HOPF BIFURCATION IN A DELAYED MODEL FOR TUMOR-IMMUNE SYSTEM COMPETITION WITH NEGATIVE IMMUNE RESPONSE

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The dynamics of the model for tumor-immune system competition with negative immune response and with one delay are investigated. We show that the asymptotic behavior depends crucially on the time delay parameter. We are particularly interested in the study of the Hopf bifurcation problem to predict the occurrence of a limit cycle bifurcating from the nontrivial steady state, by using the delay as a parameter of bifurcation. The obtained results provide the oscillations given by the numerical study in M. Gałach (2003), which are observed in reality by Kirschner and Panetta (1998).

1. Introduction

We consider in this paper a model which provides a description of tumor cells in competition with the immune system. This description is described by many authors, using ordinary and delayed differential equations to model the competition between immune system and tumor. In particular [19, 23, 24] other similar models can be found in the literature, (see [16, 25, 28]) that provide a description of the modelling, analysis, and control of tumor immune system interaction.

Other authors use kinetic equations to model the competition between immune system and tumor. Although they give a complex description in comparison with other simplest models, they are, for example, needed to model the differences of virulence between viruses, (see [1–5, 10]). Several other fields of biology use kinetic equations, for instance, [12, 13] give a kinetic approach to describe population dynamics, [2] deals with the development of suitable general mathematical structures including a large variety of Boltzmann-type models.

The reader, interested in a more complete bibliography about the evolution of a cell and the pertinent role that has cellular phenomena to direct the body towards the recovery or towards the illness, is addressed to [15, 20]. A detailed description of virus, antivirus, body dynamics can be found in the following references [8, 14, 26, 27].

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$$E + T \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \begin{array}{c} \overset{k_2}{\nearrow} \\ \underset{k_3}{\searrow} \end{array} \begin{array}{c} E + T^* \\ E^* + T \end{array}$$

Figure 2.1. Kinetic scheme describing interactions between ECs and TCs (see [19]).

The mathematical model with which we are dealing, was proposed in a recent paper by Gałach [19]. In this paper the author developed a new simple model with one delay of tumor immune system competition, this idea is inspired from [24] and he recalled some numerical results in [24] in order to compare them with those obtained in his paper [19].

2. Mathematical model

The model proposed in [24] describes the response of effector cells (ECs) to the growth of tumor cells (TCs). This model differs from others because it takes into account the penetration of TCs by ECs, which simultaneously causes the inactivation of ECs. It is assumed that interactions between ECs and TCs in vitro can be described by the kinetic scheme shown in Figure 2.1, where E, T, C, E^*, and T^* are the local concentrations of ECs, TCs, EC-TC complexes, inactivated ECs, and "lethally hit" TCs, respectively, k_1 and k_{-1} denote the rates of bindings of ECs to TCs and the detachment of ECs from TCs without damaging them, k_2 is the rate at which EC-TC interactions program TCs for lysis, and k_3 is the rate at which EC-TC interaction inactivate ECs.

Kuznetsov and Taylor model is as follows:

$$\begin{aligned} \frac{dE}{dt} &= s + F(C,T) - d_1E - k_1ET + (k_{-1} + k_2)C, \\ \frac{dT}{dt} &= aT(1 - bT) - k_1ET + (k_{-1} + k_3)C, \\ \frac{dC}{dt} &= k_1ET - (k_{-1} + k_2 + k_3)C, \\ \frac{dE^*}{dt} &= k_3C - d_2E^*, \\ \frac{dT^*}{dt} &= k_2C - d_3T^*, \end{aligned} \tag{2.1}$$

where s is the normal (i.e., not increased by the presence of the tumor) rate of the flow of adult ECs into the tumor site, $F(C,T)$ describes the accumulation of ECs in the tumor site, d_1, d_2, and d_3 are the coefficients of the processes of destruction and migration for E, E^*, and T^*, respectively, a is the coefficient of the maximal growth of tumor, and b is the environment capacity.

In [24] it is claimed that experimental observations motivate the approximation $dC/dt \approx 0$. Therefore, it is assumed that $C \approx KET$, where $K = k_1/(k_2 + k_3 + k_{-1})$, and the model can be reduced to two equations which describe the behavior of ECs and TCs only. Moreover, in [19] it is suggested that the function F should be in the following form:

$F(C,T) = F(E,T) = \theta ET$. Therefore, the model (2.1) takes the form

$$\frac{dE}{dt} = s + \alpha_1 ET - dE, \qquad \frac{dT}{dt} = aT(1-bT) - nET, \tag{2.2}$$

where $\alpha_1 = \theta - m$, and a, b, s have the same meaning as in (2.1); $n = K/k_2$, $m = K/k_3$, $d = d_1$. All coefficients except α_1 are positive. The sign of α_1 depends on the relation between θ and m. If the stimulation coefficient of the immune system exceeds the neutralization coefficient of ECs in the process of the formation of EC-TC complexes, then $\alpha_1 > 0$. We use the dimensionless form of model (2.2):

$$\frac{dx}{dt} = \sigma + \omega xy - \delta x, \qquad \frac{dy}{dt} = \alpha y(1-\beta y) - xy, \tag{2.3}$$

where x denotes the dimensionless density of ECs, y stands for dimensionless density of the population of TCs, $\alpha = a/Kk_2T_0$, $\beta = bT_0$, $\delta = d/Kk_2T_0$, $\sigma = s/nE_0T_0$, and $\omega = \alpha_1/n$ is immune response to the appearance of the tumor cells, and E_0 and T_0 are the initial conditions. In [19], the author studies the existence, uniqueness, and nonnegativity of solutions and he show the nonexistence of nonnegative periodic solution of system (2.3).

For $\omega < 0$, $\alpha\delta > \sigma$, and $\alpha^2(\beta\delta - \omega)^2 + 4\alpha\beta\sigma\omega > 0$, (2.3) has two possible nonnegative steady states P_0 and P_2, where the first is unstable and the second is stable (see [19]).

The delayed mathematical model corresponding to (2.3) is given by the following system [19]:

$$\frac{dx}{dt} = \sigma + \omega x(t-\tau)y(t-\tau) - \delta x, \qquad \frac{dy}{dt} = \alpha y(1-\beta y) - xy, \tag{2.4}$$

where the parameter τ is the time delay which the immune system needs to develop a suitable response after the recognition of nonself cells (see [19]). Time delays in connection with the tumor growth also appear in [6, 7, 9, 17, 18].

The existence and uniqueness of solutions of system (2.4) for every $t > 0$ are established in [19], and in the same paper it is shown that

(1) if $\omega \geq 0$, these solutions are nonnegative for any nonnegative initial conditions (biologically realistic case);

(2) if $\omega < 0$, there exists a nonnegative initial condition such that the solution becomes negative in a finite time interval.

Our goal in this paper is to consider the case (2) when the immune response is negative (i.e., $\omega < 0$) with the following conditions: $\alpha\delta > \sigma$ and $\alpha^2(\beta\delta - \omega)^2 + 4\alpha\beta\sigma\omega > 0$. We study the asymptotic behavior of the possible steady states P_0 and P_2 with respect to the delay τ. We establish that, the Hopf bifurcation may occur by using the delay as a parameter of bifurcation. The case (1) when the immune response is positive (i.e., $\omega > 0$) is treated in [29].

This paper is organized as follows. In Section 3, we establish some results on the stability of the possible steady states (trivial and nontrivial) of the delayed system (2.4). The existence of a critical value of the delay in which the nontrivial steady state changes stability is investigated. The main result of this paper is given in Section 4. Based on the Hopf bifurcation theorem, we show the occurrence of Hopf bifurcation as the delay cross some critical value of the parameter delay.

3. Steady states and stability for positive delays

Consider system (2.4), and suppose that $\omega < 0$, $\alpha\delta > \sigma$, and $\alpha^2(\beta\delta - \omega)^2 + 4\alpha\beta\sigma\omega > 0$.

Then, system (2.4) has two equilibrium points: $P_0 = (\sigma/\delta, 0)$ and $P_2 = (x_2, y_2)$, where

$$x_2 = \frac{-\alpha(\beta\delta - \omega) + \sqrt{\Delta}}{2\omega}, \qquad y_2 = \frac{\alpha(\beta\delta + \omega) - \sqrt{\Delta}}{2\alpha\beta\omega} \tag{3.1}$$

with $\Delta = \alpha^2(\beta\delta - \omega)^2 + 4\alpha\beta\sigma\omega$.

The linearized system around P_0 takes the form

$$\frac{dx}{dt} = \omega\frac{\sigma}{\delta}y(t-\tau) - \delta x, \qquad \frac{dy}{dt} = \left(\alpha - \frac{\sigma}{\delta}\right)y, \tag{3.2}$$

which leads to the characteristic equation

$$W(\lambda) = \left(\lambda + \frac{\sigma}{\delta} - \alpha\right)(\lambda + \delta). \tag{3.3}$$

Then, we have the following result.

Proposition 3.1. *Under the hypotheses $\omega < 0$ and $\alpha\delta > \sigma$, the equilibrium point P_0 is unstable for all $\tau > 0$.*

Proof. The characteristic equation (3.3) has two roots: $\lambda_1 = -\sigma/\delta + \alpha$ and $\lambda_2 = -\delta$ which are independent of τ. As $\alpha\delta > \sigma$, we have $\lambda_1 > 0$. From [21], the equilibrium point P_0 is unstable for all $\tau > 0$. □

In the next, we will study the stability of the nontrivial equilibrium point P_2.

Let $u = x - x_2$ and $v = y - y_2$, by linearizing system (2.4) around the nontrivial equilibrium point P_2, we obtain the following linear system:

$$\frac{du}{dt} = \omega x_2 v(t-\tau) - \omega y_2 u(t-\tau) - \delta u, \qquad \frac{dv}{dt} = -y_2 u + (\alpha - 2\alpha\beta y_2 - x_2)v. \tag{3.4}$$

The characteristic equation of (3.4) has the form

$$W(\lambda, \tau) = \lambda^2 + p\lambda + r + (s\lambda + q)e^{-\lambda\tau} = 0, \tag{3.5}$$

where $p = \delta + \alpha\beta y_2 > 0$, $r = \delta\alpha\beta y_2 > 0$, $s = -\omega y_2 < 0$, and $q = \alpha\omega y_2(1 - 2\beta y_2)$.

The stability of the equilibrium point P_2 is a result of the localization of the roots of the equation

$$W(\lambda, \tau) = 0, \tag{3.6}$$

then we have the following theorem.

Theorem 3.2. *Assume $\alpha\delta > \sigma$, $\alpha > 0$, and $\beta > 0$ are close enough to 0. Then, there exists $\tau_l > 0$ such that P_2 is asymptotically stable for $\tau < \tau_l$ and unstable for $\tau > \tau_l$, where*

$$\tau_l = \frac{1}{\zeta_l}\arccos\left\{\frac{q(\zeta_l^2 - r) - ps\zeta_l^2}{s^2\zeta_l^2 + q^2}\right\},$$
$$\zeta_l^2 = \frac{1}{2}(s^2 - p^2 + 2r) + \frac{1}{2}\left[(s^2 - p^2 + 2r)^2 - 4(r^2 - q^2)\right]^{1/2}. \tag{3.7}$$

For the proof of Theorem 3.2, we need the following lemma.

Lemma 3.3 [11]. *Consider the equation*

$$\lambda^2 + p\lambda + r + (s\lambda + q)e^{-\lambda\tau} = 0, \tag{3.8}$$

where p, r, q, and s are real numbers.

Let the hypotheses

(H_1) $p + s > 0$;

(H_2) $q + r > 0$;

(H_3) $r^2 - q^2 < 0$ *or* ($s^2 - p^2 + 2r > 0$ *and* $(s^2 - p^2 + 2r)^2 = 4(r^2 - q^2)$).

If (H_1)–(H_3) *hold, then when $\tau \in [0, \tau_l)$ all roots of (3.8) have negative real parts, when $\tau = \tau_l$, (3.8) has a pair of purely imaginary roots $\pm i\zeta_l$, and when $\tau > \tau_l$, (3.8) has at least one root with positive real part, where τ_l and ζ_l are defined in Theorem 3.2.*

Proof of Theorem 3.2. From the expressions of p, q, s, and r, we have $p + s > 0$ and

$$q + r = -\alpha(\omega + \delta\beta)y_2 + 2(\alpha\delta - \sigma). \tag{3.9}$$

As β is close enough to 0, we have $\omega/\beta < -\delta$.

From the hypothesis $\alpha\delta > \sigma$, we deduce that $q + r > 0$.

Therefore, the hypotheses (H_1), (H_2) of Lemma 3.3 are satisfied. Then all roots of the characteristic equation (3.5) have negative real parts for $\tau = 0$, and the steady state P_2 is asymptotically stable for $\tau = 0$. By Rouche's theorem, it follows that the roots of (3.5) have negative real parts for some critical value of the delay τ.

We want to determine if the real part of some root increases to reach zero and eventually becomes positive as τ varies. If $i\zeta$ is a root of (3.5), then

$$-\zeta^2 + ip\zeta + is\zeta(\cos(\tau\zeta) + i\sin(\tau\zeta)) + r + q(\cos(\tau\zeta) + i\sin(\tau\zeta)) = 0. \tag{3.10}$$

Separating the real and imaginary parts, we have

$$-\zeta^2 + r = -q\cos(\tau\zeta) + s\zeta\sin(\tau\zeta), \qquad p\zeta = -s\zeta\cos(\tau\zeta) - q\sin(\tau\zeta). \tag{3.11}$$

It follows that ζ satisfies

$$\zeta^4 - (s^2 - p^2 + 2r)\zeta^2 + (r^2 - q^2) = 0. \tag{3.12}$$

The two roots of the above equation can be expressed as follows:

$$\zeta^2 = \frac{1}{2}(s^2 - p^2 + 2r) \pm \frac{1}{2}\left[(s^2 - p^2 + 2r)^2 - 4(r^2 - q^2)\right]^{1/2}. \tag{3.13}$$

As $r^2 - q^2 = \alpha^2 y_2^2(\delta^2\beta^2 - \omega^2(1-2\beta y_2)^2)$, the sign of $r^2 - q^2$ is deduced from the sign of $(\delta\beta - \omega^2(1-2\beta y_2)) = (2\alpha\beta\delta - \sqrt{\Delta})/\alpha$ which is negative (because β is very small and $\alpha > 0$).

Therefore, $r^2 - q^2 < 0$, and the hypothesis (H_3) of Lemma 3.3 is satisfied.

From Lemma 3.3, the unique solution of (3.12) has the following form:

$$\zeta_l^2 = \frac{1}{2}(s^2 - p^2 + 2r) + \frac{1}{2}\left[\left(s^2 - p^2 + 2r\right)^2 - 4\left(r^2 - q^2\right)\right]^{1/2} \tag{3.14}$$

and there exists a unique critical value

$$\tau_l = \frac{1}{\zeta_l}\arccos\left\{\frac{q(\zeta_l^2 - r) - ps\zeta_l^2}{s^2\zeta_l^2 + q^2}\right\} \tag{3.15}$$

such that the equilibrium point P_2 is asymptotically stable for $\tau \in [0,\tau_l)$ and unstable for $\tau > \tau_l$. For $\tau = \tau_l$, the characteristic equation (3.5) has a pair of purely imaginary roots $\pm i\zeta_l$. □

In the next sections, we will study the occurrence of Hopf bifurcation when the delay passes trough the critical value of the delay $\tau = \tau_l$.

Let $z(t) = (u(t), v(t)) = (x(t), y(t)) - (x_2, y_2)$, then system (2.4) is written as a functional differential equation (FDE) in $C := C([-\tau, 0], \mathbb{R}^2)$:

$$\frac{dz(t)}{dt} = L(\tau)z_t + f(z_t, \tau), \tag{3.16}$$

where $L(\tau) : C \to \mathbb{R}^2$ is a linear operator and $f : C \times \mathbb{R} \to \mathbb{R}^2$ are given, respectively, by

$$\begin{aligned} L(\tau)\varphi &= \begin{pmatrix} \omega y_2\varphi_1(-\tau) + \omega x_2\varphi_2(-\tau) - \delta\varphi_1(0) \\ -y_2\varphi_1(0) + (\alpha - 2\alpha\beta y_2 - x_2)\varphi_2(0) \end{pmatrix}, \\ f(\varphi,\tau) &= \begin{pmatrix} \sigma + \omega\varphi_1(-\tau)\varphi_2(-\tau) + \omega x_2 y_2 - \delta x_2 \\ -\alpha\beta\varphi_2^2(0) + \alpha y_2 - \alpha\beta y_2^2 - \varphi_1(0)\varphi_2(0) - x_2 y_2 \end{pmatrix} \end{aligned} \tag{3.17}$$

for $\varphi = (\varphi_1, \varphi_2) \in C$.

4. Hopf bifurcation occurrence

According to the Hopf bifurcation theorem [22], we come to the main result of this paper.

THEOREM 4.1. *Assume $\alpha\delta > \sigma$, $\alpha > 0$, $\beta > 0$, and β are close enough to* 0. *There exists $\varepsilon_1 > 0$ such that, for each $0 \le \varepsilon < \varepsilon_1$, (3.16) has a family of periodic solutions $p_l(\varepsilon)$ with period $T_l = T_l(\varepsilon)$, for the parameter values $\tau = \tau(\varepsilon)$ such that $p_l(0) = P_2$, $T_l(0) = 2\pi/\zeta_l$, and $\tau(0) = \tau_l$, where τ_l and ζ_l are given, respectively, in (3.7).*

Proof. We apply the Hopf bifurcation theorem introduced in [22]. From the expression of f in (3.16), we have

$$f(0,\tau) = 0, \quad \frac{\partial f(0,\tau)}{\partial\varphi} = 0, \quad \forall \tau > 0. \tag{4.1}$$

From (3.5) and Theorem 3.2, the characteristic equation (3.5) has a pair of simple imaginary roots: $\lambda_l = i\zeta_l$ and $\overline{\lambda}_l = -i\zeta_l$ at $\tau = \tau_l$.

From (3.5), $W(\lambda_l, \tau_l) = 0$ and $(\partial/\partial\lambda)W(\lambda_l, \tau_l) = 2i\zeta_l + p + (s - \tau(is\zeta_l + q))e^{-i\zeta_l\tau_l} \neq 0$. According to the implicit function theorem, there exists a complex function $\lambda = \lambda(\tau)$ defined in a neighborhood of τ_l, such that $\lambda(\tau_l) = \lambda_l$ and $W(\lambda(\tau), \tau) = 0$ and

$$\lambda'(\tau) = -\frac{\partial W(\lambda,\tau)/\partial\tau}{\partial W(\lambda,\tau)/\partial\lambda}, \quad \text{for } \tau \text{ in a neighborhood of } \tau_l, \tag{4.2}$$

$$\lambda'(\tau) = \frac{\lambda(s\lambda + q)e^{-\lambda\tau}}{2\lambda + p + (s - \tau s\lambda - \tau q)e^{-\lambda\tau}}. \tag{4.3}$$

From (3.5), (3.11), and (4.3), we obtain the following expression of $\lambda'(\tau)$ for τ in a neighborhood of τ_l:

$$\lambda'(\tau) = -\lambda\frac{s\lambda^3 + (s^2p + q)\lambda^2 + (sr + pq)\lambda + qr}{\tau s\lambda^3 + (s + \tau(sp + q))\lambda^2 + (2q + \tau(sr + pq))\lambda + pq - sr + qr}. \tag{4.4}$$

Let $\lambda(\tau) = \kappa(\tau) + i\zeta(\tau)$ (where κ and ζ are the real and imaginary parts of λ, resp.). From (4.4), we have

$$\begin{aligned}&\kappa'(\tau)_{/\tau=\tau_l}\\ &\quad= \zeta_l^2\frac{s^2\zeta_l^4 + (sqr(\tau - 1) + 2q^2)\zeta_l^2 + sr^2(q - sr) + pq^2(p + r) - qr(2q + \tau(sr + pq))}{A^2 + B^2},\end{aligned} \tag{4.5}$$

where

$$A = -(s + \tau(sp + q))\zeta_l^2 + pq - sr + qr, \qquad B = -\tau s\zeta_l^2 + (2q + \tau(sr + pq))\zeta_l. \tag{4.6}$$

From the expression of r and as β is close to 0, then r is very small.

From (4.5), we conclude that,

$$\kappa'(\tau)_{/\tau=\tau_l} > 0. \tag{4.7}$$

Then, the transversality condition is verified, which completes the proof of Theorem 4.1. □

5. Discussions

In [19], a numerical analysis shows that the characteristic equation (3.5) of the linearized system of system (2.4) around the nontrivial steady state P_2 has a purely imaginary root for some $\tau = \tau_0$, and the switching of stability may occur by using the Mikhailov hodograph.

In this paper, we give an analytical study of stability (with respect to the time delay τ) of the possible steady states P_0 and P_2 for the negative values of the parameter ω, and we study each case separately.

In Section 4, we prove that system (2.4) has a family of periodic solutions bifurcating from the nontrivial steady state for small and large time delay.

The results proposed in this paper should hopefully improve the understanding of the qualitative properties of the description delivered by model (2.4). So far we have now a description of stability properties and Hopf bifurcation with a detailed analysis of the influence of delays terms.

The studies of direction of Hopf bifurcation and the case when $\omega < 0$ with other cases are our aims in the next papers.

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