

## Dynamics Analysis and Limit Cycle in a Delayed Model for Tumor Growth with Quiescence

R. Yafia

Université Chouaib Doukkali  
Faculté des Sciences, Département de Mathématiques et Informatique  
B.P:20, El Jadida, Morocco  
yafia\_radouane@hotmail.com

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**Abstract.** The model analyzed in this paper is based on the unstructured model set forth by Gyllenberg and Webb (1989) without delay, which describes an interaction between the proliferating and quiescent cells tumor. In the present paper we consider the model with one delay and a unique positive equilibrium  $E^*$  and the other is trivial. Their dynamics are studied in terms of the local stability of the two equilibrium points and of the description of the Hopf bifurcation at  $E^*$ , that is proven to exist as the delay (taken as a parameter) crosses some critical value. We suggest to examine in laboratory experiments how to employ these results for containing tumor growth.

**Keywords:** tumor growth with quiescence, delayed differential equations, stability, Hopf bifurcation, periodic solutions.

### 1 Introduction and mathematical model

In this paper, we are interested by a non linear unstructured model with quiescence proposed by Gyllenberg and Webb (see [1]) which employs quiescence as a mechanism to explain characteristic sigmoid growth curves. The authors consider two situations: the unstructured quiescent model and the structured one. In a series of papers (see [1–4]) the authors develop and analyze the model.

The asymptotic behavior of the structured model has been treated also by A. Grabosh in [5] by functional analytic methods and the semi group theory. In [6], the author proposes a generalization of the model and presents some sim-

plifications of A. Grabosh approach, using a perturbation argument based on the theory of semi group.

The mathematical model proposed in this paper describes the tumor growth system interaction and is given by a system of two differential equations with one delay :

$$\begin{cases} \frac{dP(t)}{dt} = bP(t - \tau) - r_P(N(t))P(t) + r_Q(N(t))Q(t), \\ \frac{dQ(t)}{dt} = r_P(N(t))P(t) - (\mu_Q + r_Q(N(t)))Q(t). \end{cases} \quad (1)$$

In biological terms,  $P(t)$  (resp.  $Q(t)$ ) is the number of proliferating (resp. quiescent) cells at time  $t$ .  $N(t) = P(t) + Q(t)$  is the total number of cells in the tumor (or the size of the tumor) at time  $t$ ;  $b = \beta - \mu_P > 0$  is the intrinsic rate of the proliferating cells (where  $\beta > 0$  is the division rate of the proliferating cells and  $\mu_P \geq 0$  is the death rate of cells of the proliferating cells),  $\mu_Q \geq 0$  is the mortality rate of the quiescent cells.  $r_P(N)$  is the (nonlinear) transition rate from the proliferating class to the quiescent class and  $r_Q(N)$  is the (nonlinear) transition rate from the quiescent class to the proliferating class. For this tumor population, one suppose that  $r_P(N)$  is nondecreasing and  $r_Q(N)$  is nonincreasing,  $r_P(N)$  and  $r_Q(N)$  are Lipschitz continuous on bounded sets of  $N$  in  $\mathbb{R}$  (see Gyllenberg and Webb [1]) and the constant  $\tau$  is the time delay which the proliferating cells needs to divide. Time delays in connection with the tumor growth also appear in Bodnar and Forys [7] and [8], Byrne [9], Forys and Kolev [10] and Forys and Maciniak-Czochra [11] and Galach [12] and Mackey *et al.* [13–20] and Agur *et al.* [21].

For  $\tau = 0$  system (1) becomes a system of ordinary differential equations given by:

$$\begin{cases} \frac{dP}{dt} = bP - r_P(N)P + r_Q(N)Q, \\ \frac{dQ}{dt} = r_P(N)P - (\mu_Q + r_Q(N))Q. \end{cases} \quad (2)$$

In [1], the authors study the existence, uniqueness and nonnegativity of solutions and they show that, under an appropriate hypotheses and using essentially the Poincare-Bendixon theorem, the nontrivial steady state  $E^*$  is globally asymptotically stable for the system (2).

In the absence of the quiescent cells, the proliferating cells in (2) follows the logistic equation  $\dot{P}(t) = bP(t)$  and the tumor becomes a malignant tumor for  $b > 0$  and becomes benign for  $b < 0$ . In the absence of proliferating cells the quiescent cells are automatically absent.

The reader interested in a more complete bibliography about the evolution of a cell, and the pertinent role that have cellular phenomena to direct the body towards the recovery or towards the illness, is addressed to [22, 23]. A detailed description of virus, antivirus, body dynamics can be found in the following references [24–27].

Our goal in this paper is to consider the case when system (1) has the unique trivial steady state and the other case when system (1) has trivial and non trivial steady states, therefore also the steady states of system (2). Taking the delay  $\tau > 0$  as a parameter, our purpose is to relate the dynamics of the two systems (without and with delay) in the neighborhood of the non trivial steady state  $E^*$  and determine the role of the delay term. To accomplish this, the local stability of  $E^*$  which is the most biologically meaningful one is established, both as an equilibrium of (1) and system (2). For (1), we prove that the Hopf bifurcation occurs at  $E^*$  as the delay crosses some critical value  $\tau_0$  and the periodic orbit may appear, which is not the case for system (2), when  $E^*$  is globally asymptotically stable for  $\tau = 0$ .

This paper is organized as follows. In Section 2, the local stability of the possible steady states of the delayed system (1) is addressed, using the delay as a parameter. Using the Hopf bifurcation theorem for delay differential equations, the study of the existence of limit cycle at the positive steady state is showed in Section 3. In Section 4, we give a short discussions.

## 2 Steady states and stability for positive delays

Consider the system (1), and define the functions  $f: \mathbb{R}^+ \rightarrow \mathbb{R}$  by

$$f(x) = \mu_Q r_P(x) - b(\mu_Q + r_Q(x))$$

and  $g: \mathbb{R}^+ \rightarrow \mathbb{R}$  by

$$g(x) = b - \mu_Q - r_P(x) - r_Q(x).$$

Let the hypotheses:

- (A<sub>1</sub>)  $f(0) < 0$ ,
- (NA<sub>1</sub>)  $f(0) > 0$ ,
- (A<sub>2</sub>)  $f(+\infty) > 0$ ,
- (A<sub>3</sub>)  $g(x) < 0$  for all  $x \geq 0$ ,
- (NA<sub>3</sub>)  $g(x) > 0$  for all  $x \geq 0$ .

**Proposition 1.** (i) Under the hypothesis (NA<sub>1</sub>),  $(0, 0)$  is the unique equilibrium point of system (1).

(ii) Under the hypotheses (A<sub>1</sub>) and (A<sub>2</sub>), system (1) has a positive non trivial equilibrium point  $E^* = (P^*, Q^*)$  and the trivial equilibrium point  $(0, 0)$ ; where  $P^*$  is the unique solution of equation  $f((1 + \frac{b}{\mu_Q})x) = 0$  and  $Q^* = \frac{b}{\mu_Q}P^*$ .

*Proof.* From the system (1) and the monotonicity of the functions  $r_P$  and  $r_Q$ , we deduce the results.  $\square$

In the next, we study the stability of the possible steady states with respect to the delay parameter  $\tau$ .

The following theorem gives the stability result for the trivial steady state  $(0, 0)$ , when its the unique equilibrium point of (1).

**Theorem 1.** Assume the hypotheses (NA<sub>1</sub>) and (A<sub>3</sub>). Then, the trivial equilibrium point  $(0, 0)$  of system (1) is asymptotically stable for all  $\tau \geq 0$ .

For the proof of Theorem 1, we need the following lemma.

**Lemma 1.** [28] Consider the equation

$$\lambda^2 + a\lambda + e + (c\lambda + d)e^{-\lambda\tau} = 0, \quad (3)$$

where  $a, b, c$  and  $d$  are real numbers. Let the hypotheses:

- (H<sub>1</sub>)  $a + c > 0$ ,
- (H<sub>2</sub>)  $e + d > 0$ ,
- (H<sub>3</sub>)  $c^2 - a^2 + 2e < 0$  and  $e^2 - d^2 > 0$   
or  $(c^2 - a^2 + 2e)^2 < 4(e^2 - d^2)$ ,

$$\begin{aligned}
 (\mathbf{H}_4) \quad & e^2 - d^2 < 0 \quad \text{or} \quad c^2 - a^2 + 2e > 0 \\
 & \text{and} \quad (c^2 - a^2 + 2e)^2 = 4(e^2 - d^2).
 \end{aligned}$$

(i) If  $(\mathbf{H}_1)$ – $(\mathbf{H}_3)$  hold, then all roots of equation (3) have negative real parts for all  $\tau \geq 0$ .

(ii) If  $(\mathbf{H}_1)$ ,  $(\mathbf{H}_2)$  and  $(\mathbf{H}_4)$  hold, then there exists  $\tau_0 > 0$  such that, when  $\tau \in [0, \tau_0)$  all roots of equation (3) have negative real parts, when  $\tau = \tau_0$  equation (3) has a pair of purely imaginary roots  $\pm i\zeta_+$ , and when  $\tau > \tau_0$  equation (3) has at least one root with positive real part, where  $\tau_0$  and  $\zeta_+$  are given by

$$\begin{aligned}
 \tau_0 &= \frac{1}{\zeta_+} \arccos \left\{ \frac{d(\zeta_+^2 - e) - ac\zeta_+^2}{c^2\zeta_+^2 + d^2} \right\}, \\
 \zeta_+^2 &= \frac{1}{2}(c^2 - a^2 + 2e) \pm \frac{1}{2}[(c^2 - a^2 + 2e)^2 - 4(e^2 - d^2)]^{\frac{1}{2}}.
 \end{aligned}$$

*Proof.* of Theorem 1.

The linearized system of (1) at the trivial steady state  $(0, 0)$  is

$$\begin{cases} \frac{dP(t)}{dt} = bP(t - \tau) - r_P(0)P(t) + r_Q(0)Q(t), \\ \frac{dQ(t)}{dt} = r_P(0)P(t) - (\mu_Q + r_Q(0))Q(t). \end{cases} \quad (4)$$

The associated characteristic equation of (4) has the following form:

$$\Delta_0(\lambda, \tau) = \lambda^2 + a\lambda + e + (c\lambda + d)e^{-\lambda\tau} = 0, \quad (5)$$

where  $a = \mu_Q + r_P(0) + r_Q(0)$ ,  $c = -b$ ,  $e = \mu_Q r_P(0)$  and  $d = -b(\mu_Q + r_Q(0))$ .

From the hypotheses  $(\mathbf{NA}_1)$  and  $(\mathbf{A}_3)$ , we deduce the hypotheses  $(\mathbf{H}_1)$  and  $(\mathbf{H}_2)$  of Lemma 1.

**Lemma 2.** *Under the hypotheses  $(\mathbf{NA}_1)$  and  $(\mathbf{A}_3)$ , then, the hypothesis  $(\mathbf{H}_3)$  of Lemma 1 is satisfied.*

From Lemma 2 and Lemma 1 (i), we conclude that all roots of equation (5) have negative real parts for all  $\tau \geq 0$ . Then the trivial equilibrium point  $(0, 0)$  is asymptotically stable for all  $\tau \geq 0$  (see [29]).  $\square$

*Proof.* of Lemma 2.

From the expressions of  $a$ ,  $b$ , and  $c$ , we have:

$$c^2 - a^2 + 2e = b^2 - (\mu_Q + r_Q(0))^2 - 2r_P(0)r_Q(0) - r_P^2(0).$$

From the hypothesis  $(\mathbf{NA}_1)$ , we have:

$$b < \frac{\mu_Q r_P(0)}{\mu_Q + r_Q(0)} \quad \text{as} \quad \mu_Q < \mu_Q + r_Q(0),$$

we deduce that  $b < r_P(0)$ . Then

$$c^2 - a^2 + 2e < -(\mu_Q + r_Q(0))^2 - 2r_P(0)r_Q(0) < 0.$$

From the expressions of  $e$  and  $d$ , we have

$$e^2 - d^2 = (\mu_Q r_P(0))^2 - b^2(\mu_Q + r_Q(0))^2$$

and from the hypothesis  $(\mathbf{NA}_1)$ , we deduce that  $e^2 - d^2 > 0$ , and the hypothesis  $(\mathbf{H}_3)$  of Lemma 1 is satisfied.  $\square$

The following theorem gives a result of instability of the trivial steady state when the non trivial steady state  $E^*$  exists.

**Theorem 2.** *Assume the hypotheses  $(\mathbf{A}_1)$  and  $(\mathbf{NA}_3)$ . Then, the trivial steady state of system (1) is unstable for all  $\tau > 0$ .*

*Proof.* Under the hypothesis  $(\mathbf{A}_1)$  and  $(\mathbf{NA}_3)$ , the hypothesis  $(\mathbf{H}_1)$  and  $(\mathbf{H}_2)$  of Lemma 1 are not satisfied. From the characteristic equation (5), the trivial steady state is unstable for  $\tau = 0$ .

Then its unstable for all  $\tau > 0$  (see [29]).  $\square$

In the next, we study the change of stability of the non trivial steady state  $E^*$ .

By the translation  $z(t) = (u(t), v(t)) = (P(t), Q(t)) - E^* \in \mathbb{R}^2$ , (1) is written as an FDE in  $C := C([- \tau, 0], \mathbb{R}^2)$  as

$$\frac{dz}{dt}(t) = L(\tau)z_t + f_0(z_t, \tau), \tag{6}$$

where  $L(\tau): C \rightarrow \mathbb{R}^2$ ,  $f_0: C \times \mathbb{R}^+ \rightarrow \mathbb{R}^2$  are given by

$$L(\tau)(\varphi) = \begin{pmatrix} b\varphi_1(-\tau) + (-r_P(N^*) - r'_P(N^*)P^* + r'_Q(N^*)Q^*)\varphi_1(0) \\ + (r_Q(N^*) - r'_P(N^*)P^* + r'_Q(N^*)Q^*)\varphi_2(0) \\ (r_P(N^*) + r'_P(N^*)P^* - r'_Q(N^*)Q^*)\varphi_1(0) \\ - (\mu_Q + r_Q(N^*) - r'_P(N^*)P^* + r'_Q(N^*)Q^*)\varphi_2(0) \end{pmatrix},$$

$$f_0(\varphi, \tau) = \begin{pmatrix} bP^* - r_P(\varphi_1(0) + \varphi_2(0) + N^*)(\varphi_1(0) + P^*) \\ + r_Q(\varphi_1(0) + \varphi_2(0) + N^*)(\varphi_2(0) + Q^*) \\ - (-r_P(N^*) - r'_P(N^*)P^* + r'_Q(N^*)Q^*)\varphi_1(0) \\ - (r_Q(N^*) - r'_P(N^*)P^* + r'_Q(N^*)Q^*)\varphi_2(0) \\ r_P(\varphi_1(0) + \varphi_2(0) + N^*)(\varphi_1(0) + P^*) \\ - (\mu_Q + r_Q(\varphi_1(0) + \varphi_2(0) + N^*))(\varphi_2(0) + Q^*) \\ - (r_P(N^*) + r'_P(N^*)P^* - r'_Q(N^*)Q^*)\varphi_1(0) \\ + (\mu_Q + r_Q(N^*) - r'_P(N^*)P^* + r'_Q(N^*)Q^*)\varphi_2(0) \end{pmatrix},$$

where  $N^* = P^* + Q^*$  and  $\varphi = (\varphi_1, \varphi_2) \in C$ .

The characteristic equation of the linear equation

$$\dot{z}(t) = L(\tau)z_t \quad (7)$$

is given by

$$\Delta_1(\lambda, \tau) = \lambda^2 + p\lambda + r + (s\lambda + q)e^{-\lambda\tau} = 0, \quad (8)$$

where  $p$ ,  $s$ ,  $r$ , and  $q$  have the following expressions:

$$\begin{aligned} p &= \mu_Q + r_P(N^*) + r_Q(N^*), & s &= -b, \\ r &= \mu_Q(r_P(N^*) + r'_P(N^*)P^* - r'_Q(N^*)Q^*), \\ q &= -b(\mu_Q + r_Q(N^*) - r'_P(N^*)P^* + r'_Q(N^*)Q^*). \end{aligned}$$

Let the hypothesis:

(**A<sub>4</sub>**)  $0 < \frac{\mu_Q}{b} < G(x, y)$  for all  $x, y > 0$ , where the function  $G: \mathbb{R}^{+2} \rightarrow [0, 1[$  is defined by:

$$G(x, y) = \frac{r'_P(x+y)x - r'_Q(x+y)y}{2r_P(x+y) + r'_P(x+y)x - r'_Q(x+y)y}.$$

The following theorem gives the result of change of stability of the non trivial steady state.

**Theorem 3.** *Assume the hypotheses (A<sub>1</sub>)–(A<sub>4</sub>) and the functions  $r_P$  (increasing function) and  $r_Q$  (decreasing function) are of class  $C^1$ . Then, there exists a critical value  $\tau_0$  of the time delay, such that the non trivial steady state  $E^*$  is asymptotically stable for  $\tau \in [0, \tau_0[$  and unstable for  $\tau > \tau_0$ , where*

$$\tau_0 = \frac{1}{\zeta_+} \arccos \left\{ \frac{q(\zeta_+^2 - r) - ps\zeta_+^2}{s^2\zeta_+^2 + q^2} \right\}, \quad (9)$$

and

$$\zeta_+^2 = \frac{1}{2}(s^2 - p^2 + 2r) + \frac{1}{2}[(s^2 - p^2 + 2r)^2 - 4(r^2 - q^2)]^{\frac{1}{2}}. \quad (10)$$

*Proof.* The hypotheses (A<sub>1</sub>) and (A<sub>2</sub>) imply the existence of the non trivial steady state  $E^*$ .

From the expressions of  $p$ ,  $s$ ,  $r$  and  $q$  we have that:

$$p + s = -b + \mu_Q + r_P(N^*) + r_Q(N^*)$$

and

$$q + r = (\mu_Q + b)(r'_P(N^*)P^* - r'_Q(N^*)Q^*)$$

(because  $N^* = P^* + Q^*$  is the solution of the equation  $f(x) = 0$ ).

From the hypothesis (A<sub>3</sub>) and the monotonicity property of  $r_P$  and  $r_Q$ , we deduce the inequalities of the hypotheses (H<sub>1</sub>) and (H<sub>2</sub>) of Lemma 1 (with  $p = a$ ,  $r = e$ ,  $s = c$  and  $q = d$ ).

By Rouché's theorem, it follows that the roots of equation (8) have negative real parts for the delay  $\tau$  small than some critical value of the delay.

We want to determine if the real part of some root increase to reach zero and eventually becomes positive as  $\tau$  varies. If  $i\zeta$  is a root of equation (8), then

$$-\zeta^2 + ip\zeta + is\zeta(\cos(\tau\zeta) + i\sin(\tau\zeta)) + r + q(\cos(\tau\zeta) + i\sin(\tau\zeta)) = 0. \quad (11)$$

Separating the real and imaginary parts, we have

$$\begin{cases} -\zeta^2 + r = -q \cos(\tau\zeta) + s\zeta \sin(\tau\zeta), \\ p\zeta = -s\zeta \cos(\tau\zeta) - q \sin(\tau\zeta). \end{cases} \quad (12)$$

It follows that  $\zeta$  satisfies

$$\zeta^4 - (s^2 - p^2 + 2r)\zeta^2 + (r^2 - q^2) = 0. \quad (13)$$

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

$$\zeta^2 = \frac{1}{2}(s^2 - p^2 + 2r) \pm \frac{1}{2}[(s^2 - p^2 + 2r)^2 - 4(r^2 - q^2)]^{\frac{1}{2}}. \quad (14)$$

We are now in a position to calculate  $r^2 - q^2$ .

From the expressions of  $r$  and  $q$ , we have:

$$\begin{aligned} r^2 - q^2 &= (\mu_Q + b)(r'_P(N^*)P^* - r'_Q(N^*)Q^*) \\ &\quad \times (2\mu_Q r_P(N^*) + (\mu_Q - b)(r'_P(N^*)P^* - r'_Q(N^*)Q^*)). \end{aligned}$$

From the monotonicity property of the functions  $r_P$  and  $r_Q$ , we have:

$$(\mu_Q + b)(r'_P(N^*)P^* - r'_Q(N^*)Q^*) > 0.$$

From the hypothesis (**A**<sub>4</sub>), we have:

$$2\mu_Q r_P(N^*) + (\mu_Q - b)(r'_P(N^*)P^* - r'_Q(N^*)Q^*) < 0$$

and the hypothesis (**H**<sub>4</sub>) of Lemma 1 is satisfied.

From Lemma 1, the unique solution of equation (8) has the following form

$$\zeta_+^2 = \frac{1}{2}(s^2 - p^2 + 2r) + \frac{1}{2}[(s^2 - p^2 + 2r)^2 - 4(r^2 - q^2)]^{\frac{1}{2}}$$

and there exists a unique critical value of the time delay

$$\tau_0 = \zeta_+^{-1} \arccos \left\{ \frac{q(\zeta_+^2 - r) - ps\zeta_+^2}{s^2\zeta_+^2 + q^2} \right\}$$

such that, the steady state  $z = 0$  of system (6) (i.e.  $E^*$  of system (1)) is asymptotically stable for  $\tau \in [0, \tau_0[$  and unstable for  $\tau > \tau_0$ , and we deduce (ii) of Theorem 5.  $\square$

### 3 Hopf bifurcation occurrence

In this section, we will study the occurrence of Hopf bifurcation by using the time delay as a parameter of bifurcation.

In what follows, we recall the formulation of the Hopf bifurcation Theorem for retarded differential equations.

**Theorem 4.** [29] *Let the equation*

$$\frac{dx(t)}{dt} = F(\alpha, x_t) \quad (15)$$

with  $F: \mathbb{R} \times C \rightarrow \mathbb{R}^n$ ,  $F$  of class  $\mathcal{C}^k$ ,  $k \geq 2$  and  $F(\alpha, 0) = 0 \forall \alpha \in \mathbb{R}$  and  $C = C([-r, 0], \mathbb{R}^n)$  the space of continuous functions from  $[-r, 0]$  to  $\mathbb{R}^n$ . As usual,  $x_t$  is the function defined from  $[-r, 0]$  into  $\mathbb{R}^n$  by  $x_t(\theta) = x(t + \theta)$ ,  $r \geq 0$  and  $n \in \mathbb{N}^*$ .

We will make the following assumptions:

(**M<sub>0</sub>**)  $F$  of class  $\mathcal{C}^k$ ,  $k \geq 2$  and  $F(\alpha, 0) = 0 \forall \alpha \in \mathbb{R}$ , and the map  $(\alpha, \varphi) \rightarrow D_\varphi^k F(\alpha, \varphi)$  sends bounded sets into bounded sets.

(**M<sub>1</sub>**) The characteristic equation

$$\det \Delta(\alpha, \lambda) = \lambda Id - D_\varphi F(\alpha, 0) \exp(\lambda(\cdot)Id) \quad (16)$$

of the linearized equation of (15) around the equilibrium  $v = 0$ :

$$\frac{dv(t)}{dt} = D_\varphi F(\alpha, 0)v_t \quad (17)$$

has in  $\alpha = \alpha_0$  a simple imaginary root  $\lambda_0 = \lambda(\alpha_0) = i$ , all others roots  $\lambda$  satisfy  $\lambda \neq m\lambda_0$  for  $m \in \mathbb{Z}$ .

((**M<sub>1</sub>**) implies notably that the root  $\lambda_0$  lies on a branch of roots  $\lambda = \lambda(\alpha)$  of equation (16), of class  $\mathcal{C}^{k-1}$ ).

(**M<sub>2</sub>**)  $\lambda(\alpha)$  being the branch of roots passing through  $\lambda_0$ , we have

$$\frac{\partial}{\partial \alpha} \operatorname{Re} \lambda(\alpha)|_{\alpha=\alpha_0} \neq 0 \quad (18)$$

Under the assumptions ( $M_0$ ), ( $M_1$ ) and ( $M_2$ ), there exist constants  $\varepsilon_0 > 0$  and  $\delta_0$  and functions  $\alpha(\varepsilon)$ ,  $T(\varepsilon)$  and a  $T(\varepsilon)$ -periodic function  $x^*(\varepsilon)$ , such that:

- (i) All of these functions are of class  $\mathcal{C}^{k-1}$  with respect to  $\varepsilon$ , for  $\varepsilon \in [0, \varepsilon_0[$ ,  
 $\alpha(0) = \alpha_0$ ,  $T(0) = 2\pi$ ,  $x^*(0) = 0$ ;
- (ii)  $x^*(\varepsilon)$  is a  $T(\varepsilon)$ -periodic solution of (15), for the parameter value equal  
 $\alpha(\varepsilon)$ ;
- (iii) For  $|\alpha - \alpha_0| < \delta_0$  and  $|T - 2\pi| < \delta_0$ , any  $T$ -periodic solution  $p$ , with  
 $\|p\| < \delta_0$ , of (15) for the parameter value  $\alpha$ , there exists  $\varepsilon \in [0, \varepsilon_0[$  such  
 that  $\alpha = \alpha(\varepsilon)$ ,  $T = T(\varepsilon)$  and  $p$  is, up to a phase shift, equal to  $x^*(\varepsilon)$ .

The next theorem gives a result on the existence of limit cycle of system (1) at the non trivial steady state  $E^*$ .

**Theorem 5.** Assume the hypotheses  $(\mathbf{A}_1)$ – $(\mathbf{A}_4)$  and the functions  $r_P$  and  $r_Q$  are of class  $\mathcal{C}^1$ .

Then, there exists  $\varepsilon_0 > 0$  such that, for each  $0 \leq \varepsilon < \varepsilon_0$ , equation (1) 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  $p_l(0) = E^*$ ,  $T_l(0) = \frac{2\pi}{\zeta_+}$  and  $\tau(0) = \tau_0$ , where  $\tau_0$  and  $\zeta_+$  are given respectively in equations (9) and (10).

*Proof.* We apply the Hopf bifurcation Theorem 4. From the expression of  $f_0$  in (6), we have,

$$f_0(0, \tau) = 0 \quad \text{and} \quad \frac{\partial f_0(0, \tau)}{\partial \varphi} = 0 \quad \text{for all } \tau > 0.$$

From (8), (9), (10) and Theorem 5, we have:

$$\Delta_1(i\zeta, \tau) = 0 \quad \iff \quad \zeta = \zeta_+ \quad \text{and} \quad \tau = \tau_0.$$

Thus, the characteristic equation (8) has a pair of simple imaginary roots  $\lambda_0 = i\zeta_+$  and  $\bar{\lambda}_0 = -i\zeta_+$  at  $\tau = \tau_0$ .

Lastly, we need to verify the transversality condition.

From (8),

$$\Delta_1(\lambda_0, \tau_0) = 0 \quad \text{and} \quad \frac{\partial}{\partial \lambda} \Delta_1(\lambda_0, \tau_0) \neq 0.$$

According to the implicit function theorem, there exists a complex function  $\lambda = \lambda(\tau)$  defined in a neighborhood of  $\tau_0$ , such that  $\lambda(\tau_0) = \lambda_0$  and  $\Delta_1(\lambda(\tau), \tau) = 0$  and

$$\lambda'(\tau) = -\frac{\partial \Delta_1(\lambda, \tau)/\partial \tau}{\partial \Delta_1(\lambda, \tau)/\partial \lambda}, \quad \text{for } \tau \text{ in a neighborhood of } \tau_0. \quad (19)$$

Let  $\lambda(\tau) = \mu(\tau) + i\nu(\tau)$ . From (19) we have:

$$\mu'(\tau)|_{\tau=\tau_0} = \zeta_+ \frac{\zeta_+ p A + (\zeta_+^2 - r) B}{A^2 + B^2},$$

where

$$A = -\tau_0 \zeta_+^2 + p + \tau_0 r + s \cos(\tau_0 \zeta_+)$$

and

$$B = \zeta_+ (2 + \tau_0 p) - s \sin(\tau_0 \zeta_+).$$

From equation (8), we have:

$$\begin{aligned} \cos(\tau_0 \zeta_+) &= \frac{q(\zeta_+^2 - r) - ps\zeta_+^2}{s^2\zeta_+^2 + q^2} \\ \sin(\tau_0 \zeta_+) &= -\frac{s}{q} \cos(\tau_0 \zeta_+) - \frac{p}{q} \zeta_+. \end{aligned}$$

Then

$$\begin{aligned} \mu'(\tau)|_{\tau=\tau_0} &= \frac{\zeta_+^2}{A^2 + B^2} (3s^2\zeta_+^4 + (2q^2 - 4rs^2 + 2spq)\zeta_+^2 - 2rq^2 - 2spqr + s^2r^2). \end{aligned} \quad (20)$$

From the characteristic equation (8),  $\zeta_+$  is a solution of the following equation

$$\zeta^4 - (s^2 - p^2 + 2r)\zeta^2 + r^2 - q^2 = 0. \quad (21)$$

From equations (20) and (21), we conclude that

$$\mu'(\tau)|_{\tau=\tau_0} \neq 0.$$

□

#### 4 Discussions

In [1], the following conditions of global stability of the non trivial steady states  $E^*$  for  $\tau = 0$  were proposed

$$\begin{aligned} b - \mu_Q - r_P(N) - r_Q(N) &< 0, \quad \forall N > 0, \\ \mu_Q r_P(0) &< b(\mu_Q + r_Q(0)), \\ b\left(1 + \frac{r_Q(+\infty)}{\mu_Q}\right) &< r_P(+\infty). \end{aligned}$$

Therefore, for any non trivial solution  $(P(t), Q(t))$  with nonnegative initial conditions of system (2) goes to  $E^*$  when  $t \rightarrow +\infty$ , which means that the tumor is always a benign tumor, but in the reality this is not the case it may be a malignant tumor or take an oscillatory form (see [30–32]).

In this paper we introduce a parameter families time delay ODE systems (1) in order to achieve a better compatibility with reality. We give an analytical study of stability (with respect to the time delay  $\tau$ ) of the possible steady states 0 and  $E^*$  for the positive values of the parameter delay  $\tau$  and we study each case separately.

In the end, we prove that, system (1) has a family of periodic solutions bifurcating from the non-trivial steady state, using the time delay as a parameter of bifurcation. We prove that the stationary point  $E^*$  is stable focus, when  $\tau < \tau_0$ . When  $\tau > \tau_0$ , it turns into unstable focus. Physiologically it means, that the system (1) has a stable positive position  $E^*$ , when  $\tau < \tau_0$ . In this case the growth of the tumor is stopped by the medical cure (chemotherapy or irradiation). After extension of influence of the medical cure (the parameter  $\tau$ ) the stable positive equilibrium is lost and the tumor starts oscillate. Because of those oscillations the tumor can disappear or the patient can dye.

The results proposed in this paper should hopefully improve the understanding of the qualitative properties of the description delivered by model (1). So far we have now a description of stability properties and Hopf bifurcation with a detailed analysis of the influence of delays terms.

For the studies of direction of Hopf bifurcation and stability of the periodic orbits and the same analysis for structural population dynamics [1] are our aims in the next paper.

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