Math. Model. Nat. Phenom.
Vol. 5, No. 7, 2010, pp. 29-34
DOI:10.1051/mmnp/20105705

Global Existence of Periodic Solutions in a Delayed Tumor-Immune Model

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Abstract. This paper is devoted to the study of global existence of periodic solutions of a delayed tumor-immune competition model. Also some numerical simulations are given to illustrate the theoretical results.

Key words: tumor-immune model, delayed differential equations, Hopf bifurcation, periodic solutions
AMS subject classification: 37G15, 92D25

1. Introduction

The Hopf bifurcation theorem is a tool for establishing the existence of periodic solutions. However, these periodic solutions are generally local. Therefore, it is an important subject to investigate if nonconstant periodic solutions exist globally. In this paper we use a method to prove the global existence of periodic solutions given by Wu [4] to study the following delayed tumor-immune competition model [2, 3]:

$$\begin{cases} \frac{dE}{dt} = \sigma + \omega E(t-\tau)T(t-\tau) - \delta E(t), \\ \\ \frac{dT}{dt} = \alpha T(t)(1-\beta T(t)) - E(t)T(t), \end{cases} \tag{1.1}$$

with

$$\begin{cases} E(\theta) = \phi_1(\theta) \geq 0, \quad E(\theta) = \phi_2(\theta) \geq 0, \quad \theta \in [-\tau, 0], \quad \phi_i \in \mathcal{C}([-\tau,0],\mathbb{R}), i = 1,2, \\ \\ E(0) > 0, \quad T(0) > 0, \end{cases} \tag{1.2}$$

*Corresponding author. E-mail: a.kaddar@yahoo.fr where E, T are respectively the local concentrations of the effector cells (ECs) and the tumor cells (TCs), σ is the normal rate of the flow of adult ECs into the tumor site, ω is the immune response to the appearance of the TCs, δ characterizes death or migration of ECs, α is the coefficient of the maximal growth of tumor, β is the environment capacity and τ is the time needed for the immune system to develop a chemical and cell mediated response to the presence of the tumor. All coefficient except ω are positive.

2. Local stability and local Hopf bifurcation

In this section, we discuss the local stability of the possible steady states and the existence of local Hopf bifurcation of system (1.1)-(1.2) by analyzing the corresponding characteristic equation (see, for example, [6]). It is easy to show that if the following condition holds: $\omega > 0$, and $\alpha\delta > \sigma$, then system (1.1)-(1.2) has two positive steady states $(\frac{\sigma}{\delta}, 0)$ and (E^*, T^*), where $E^* = \frac{-\alpha(\beta\delta-\omega)+\sqrt{\Delta}}{2\omega}$, $T^* = \frac{\alpha(\beta\delta+\omega)-\sqrt{\Delta}}{2\alpha\beta\omega}$ with

$$\Delta := \alpha^2(\beta\delta - \omega)^2 + 4\alpha\beta\sigma\omega > 0. \tag{2.1}$$

Proposition 1. *Under the hypotheses*

(S1) $\omega > 0$,

(S2) $\alpha\delta > \sigma$,

the steady state $(\frac{\sigma}{\delta}, 0)$ *is unstable for all* $\tau \geq 0$.

Proof. The characteristic equation for the system (1.1)-(1.2) at $(\frac{\sigma}{\delta}, 0)$ is given by

$$\lambda^2 + (\delta - \alpha + \frac{\sigma}{\delta})\lambda + (-\alpha + \frac{\sigma}{\delta}) = 0. \tag{2.2}$$

From (S2) in Proposition 1, we have $-\alpha + \frac{\sigma}{\delta} < 0$. Hence, according to the Routh-Hurwitz criterion, the steady state $(\frac{\sigma}{\delta}, 0)$ is unstable for all $\tau \geq 0$.

In what follows, we study stability of the nontrivial steady state (E^*, T^*) for various values of the time delay τ. The characteristic equation associated with the system (1.1)-(1.2) at (E^*, T^*) takes the general form

$$\lambda^2 + p\lambda + r + (s\lambda + q)exp(-\lambda\tau) = 0, \tag{2.3}$$

where $p = \delta + \alpha\beta T^*$, $r = \alpha\beta\delta T^*$, $s = -\omega T^*$, and $q = \alpha\omega T^*(1 - 2\beta T^*)$.

Proposition 2. *For* $\tau = 0$, *suppose that (S1) and (S2) holds. If one of the following conditions*

(S3) $\frac{\omega}{\beta} \leq \alpha$,

(S4) β *is close enough to 0,*

is satisfied, then the equilibrium (E^*, T^*) *is locally asymptotically stable.*

Proof. When $\tau = 0$, the characteristic equation (2.3) reads as

$$\lambda^2 + (p+s)\lambda + (r+q) = 0. \tag{2.4}$$

We have $r + q = T^*\sqrt{\Delta} > 0$, with Δ is given by (2.1) and $p + s = \delta + (\alpha\beta - \omega)T^*$. In view of hypothesis (S3), it is clear that $p + s > 0$. According to the Routh-Hurwitz criterion, the steady state (E^*, T^*) is locally asymptotically stable. If $\beta = 0$, we have $T^* = \frac{\alpha\delta-\sigma}{\alpha\omega}$. Then $p+s = \frac{\sigma}{\alpha} > 0$. Consequently, the hypothesis (S4) implies that (E^*, T^*) is locally asymptotically stable.

When $\tau > 0$, Cooke and Grossman [1] proved that if there are real values of ν_0 given by $\nu_0 = \sqrt{\frac{A\pm\sqrt{A^2-4B}}{2}}$, where $A = s^2 - p^2 + 2r$, and $B = r^2 - q^2$, then stability of the equilibrium is altered for critical values of τ depending on ν_0. For our model we apply this result and the Hopf bifurcation theorem introduced in [6] to prove the following result:

Theorem 3. *Under the hypotheses (S1), (S2) and (S4), there exist* τ_n, $n = 0, 1, 2...$ *such that*

(i) (E^*, T^*) *is asymptotically stable for* $\tau < \tau_0$ *and unstable for* $\tau > \tau_0$.

(ii) System (1.1)-(1.2) undergoes a Hopf bifurcation at (E^*, T^*) *when* $\tau = \tau_n$,

where

$$\tau_n = \frac{1}{\nu_0}\arccos\frac{q(\nu_0^2 - r) - ps\nu_0^2}{s^2\nu_0^2 + q^2} + \frac{2n\pi}{\nu_0}, \tag{2.5}$$

and

$$\nu_0^2 = \frac{1}{2}(s^2 - p^2 + 2r) + \frac{1}{2}\sqrt{(s^2 - p^2 + 2r)^2 - 4(r^2 - q^2)}. \tag{2.6}$$

3. Global existence of periodic solutions

In this section, we investigate global continuation of periodic solutions bifurcated from the point (E^*, τ_n), $n = 1, 2...$ for system (1.1)-(1.2) by applying the method given by Wu [4].

Lemma 4. *Let* (E, T) *denote the solution of system (1.1)-(1.2). Then*

(i) $E(t) > 0, \quad T(t) > 0,$ *for all* $t \geq 0$,

(ii) $E(t) \leq M_1, \quad T(t) \leq M_2,$ *for all* t *sufficiently large,*

where $M_1 = E(0)\exp(\frac{\omega}{\delta M_2}\exp(\delta\tau))$, *and* $M_2 = \max(\frac{1}{\beta}, T(0))$.

Proof. Let (E, T) denote the solution of system (1.1)-(1.2). Then we obtain

$$\begin{cases} E(t) = \exp(-\delta t)\{E(0) + \int_0^t [\sigma + \omega E(s-\tau)T(s-\tau)]\exp(\delta s)ds\}, \\ T(t) = T(0)\exp(\int_0^t [\alpha(1-\beta T(s)) - E(s)]ds). \end{cases} \tag{3.1}$$

(i) It is true because $E(0) > 0, \quad T(0) > 0, \quad and \quad E(\theta) \geq 0, \quad for \quad \theta \in [-\tau, 0).$
(ii) Now, we want to show that $T(t)$ is bounded. From the second equation of system (1.1)-(1.2), we have $\frac{dT}{dt} \leq \alpha T(t)(1-\beta T(t))$. Thus, $T(t)$ may be compared with solution of

$$\frac{dX}{dt} = \alpha X(t)(1-\beta X(t)), \quad X(0) = T(0).$$

This concludes the proof. By using the generalized Gronwall Lemma, we get

$$E(t) \leq E(0)\exp(\frac{\omega}{\delta M_1} e^{\delta\tau}). \tag{3.2}$$

Then $E(t)$ is uniformly bounded for bounded M_1.

Lemma 5. *System (1.1)-(1.2) has no nontrivial τ-periodic solution.*

Proof. By contradiction, suppose that system (1.1)-(1.2) has a nontrivial τ-periodic solution. Then the following system of ordinary differential equations has periodic solution:

$$\begin{cases} \frac{dE}{dt} = \sigma + \omega E(t)T(t) - \delta E(t), \\ \frac{dT}{dt} = \alpha T(t)(1-\beta T(t)) - E(t)T(t). \end{cases} \tag{3.3}$$

Denote $P(E,T) = \sigma + \omega ET - \delta E$, $Q(E,T) = \alpha T(1-\beta T) - ET$, and $B(E,T) = \frac{1}{T}$, then we have $\frac{\partial(BP)}{\partial E} + \frac{\partial(BQ)}{\partial T} = \omega - \frac{\delta}{T} - \alpha\beta$. By (S3) in Proposition 2, we have that $\frac{\partial(BP)}{\partial E} + \frac{\partial(BQ)}{\partial T} < 0$. Due to Dulac's criterion ([5]), we conclude that the system (3.3) has no periodic solution. The conclusion follows.

For simplicity of notations, setting $z = (E, T)$, we may rewrite system (1.1)-(1.2) as the following functional differential equation:

$$\frac{dz}{dt} = F(z(t), z(t-\tau)), \tag{3.4}$$

note that F satisfies the hypotheses $(A1)$ and $(A2)$ in ([4], p. 4813-4814). Following the work of Wu [4], we need to define $X = C([-\tau, 0], \mathbb{R}^2)$, $\Sigma = Cl\{(z, \tau, p) \in X \times \mathbb{R} \times \mathbb{R}^+$: z is a p-periodic solution of system (3.4)$\}$, and let $l(E^*, \tau_n, \frac{2\pi}{\omega_0})$ denote the connected component of $(E^*, \tau_n, \frac{2\pi}{\omega_0})$ in Σ, where ω_0 and τ_n are defined respectively in (2.5) and (2.6).

Lemma 6. *$l(E^*, \tau_n, \frac{2\pi}{\omega_0})$ is unbounded.*

Proof. We consider τ as a parameter. The characteristic matrix corresponding to E^* is

$$\Delta_{(E^*,\tau)}(\lambda) = \begin{pmatrix} \lambda - \omega T^* \exp(-\lambda\tau) & -\omega E^* \exp(-\lambda\tau) \\ T^* & \lambda - (\alpha - 2\alpha\beta T^* - E^*) \end{pmatrix}. \tag{3.5}$$

It is clearly continuous with respect to $(\lambda, \tau) \in \mathbb{C} \times \mathbb{R}_+$. This justifies hypothesis $(A3)$ in ([4], p. 4814) for the considered system (3.4). A stationary solution $(E^*, \overline{\tau})$ is called a center if $\det(\Delta_{(E^*,\overline{\tau})}(im\frac{2\pi}{\omega_0})) = 0$ for some positive integer m. A center $(E^*, \overline{\tau})$ is said to be isolated if it is the only center in some neighborhood of $(E^*, \overline{\tau})$.

It follows from the discussion regarding the local Hopf bifurcation in Section 2 that (E^*, τ_n) is an isolated center and from the implicit function theorem, there exist $\varepsilon > 0$, $\nu > 0$ and a smooth curve $\lambda : (\tau - \nu, \tau + \nu) \to \mathbb{C}$ such that $\det(\Delta_{(E^*,\tau_n,\frac{2\pi}{\omega_0})}(\lambda) = 0$, $|\lambda(\tau_n) - \omega_0| < \varepsilon$ for all $\tau \in (\tau - \nu, \tau + \nu)$ and $\lambda(\tau_n) = i\omega_0$, $\frac{dRe(\lambda)}{d\tau}|_{\tau=\tau_n} > 0$. Let

$$\Omega_\varepsilon := \{(u,p); 0 < u < \varepsilon, |p - \frac{2\pi}{\omega_0}| < \varepsilon\}.$$

Clearly, if $|\tau - \tau_n| < \nu$ and $(u,p) \in \partial\Omega_\varepsilon$ such that $\det(\Delta_{(E^*,\tau,p)}(u + i\frac{2\pi}{\omega_0}))) = 0$, then $\tau = \tau_n$, and $u = 0$. This justifies hypothesis $(A4)$ in ([4], p. 4814) for $m = 1$. Moreover, if we put $H_1^{\pm}(E^*, \tau_n, \frac{2\pi}{\omega_0})(u,p) := \det(\Delta_{(0,\tau_n\pm\nu,p)}(u + im\frac{2\pi}{p})))$, then for $m = 1$, we have the crossing number of (E^*, τ, p)

$$\Gamma(E^*, \tau_n, \frac{2\pi}{\omega_0}) = deg_B(H_1^-, \Omega_\varepsilon, 0) - deg_B(H_1^+, \Omega_\varepsilon, 0) = -1,$$

where deg_B denotes the classical Brouwer degree. By Theorem 3.3 in [4], we conclude that the connected component $l(E^*, \tau_n, \frac{2\pi}{\omega_0})$ is unbounded.

Theorem 7. *Suppose that hypotheses (S1), (S2) and (S3) in Proposition 1 hold. Then for each* $\tau > \tau_n$ $(n = 1, 2...)$, *system (1.1)-(1.2) has at least* $n + 1$ *periodic solutions.*

Proof. It is sufficient to verify that the projection of $l(E^*, \tau_n, \frac{2\pi}{\omega_0})$ onto τ-space is $[\tau^*, +\infty)$, where $\tau^* \leq \tau_n$, $n = 1, 2, 3...$ Lemma 5 implies that the projection of $l(E^*, \tau_n, \frac{2\pi}{\omega_0})$ onto z-space is bounded. Also, note that the proof of Lemma 5 implies that the system (1.1)-(1.2) with $\tau = 0$, has no nonconstant periodic solution. Therefore, the projection of $l(E^*, \tau_n, \frac{2\pi}{\omega_0})$ onto the τ-space is bounded below. By the definition of τ_n, we know that $\tau_n > \frac{2\pi}{\omega_0}$ for each $n \geq 1$. To obtain a contradiction, we assume that the projection of $l(E^*, \tau_n, \frac{2\pi}{\omega_0})$ onto the τ-space is bounded. Then there exists $\overline{\tau} > \tau_n$ such that the projection of $l(E^*, \tau_n, \frac{2\pi}{\omega_0})$ onto the τ-space is included in the interval $[0, \overline{\tau})$. Inequality $\frac{2\pi}{\omega_0} < \tau_n$ and Lemma 5 imply that $0 < p < \overline{\tau}$ for $(z(t), \tau, p)$ belonging to $l(E^*, \tau_n, \frac{2\pi}{\omega_0})$. Applying Lemma 4 we have that $l(E^*, \tau_n, \frac{2\pi}{\omega_0})$ is bounded. This contradicts Lemma 6 and hence that the projection of $l(E^*, \tau_n, \frac{2\pi}{\omega_0})$ into the τ-space is $[\tau^*, +\infty)$, where $\tau^* \leq \tau_n$, $n = 1, 2, 3...$ The proof is complete.

4. Numerical application

In this section, we give a numerical simulation supporting the theoretical analysis given in Sections 2 and 3. Consider the following parameters: $\alpha = 1.636$, $\beta = 0.002$, $\delta = 0.3747$, $\sigma = 0.1181$, $\omega = 0.01184$. System (1.1)-(1.2) has two steady states $(0.3152, 0)$ and $(E^*, T^*) = (1.5535, 25.2260)$, and from Theorem 3, the critical delay $\tau_0 = 0.3854$. Thus we know that when $0 \le \tau < \tau_0$, (E^*, T^*) is asymptotically stable. When τ passes through the critical value τ_0, (E^*, T^*) loses its stability and a family of a global periodic solutions with period $P(0) = 9.8054$ bifurcating from E^* occurs (see Fig.1).

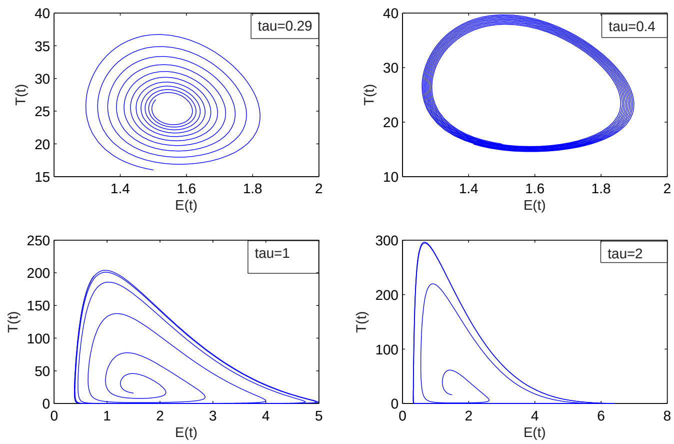

Figure 1: The steady state (E^*, T^*) is unstable when $\tau \ge 0.3854$ and a bifurcation of a periodic solution from (E^*, T^*) occurs.

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