quad f_{211} = 2b_1 \text{Re}(v_2 v_3 e^{\lambda_2 \tau_{11}}), \quad f_{202} = \overline{f}_{220}, \\
f_{320} &= f_{311} = f_{302} = 0
\end{align*}
\]

\[
f_{121} = -a_2 (2v_1 w_{211}(0) + \overline{w}_{220}(0) + 2v_2 w_{111}(0) + \overline{w}_{120}(0))
\]

\[
f_{221} = b_1 (2v_3 w_{211}(-\tau_{11}) + \overline{w}_{220}(-\tau_{11}) + 2v_2 e^{\lambda_2 \tau_{11}} w_{311}(0) + \overline{w}_{2} e^{\lambda_1 \tau_{11}} w_{320}(0))
\]

\[
f_{321} = 0;
\]

and
\[
w_{20}(\theta) = (w_{120}(\theta), w_{220}(\theta), w_{320}(\theta))^T, \quad w_{11}(\theta) = (w_{111}(\theta), w_{211}(\theta), w_{311}(\theta))^T,
\]

\[
w_{20}(\theta) = -\frac{g_{20}}{\lambda_1} h(0)e^{\lambda_1 \theta} - \frac{g_{20}}{3\lambda_1} h(0)e^{2\lambda_1 \theta} + E_1 e^{2\lambda_1 \theta}
\]

\[
w_{11}(\theta) = \frac{g_{11}}{\lambda_1} h(0)e^{\lambda_1 \theta} - \frac{g_{11}}{\lambda_1} h(0)e^{2\lambda_2 \theta} + E_2,
\]

and
\[
E_1 = (E_{11}, E_{12}, E_{13})^T, \quad E_2 = (E_{21}, E_{22}, E_{23})^T,
\]

where
\[
E_{11} = \frac{a_2 x_0 E_{12} + f_{120}}{2\lambda_1}, \quad E_{12} = \frac{2\lambda_1 f_{220} - b_2 f_{120}}{2\lambda_1 (2\lambda_1 + b_3 - b_1 y_0 e^{2\lambda_1 \tau_{11}}) - a_2 b_2 x_0}, \\
E_{13} = \frac{q_2 E_{11}}{2\lambda_1 + q_2}, \quad E_{21} = -\frac{(b_3 - b_1 y_0) E_{22} - f_{211}}{b_2}, \quad E_{22} = \frac{f_{111}}{a_2 x_0}, \quad E_{23} = E_{21}.
\]

We can explicitly compute the following quantities \( C_{11}(0), \mu_{21}, T_{21}, \beta_{21} \):

\[
C_{11}(0) = \frac{i}{2\omega_{11}}(g_{20} g_{11} - 2|g_{11}|^2 - \frac{1}{3}|g_{20}|^2) + \frac{g_{21}}{2}
\]

\[
\mu_{21} = -\frac{\text{Re} C_{11}(0)}{\text{Re} \lambda'(0)}
\]

\[
T_{21} = -\frac{\text{Im} C_{11}(0) + \mu_{21} \text{Im} \lambda'(0)}{\omega_{11}}
\]

\[
\beta_{21} = 2\text{Re} (C_{11}(0)).
\]

In summary, this leads to the following result:
Theorem 3.2. In formulas (26), $\mu_{21}$ determines the directions of the Hopf bifurcations: if $\mu_{21} > 0 (< 0)$ the Hopf bifurcation is supercritical (subcritical) and the bifurcating periodic solutions exist for $\tau_1 > \tau_{11} (< \tau_{11})$; $\beta_{21}$ determines the stability of the bifurcation periodic solutions: the solutions are orbitally stable (unstable) if $\beta_{21} < 0 (> 0)$ and $T_{21}$ determines the periodic solutions: the period increases (decreases) if $T_{21} > 0 (< 0)$.

In (26) $Re(\lambda'(0))$ and $Im(\lambda'(0))$ are given by

$$Re(\lambda'(0)) = Re\left(\frac{d\lambda}{d\tau_1}\right)_{\lambda=i\omega_0, \tau=\tau_{11}}$$
$$Im(\lambda'(0)) = Im\left(\frac{d\lambda}{d\tau_1}\right)_{\lambda=i\omega_0, \tau=\tau_{11}}$$

where

$$\frac{d\lambda}{d\tau_1} = \frac{(r_1\lambda^2 + r_0\lambda - r_1)e^{-\lambda\tau_1}}{3\lambda^2 + 2p_2\lambda + p_1 - (r_1\lambda + r_0)\tau_1}.$$ 

4. Numerical simulations.

For the numerical simulations we use Maple 9.5. In this section, we consider system (6) with $a_1 = 2.5$, $a_2 = 1$, $b_1 = 1$, $b_2 = 0.4$, $b_3 = 0.95$, $b_4 = 2$. We obtain: $x_0 = 0.1524390244$, $y_0 = 2.5$.

In the first case, $k_1(s) = \delta(s - \tau_1)$, $k_2(s) = \delta(s - \tau_2)$, for $\tau_2 = 0.01$, we have: $\omega_0 = 0.6124295863$, $\mu_2 = 630.5712553$, $\beta_2 = 125.5070607$, $T_2 = 10.25944116$, $\tau_{10} = 9.541873607$. Then the Hopf bifurcation is supercritical and the bifurcating periodic solutions exist for $\tau > \tau_{10}$; the solutions are orbitally unstable and the period of the solution increases. The waveforms are displayed in Fig1 and Fig2 and the phase plane diagram of the state variables $x(t)$, $y(t)$ is displayed in Fig3:
In the second case, $k_1(s) = \delta(s - \tau_1)$, $k_2(s) = q_2 e^{-q_2 s}$ for $q_2 = 0.1$, we have: $\omega_{01} = 0.2235621332$, $\mu_{21} = 7.926079992$, $\beta_{21} = 0.0409704658$, $T_{21} = 0.3275619874$, $\tau_{11}^* = 10.3858942$. Then the Hopf bifurcation is supercritical and the bifurcating periodic solutions exist for $\tau_1 > \tau_{11}^*$; the solutions are orbitally unstable and the period of the solution increases. The waveforms are displayed in Fig5 and Fig6 and the phase plane diagram of the state variables $x(t), y(t)$ is displayed in Fig7:
For $q_2 = 0.1$, we have: $\omega_{01} = 0.9506753825$, $\mu_{21} = -0.6058263333$, $\beta_{21} = -0.001118156944$, $T_{21} = -0.07864963978$, $\tau_{11} = 23.03933807$. Then the Hopf bifurcation is subcritical and the bifurcating periodic solutions exist for $\tau_1 > \tau_{11}$; the solutions are orbitally stable and the period of the solution decreases. The waveforms are displayed in Fig5 and Fig6 and the phase plane diagram of the state variables $x(t)$, $y(t)$ is displayed in Fig7 and Fig8:
5. Conclusions.

This paper was focused on mathematical analysis of a model which describes the interaction between immune system and the tumor cells. The model is an improved one by using the delay kernel. Taking the average time delay as a parameter, it has been proved that the Hopf bifurcation occurs when this parameter passes through a critical value. In a future work it will be studied the mathematical aspects of the effect of immunotherapy on the development of the cancer.
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