PERIODIC SOLUTIONS IN A TUMOR-IMMUNE COMPETITION SYSTEM WITH TIME-DELAY AND CHEMOTHERAPY EFFECTS

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Abstract. The main purpose of this paper is to analyze the dynamics of the system of time-delay differential equations (DDEs)

$$\dot{T}(t) = T(t)f(t, T(t)) - \gamma E(t)T(t),$$
$$\dot{E}(t) = \sigma + \frac{pE(t)T(t-\tau_1)}{g + aT(t-\tau_1)} - \frac{mE(t)T(t-\tau_2)}{g + aT(t-\tau_2)} - \eta E(t),$$

where $T = T(t)$ and $E = E(t)$ represent the concentrations of tumor and effector cells at the time t. The coefficients σ, μ, γ, and η are all positive, and $f(t, T)$ represents the relative growth rate of tumor cells, corresponding to a generalized logistic growth function that describes periodic time chemotherapeutic effects. The parameter $\tau_1 \in \mathbb{R}_{\geq 0}$ is the response time delay of the immune system (mediated by effector cells) to an invasion of tumor cells, while $\tau_2 \in \mathbb{R}_{\geq 0}$ represents the time delay of tumor cells in response to the appearance of effector cells.

1. Introduction

A tumor is an abnormal growth of body tissue that the immune system can normally control in most cases. The formation of a tumor often occurs due to an immune system issue in the body [1]. Many works in the literature describe tumor growth, e.g., The tumor growth curves are classically exponential, logistic, and Gompertz using a population approach. In analyzing the Gompertz model, several studies have reported a striking correlation between the two parameters of the model, which could be used to reduce dimensionality and improve predictive power. Candidate models of tumor growth included exponential, logistic, and Gompertz models. The exponential and more notable logistic models failed to describe the experimental data, whereas the Gompertz model generated better fits [2].

Several mathematical models have been developed for the interactions between the immune system and a growing tumor. In [3] for $T := T(t)$ and $E := E(t)$ functions depending of time representing the concentrations of tumor and effector cells at time t, the authors consider a logistic relative growth rate, i. e. $f(T) = r\left(1 - \frac{T}{K}\right)$, where r and K are the maximal growth rate and the carrying capacity of the biological environment of the tumor cells, the following

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system is obtained:

$$\begin{aligned}\dot{T} &= rT\Big(1-\frac{T}{K}\Big)-\gamma E(t)T(t),\\ \dot{E} &= \sigma+\frac{pE(t)T(t-\tau)}{g+aT(t-\tau)}-E(t)\big(mT(t)+\eta\big).\end{aligned} \tag{1}$$

This manuscript considers the following periodic tumor-immune system with delays inspired by the work of J. Li et. al. [4]

$$\begin{aligned}\dot{T}(t) &= T(t)f(t,T(t))-\gamma E(t)T(t),\\ \dot{E}(t) &= \sigma+\frac{pE(t)T(t-\tau_1)}{g+aT(t-\tau_1)}-\frac{mE(t)T(t-\tau_2)}{g+aT(t-\tau_2)}-\eta E(t),\end{aligned} \tag{2}$$

Table 1. Description of parameters of Eq. (2).

Variables/Parameters	**Interpretation**
$T(t)$	Concentrations of tumor cells (T-cells) at time t
$E(t)$	Concentrations of effector cells (E-cells) at time t
$Tf(t,T)$	Time variable growth rate function of the tumor cells
γ	Rate at which effector cells damage (kill) the tumor cells
σ	Constant input of effector cells
$pET/(g+aT)$	Recruiment term of E-cells by stimulation of T-cells
p	Maximum recruitment coefficient of E-cells cells by stimulation of T-cells
$mET/(g+aT)$	Neutralization term of E-cells by stimulation of T-cells
m	Maximum decline rate of E-cells by T-cells
g, a	Parameters associated to the Holling's type functional response $\frac{T}{g+aT}$. g^{-1}-rate attack. a-handling time

for which, in the absence of effector cells, the relative growth rate of tumor cells is given by the time-periodic Richards-type equation, see [5]

$$f(t,T)=r\Big[\frac{(1-T^{\beta})}{\beta}-b(t)\Big],$$

where $r>0$ is the Malthusian parameter of the tumor cells, $b(t)\in C(\mathbb{R}/q\mathbb{Z})$ (continuous and q-periodic function) that represents chemotherapeutic effects on the tumor cell mass, see [6] and $0<\beta\le 1$ is a real parameter that provides well-known growth functions like

$$\text{Logistic relative growth rate } (\beta=1) \quad \Rightarrow \quad f(r,T)=r\big[(1-T)-b(t)\big],$$

$$\text{Gompertz relative growth rate } (\beta\searrow 0) \quad \Rightarrow \quad f(r,T)=r\big[\ln\frac{1}{T}-b(t)\big].$$

Notice that, without loss of generality, we assumed that the carrying capacity of the biological environment of the tumor cells is equal to 1.

In this study, we focus mainly on the effects of time delays on the dynamics of tumor and effector cell concentrations and the existence of periodic solutions of (2) as a continuation of specific equilibrium solutions. The rest of the paper is organized into five sections and one appendix. In Section 2 we introduce some well-known results on the existence and stability of equilibria solutions and periodic solutions for delayed systems. In this section 3, we obtain the equilibrium points for equation 2 in terms of the different parameters associated with this system. In sections 4 and 5 we present our main results: First, we provide an explicit interval of delay parameters for the local stability of two of the equilibrium points in the delayed autonomous. Secondly, we state and prove two results about the existence of periodic solutions of (2) via the continuation method adapted to our work. In Section 6 we perform some computational results, often using graphs and phase portraits, to visually validate the theoretical findings from the stability and bifurcation analysis.

2. Theoretical Background

This section presents the theoretical background for the main aspects discussed in this document. Firstly, we analyze the linear stability of the equilibria of (2) together with the stability switch curves in the plane $(\tau_1, \tau_2) \in \mathbb{R}^2_+$. Secondly, we provide a theoretical scenario that will allow us to study the existence of ω-periodic solutions of (2) considered as a perturbation of an autonomous nondelayed system.

On the stability of equilibria for delayed linear systems with two delays. We finish this section with the following general result on the following linear delay system

$$\dot{Y} = A_0 Y + A_1 Y(t-\tau_1) + A_2 Y(t-\tau_2), \tag{3}$$

with $A_0, A_1, A_2 \in \mathbb{M}_{2\times 2}$ constant real matrices, $Y \in \mathbb{R}^2$ and $\tau_1, \tau_2 \geq 0$. Assume that $\det A_1 = \det A_2 = 0$. Following the results in Appendix B, the associated characteristic equation is given by:

$$\mathcal{P}(\lambda, \tau_1, \tau_2) = 0, \quad \text{with} \quad \mathcal{P}(\lambda, \tau_1, \tau_2) = p_0(\lambda) + p_1(\lambda)e^{-\lambda\tau_1} + p_2(\lambda)e^{-\lambda\tau_2} + p_3(\lambda)e^{\lambda(\tau_1+\tau_2)} \tag{4}$$

where

$$\begin{aligned} p_0(\lambda) &= \lambda^2 - (trA_0)\lambda + \det A_0, \\ p_1(\lambda) &= C_{A_0A_1} - (trA_1)\,\lambda, \qquad\qquad \text{and} \qquad C_{A_iA_j} = \det(A_i^1|A_j^2) + \det(A_j^1|A_i^2), \\ p_2(\lambda) &= C_{A_0A_2} - (trA_2)\,\lambda, \\ p_3(\lambda) &= C_{A_1A_2}, \end{aligned} \tag{5}$$

Here, $\det(a^1|b^2)$ denotes the matrix with the first column and the second column of the matrices.

$$A = [a^1, a^2] \quad \text{and} \quad B = [b^1, b^2],$$

respectively. Notice that the analytic function $p_i(\lambda)$ satisfies the following

a. $\deg(p_0(\lambda)) = 2 > 1 \geq \deg(p_i(\lambda))$ with $i = 1, 2, 3$.
b. $p_i(\lambda)$ have no common factors.

c. For all $s \in \mathbb{R}$, $p_l(is) \neq 0$, for $l = 1, 2, 3$.
d. On $\mathbb{C}$ we have

$$\lim_{|\lambda|\to\infty} \sup \left(\left|\frac{p_1(\lambda)}{p_0(\lambda)}\right| + \left|\frac{p_2(\lambda)}{p_0(\lambda)}\right| + \left|\frac{p_3(\lambda)}{p_0(\lambda)}\right| \right) = 0.$$

We need the following condition

H1) Finite number of characteristic roots on $\mathbb{C}_+ = \{\lambda \in \mathbb{C} : \mathrm{Re}(\lambda) > 0\}$
H2) $\lambda = 0$ is not a characteristic root for any τ_1, τ_2, i.e., $p_0(0) + p_1(0) + p_2(0) + p_3(0) \neq 0$.

In the following, we present some well-known results on the solutions $\lambda = \lambda(\tau_1, \tau_2)$ of (4). The simplest case emerges when both delays are zero. Direct and easy computations prove the following.

Lemma 1. *For $\tau_1 = \tau_2 = 0$, the roots $\lambda = \lambda(0,0)$ satisfy the quadratic equation*

$$P(\lambda, 0, 0) = \lambda^2 - tr\mathcal{A}\,\lambda + \det \mathcal{A},$$

with $\mathcal{A} = A_0 + A_1 + A_2$. Moreover, if

$$tr\mathcal{A} < 0 \quad \textit{and} \quad \det \mathcal{A} > 0,$$

the trivial solution $Y(t) = \mathbf{0}$ of (3) is locally asymptotically stable. Meanwhile, if

$$tr\mathcal{A} > 0, \quad \textit{or} \quad tr\mathcal{A} = 0 \quad \textit{and} \quad \det \mathcal{A} < 0.$$

hold, is unstable.

On the stability switching curves. In the next lines, we present some well-known results about the stability switching curves of delayed systems with two delays and delay-independent coefficients; see [7]

Lemma 2. *Assume $\tau_1, \tau_2 \in \mathbb{R}_+$. As (τ_1, τ_2) varies continuously in $\mathbb{R}^2_+$ the number of characteristic roots (including their multiplicities) of $P(\lambda, \tau_1, \tau_2)$ on $\mathbb{C}_+$, can change only if a characteristic roots appear on or cross the imaginary axis.*

From this result, we are looking for solutions of (4) of the form $\lambda = i\vartheta$ with $\vartheta \in \mathbb{R}_+$

Periodic solutions. The end of this section is devoted to establish a general abstract result for the existence of ω-periodic solutions of the system

$$X'(t) = \Phi(X(t), y), \tag{6}$$

where the parameter y belongs to an appropriate Banach space Y. In more precise terms, let C_ω denote the set of continuous ω-periodic functions $X : \mathbb{R} \to \mathbb{R}^n$ and $C^1_\omega := C_\omega \cap C^1(\mathbb{R}, \mathbb{R}^n)$. Assume that $\mathcal{O} \subset C_\omega \times Y$ is open and $\Phi : \mathcal{O} \to C_\omega$ is a continuously Fréchet differentiable operator, then the operator $\mathcal{F} : C^1_\omega \times Y \to \mathbb{R}^n$ given by

$$\mathcal{F}(X, y) := X' - \Phi(X, y)$$

is well defined and continuously differentiable. For instance, with system (2) in mind, we may set $b(t) := b_0 + \varphi(t)$ with $\varphi \in C_\omega$, $\tau := (\tau_1, \tau_2)$ and $Y := C_\omega \times \mathbb{R}^2$. The right-hand side of the system, which is generically written as $F(t, X(t), X(t-\tau_1), X(t-\tau_2))$, can be equivalently expressed in the form $\Phi(X, \varphi, \tau)$ with the help of the continuous operators $X \mapsto X_{\tau_j}$ defined on C_ω by $X_{\tau_j}(t) := X(t-\tau_j)$ for $j=1,2$. When $y=(\varphi,\tau)=0$, the system is autonomous and has no delay; given an equilibrium point X_0, our goal consists in finding a smooth branch of ω-periodic solutions $X = X(y)$ such that $X(0) = X_0$. The following result is a direct consequence of the Implicit Function Theorem, combined with the Fredholm alternative:

Theorem 3. *In the previous context, let X_0 be a solution of the system $\mathcal{F}(X,0)=0$ and assume that the linear system*

$$Z'(t) = D_X\Phi(X_0,0)Z(t),$$

where D_X denotes the Fréchet partial derivative with respect to X, has no nontrivial ω-periodic solutions. Then there exist open sets $\mathcal{V},\mathcal{W}$ with $0\in\mathcal{V}\subset Y$, $X_0\in\mathcal{W}\subset C_\omega$ and a unique smooth function $X:\mathcal{V}\to\mathcal{W}$ such that $X(0)=X_0$ and $X(y)$ is a solution of (6) for each $y\in\mathcal{V}$.

Focusing on the application to (2), it shall be useful to recall the following simple criterion:

Lemma 4. *Let $M\in\mathbb{R}^{n\times n}$ and consider the linear operator $L : C^1_\omega \to C_\omega$ given by $LZ := Z' - MZ$. Then $\ker(L) = \{0\}$ if and only if $\pm\frac{2k\pi}{\omega}i$ is not an eigenvalue of M for any $k\in\mathbb{N}_0$.*

3. Basic Results

In this section, we study some basic results on the system (2). Firstly, let us define $X := (T,E)^{tr}$. Under this notation,

$$X(t) = (T(t),E(t))^{tr},\quad X_{\tau_1}(t) := X(t-\tau_1),\quad X_{\tau_2}(t) := X(t-\tau_2),$$

is a solution of (2) if $X = X(t)$ satisfies the non-autonomous delayed system

$$\dot{X}(t) = F(t,X(t),X_{\tau_1}(t),X_{\tau_2}(t)), \tag{7}$$

with $F(t,X(t),X_{\tau_1}(t),X_{\tau_2}(t))$ given by

$$F(t,X,X_{\tau_1},X_{\tau_2}) = \begin{pmatrix} T\big(f(t,T)-\gamma E\big) \\ \sigma + E\big(ph(T_{\tau_1}) - mh(T_{\tau_2}) - \eta\big)\end{pmatrix} \quad \text{with} \quad h(s) = \frac{s}{g+as}. \tag{8}$$

We prove this for our system (7) subject to the initial condition.

$$T(s) = \Psi_1(s),\quad E(s) = \Psi_2(s),$$
$$\Psi_1(s),\Psi_2(s)\geq 0,\ s\in[-\tau,0],\quad \Psi_1(0),\Psi_2(0)\geq 0,$$

where $\Psi(s) := (\Psi_1(s),\Psi_1(s)) \in C([-\tau,0],\mathbb{R}^2_+)$ the Banach space of continuous functions mapping $[-\tau,0]$ to $\mathbb{R}^2_+$ with $\tau = \max\{\tau_1,\tau_2\}$, $\|\Psi\| = \sup_{-\tau\leq s\leq 0}|\Psi_i(s)|$ and $\mathbb{R}^2_+ = \{(x_1,x_2)|\, x_i\geq 0)\}$. In addition, (8) is a Lipschitz continuous function, then, locally, there exists a unique solution $X = X(t,\Psi)$ for any continuous initial function Ψ.

3.1. **Two fundamental properties.** Let us start with an analogous result of Lemma 1 and Lemma 5 in [8] about the positivity and maximal interval of existence of solutions with non-negative initial conditions and the non-existence of non-negative periodic orbits in (2) for $\tau_1,\tau_2\geq 0$.

Theorem 5. *Any solution $X(t,\Phi)$ of (2) globally defined for all $\Phi \in C([-\tau,0],\mathbb{R}^2_+)$ and is positive, i.e., $T(t) \geq 0$ and $E(t) \geq 0$ for all $t \in \mathbb{R}$.*

Proof. From the existence and uniqueness theorem, for each $X_0 = (\Psi_1(0),\Psi_2(0))$, with $\Psi_1(0),\Psi_2(0) \geq 0$, there exists a unique solution $X(t)$ of (2) satisfying $X(0) = X_0$, defined in some interval $(0,\omega_+)$ with $\omega_+ \leq \infty$. Let us define the function

$$\mathcal{K}(t) := \int_0^t (f(s,T(s)) - \gamma E(s))\, ds.$$

A direct computation of the first equation of (2) shows that

$$\frac{d}{dt}(\exp[-\mathcal{K}(t)]T(t)) = \exp[-\mathcal{K}(t)]\big(-\mathcal{K}(t)T(t)+\mathcal{K}(t)T(t)\big) = 0 \quad \Rightarrow \quad T(t) = \Psi(0)\exp\Big[\mathcal{K}(t)\Big].$$

That is,

$$T(t) = \Psi(0)\exp\Big[\int_0^t (f(s,T(s)) - \gamma E(s))\, ds,$$

showing that $T(t) \geq 0$ for all $t \in (0,\omega_+)$. Similarly, from the second equation of (2) we have

$$\dot{E}(t) \geq E\big(ph(T_{\tau_1}) - mh(T_{\tau_2}) - \eta\big),$$

therefore,

$$\dot{E}(t) \geq \Psi_2(0)\exp\Big[\int_0^t \big(ph(T_{\tau_1}) - mh(T_{\tau_2}) - \eta\big)\, ds\Big].$$

and then $E(t) \geq 0$ for all $t \in (0,w_+)$. Since $T(t)$ and $E(t)$ are positive and well-defined for all $t \in (0,w_+)$ for some $w_+ \leq \infty$, we have

$$T'(t) \leq T(t)f(t,T(t)) \quad \Rightarrow \quad T(t) \leq T_M := \max\Big\{T(0), [(1-\beta b_{\min})/r]^{1/\beta}\Big\}.$$

where $b_{\min} := \min b(t)$. Coming back to the equation of $E(t)$, we have

$$E'(t) \leq \sigma + \kappa E(t), \quad \text{with} \quad \kappa = \begin{cases} -\eta & \text{if} \quad m \geq p, \\ (p-m)h(T_M) - \eta & \text{if} \quad m < p, \end{cases}$$

therefore

$$E(t) \leq \exp[\kappa t]\Big(E(0) + \sigma\int_0^t \exp[-\kappa s]\, ds\Big).$$

The previous computations imply that $\omega_+ = \infty$, otherwise if $\omega_+ < \infty$, from the classical results of the continuation of solutions we have $\lim\limits_{t\to\omega_+^-} |X(t)| = \infty$ which is a contradiction. $\square$

Remark 1. *Alternatively, the global definition of any solution can be established by the following argument:*

$$\dot{E}(t) \leq \sigma + pE(t),$$

implying that $E(t)$ globally defined. Then, for $T(t)$ we have

$$\dot{T}(t) \leq T(t)(\kappa - \gamma E(t)), \quad \textit{with} \quad k := \max_{\mathbb{R}\times\mathbb{R}^+} f(t,T),$$

proving that $T(t)$ is globally defined.

Lemma 6. *Assume* $\tau = (0,0)$. *Then, there are no non-negative and non-trivial periodic solutions of the system* (18).

Proof. For $X = (T,E)^{tr}$, consider the auxiliary scalar function $L : \mathbb{R}^2_+ \to \mathbb{R}_+$, $L(X) = \frac{1}{TE}$. Define the vector field $\tilde{F} : \mathbb{R}^2_+ \to \mathbb{R}^2_+$, $X \to \tilde{F}(X)$ given by

$$\tilde{F}(X) = L(X)F(X) = \begin{pmatrix} \frac{f(T)}{E} - \gamma \\ \frac{\sigma}{TE} + \frac{p}{g+aT} - \frac{mT+\eta}{T} \end{pmatrix}$$

Then, the divergence of $\tilde{F}$ is computed as

$$\nabla \cdot \tilde{F}(X) = -\frac{1}{E}\Big(r\beta T^{\beta-1} + \frac{\sigma}{TE}\Big) < 0,$$

by Dulac-Bendixson Theorem, it follows that (18) does not admit closed orbits in $\mathbb{R}^2_+$ □

Let us begin with some results on the existence and stability of equilibrium points for the associated autonomous system, i.e., when $b(t) = \hat{b}$ for all $t \in \mathbb{R}$, with $\hat{b} \in \mathbb{R}^+$. In this case, we have the autonomous time-delayed system

$$\begin{aligned} \dot{T} &= T\big(f(T) - \gamma E\big), \\ \dot{E} &= \sigma + E\big(p\,h(T_{\tau_1}) - m\,h(T_{\tau_2}) - \eta\big), \end{aligned} \tag{9}$$

where the relative tumor growth function (for $0 < \beta$) is given by

$$f(T) := r(b - T^{\beta}), \tag{10}$$

with $r \to r/\beta$ and $b := 1 - \beta\hat{b}$. In addition, from now on we shall assume that $b > 0$, that is:

$$\hat{b} < 1/\beta \quad \text{for any } \beta > 0.$$

3.2. **Equilibrium points.** The possible equilibrium points (T,E) of (9) are given by the solutions of the following system

$$\begin{aligned} T\big(f(T) - \gamma E\big) &= 0, \\ \sigma + E\Big(\frac{(p-m)T}{g+aT} - \eta\Big) &= 0. \end{aligned} \tag{11}$$

We are only interested in solutions of (11) lying in the first quadrant of the TE-plane. i.e., points (T,E) satisfying $T \geq 0$ and $E \geq 0$. Any equilibrium point that fulfills this condition shall be called an *admissible equilibrium point*. The most simple equilibrium point is obtained when $T = 0$. Indeed, in this case, we have that $(0, \sigma/\eta)$ is an equilibrium point (for any function $f(T)$), known as *tumor-free equilibrium point*.

Otherwise, for $T \neq 0$, any solution of (11) must satisfy

$$f(T) = \gamma E, \quad \text{and} \quad \sigma = E\big(\eta + \frac{(m-p)T}{g+aT}\big). \tag{12}$$

From the left-hand equation in (12) we deduce that $f(T) \geq 0$. Therefore, from the formula (10), any solution (T,E) of (12) satisfies $T \in [0, b^{1/\beta}]$. Easy computations show that

$$\sigma\gamma = f(T)\big(\eta + \frac{(m-p)T}{g+aT}\big),$$
$$= \eta f(T) + \frac{(m-p)Tf(T)}{g+aT},$$

from which it follows that the solutions of the equation

$$\eta f(T) = \sigma\gamma - \frac{(m-p)Tf(T)}{g+aT},$$

namely

$$\eta r(b - T^\beta) = \sigma\gamma - \Big(\frac{m-p}{g+aT}\Big) rT(b-T^\beta) \tag{13}$$

provide the first component of possible non-tumor-free equilibrium points of system (9). To avoid parameter overload, we introduce the scaling given by

$$\sigma \to \frac{\sigma\gamma}{\eta r}, \quad m \to \frac{m}{\eta g}, \quad p \to \frac{p}{\eta g}, \quad a \to \frac{a}{g} \quad \text{and call} \quad \mu := m - p, \tag{14}$$

After some direct and easy computations, (13) can be rewritten as follows

$$S(T,\mu,a) = b - \sigma, \quad \text{with} \quad S(T,\mu,a) = T[(a+\mu)T^\beta + T^{\beta-1} - (b(\mu+a) - a\sigma)] \tag{15}$$

In conclusion, any possible admissible equilibrium point (T,E) of (9) that is not the tumor-free equilibrium point, satisfies

$$0 < T \leq b^{1/\beta}, \quad E = f(T)/\gamma, \quad \text{and} \quad S(T,\mu,a) = b - \sigma.$$

Remark 2. *The next results consider the case $a = 0$. Following the section of numerical simulations in* [9] *the parameter g is of the order 10^6 (pretty large) with respect to the other parameter in the model. Then, after the scaling process, the value $a \to a/g = O(10^{-6})$, is quite small.*

For $a = 0$, the function $S(T,\mu,0)$ is given by

$$S(T,\mu,0) = \mu(T^\beta - b)T + T^\beta.$$

Appendix A provides mathematical properties of $S(T,\mu,0)$ useful for obtaining the following results on the equation (15) in this case.

Proposition 7. *Let $\beta, b \in (0,1)$ and let us assume $a = 0$, in addition to the following conditions*

$$b \leq \sigma, \quad \textit{and} \quad \mu \leq \mu_c := \Big(\frac{1}{b}\Big(\frac{1-\beta}{1+\beta}\Big)^{\beta-1}\Big)^{\frac{1}{\beta}}. \tag{16}$$

Then, equation (15) *has no solutions lying in* $[0, b^{1/\beta}]$ *i.e., the tumor-free equilibrium point* $(0, \sigma/\eta)$ *is the only admissible equilibrium point of* (9).

Proof. As we know, if (T,E) is any admissible equilibrium point of (9) besides the tumor-free equilibrium point, then it satisfies

$$S(T,\mu,a) = b - \sigma, \quad \text{with} \quad 0 < T \leq b^{1/\beta}.$$

If $a = 0$, we have $S(T,\mu,0) = \mu(T^{\beta} - b)T + T^{\beta}$. The result follows directly from Lemma 17 and Lemma 18 in Appendix A. □

Proposition 8. *Let $\beta, b \in (0,1)$ and assume that $a = 0$. Suppose that one of the following conditions holds*

$$\dagger) \quad \sigma < b \quad \textit{and} \quad \mu \leq 0, \quad \textit{or} \quad \ddagger) \quad \sigma \leq b \quad \textit{and} \quad 0 < \mu \leq \mu_c.$$

Then, equation (15) has exactly one solution T_* on $]0, b^{1/\beta}]$ (which is simple), given implicitly as the solution of

$$\mu(T_*^{\beta} - b)T_* + T_*^{\beta} = b - \sigma. \tag{17}$$

Consequently, the only admissible equilibrium points of (9) are $(0, \sigma/\eta)$ and (T_*, E_*) with $E_* := r(b - T_*^{\beta})/\gamma$.

Proof. Let $h_0 := b - \sigma$, then $0 \leq h_0 \leq b$. The proof follows as a direct consequence of Lemma 17 case 2a. and Lemma 18 case b. in Appendix A. □

Remark 3. *In the case $\beta = 1$, we have*

$$T_* = b - \sigma, \quad \textit{and} \quad E_* = \frac{r\sigma}{\gamma} \quad \textit{if} \quad \mu = 0,$$

$$T_* = \frac{\mu b - 1 + \sqrt{(1+\mu b)^2 - 4\mu\sigma}}{2\mu}, \quad \textit{and} \quad E_* = \frac{r}{2\gamma}\Big(b + \frac{1 - \sqrt{(1+\mu b)^2 - 4\mu\sigma}}{\mu}\Big) \quad \textit{if} \quad \mu < 0.$$

In particular,

$$T_* = \big(1 - \sqrt{\frac{\sigma}{b}}\big)b, \quad \textit{and} \quad E_* = \frac{r\sqrt{\sigma b}}{\gamma}, \quad \textit{if} \quad \mu = -b^{-1}.$$

On the other hand, for each fixed $\mu > \mu_c$, let $T_{L,R}(\mu)$ be the two solutions of

$$T^{\beta-1}(\beta + \mu(1+\beta)T) = \mu b, \quad \text{with} \quad 0 < T_L(\mu) < \frac{\mu(1-\beta)}{1+\beta} < T_R(\mu) < b^{1/\beta},$$

and define the following quantities

$$H_L := \mu(T_L^{\beta}(\mu) - b)T_L(\mu) + T_L^{\beta}(\mu), \quad \text{and} \quad H_R := \mu(T_R^{\beta}(\mu) - b)T_R(\mu) + T_R^{\beta}(\mu),$$

In Appendix A it is shown that $H_R < H_L$ and, in particular, if $\mu \geq \mu_{bif} := \dfrac{1}{\beta\big[b(1-\beta)^{1-\beta}\big]^{1/\beta}}$, then $H_R \leq 0$ with

$$H_R = 0 \quad \Leftrightarrow \quad T_R(\mu_{bif}) = [(1-\beta)b]^{1/\beta}.$$

Remark 4. *Direct computation shows that for all $]0,1]$ we have*

$$\mu_c < \mu_{bif}, \quad \textit{and} \quad \mu_c \to \frac{1}{b}, \quad \mu_{bif} \to \frac{1}{b} \quad \textit{as} \quad \beta \to 1$$

$$T_* = \frac{\mu b - 1 + \sqrt{(1+\mu b)^2 - 4\mu\sigma}}{2\mu}, \quad \textit{and} \quad E_* = \frac{r}{2\gamma}\Big(b + \frac{1 - \sqrt{(1+\mu b)^2 - 4\mu\sigma}}{\mu}\Big) \quad \textit{if} \quad \mu < 0.$$

In particular,

$$T_* = \big(1 - \sqrt{\frac{\sigma}{b}}\big)b, \quad \textit{and} \quad E_* = \frac{r\sqrt{\sigma b}}{\gamma}, \quad \textit{if} \quad \mu = -b^{-1}.$$

Proposition 9. *Let $\beta, b \in]0,1[$, $h_0 := b - \sigma$, and let us assume $a = 0$.*

1. *For $\mu_c < \mu \leq \mu_{bif}$, it holds:*
   - I) *If $h_0 = H_R$, then there are exactly two solutions of* (15) *on* $[0, b^{1/\beta}]$.
   - II) *If $H_R < h_0 < H_L$, then there are exactly three solutions of* (15) *on* $[0, b^{1/\beta}]$.
   - III) *If $H_L = h_0$, then there are exactly two solutions of* (15) *on* $[0, b^{1/\beta}]$.
   - IV) *If $0 \leq h_0 < H_R$ or $H_L < h_0$, then there is exactly one solution of* (15) *on* $[0, b^{1/\beta}]$.

2. *For $\mu > \mu_{bif}$, it holds:*
   - I) *If $h_0 = H_R$, then there are exactly one solution of* (15) *on* $[0, b^{1/\beta}]$.
   - II) *If $H_R < h_0 \leq 0$, then there are exactly two solutions of* (15) *on* $[0, b^{1/\beta}]$.
   - III) *If $0 < h_0 < H_L$, then there are exactly three solutions of* (15) *in* $[0, b^{1/\beta}]$.
   - IV) *If $h_0 = H_L$, then there are exactly two solutions of* (15) *in* $[0, b^{1/\beta}]$.
   - V) *If $h_0 < H_R$ there are no solutions pf* (15), *while if $H_L < h_0$, there is exactly one solution of* (15) *on* $[0, b^{1/\beta}]$.

4. Main results

This section presents some results about the dynamics and stability of the feasible equilibrium points for the autonomous delayed system (9), given by

$$\dot{X} = \mathcal{F}(X, X_{\tau_1}, X_{\tau_2}) \quad \text{with} \quad \mathcal{F}(X_{\tau_0}, X_{\tau_1}, X_{\tau_2}) = \begin{pmatrix} T\big(f(T) - \gamma E\big) \\ \sigma + E\big(ph(T_{\tau_1}) - mh(T_{\tau_2}) - \eta\big) \end{pmatrix}, \tag{18}$$

where $X_{\tau_i} = (T_{\tau_i}, E_{\tau_i})^{tr}$. For convenience, here we denote $X_{\tau_0} = X = (T, E)$, that is, $\tau_0 = 0$. Notice that at each equilibrium point $\hat{X} = (\hat{T}, \hat{E})$, the associated linear system is given by

$$\dot{Y} = A_0 Y + A_1 Y_{\tau_1} + A_2 Y_{\tau_2}, \tag{19}$$

with $A_i = D_{X_{\tau_i}}\mathcal{F}(\hat{X})$. Moreover,

$$A_0 = \begin{pmatrix} f(\hat{T}) - \gamma\hat{E} + \hat{T}f'(\hat{T}) & -\gamma\hat{T} \\ 0 & (p-m)h(\hat{T}) - \eta \end{pmatrix},$$

and

$$A_1 = \begin{pmatrix} 0 & 0 \\ p\,h'(\hat{T})\hat{E} & 0 \end{pmatrix}, \qquad A_2 = \begin{pmatrix} 0 & 0 \\ -m\,h'(\hat{T})\hat{E} & 0 \end{pmatrix}.$$

From Appendix B, the corresponding characteristic function $\mathcal{P}_a(\lambda, \tau_1, \tau_2)$ of (19) is given by

$$\mathcal{P}_a(\lambda, \tau_1, \tau_2) := P(\lambda) + e^{-\tau_1\lambda}Q(\lambda) + e^{-2\tau_1\lambda}\det A_1 + e^{-\tau_2\lambda}H(\lambda, \tau_1) + e^{-2\tau_2\lambda}\det A_2,$$

with

$$P(\lambda) = \lambda^2 - (trA_0)\lambda + \det A_0$$
$$Q(\lambda) = C_{A_0A_1} - (trA_1)\,\lambda, \qquad \text{and} \qquad C_{A_iA_j} = \det(A_i^1|A_j^2) + \det(A_j^1|A_i^2), \quad (20)$$
$$H(\lambda,\tau_1) = e^{-\lambda\tau_1}C_{A_1A_2} + C_{A_0A_2} - (trA_2)\,\lambda,$$

where, A_i^1, A_i^2 denoted the first and the second column of A_i respectively. Direct computations show that

$$trA_0 = f(\hat{T}) - \gamma\hat{E} + \hat{T}f'(\hat{T}) + (p-m)h(\hat{T}) - \eta, \quad trA_1 = trA_2 = 0$$
$$\det A_0 = \big(f(\hat{T}) - \gamma\hat{E} + \hat{T}f'(\hat{T})\big)\big((p-m)h(\hat{T}) - \eta\big), \quad \det A_1 = \det A_2 = 0.$$

and

$$C_{A_0A_1} = \gamma p h'(\hat{T})\hat{T}\hat{E}, \quad C_{A_0A_2} = -\gamma m h'(\hat{T})\hat{T}\hat{E}, \quad \text{and} \quad C_{A_1A_2} = 0.$$

In consequence,

$$\mathcal{P}_a(\lambda,\tau_1,\tau_2) = P(\lambda) + \gamma h'(\hat{T})\hat{T}\hat{E}\big(pe^{-\tau_1\lambda} - me^{-\tau_2\lambda}\big) \qquad (21)$$

4.1. **Stability of the tumor-free equilibrium point.** For any $a \in \mathbb{R}^+$, the characteristic equation (21) at the tumor-free equilibrium point $(0,\sigma/\eta)$ is given explicitly by

$$P_a(\lambda,\tau_1) = 0 \quad \Leftrightarrow \quad (\lambda+\eta)(\lambda - rb + \frac{\gamma\sigma}{\eta}) = 0. \qquad (22)$$

Theorem 10. *Define the parameter $\Delta := \gamma\sigma - rb\eta$. Then, for all $\tau_1, \tau_2 \geq 0$, it follows*

1. *If $\Delta < 0$ then the equilibrium $(0,\sigma/\eta)$ is unstable.*
2. *If $\Delta = 0$ then $(0,\sigma/\eta)$ is locally stable.*
3. *If $\Delta > 0$ then $(0,\sigma/\eta)$ is locally asymptotically stable.*

4.2. **Stability analysis of non-tumor-free equilibrium points.** In what follows, the stability properties of the equilibrium point (T_*,E_*) are discussed. Recall that for $a=0$, (T_*,E_*) is the only solution of (15), with T_* solution of equation (17) and $E_* := r(b - T_*^\beta)/\gamma$. With this, we observe the following consequence, predicted by Proposition 8.

Remark 5. *As (T_*,E_*) is a simple solution of equation (15) at $a=0$, it is natural the analytical extension of this solution to $a \geq 0$ small. Therefore, from now on, we will refer to*

$$(T_{*,a}, E_{*,a}),$$

as the equilibrium point for a positive small a, and under the remaining set of restrictions given on the parameters by Proposition 8.

Moreover, the characteristic function for $(T_{*,a},E_{*,a})$ is given by

$$\mathcal{P}_a(\lambda,\tau_1,\tau_2) = (\lambda - \lambda_{1,a}^*)(\lambda - \lambda_{2,a}^*) + h'\big(T_{*,a}\big)f(T_{*,a})T_{*,a}\big(pe^{-\tau_1\lambda} - me^{-\tau_2\lambda}\big), \qquad (23)$$

where

$$\lambda_{1,a}^* = T_{*,a}f'(T_{*,a}) < 0 \quad \text{and} \quad \lambda_{2,a}^* = (p-m)h(T_{*,a}) - \eta. \qquad (24)$$

Let us define $\mathscr{D}_{*,a} := \mathcal{P}_a(0,\tau_1,\tau_2)$ which corresponds to

$$\begin{aligned}\mathscr{D}_{*,a} &= \lambda^*_{1,a}\lambda^*_{2,a} + h'\big(T_{*,a}\big)f(T_{*,a})T_{*,a}(p-m),\\ &= (p-m)T_{*,a}\big(f'(T_{*,a})h(T_{*,a}) + h'(T_{*,a})f(T_{*,a})\big) - \eta T_{*,a}f'(T_{*,a}).\end{aligned} \tag{25}$$

By the set of scale parameters (14), $\lambda^*_{2,a}$, and $\mathscr{D}_{*,a}$ are given explicitly by

$$\lambda^*_{2,a} = -\eta\Big(\frac{\mu T_{*,a}}{1+aT_{*,a}}+1\Big) \quad \text{and} \quad \mathscr{D}_{*,a} = -\eta T_{*,a}\Big(\Big(\frac{\mu T_{*,a}}{1+aT_{*,a}}+1\Big)f'(T_{*,a}) + \frac{\mu f(T_{*,a})}{(1+aT_{*,a})^2}\Big),$$

for all $\tau = (\tau_1,\tau_2) \in \mathbb{R}^+$. In particular, for $a = 0$ we have

$$\lambda^*_{2,0} = -\eta\big(\mu T_* + 1\big) \quad \text{and} \quad \mathscr{D}_{*,0} = -\eta T_*\big(\big(\mu T_* + 1\big)f'(T_*) + \mu f(T_*)\big), \tag{26}$$

where $T_* = T_{*,0}$ is the unique solution of (17). The first result on the stability of (T_*, E_*) is the following.

Lemma 11. *Let $a \geq 0$ be small and assume that Proposition 8 is valid for $a = 0$. If $\mathscr{D}_{0,*} < 0$ then the equilibrium $(T_{*,a}, E_{*,a})$ is unstable for all $\tau_1, \tau_2 \geq 0$.*

Proof. Direct calculations show that

$$\mathcal{P}_0(0,\tau_1,\tau_2) = \mathscr{D}_{0,*} < 0, \quad \text{and} \quad \lim_{\lambda\to\infty} \mathcal{P}_0(0,\tau_1,\tau_2) = \infty,$$

for all, for all $\tau_1, \tau_2 \geq 0$. Then by the Intermediate Value Theorem, there exists $\lambda_0 > 0$ such that $\mathcal{P}_0(\lambda_0,\tau_1,\tau_2) = 0$. By continuity and for $a > 0$ small, the characteristic equation $\mathcal{P}_a(\lambda,\tau_1,\tau_2) = 0$ has a real positive solution λ_a. This shows that $(T_{*,a}, E_{*,a})$ is unstable. $\square$

From now on, we will establish sufficient conditions for the local stability of this equilibrium. Let us begin with the following result.

Theorem 12. *Let $a, \tau_1, \tau_2 \geq 0$ be small.*

1. *If condition †) in Proposition 8 holds, then $(T_{*,a}, E_{*,a})$ is a locally asymptotically stable equilibrium point of (9).*
2. *If condition ‡) in Proposition 8 holds, then (T_*, E_*) is locally asymptotically stable (stable node), provided that one of the following conditions holds:*
   a. $\sigma \leq \dfrac{b\beta}{1+\beta} < b.$
   b. $\dfrac{b\beta}{1+\beta} < \sigma < \sigma_\Delta$ *and* $0 < \mu_\Delta(\sigma) < \mu < \mu_c$ *where*

$$\sigma_\Delta = \frac{b\beta}{1+\beta}\Big(1 + \mu_c\Big(\frac{b}{1+\beta}\Big)^{1/\beta}\Big) \quad \textit{and} \quad \mu_\Delta(\sigma) = \frac{1}{b\beta}\Big(\frac{1+\beta}{b}\Big)^{1/\beta}\big((1+\beta)\sigma - b\beta\big).$$

Proof. For $\tau = (0,0)$, it is easy to see that, for all $a \geq 0$ we have

$$\begin{aligned}\mathcal{P}_a(\lambda,0,0) &= (\lambda - \lambda^*_{1,a})(\lambda - \lambda^*_{2,a}) + \gamma(p-m)h'\big(T_{*,a}\big)T_{*,a}E_{*,a},\\ &= \lambda^2 - (\lambda^*_{1,a} + \lambda^*_{2,a})\lambda + \mathscr{D}_{*,a}.\end{aligned}$$

where $\lambda^*_{1,a}, \lambda^*_{2,a}$ and $\mathscr{D}_{*,a}$ given by (24) and (25) respectively. Moreover,

$$(\lambda_{1,a}+\lambda_{2,a})^2 - 4\mathscr{D}_{*,a} = (\lambda_{1,a}-\lambda_{2,a})^2 + \frac{4\mu\eta T_{*,a} f(T_{*,a})}{(1+aT_{*,a})^2}.$$

On the other hand, in particular, for $a=0$ we can rewrite equation (17), as follows

$$\mu(T_*^\beta - b)T_* + T_*^\beta = b-\sigma \quad \Leftrightarrow \quad (1+\mu T_*)(b-T_*^\beta) = \sigma,$$

then $1+\mu T_* > 0$ for all $\mu \in \mathbb{R}$. Now, from (26) and the condition †) in Proposition 8 we deduce that

$$\lambda^*_{1,0} + \lambda^*_{2,0} < 0 \quad \text{and} \quad \mathscr{D}_{*,0} > 0.$$

Consequently, $\mathcal{P}_0(\lambda, 0, 0)$ has two distinct roots, both with negative real part. This implies that (T_*, E_*) is locally asymptotically stable for small $\tau_1, \tau_2 \geq 0$. The previous result and a simple argument of continuity complete the proof of part 1. of the theorem.

For part 2a. Let us assume that condition ‡) is met. Firstly, for all $\mu > 0$ we have

$$\lambda_{1,a} + \lambda^*_{2,a} < 0 \quad \text{and} \quad (\lambda_{1,a}+\lambda_{2,a})^2 - 4\mathscr{D}_{*,a} > 0.$$

Therefore, the roots of $\mathcal{P}_0(\lambda,0,0)$ are real. Our attention now turns to the analysis of the positivity of $\mathscr{D}_{*,a}$, which can be considered a function of $\mathscr{D}_{*,a}(\mu)$. Notice that

$$\mathscr{D}_{*,0}(\mu) : = -\eta T_* \big(\mu f(T_*) + f'(T_*)\big(1+\mu T_*\big)\big), \tag{27}$$

where $T_* = T_*(\mu)$ is the only solution of (17). Recall that the positive sign of $\mathscr{D}_{*,0}(\mu)$ implies the local asymptotical stability of (T_*, E_*). With this in mind, we proceed as follows. Since for all $0 < \mu < \mu_c$ we have

$$T_*^\beta(0) = b - \sigma < T_*^\beta(\mu) < T_*^\beta(\mu_c),$$

therefore,

$$\text{If} \quad \frac{b}{1+\beta} \leq b-\sigma \quad \Leftrightarrow \quad \sigma \leq \frac{b\beta}{1+\beta}, \quad \text{then} \quad \frac{b}{1+\beta} < T_*^\beta.$$

As a consequence, $\mathscr{D}_{*,0}(\mu) > 0$, for all $\beta \in]0,1[$ and $0<\mu<\mu_c$. Proof of part 2b: Notice that there exists $\mu_\Delta > 0$ such that (17) has the solution $T = \Big(\dfrac{b}{1+\beta}\Big)^{1/\beta}$. In fact,

$$\mu\Big(\frac{b}{1+\beta} - b\Big)\Big(\frac{b}{1+\beta}\Big)^{1/\beta} + \frac{b}{1+\beta} = b-\sigma,$$

This implies,

$$\mu = \mu_\Delta(\sigma) := \frac{1+\beta}{b\beta}\Big(\frac{1+\beta}{b}\Big)^{1/\beta}\Big(\sigma - \frac{b\beta}{1+\beta}\Big),$$

which, in turn, implies $\sigma > \dfrac{b\beta}{1+\beta}$. At this point, we compare the value $\mu_\Delta(b)$ with respect to μ_c. Then, straightforward computations show that

$$\mu_\Delta(b) = \frac{1}{\beta}\Big(\frac{1+\beta}{b}\Big)^{1/\beta} > \mu_c \quad \Leftrightarrow \quad (1-\beta)^{\frac{1-\beta}{\beta}} > \frac{\beta}{(1+\beta)}.$$

It is an easy exercise to prove that the last inequality is true for all $\beta \in [0,1]$. Therefore, we deduce the existence of a unique $\sigma = \sigma_\Delta$ such that $\mu_\Delta(\sigma_\Delta) = \mu_c$ for all $\beta \in]0,1[$. Moreover,

$$\sigma_\Delta = \frac{b\beta}{1+\beta}\Big(1 + \mu_c\Big(\frac{b}{1+\beta}\Big)^{1/\beta}\Big).$$

Finally, following the proof of part 2a. for all $\frac{b\beta}{1+\beta} < \sigma < \sigma_\Delta$ and $0 < \mu_\Delta < \mu < \mu_c$ we have

$$T_*(\mu_\Delta) = \Big(\frac{b}{1+\beta}\Big)^{1/\beta} < T_*(\mu),$$

proving that $\mathscr{D}_{*,0}(\mu) > 0$. Taken $a \geq 0$ sufficiently small, the continuity of the function $\mathscr{D}_{*,a}(\mu)$ with respect a, complete the proof. $\square$

Lemma 13. *Assume $a, \tau_1.\tau_2 \geq 0$ to be small. If $\beta = 1$ and $\sigma < b$, then $(T_{*.a}, E_{*.a})$ is locally asymptotically stable for all $\mu \in \mathbb{R}^+$. Moreover, if $\mu \geq 0$ is small, the same conclusion holds for all $\beta \in]0,1[$ and $\sigma < b$.*

Proof. Let $a = 0$, $\tau = (0,0)$ and assume that $\sigma < b$. A direct computation shows that the function $\mathscr{D}_{*,0}(\mu)$ can be written as

$$\begin{aligned}
\mathscr{D}_{*,0}(\mu) &= -\eta T_*\big(f'(T_*) + \mu(f(T_*) + T_* f'(T_*))\big) \\
\mathscr{D}_{*,0}(\mu) &= r\eta\big((\beta-1)T_*^\beta + b - \sigma + \mu\beta T_*^{\beta+1})).
\end{aligned}$$

Then, for $\beta = 1$ we have $\mathscr{D}_{*,a}(\mu) > 0$ for all $\mu \geq 0$ and $a \geq 0$ sufficiently small. Finally, if $\mu = 0$ then $T_*^\beta = b - \sigma$, therefore

$$\mathscr{D}_{*,0}(0) = r\eta\big((\beta-1)(b-\sigma) + b - \sigma\big) = r\beta\eta(b-\sigma) > 0.$$

A simple argument of continuity completes the proof. $\square$

4.3. **Local stability for non-small delays.** This section is devoted to exploring the stability of $(T_{*,a}, E_{*,a})$ for small $a \geq 0$ and $\tau_1, \tau_2 \geq 0$ that are not necessarily small. For simplicity in the following computations, we rewrite the characteristic function (23) as follows

$$\mathcal{P}_a(\lambda, \tau_1, \tau_2) = P(\lambda) + R(pe^{-\tau_1\lambda} - me^{-\tau_2\lambda}),$$

with $P(\lambda) = (\lambda - \lambda^*_{1,a})(\lambda - \lambda^*_{2,a})$ and $R := f(T_{*,a})h'(T_{*,a})T_{*,a}$. Let us assume that $\lambda = x + iy$, $x, y \in \mathbb{R}$ is a solution of (23). Dividing the equation into the real and imaginary parts, we obtain

$$\begin{aligned}
P(x) - y^2 + R\big(p\cos(\tau_1 y)e^{-\tau_1 x} - m\cos(\tau_2 y)e^{-\tau_2 x}\big) &= 0, \\
2xy - (\lambda^*_{1,a} + \lambda^*_{2,a})y - R\big(p\sin(\tau_1 y)e^{-\tau_1 x} - m\sin(\tau_2 y)e^{-\tau_2 x}\big) &= 0.
\end{aligned} \tag{28}$$

Notice that if $\tau_1 = \tau_2 = \tau$ we obtain

$$\mathcal{P}_a(\lambda, \tau) = P(\lambda) - Ne^{-\tau\lambda}, \tag{29}$$

with $N := (m-p)R$ which can be divided into [1]

$$\begin{aligned} P(x) - y^2 - N\cos(\tau y)e^{-\tau x} &= 0, \\ 2xy - (\lambda^*_{1,a} + \lambda^*_{2,a})y + N\sin(\tau y)e^{-\tau x} &= 0. \end{aligned} \tag{30}$$

We begin our analysis considering the characteristic function (29). To this end, we apply Theorems A, B, and C in the Appendix.

Theorem 14. *Assume that $a \geq 0$ is sufficiently small. If condition †) in Proposition 8 holds and*

$$f'(T_*)(\mu T_* + 1) - \mu f(T_*) < 0,$$

then $(T_{*,a}, E_{*,a})$ is a locally asymptotically stable equilibrium point of (9) for all values of τ satisfying

$$0 \leq \tau < \frac{T_{*,a}f'(T_{*,a}) - \eta\Big(\frac{\mu T_*}{1+aT_{*,a}} + 1\Big)}{\frac{\mu\eta T_{*,a}f(T_{*,a})}{(1+aT_{*,a})^2}} \approx \frac{T_* f'(T_*) - \eta(\mu T_* + 1)}{\mu\eta T_* f(T_*)}.$$

Moreover, for $a = 0$, there exists $\tau_c > 0$ given by

$$\tau_c = \frac{1}{\hat{y}}\arctan\Big[-\frac{(\lambda^*_{1,0} + \lambda^*_{2,0})\hat{y}}{\lambda^*_{1,0}\lambda^*_{2,0} - \hat{y}^2}\Big]$$

with $\hat{y}$ the smallest positive solution of

$$G(y) = y^4 + \Big(\big(\lambda^*_{1,0}\big)^2 + \big(\lambda^*_{2,0}\big)^2\Big)y^2 + \big(\lambda^*_{1.0}\lambda^*_{2,0}\big)^2 - N^2,$$

with $N = \eta\mu T_* f(T_*)$ for which $\tau < \tau_0$ the equilibrium point (T_*, E_*) is asymptotically stable and for $\tau < \tau_0$ is unstable. Furthermore, as τ increases through τ_0, (T_*, E_*) bifurcates into stable periodic solutions with small amplitude.

Proof. Let us begin with the proof of part 1. Consider $\lambda^*_{1,a}$ and $\lambda^*_{2,a}$ to be given by (24) namely

$$\lambda^*_{1,a} = T_{*,a}f'(T_{*,a}) < 0 \quad \text{and} \quad \lambda^*_{2,a} = -\eta\Big(\frac{\mu T_{*,a}}{1 + aT_{*,a}} + 1\Big).$$

Recall that $\lambda^*_{2,0} < 0$ for all $\mu \in \mathbb{R}$. Define the function $\mathcal{K}(a) := \lambda^*_{1,a}\lambda^*_{2,a} + N$, explicitly given by

$$\mathcal{K}(a) := -\eta T_{*,a}\Big[f'(T_{*,a})\Big(\frac{\mu T_{*,a}}{1 + aT_{*,a}} + 1\Big) - \Big(\frac{\mu f(T_{*,a})}{(1 + aT_{*,a})^2}\Big)\Big],$$

with

$$\mathcal{K}(0) = -\eta T_*\big(f'(T_*)(\mu T_* + 1) - \mu f(T_*)\big).$$

By hypothesis $\mathcal{K}(0) > 0$ we deduce the following:

1. $\lambda^*_{2,a} < 0$ and $\lambda^*_{1,a} + \lambda^*_{2,a} < 0$,
2. $\mathcal{K}(a) = \lambda^*_{1,a}\lambda^*_{2,a} + N < 0 \quad \Leftrightarrow \quad \lambda^*_{1,a}\lambda^*_{2,a} < -N$,

[1] In the set of scale parameters (14) we have $N = \dfrac{\eta\mu T_{*,a}f(T_{*,a})}{(1 + aT_{*,a})^2}$. Further, for $a = 0$, $N = \eta\mu T_* f(T_*)$.

for all $a \geq 0$ and sufficiently small. By continuity and Theorem A., the equilibrium point $(T_{*,a}, E_{*,a})$ is asymptotically stable for all $\tau \in [0, \tau_a)$ with

$$\tau_a = \frac{\lambda_{1,a}^* + \lambda_{2,a}^*}{N} = \frac{T_{*,a} f'(T_{*,a}) - \eta\Big(\frac{\mu T_*}{1+aT_{*,a}} + 1\Big)}{\frac{\mu\eta T_{*,a} f(T_{*,a})}{(1+aT_{*,a})^2}},$$

for all $a \geq 0$ and sufficiently small, where $\tau_a \approx \tau_0 := \dfrac{T_* f'(T_*) - \eta(\mu T_* + 1)}{\mu\eta T_* f(T_*)}$.

Now, for the calculation of τ_c for which (30) has a solution of the form $\lambda = iy$ (i.e., $x = 0$) we have (for $a = 0$)

$$\begin{aligned} \lambda_{1,0}^*\lambda_{2,0}^* - y^2 - N\cos(\tau y) = 0, \\ -(\lambda_{1,0}^* + \lambda_{2,0}^*)y + N\sin(\tau y) = 0, \end{aligned} \tag{31}$$

implying that $G(y) = 0$ with G the quadratic function in y^2 given by

$$G(y) := y^4 + \Big((\lambda_{1,0}^*)^2 + \big(\lambda_{2,0}^*\big)^2\Big)y^2 + (\lambda_{1,0}^*\lambda_{2,0}^* - N)(\lambda_{1,0}^*\lambda_{2,0}^* + N).$$

where $N = \eta\mu T_* f(T_*)$. Since $G(0) = (\lambda_{1,0}^*\lambda_{2,0}^* - N)(\lambda_{1,0}^*\lambda_{2,0}^* + N) < 0$ there exist $\hat{y} > 0$ such that $G(\hat{y}) = 0$ moreover, $\hat{y}$ is given explicitly by

$$\hat{y} = \sqrt{\frac{-\Big[(\lambda_{1,0}^*)^2 + \big(\lambda_{2,0}^*\big)^2\Big] + \sqrt{\Big[(\lambda_{1,0}^*)^2 + \big(\lambda_{2,0}^*\big)^2\Big]^2 - 4\Big((\lambda_{1.0}^*\lambda_{2,0}^*)^2 - N^2\Big)}}{2}}$$

From (31) we deduce

$$\tan(\tau y) = -\frac{(\lambda_{1,0}^* + \lambda_{2,0}^*)y}{\lambda_{1,0}^*\lambda_{2,0}^* - y^2}$$

The critical value τ_c is given by

$$\tau_c := \tau_0 \quad \text{where} \quad \tau_k := \frac{1}{\hat{y}}\arctan\Big[-\frac{(\lambda_{1,0}^* + \lambda_{2,0}^*)\hat{y}}{\lambda_{1,0}^*\lambda_{2,0}^* - \hat{y}^2}\Big] + \frac{2k\pi}{\hat{y}}, \quad k = 0, 1, 2, \ldots$$

The conclusion of the existence of a Hopf bifurcation at the critical time-delay value τ_0 follows from Theorem C. This completes the proof. □

Stability for non equal time delays. The next lines provides the general frame where the stability of the equilibrium point $(T_{*,a}, E_{*,a})$ is guaranteed for $\tau_1, \tau_2 \in \mathbb{R}_+^2$. From system (28) we have

$$\begin{aligned} \mathcal{Q}_0(x,y) + Rp\cos(\tau_1 y)e^{-\tau_1 x} &= Rm\cos(\tau_2 y)e^{-\tau_2 x}, \\ \mathcal{Q}_1(x,y) - Rp\sin(\tau_1 y)e^{-\tau_1 x} &= -Rm\sin(\tau_2 y)e^{-\tau_2 x}, \end{aligned}$$

where

$$\mathcal{Q}(x,y) = P(x) - y^2 \quad \text{and} \quad \mathcal{Q}_1(x,y) = 2xy - (\lambda_{1,a}^* + \lambda_{2,a}^*)y.$$

A direct calculation shows that

$$\mathcal{Q}_0^2(x,y) + \mathcal{Q}_1^2(x,y) + 2Rp(\mathcal{Q}_0(x,y)\cos(\tau_1 y) - \mathcal{Q}_1(x,y)\sin(\tau_1 y))e^{-\tau_1 x} = (Rm)^2 e^{-2\tau_2 x} - (Rp)^2 e^{-2\tau_1 x}.$$

Now, we look for solutions of the form $\lambda = iy$ (i.e., $x = 0$). In this case, we obtain the following

$$\mathcal{Q}_0^2(y) + \mathcal{Q}_1^2(y) + 2Rp(\mathcal{Q}_0(y)\cos(\tau_1 y) - \mathcal{Q}_1(y)\sin(\tau_1 y)) = (Rm)^2 - (Rp)^2, \tag{32}$$

with

$$\mathcal{Q}_0(y) := \mathcal{Q}_0(0,y) = \lambda_{1,a}^*\lambda_{2,a}^* - y^2 \quad \text{and} \quad \mathcal{Q}_1(y) := \mathcal{Q}_1(0,y) = -(\lambda_{1,a}^* + \lambda_{2,a}^*)y.$$

Under the condition †) in Proposition 8, for all $a \geq 0$ sufficiently small we have $\lambda_{1,a}^* + \lambda_{2,a}^* < 0$ which implies $\mathcal{H}^2(y) = \mathcal{Q}_0^2(y) + \mathcal{Q}_1^2(y) > 0$. Consequently, there exists a continuous function $\varphi_1 : \mathbb{R} \to \mathbb{R}$, $y \to \varphi_1(y)$ such that

$$\mathcal{Q}_0(y) = \sqrt{\mathcal{Q}_0^2(y) + \mathcal{Q}_1^2(y)}\cos(\varphi_1(y)) \quad \text{and} \quad \mathcal{Q}_1(y) = \sqrt{\mathcal{Q}_0^2(y) + \mathcal{Q}_1^2(y)}\sin(\varphi_1(y)).$$

In this scenario, equation (32) becomes

$$(\lambda_{1,a}^*\lambda_{2,a}^* - y^2)^2 + (\lambda_{1,a}^* + \lambda_{2,a}^*)^2 y^2 + R^2(p^2 - m^2) = -2Rp\mathcal{H}(y)\cos(\tau_1 y + \varphi_1(y)). \tag{33}$$

There exists $\tau_1 \in \mathbb{R}_+$ satisfying the last equation if and only if

$$\left|(\lambda_{1,a}^*\lambda_{2,a}^* - y^2)^2 + (\lambda_{1,a}^* + \lambda_{2,a}^*)^2 y^2 + R^2(p^2 - m^2)\right| \leq 2Rp\mathcal{H}(y). \tag{34}$$

Define $I \in \mathbb{R}_+$ so that condition (34) is met. For each $\hat{y} \in I$ define the function

$$\vartheta(\hat{y}) := \arccos\Big(- \frac{(\lambda_{1,a}^*\lambda_{2,a}^* - \hat{y}^2)^2 + (\lambda_{1,a}^* + \lambda_{2,a}^*)^2\hat{y}^2 + R^2(p^2 - m^2)}{2Rp\sqrt{(\lambda_{1,a}^*\lambda_{2,a}^* - \hat{y}^2)^2 + (\lambda_{1,a}^* + \lambda_{2,a}^*)^2\hat{y}^2)}}\Big), \quad \vartheta \in [0, \pi]$$

Finally, from (33) we have

$$\tau_{1,s}^{\pm}(\hat{y}) := \frac{\pm\vartheta(\hat{y}) - \varphi_1(\hat{y})}{\hat{y}} + \frac{2s\pi}{\hat{y}}, \quad s \in \mathbb{Z}. \tag{35}$$

From this, it is possible to obtain an explicit formula for $\tau_2 = \tau_2(\hat{y})$ throughout the system (28) as follows

$$\tan(\tau_2\hat{y}) = \frac{Rp\sin(\tau_1(\hat{y})\hat{y}) - \mathcal{Q}_1(\hat{y})}{\mathcal{Q}_0(\hat{y}) + Rp\cos(\tau_1(\hat{y})\hat{y})},$$

then,

$$\tau_{2,k}^{\pm}(\hat{y}) := \frac{1}{\hat{y}}\arctan\Big[\frac{Rp\sin(\tau_1^{\pm}(\hat{y})\hat{y}) - \mathcal{Q}_1(\hat{y})}{\mathcal{Q}_0(\hat{y}) + Rp\cos(\tau_1^{\pm}(\hat{y})\hat{y})}\Big] + \frac{2k\pi}{\hat{y}}, \quad k \in \mathbb{Z}. \tag{36}$$

The previous computation provides the proof of the following result.

Theorem 15. *(Stability crossing curves) Assume that $a \geq 0$ is sufficiently small and that the condition †) in Proposition 8. Let $I \in \mathbb{R}_+$ be the set where* (34) *holds. The stability of the equilibrium point $(T_{*,a}, E_{*,a})$ changes if $(\tau_1, \tau_2) \in \mathbb{R}_+$ crosses the curves*

$$\mathcal{C}_{s,k} = \left\{(\tau_1^{\pm}(y), \tau^{\pm}(y)) \in \mathbb{R}_+^2 : y \in I, s, k \in \mathbb{Z}\right\}.$$

with $\tau_1^{\pm}, \tau_2^{\pm}$ given by (35) *y* (36) *respectively.*

5. Continuation

In this section, we shall prove the existence of ω-periodic solutions for small perturbations of the autonomous undelayed system. Keeping in mind Theorem 3 consider any equilibrium point $(\hat{T},\hat{E})$ of (2) for $\varphi = 0$ and $\tau_1 = \tau_2 = 0$ and compute the partial derivative of Φ at $(\hat{T},\hat{E},0)$. which is given by

$$D_{(T,E)}\Phi(\hat{T},\hat{E},0)Z = \lim_{h\to 0} \frac{\Phi((\hat{T},\hat{E}+hZ,0) - \Phi((\hat{T},\hat{E},0)}{h},$$

that is,

$$D_{(T,E)}\Phi(T^*,E^*,0)Z = MZ,$$

where M is the matrix given by

$$M := \begin{pmatrix} f(\hat{T}) - \hat{T}f'(\hat{T}) - \gamma\hat{E} & -\gamma\hat{T} \\ (p-m)\hat{E}h'(\hat{T}) & (p-m)h(\hat{T}) - \eta \end{pmatrix}.$$

Let us first assume that $(\hat{T},\hat{E})$ is the tumor-free equilibrium point, that is, $(\hat{T},\hat{E}) = (0,\sigma/\eta)$. Then

$$M_{|_{(0,\sigma/\eta)}} := \begin{pmatrix} rb - \gamma\sigma/\eta & 0 \\ \sigma(p-m)h'(0)/\eta & -\eta \end{pmatrix}.$$

To conclude our analysis, let us proceed with an strictly positive equilibrium $(\hat{T},\hat{E})$ given as a solution of the system (12), that is,

$$f(\hat{T}) = \gamma\hat{E}, \quad \text{and} \quad \sigma = \hat{E}\big(\eta + (m-p)h(\hat{T})\big),$$

with $\hat{T},\hat{E} > 0$. In particular, for $a = 0$, from Proposition 17 we deduce that $\hat{T} = T_*$ under some appropriate conditions. In addition, the corresponding matrix is

$$M_{|_{(\hat{T},\hat{E})}} := \begin{pmatrix} \hat{T}f'(\hat{T}) & -\gamma\hat{T} \\ (p-m)\hat{E}h'(\hat{T}) & -\sigma/\hat{E} \end{pmatrix}$$

Thus, taking into account Lemma 4, existence of ω-periodic solution for all values of ω is deduced in both cases.

Theorem 16. *Let (T^*,E^*) be an admissible equilibrium of (2) with $b \equiv b_0$. Then there exist constants $\varphi^*, \tau_j^* > 0$ and $r^* > 0$ such that the system (2) has at least one ω-periodic solution (T,E) with $\|(T-T^*, E-E^*)\|_\infty < r^*$, provided that $\|\varphi\|_\infty < \varphi^*, \tau_1 < \tau_1^*$ and $\tau_2 < \tau_2^*$.*

Proof. From the previous calculations, when $T^* = 0$, it is verified that the matrix $M_{|_{(0,\sigma/\eta)}}$ has only real eigenvalues given by

$$\lambda_1 = rb - \gamma\sigma/\eta, \quad \text{and} \quad \lambda_2 = -\eta.$$

On the other hand, for $T^* > 0$ it is seen that the trace of the matrix $M_{|_{(T^*,E^*)}}$ is strictly negative, indeed,

$$tr(M_{|_{(T^*,E^*)}}) = -r\beta[T^*]^\beta - \sigma/E^* < 0,$$

which, in particular, implies that it has no pure imaginary eigenvalues. Thus, in both cases, the conclusion follows from lemma 4. □

6. Numerical Validation

Section in construction.

Appendix A

In Section 3 for each $\beta \in]0,1]$ we consider the function

$$h_\mu(T) := S(T,\mu,0) = \mu(T^\beta - b)T + T^\beta,$$

with $0 \le T < b^{1/\beta}$ and $\mu \in \mathbb{R}$. This function provides the first component of non-trivial and admissible equilibrium points (T,E) (with $T,E > 0$) of the system (9) as solutions of the algebraic equation

$$h_\mu(T) = h_0. \qquad (\blacktriangle)$$

with $h_0 \in \mathbb{R}$. In the following lines, we present mathematically and numerically some algebraic properties of h_μ which are important to study the number of solutions of $(\blacktriangle)$. Firstly, notice that

$$\begin{aligned} h'_\mu(T) &= T^{\beta-1}(\beta + \mu(1+\beta)T) - \mu b, \\ h''_\mu(T) &= \beta T^{\beta-2}(\beta - 1 + \mu(1+\beta)T), \\ h'''_\mu(T) &= \beta(\beta-1)T^{\beta-3}(\beta - 2 + \mu(1+\beta)T). \end{aligned}$$

In addition,

$$h_\mu(b^{1/\beta}) = b, \qquad \text{and} \qquad h'_\mu(b^{1/\beta}) = \beta b\big(b^{-1/\beta} + \mu\big).$$

Let us start our analysis by assuming the case $\mu < 0$. Straightforward computations show the following:

†) $h''_\mu(T) < 0$ for all $T > 0$. Then, $h_\mu(T)$ is a smooth concave function, and satisfies

$$\lim_{T\to 0^+} h'_\mu(T) = \begin{cases} 0, & \text{if} \quad \beta = 1, \\ \infty, & \text{if} \quad 0 < \beta < 1, \end{cases} \qquad \text{and} \qquad \lim_{T\to\infty} h'_\mu(T) = -\infty.$$

In consequence, there exists exactly one (positive) critical point T_Δ given implicitly by the equation

$$T_\Delta^{\beta-1}(\beta + \mu(1+\beta)T_\Delta) = \mu b. \tag{37}$$

†) $h_\mu(T) > 0$ for all $0 < T < b^{1/\beta}$. Furthermore, from (37) we deduce that

$$h_\mu(T_\Delta) = T_\Delta^\beta\big(1 - \beta - \mu\beta T_\Delta\big).$$

Finally, it is clear that $b^{1/\beta} \lesseqgtr T_\Delta$ if $b^{-1/\beta} \gtreqless -\mu$. The following Lemma is easily deduced from the properties of $h_\mu(T)$.

Lemma 17. *Let us assume $\mu < 0$. Then*

1. *If $h_0 < 0$, then there are no solutions of $(\blacktriangle)$ in $[0, b^{1/\beta}]$.*
2. a. *If $0 \le h_0 \le b$, then there is exactly one solution of $(\blacktriangle)$ in $[0, b^{1/\beta}]$.*

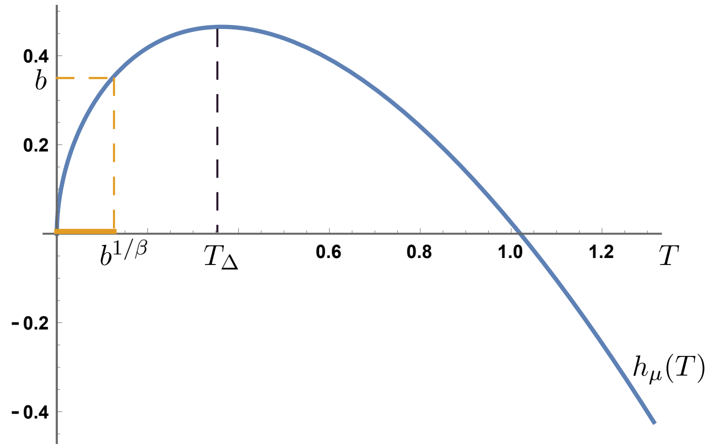

FIGURE 1. Graph of $h_\mu(T)$ with parameters $\mu = -1.5$, $b = 0.35$, and $\beta = 0.5$. For these values, $h'_\mu(b^{1/\beta}) \approx 1.17$, therefore $b^{1/\beta} < T_\Delta$. If $0 < h_0 \le b$ there exists exactly one solution of ($\blacktriangle$) on $]0, b^{1/\beta}]$ and no solutions if $h_0 > b$.

b. *If $b < h_0$ and satisfies*

$$h_0 \le T_\Delta^\beta\big(1 - \beta - \mu\beta T_\Delta\big),$$

with T_Δ the only positive solution of (37)*. Then, there are at most two solutions of* ($\blacktriangle$) *in* $[0, b^{1/\beta}]$ *if* $b^{1/\beta} \ge T_\Delta$ *and there are no solutions in* $[0, b^{1/\beta}]$ *if* $b^{1/\beta} < T_\Delta$.

Remark 6. *Since for all $\mu < 0$, the function h is concave, namely $h''_\mu(T) < 0$ for all $T > 0$, it follows that*

$$\mu \le -b^{-1/\beta} \quad \Leftrightarrow \quad b^{1/\beta} \ge T_\Delta, \quad \textit{and} \quad -b^{-1/\beta} < \mu < 0 \quad \Leftrightarrow \quad b^{1/\beta} < T_\Delta.$$

Next, we proceed with the case $\mu > 0$. Firstly, note that

$$\lim_{T\to 0^+} h'_\mu(T) = \begin{cases} 0, & \text{if} \quad \beta = 1, \\ \infty, & \text{if} \quad 0 < \beta < 1, \end{cases} \qquad \text{and} \quad \lim_{T\to\infty} h'_\mu(T) = \infty.$$

In addition, $h'_\mu(T)$ admits exactly one positive critical point $T_\star$. Indeed,

$$h''_\mu(T_\star) = 0 \quad \Leftrightarrow \quad \beta - 1 + \mu(1+\beta)T_\star = 0, \quad \Leftrightarrow \quad T_\star = \frac{1-\beta}{\mu(1+\beta)}.$$

Moreover,

$$h'''_\mu(T_\star) = \beta(1-\beta)T_\star^{\beta-3} > 0, \quad \text{and} \quad h'_\mu(T_\star) = \left(\frac{1-\beta}{\mu(1+\beta)}\right)^{\beta-1} - \mu b.$$

The last left-hand inequality implies that $T_\star$ is a global minimum of $h'_\mu(T)$ on $\{T \in \mathbb{R} : T \ge 0\}$. These computations provide the elements for the proof of the following result

Lemma 18. *Assume that*

$$0 < \mu \le \mu_c := \left(\frac{1}{b}\left(\frac{1-\beta}{1+\beta}\right)^{\beta-1}\right)^{\frac{1}{\beta}}.$$

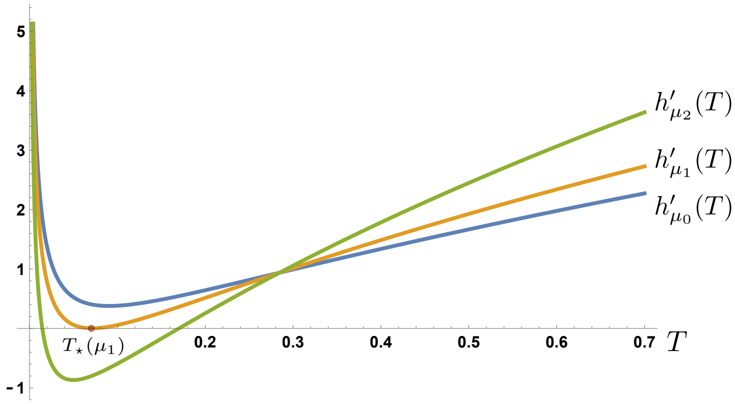

FIGURE 2. Graph of $h'_\mu(T)$ with parameters $b = 0.8$, and $\beta = 0.5$ for $T \in]0, 0.7]$. Three different values of μ are considered: $\mu_n = 3.68+n$, $n \in \{0, 1, 2\}$. Notice that $\mu_1 \approx \mu_c = 75/16$. For $\mu < \mu_c$, $h'_\mu(T) > 0$ for all $T > 0$. Instead, if $\mu > \mu_c$, $h'_\mu(T)$ have exactly two positive zeros.

Then,

a. *If* $h_0 < 0$, *there are no solutions of* (▲) *for all* $T \geq 0$.
b. *If* $0 \leq h_0$ *there exist exactly one solution of* (▲) *on the set* $T \geq 0$. *In particular, if* $h_0 \leq b$ *the solution lying on* $[0, b^{1/\beta}]$.

Proof. For each $\mu > 0$, the previous computations shows that $h'_\mu(T)$ has a global minimum at $T = T_\star = \dfrac{1-\beta}{\mu(1+\beta)}$. Furthermore,

$$h'_\mu(T_\star) = \Big(\frac{1-\beta}{\mu(1+\beta)}\Big)^{\beta-1} - \mu b \geq 0 \quad \text{if and only if} \quad \mu \leq \Big(\frac{1}{b}\Big(\frac{1-\beta}{1+\beta}\Big)^{\beta-1}\Big)^{\frac{1}{\beta}},$$

hence, $h_\mu(T)$ is a monotone-increasing continuous function. Since $h_\mu(0) = 0$, we have that $h_\mu(T)$ is non-negative, proving already statement a. and the first part of statement b. Finally, since $h_\mu([0, b^{1/\beta}]) \subseteq [0, b]$ clearly the solution of (▲) for $0 \leq h_0 \leq b$ lying on $[0, b^{1/\beta}]$. □

Let us consider the function $l :]0, \infty[\to \mathbb{R}$, $\mu \to l(\mu) := \min_{T>0} h'_\mu(T)$. Since $T_\star = T_\star(\mu)$ is the global minimum of $h'_\mu(T)$ on $\{T \in \mathbb{R} : T \geq 0\}$, it follows

$$\begin{aligned} l(\mu) = h'_\mu(T_\star(\mu)) = T_\star^{\beta-1}(\mu) - \mu b &= \mu^{1-\beta}\Big(\frac{1-\beta}{1+\beta}\Big)^{\beta-1} - \mu b, \\ &= \mu b\Big(\Big(\frac{\mu_c}{\mu}\Big)^{\beta} - 1\Big). \end{aligned}$$

In consequence, $l(\mu)$ is monotone decreasing for all $\mu > 0$ satisfying

$$l(\mu_c) = 0, \quad \text{and} \quad \lim_{\mu\to\infty} l(\mu) = -\infty.$$

It should be pointed out that $h''_\mu(T)$ has only one sign change (precisely at $T_\star$). In fact,

$$h'''_\mu(T_\star) > 0, \quad \lim_{T\to 0} h''_\mu(T) = -\infty, \quad \text{and} \quad \lim_{T\to\infty} h''_\mu(T(\mu)) = 0.$$

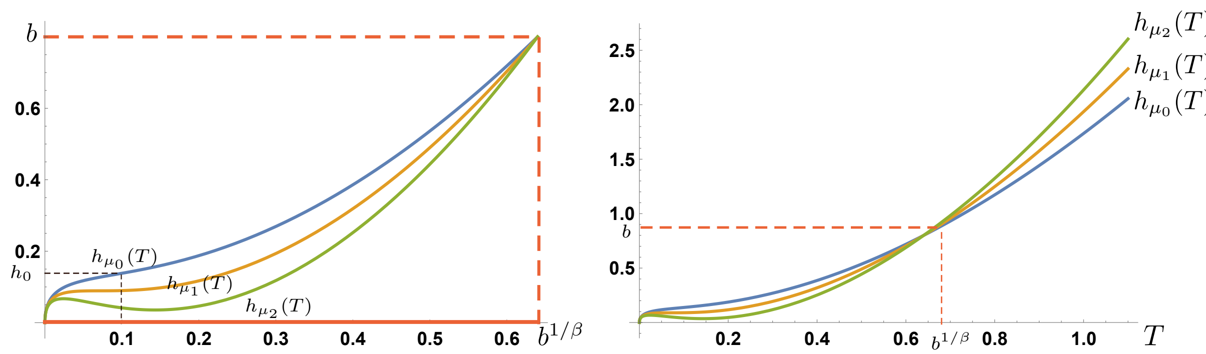

FIGURE 3. Graph of $h_\mu(T)$ with parameters $b = 0.8$, and $\beta = 0.5$. (Left) $T \in]0, b^{1/\beta}]$. (Right) $T \in]0, 1.2]$. Three different values of μ are considered: $\mu_n = 3.68 + n$, $n \in \{0, 1, 2\}$. Notice that $\mu_1 \approx \mu_c = 75/16$. For $\mu \le \mu_c$, there is exactly one solution of ($\blacktriangle$) if $0 \le h_0 \le b$ lying on $[0, b^{1/\beta}]$.

Combining the previous results it is deduced that $h'_\mu(T)$ have exactly two zeros, which shall be called $T_L = T_L(\mu)$ and $T_R = T_R(\mu)$ for all $\mu_c < \mu$. Furthermore, [2]

$$0 < T_L < T_* < T_R, \quad \text{and} \quad h''_\mu(T_L) < 0 < h''_\mu(T_R).$$

Now, it is important to highlight the behavior of the zeros of $h'_\mu(T)$ for $\mu > \mu_c$. Firstly, notice that

$$h'_\mu(T_R) = 0 \quad \Leftrightarrow \quad \mu\big((1+\beta)T_R^\beta - b\big) + \beta T_R^{\beta-1} = 0 \quad \Rightarrow \quad T_R^\beta < \frac{b}{1+\beta} < b,$$

implying that $0 < T_L < T_\star < T_R < b^{1/\beta}$.

Next, define the function

$$\begin{aligned} H_L : [\mu_c, \infty[&\to \mathbb{R} \\ \mu &\to h_\mu(T_L(\mu)), \end{aligned}$$

which provides the value of $h_\mu(T)$ over the critical point T_L for all $\mu_c \le \mu$. A direct computation proves that

$$T_L(\mu_c) = T_\star(\mu_c) = \Big(b\Big(\frac{1-\beta}{1+\beta}\Big)\Big)^{1/\beta}, \quad \text{and} \quad T_\star^\beta(\mu_c) - \mu_c b\, T_\star(\mu_c) = 0.$$

From here, we deduce

$$H(\mu_c) = \mu_c T_\star^{1+\beta}(\mu_c) = b\Big(\frac{1-\beta}{1+\beta}\Big)^{1+\beta} < b, \quad \text{and} \quad H'(\mu) = \big(T_L^\beta(\mu) - b\big)T_L(\mu) < 0.$$

[2]The inequalities (6) follow as result of all mentioned properties of $h'_\mu(T)$ and $h''_\mu(T)$.

In consequence, $H_L(\mu) < b$ for all $\mu_c < \mu$. Likewise, denoting $H_R(\mu) := h_\mu(T_R(\mu))$, by the monotonicity properties of $h''_\mu(T)$, it follows that $H_R(\mu) < b$, for all $\mu_c < \mu$.

To sum up, for all $b, \beta \in [0, 1[$ fixed, the function $h_\mu(T) = \mu(T^\beta - b)T + T^\beta$ satisfies:

- ▷ $h'_\mu(T)$ has exactly two zeros $T_L(\mu)$, $T_R(\mu)$ such that
$$0 < T_L(\mu) < T_\star(\mu) = \frac{1-\beta}{\mu(1+\beta)} < T_R(\mu) < b^{1/\beta}.$$
- ▷ $h''_\mu(T)$ has exactly a simple zero at $T_\star(\mu)$ and
$$h''_\mu(T_L) < 0 < h''_\mu(T_R),$$
- ▷ If $H_R(\mu) := h_\mu(T_R(\mu))$ and $H_L(\mu) := h_\mu(T_L(\mu))$, then $H_R(\mu) < H_L(\mu)$,

for all $\mu > \left(\frac{1}{b}\left(\frac{1-\beta}{1+\beta}\right)^{\beta-1}\right)^{\frac{1}{\beta}}$.

Bifurcation point. The next lines are devoted to show the existence of $\hat{\mu} > \mu_c$ and $\hat{T} > 0$ such that $h_\mu(T)$ has a saddle-node bifurcation point at $(\hat{T}, \hat{\mu})$. Moreover,
$$T_R(\mu) \to \hat{T} = [(1-\beta)b]^{1/\beta} \quad \text{if} \quad \mu \to \hat{\mu} := \frac{1}{\beta[b(1-\beta)^{1-\beta}]^{1/\beta}}.$$

Proposition 19. *Let us consider $b, \beta \in]0, 1[$, Then, the following properties hold*

1. *There exists a unique $\hat{T} \in]0, b^{1/\beta}[$ and $\hat{\mu} > \mu_c$ such that*
$$\begin{aligned} h_{\hat{\mu}}(\hat{T}) &= 0, \\ h'_{\hat{\mu}}(\hat{T}) &= 0. \end{aligned} \tag{38}$$
Moreover, $\hat{T}$ and $\hat{\mu}$ are given by
$$\hat{T} = T_{bif} := \big[(1-\beta)b\big]^{1/\beta} \quad \textit{and} \quad \hat{\mu} = \mu_{bif} := \frac{1}{\beta\big[b(1-\beta)^{1-\beta}\big]^{1/\beta}}.$$
2. *The equation $h_\mu(T) = 0$ has a fold bifurcation at (T_{bif}, μ_{bif}).*

Proof. Let us consider the system
$$\begin{aligned} h_{\hat{\mu}}(\hat{T}) &= 0, \\ h'_{\hat{\mu}}(\hat{T}) &= 0. \end{aligned} \quad \Leftrightarrow \quad \begin{aligned} T^\beta\big(1+\mu T\big) &= \mu b T, \\ T^{\beta-1}(\beta + \mu(1+\beta)T) &= \mu b. \end{aligned} \tag{39}$$
As we know, the existence of zeros of $h'_\mu(T)$ is only possible if $\mu \geq \mu_c$. Moreover, from expressions (39) we have
$$T^\beta\big(1+\mu T\big) = T^\beta(\beta + \mu(1+\beta)T) \quad \Leftrightarrow \quad T^\beta\big(1-\beta-\mu\beta T\big) = 0 \quad \Leftrightarrow \quad \hat{T}(\mu) = \frac{1-\beta}{\mu\beta}.$$
By substituting this (unique) value in the first equation in (39) it holds
$$[\hat{T}(\mu)]^\beta = (1-\beta)b \quad \Rightarrow \quad \hat{T}(\mu) = \hat{T} := ((1-\beta)b)^{1/\beta}.$$

In consequence

$$\hat{\mu} = \frac{1-\beta}{\beta\hat{T}} = \frac{1}{\beta\left[b(1-\beta)^{1-\beta}\right]^{1/\beta}}.$$

A direct computation shows that $\mu_c < \hat{\mu}$. This proves the first part of the statement.

2. Recall that a parametric equation $f(x,\mu) = 0$, with $f : I \times W \subset \mathbb{R}^2 \to \mathbb{R}$ $f \in C^2(I \times W)$ has a fold bifurcation at the point (x_0, μ_0) if

$$f(x_0,\mu_0) = 0, \quad \partial_x f(x_0,\mu_0) = 0, \quad \partial_x^2 f(x_0,\mu_0) \neq 0, \quad \text{and} \quad \partial_\mu f(x_0,\mu_0) \neq 0.$$

In such a case, there exist two intervals $I_- :=]\mu_-, \mu_0[$, $I_+ :=]\mu_0, \mu_+[$ and $\varepsilon > 0$ such that

a. If $\partial_x^2 f(x_0,\mu_0) > 0$, and $\partial_\mu f(x_0,\mu_0) < 0$, then:
   †) $f(x,\mu)$ has no zeros if $x \in]x_0-\varepsilon, x_0+\varepsilon[$ and $\mu \in I_-$.
   †) $f(x,\mu)$ has exactly two zeros if $x \in]x_0-\varepsilon, x_0+\varepsilon[$ and $\mu \in I_+$.

b. If $\partial_x^2 f(x_0,\mu_0)$ or $\partial_\mu f(x_0,\mu_0)$, have reversed sign, then the previous conclusion is similar.

For the parametric equation

$$h_\mu(T) = 0, \quad \Leftrightarrow \quad h_\mu = h(T,\mu) = 0,$$

with $h :]0, b^{1/\beta}[\times]0,\infty[\to \mathbb{R}$, $(T,\mu) \to h(T,\mu)$ we have $h(\hat{T},\hat{\mu}) = 0$, $\partial_T h(\hat{T},\hat{\mu}) = 0$ but also

$$\partial_T^2 h(\hat{T},\hat{\mu}) = \frac{b}{\left[b(1-\beta)^{1-\beta}\right]^{2/\beta}} > 0, \quad \text{and} \quad \partial_\mu h_\mu(\hat{T},\hat{\mu}) = -\beta b\hat{T} < 0.$$

In consequence, there exists two intervals $I_- :=]\mu_-, \hat{\mu}[$, $I_+ :=]\hat{\mu}, \mu_+[$ and $\varepsilon > 0$ such that

‡) $h(T,\mu)$ has no zeros if $T \in]\hat{T}-\varepsilon, \hat{T}+\varepsilon[$ and $\mu \in I_-$.
‡) $h(T,\mu)$ has exactly two zeros if $T \in]\hat{T}-\varepsilon, \hat{T}+\varepsilon[$ and $\mu \in I_+$.

□

We end this appendix by pointing out this new result about the solutions of (▲)

Remark 7. *By the monotonicity properties of $h''_\mu(T)$, it is known that $T_R(\mu)$ is the only critical point of $h_\mu(T)$ for $\mu > \mu_c$ such that $h''_\mu(T_R) > 0$. Therefore, by the C^2-continuity of h_μ with respect to the parameter μ we have*

$$T_R(\mu) \to T_{bif} \quad \textit{as} \quad \mu \to \mu_{bif},$$

implying that $H_R(\mu_{bif}) = 0$.

Proposition 20. *Let us consider the equation (▲). Assume that*

$$\mu_c := \left(\frac{1}{b}\left(\frac{1-\beta}{1+\beta}\right)^{\beta-1}\right)^{\frac{1}{\beta}} < \mu \leq \mu_{bif} = \frac{1}{\beta\left[b(1-\beta)^{1-\beta}\right]^{1/\beta}}.$$

Define

$$H_L := h_\mu(T_L(\mu)) \quad \textit{and} \quad H_R := h_\mu(T_R(\mu)),$$

where $T_{L,R}(\mu)$ are only the two critical points of $h_\mu(T)$.

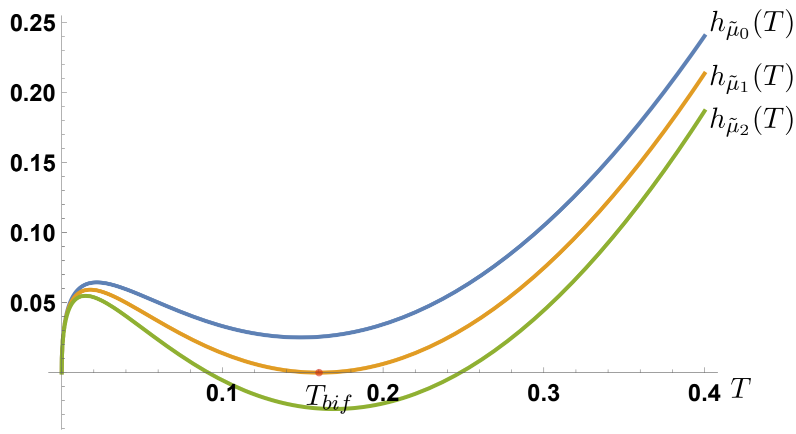

FIGURE 4. Graph of $h_\mu(T)$ with parameters $b = 0.8$, and $\beta = 0.5$. for $T \in]0, 5b^{1/\beta}/8]$. Three different values of $\tilde{\mu}$ are considered: $\tilde{\mu}_n = 5.85 + 0.4n$, $n \in \{0, 1, 2\}$. Notice that $T_{bif} = 4/25$ and $\tilde{\mu}_1 = \mu_{bif} = 25/4$. There are no solutions of $h_{\tilde{\mu}_0}(T) = 0$ and exactly two solutions of $h_{\tilde{\mu}_2}(T) = 0$.

I) *If $h_0 = H_R$, then there are exactly two solutions of* ($\blacktriangle$) *for all* $T \in [0, b^{1/\beta}]$.
II) *If $H_R < h_0 < H_L$, then there are exactly three solutions of* ($\blacktriangle$) *for all* $T \in [0, b^{1/\beta}]$.
III) *If $H_L = h_0$, there are exactly two solutions of* ($\blacktriangle$) *for all* $T \in [0, b^{1/\beta}]$.
IV) *If $0 \leq h_0 < H_R$ or $H_L < h_0$, there is exactly one solution of* ($\blacktriangle$) *for all* $T \in [0, b^{1/\beta}]$.

Finally, there exist $\varepsilon_{1,2} > 0$ and an interval $I_+ :=]\mu_{bif}, \mu_{bif} + \varepsilon_1[$ such that, if $-\varepsilon_2 < h_0 \leq 0$ the equation ($\blacktriangle$) *admits exactly two solutions for all* $T \in [0, b^{1/\beta}]$.

Remark 8. *In the current bibliography about the dynamics in a tumor immune system, the most usual growth function for the tumor cells is the Logistic growth function. In such a case*

$$h_\mu(T, \mu) = \mu T^2 + (1 - \mu b)T.$$

Moreover,

$$\lim_{\beta \to 1} \mu_c = \frac{1}{b}, \qquad \lim_{\beta \to 1} \mu_{bif} = \frac{1}{b}, \quad \textit{and} \quad 0 = T_L(1/b) = T_*\big(1/b\big) = T_R(1/b).$$

This means that there are fewer equilibrium points for the logistic growth function case. In fact:

APPENDIX B

This appendix presents some results on the linear delay system

$$(\underline{\dagger}) \qquad \dot{Y}(t) = AY(t) + BY(t - \tau_1) + CY(t - \tau_2),$$

with $A, B, C \in \mathbb{M}_{2\times 2}$ constant real matrices, $Y \in \mathbb{R}^2$ and $\tau_i \geq 0$. In the following:

- $\triangleright$ $\det A$ denotes the determinant of A.
- $\triangleright$ trA denotes the trace of A.
- $\triangleright$ $(a^1|b^2)$ is the matrix with the first column from A and the second column from B.

Define the quadratic polynomial $P(\lambda, z, w)$ in (λ, z, w) :

$$\mathcal{P}(\lambda, z, w) := \lambda^2 - (trA)\lambda + \det A + (\det B)z^2 + (\hat{c} - (trB)\lambda)z + (\det C)w^2 - \hat{d}(\lambda, z)w,$$

where

$$\hat{c} = \det(a^1|b^2) + \det(b^1|a^2) \quad \text{and} \quad \hat{d}(\lambda, z) = \det(c^1|m^2(\lambda, z)) + \det(m^1(\lambda, z)|c^2),$$

with $M(\lambda, z) = \lambda I_2 - A - zB$.

Lemma 21. *Let $\lambda \in \mathbb{C}$ and $Y_* \neq 0_{\mathbb{R}^2}$. Then $Y(t) = e^{\lambda t}Y_*$ is a solution of ($\underline{\dagger}$) if λ satisfies the associated characteristic equation*

$$\mathcal{P}(\lambda, e^{-\lambda\tau_1}, e^{-\lambda\tau_2}) = 0.$$

In particular, if $\tau = \tau_1 = \tau_2$ the characteristic equation $\mathcal{P}(\lambda, e^{-\lambda\tau}, e^{-\lambda\tau}) = 0$ is given by

$$\lambda^2 - (trA)\lambda + \det A + (\det(B + C))e^{-2\lambda\tau} + (\tilde{c} - (tr(B + C)\lambda)e^{-\lambda\tau} = 0,$$

where, $\tilde{c} = \det(a^1|(b + c)^2) + \det((b + c)^1|a^2)$.

Proof. We seek exponentially growing solutions of ($\underline{\dagger}$) of the form: $Y(t) = e^{\lambda t}Y_*$, with $Y_* \neq 0_{\mathbb{R}^2}$ and $\lambda \in \mathbb{C}$. Substituting into the equation ($\underline{\dagger}$), λ satisfies

$$e^{\lambda t}\big[\lambda I_2 - A - e^{-\lambda\tau_1}B - e^{-\lambda\tau_2}C\big]Y_* = 0 \quad \Rightarrow \quad \det\big(M - N\big) = 0,$$

with

$$M = M(\lambda, z) := \lambda I_2 - A - zB, \quad \text{and} \quad N := e^{-\lambda\tau_2}C.$$

From this, straightforward computations show that

$$\det(M - N) = \det(M) + \det(N) - \det(n^1|m^2) - \det(m^1|n^2)$$

finished the proof. ∎

Stability results and bifurcation of periodic solution for equal time-delay. Assume that for system ($\underline{\dagger}$) we have $\tau_1 = \tau_2 = \tau$, i.e., we have the delayed linear system

$$(\underline{\ddagger}) \quad \dot{Y}(t) = AY(t) + (B + C)Y(t - \tau),$$

with $A, B, C \in \mathbb{M}_{2\times 2}$ constant real matrices, $Y = Y(t) \in \mathbb{R}^2$ and $\tau \geq 0$. Additionally, suppose that the corresponding characteristic equation is of the form

$$\hat{\mathcal{P}}(\lambda, \tau) = \lambda^2 + (\lambda_1 + \lambda_2)\lambda + \lambda_1\lambda_2 - Ne^{\tau\lambda},$$

with $\lambda_i \in \mathbb{R}$ and $N \in \mathbb{R}^-$. In [10] the authors present the following theorems that provide sufficient conditions under which the trivial solution $Y(t) = 0_{\mathbb{R}^2}$ will be asymptotically stable, and the appearance of stable periodic limit cycles emerging in specific values of τ.

Teorema (A). *Assume that $\lambda_1 + \lambda_2 < 0$ and $N < \lambda_1\lambda_2 < -N$. Then $Y(t) = 0_{\mathbb{R}^2}$ is asymptotically stable for all values of τ satisfying $0 \leq \tau < \dfrac{\lambda_1 + \lambda_2}{N}$.*

Teorema (B). *Assume that $\lambda_1\lambda_2 > -N$. Then $Y(t) = 0_{\mathbb{R}^2}$ is asymptotically stable for all $\tau \geq 0$.*

Teorema (C). *(A Hopf bifurcation theorem) Assume that*

$$\lambda_1 + \lambda_2 < 0 \quad \textit{and} \quad N < \lambda_1\lambda_2 < -N$$

Then, there exists $\tau_c > 0$ given as the smallest value of τ for which

$$\hat{\mathcal{P}}(\lambda(\tau), \tau) = 0,$$

admits a solution $\lambda(\tau) = iy(\tau)$. Moreover, for $\tau < \tau_c$, $Y(t) = 0_{\mathbb{R}^2}$ is asymptotically stable, while if $\tau > \tau_c$, $Y(t) = 0_{\mathbb{R}^2}$ is unstable. Furthermore, as Furthermore, as τ increases through τ_c, $Y_2(t) = 0$ bifurcates into "small-amplitude" periodic solutions, which are stable, i.e., $Y_2(t) = 0$ loses its stability and undergoes a Hopf bifurcation.

Remark 9. *Equation $\hat{\mathcal{P}}(x + iy, \tau) = 0$ can be divided into real and imaginary parts as follows*

$$(x - \lambda_1)(x - \lambda_2) - y^2 - N\cos(\tau y)e^{-\tau x} = 0,$$
$$2xy - (\lambda_1 + \lambda_2)y + N\sin(\tau y)e^{-\tau x} = 0.$$

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