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EXISTENCE OF PERIODIC SOLUTIONS IN THE MODIFIED WHELDON MODEL OF CML

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Abstract. The Wheldon model (1975) of a chronic myelogenous leukemia (CML) dynamics is modified and enriched by introduction of a time-varying microenvironment and time-dependent drug efficacies. The resulting model is a special class of nonautonomous nonlinear system of differential equations with delays. Via topological methods, the existence of positive periodic solutions is proven. We introduce our main insight and formulate some relevant open problems and conjectures.

1. Modified Wheldon Model of CML

1.1. **Background.** Chronic myelogenous leukemia (CML) is cancer of the blood in which too many granulocytes, a type of white blood cell, are produced in the marrow, and it makes up about 10 to 15 percent of all leukemias (see, for example, [9, 10, 13, 15, 16]). In 1974 Wheldon in the paper [22] (see also [21]) introduced the following model of granulopoiesis (granulocyte production)

$$\begin{aligned} \frac{dM}{dt} &= \frac{\alpha}{1+\beta M^n(t-\tau)} - \frac{\lambda M(t)}{1+\mu B^m(t)}, \\ \frac{dB}{dt} &= -\omega B(t) + \frac{\lambda M(t)}{1+\mu B^m(t)}, \end{aligned} \tag{1.1}$$

where all parameters are positive constants. In model (1.1), $M(t)$ is the number of cells in the marrow; $B(t)$ is the number of white blood cells; β is the coupling constant for cell production loop; α is the maximum rate of cell production; λ is the maximum rate of release of mature cells from marrow; μ is the coupling constant for release loop; ω is the constant rate for loss of granulocytes from blood to tissue; τ represents mean time for stem cell maturity; n controls gain of cell production loop and m controls gain of release loop.

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A different mechanism of CML was modeled and studied by Mackey (see, for example, [6]).

$$\begin{aligned} \frac{dN}{dt} &= -\delta(t)N(t) - \beta(N(t)) + 2e^{-\delta\tau}\beta(N(t-\tau)), \\ \frac{dP}{dt} &= -\gamma P(t) + \beta(N(t)) - e^{-\delta\tau}\beta(N(t-\tau)). \end{aligned} \tag{1.2}$$

This model consists of a proliferating phase cellular population $P(t)$ and a G_0 resting phase with a population of cells $N(t)$, where

$$\beta(N) = \frac{\beta_0\theta^n N}{\theta^n + N^n} \ (n > 0).$$

This is simply a model of stem cells dynamics - daughter cells either differentiate or return to the stem cell compartment follows by another division cycle. There is only the implicit suggestion above that there are positive and negative feedback signals regulating the rates at which cells will move through these "decisions".

However, model (1.1) has a major drawback, i.e., it describes a wrong mechanism. At the (unique) nontrivial equilibrium point (M_*, B_*) of system (1.1), we have:

$$\omega B_* = \frac{\alpha}{1 + \beta M_*^n}. \tag{1.3}$$

Thus, the B-population in the Wheldon model is inversely proportional to the M-population; the latter does not have any biological explanation.

To reanimate the Wheldon model, we used Wheldon's remarks in his later work [20] to introduce a new mechanism:

$$\begin{aligned} \frac{dM}{dt} &= \frac{\alpha M(t)}{1 + \beta M^n(t-\tau_1)} - \frac{\lambda M(t)}{1 + \mu B^m(t-\tau_2)}, \\ \frac{dB}{dt} &= -\omega B(t) + \frac{\lambda M(t)}{1 + \mu B^m(t-\tau_2)}. \end{aligned} \tag{1.4}$$

This model creates a time-delay loop triggering stem cell production and a fast loop regulating release of mature cells in the blood. Studies of the model imply that the oscillatory pattern in leukemia may be bring forth in two principal ways, either by an increased cell production rate or by an increased maturation time. Note also that model (1.4) assumes that there is a direct negative feedback from mature to the precursors of those cells. Time delay τ_1 (τ in model (1.1)) represents a mean time for $M-$ cell maturity. A stimulator/inhibitor mechanism is presented by the second term in both equations, where a time delay τ_2 is a lag between when $B-$cells are initiated and when an apparent tumor progressed (the latency time) since each cell cycle phase is dependent on the completion of the previous ones.

Remark 1.1. Note that the first term in (1.1) is a decreasing function of M

$$\frac{\alpha}{1 + \beta M^n},$$

whereas in model (1.4)

$$\frac{\alpha M}{1 + \beta M^n}$$

is a one-hump function, resulting in a relationship between stem cells and white blood cells more realistic than in (1.3):

$$\omega B_* = \frac{\alpha M_*}{1+\beta M_*^n}. \tag{1.5}$$

Exposure to chemoradiation therapy will kill not only cancer cells, but other rapidly dividing cells in the body as well (e.g. the cells in the bone marrow that go on to become white blood cells), and will therefore suppress immune system [2]–[5] [9, 12, 15, 18, 19]. Note that for a new model the complete recovery is possible for sufficiently high drug dosage (see Figure 1).

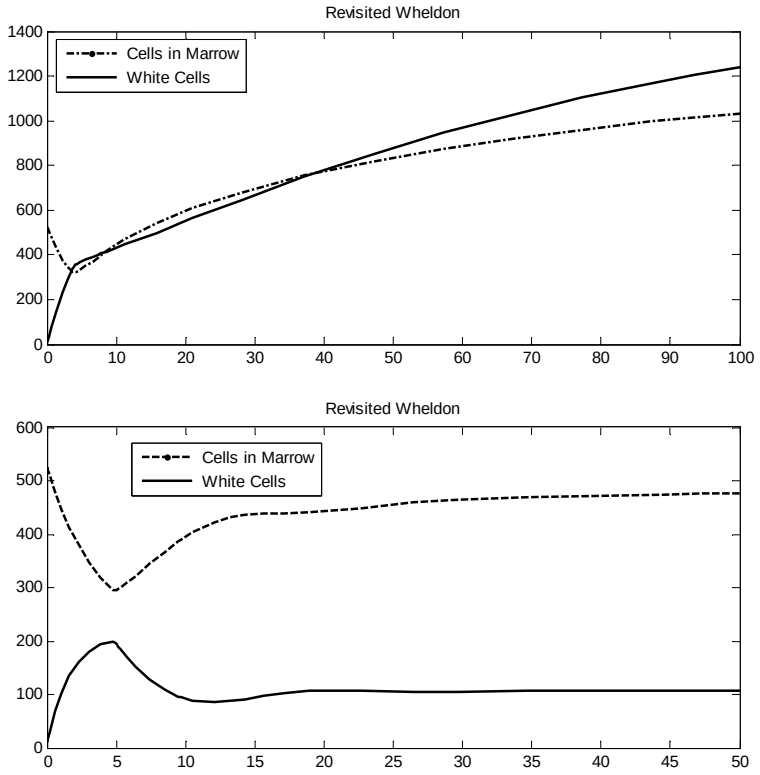

FIGURE 1. Dynamics before therapy and after therapy

It is well recognized that tumor microenvironment changes with time and in response to treatment. These fluctuations can modulate tumor progression and acquired treatment resistance (see, for example, [8, 12, 13, 18]). Henceforth, to mimic changes of the tumor microenvironment, we incorporate time-dependent parameters.

$$\begin{aligned}
\frac{dM}{dt} &= \frac{\alpha(t)M(t)}{1+\beta(t)M^n(t-\tau_1)} - \frac{\lambda(t)M(t)}{1+\mu(t)B^m(t-\tau_2)} - \delta p(t)M(t),\\
\frac{dB}{dt} &= -\omega(t)B(t) + \frac{\lambda(t)M(t)}{1+\mu(t)B^m(t-\tau_2)} - \delta q(t)B(t),
\end{aligned} \tag{1.6}$$

where $p(t) = p(c)$ and $q(t) = q(c)$ are the varying effectiveness of the drug, and $c = c(t)$ is the drug concentration at time t. Traditionally, this pharmokinetic is modeled by linear functions, namely $p(c) = \alpha c(t)$ and $g(c) = \beta c(t)$ where α and β are the appropriate drug sensitivity parameters. Clearly, $\alpha = \beta$ if the drugs are cycle-non-specific, i.e., they will be equally toxic to all types of cells. Some types of chemotherapy can be modeled based on a non-monotone one-humped functions- $p(c) = \alpha c(t)e^{-ac(t)}$ and $q(c) = \beta c(t)e^{-bc(t)}$. Throughout the paper, it shall be assumed that $\alpha(t), \beta(t), \omega(t), \lambda(t), \mu(t), p(t)$ and $q(t)$ are continuous, positive and T-periodic functions and $\tau_{1,2} > 0$ are fixed delays. The parameter δ is assumed to be 1 or 0 according the presence or absence of pharmacokinetics. Different and interesting models of CML were recently examined in [1, 7, 10, 17].

It is worth noticing that, given set of nonnegative initial conditions, the solution of problem (1.6) is globally defined and positive over $[0, +\infty)$. Indeed,

Theorem 1.2. *Let $\varphi_i : [-\tau_i, 0] \to [0, +\infty)$ be continuous functions such that $\varphi_i(0) > 0$. Then there exists a unique global positive solution of problem* (1.6) *under initial conditions*

$$\begin{aligned} M(t) &= \varphi_1(t) \quad -\tau_1 \le t \le 0, \\ B(t) &= \varphi_2(t) \quad -\tau_2 \le t \le 0. \end{aligned}$$

Proof. Set $R(t) := \ln M(t)$, then the system becomes

$$\begin{aligned} R'(t) &= \frac{\alpha(t)}{1+\beta(t)e^{nR(t-\tau_1)}} - \frac{\lambda(t)}{1+\mu(t)B^m(t-\tau_2)} - \delta p(t), \\ B'(t) &= -\omega(t)B(t) + \frac{\lambda(t)e^{R(t)}}{1+\mu(t)B^m(t-\tau_2)} - \delta q(t)B(t). \end{aligned} \tag{1.7}$$

Suppose that $M(t)$ and $B(t)$ are defined and positive for $t < t_0$, then from the inequalities $-\lambda(t) - \delta p(t) < R'(t) < \alpha(t)$ it is clear that $R(t)$ is defined up to t_0. Moreover, $B'(t) < \lambda e^{R(t)}$ and hence $B(t)$ is defined in t_0. Finally, if $B(t_0) = 0$ then $B'(t_0) > 0$, a contradiction. □

In next section we shall prove, under appropriate conditions, the existence of at least one positive T-periodic solution: namely, a pair (M, B) of C^1 functions satisfying

$$M(t+T) = M(t) > 0, \quad B(t+T) = B(t) > 0$$

for all $t \in \mathbb{R}$. In view of the preceding result, one might attempt to define a Poincaré-like operator in order to apply some fixed point theorem. However, the conditions for such a procedure seem to be very restrictive; thus we apply, instead, the Leray-Schauder degree theory [11, 14] over an appropriate open subset of $C_T \times C_T$, where C_T denotes the space of continuous and T-periodic real functions.

For the reader's convenience, we make a short account of the main properties of the degree that shall be used in this work. Let X be a Banach space, let $\Omega \subset X$ be open and bounded and denote by $cl(\Omega)$ the closure of Ω. If $\mathcal{K} : cl(\Omega) \to X$ is compact with $\mathcal{K}u \neq u$ for all $u \in \partial\Omega$, then the Leray-Schauder degree of the Fredholm operator $\mathcal{F} = Id - \mathcal{K}$ at 0 shall be denoted by $\deg(\mathcal{F}, \Omega, 0)$. Roughly speaking, this (whole) number can be regarded as an algebraic count of the zeros of $\mathcal{F}$.

(1) (Solution) If $\deg(\mathcal{F}, \Omega, 0) \neq 0$, then $\mathcal{F}$ has at least one zero in Ω.

(2) (Homotopy invariance) If $\mathcal{F}_\sigma = Id - \mathcal{K}_\sigma$ with $\mathcal{K}_\sigma : cl(\Omega) \to X$ compact such that $\mathcal{K}_\sigma u \neq u$ for all $u \in \partial\Omega$, $\sigma \in [0,1]$ and $\mathcal{K} : cl(\Omega) \times [0,1] \to X$ given by $\mathcal{K}(u,\sigma) := \mathcal{K}_\sigma(u)$ continuous, then $\deg(\mathcal{F}_\sigma, \Omega, 0)$ is independent on σ.

(3) If $\mathcal{K}(cl(\Omega)) \subset V$, with $V \subset X$ a finite dimensional subspace, then

$$\deg(\mathcal{F}, \Omega, 0) = \deg(\mathcal{F}|_{cl(\Omega)\cap V}, \Omega \cap V, 0).$$

Identifying V with $\mathbb{R}^n$, the latter term is simply the so-called *Brouwer degree*. In this paper, we only need to know that if $\Omega_0 \subset \mathbb{R}^n$ is open and bounded with $0 \in \Omega_0$, then $\deg(-Id, \Omega_0, 0) = (-1)^n$.

2. Existence of periodic solutions

2.1. Case 1: No pharmokinetic.

Theorem 2.1. *Assume that $\alpha(t), \beta(t), \lambda(t), \mu(t)$ and $\omega(t)$ are continuous, positive and T-periodic. Furthermore, assume that*

(1) $n > \frac{m}{m+1}$.
(2) $\alpha(t) > \lambda(t) > \omega(t)$ *for all* t.

Then system (1.6) *with* $\delta = 0$ *admits at least one positive T-periodic solution.*

Proof. Set $u(t) = \ln M(t)$ and $v(t) = \ln B(t)$, then (1.6) with $\delta = 0$ reads

$$u'(t) = \frac{\alpha(t)}{1+\beta(t)e^{nu(t-\tau_1)}} - \frac{\lambda(t)}{1+\mu(t)e^{mv(t-\tau_2)}} := \psi_1(u,v)(t),$$
$$v'(t) = -\omega(t) + \frac{\lambda(t)e^{u(t)-v(t)}}{1+\mu(t)e^{mv(t-\tau_2)}} := \psi_2(u,v)(t).$$

To prove the existence of T-periodic solutions of this system, we shall apply the continuation method [14]. Adapted to this case, the method guarantees the existence of solutions, provided there exists an open bounded set $\Omega \subset C_T \times C_T$ such that

(1) For $\sigma \in (0,1]$, the system

$$u'(t) = \sigma\psi_1(u,v)(t),$$
$$v'(t) = \sigma\psi_2(u,v)(t)$$

has no T-periodic solutions on $\partial\Omega$.

(2) $\deg(F, \Omega \cap \mathbb{R}^2, 0)$ is well defined and different from 0, where the function $F : \mathbb{R}^2 \to \mathbb{R}^2$ is defined by

$$F(u,v) := \frac{1}{T}\int_0^T \Big(\frac{\alpha(t)}{1+\beta(t)e^{nu}} - \frac{\lambda(t)}{1+\mu(t)e^{mv}}, \frac{\lambda(t)e^{u-v}}{1+\mu(t)e^{mv}} - \omega(t)\Big)\,dt.$$

For simplicity, we divide the proof in two steps.

First step: Let $\Omega_0 := (-R,R) \times (-R,cR) \subset \mathbb{R}^2$, where c is a fixed constant such that $\frac{1}{m+1} < c < \frac{n}{m}$. We claim that $\deg(F, \Omega_0, 0) = 1$ for $R > 0$ large enough.

Indeed, let us firstly assume that $-R \le v \le cR$, then

$$F_1(R,v) = \frac{1}{Te^{nR}}\int_0^T \frac{\alpha(t)e^{nR}}{1+\beta(t)e^{nR}} - \frac{\lambda(t)e^{nR}}{1+\mu(t)e^{mv}}\,dt.$$

As $nR > mcR$, it follows that $F_1(R, v) \le F_1(R, cR) < 0$ for $R \gg 0$. On the other hand,

$$F_1(-R, v) = \frac{1}{T}\int_0^T \frac{\alpha(t)}{1+\beta(t)e^{-nR}} - \frac{\lambda(t)}{1+\mu(t)e^{mv}}\,dt \ge \frac{1}{T}\int_0^T \frac{\alpha(t)}{1+\beta(t)e^{-nR}}\,dt - \overline{\lambda}.$$

The right-hand side term tends to $\overline{\alpha} - \overline{\lambda}$ as $R \to +\infty$; thus, as $\alpha(t) > \lambda(t)$ for all t, we deduce that $F_1(-R, v) > 0$ for $R \gg 0$.

Next, assume that $|u| \le R$, and compute

$$F_2(u, cR) = -\overline{\omega} + \frac{1}{T}\int_0^T \frac{\lambda(t)e^{u-cR}}{1+\mu(t)e^{mcR}}\,dt \le -\overline{\omega} + \int_0^T \frac{\lambda(t)e^{(1-c)R}}{1+\mu(t)e^{mcR}}\,dt \to -\overline{\omega}$$

as $R \to +\infty$ since $c(m+1) > 1$, and

$$F_2(u, -R) = -\overline{\omega} + \frac{1}{T}\int_0^T \frac{\lambda(t)e^{u+R}}{1+\mu(t)e^{-mR}}\,dt \ge -\overline{\omega} + \frac{1}{T}\int_0^T \frac{\lambda(t)}{1+\mu(t)e^{-mR}}\,dt.$$

Here, the right-hand side term tends to $\overline{\lambda} - \overline{\omega}$ as $R \to +\infty$. This quantity is positive since $\lambda(t) > \omega(t)$ for all t, so we conclude that $F_2(u, cR) < 0 < F_2(u, -R)$ for $R \gg 0$. Thus, we may define the homotopy

$$H(u, v, \sigma) := \sigma F(u, v) - (1-\sigma)(u, v),$$

which does not vanish on $\partial\Omega_0$. It follows that $\deg(F, \Omega_0, 0) = \deg(-Id, \Omega_0, 0) = (-1)^2 = 1$.

Remark 2.2. As a consequence, it is deduced that F vanishes in Ω_0. In particular, when α, β, λ and μ are positive constants we deduce that the system has a positive equilibrium, as it shall be proven in section 3 by direct computation.

Second step: Let

$$\Omega := \{(u, v) \in C_T \times C_T : \|u\|_\infty < R, -R < v(t) < cR \text{ for all } t\}.$$

We claim that if R is large enough then the T-periodic solutions of the system

$$u'(t) = \sigma\psi_1(u, v)(t),$$
$$v'(t) = \sigma\psi_2(u, v)(t)$$

with $0 < \sigma \le 1$ do not belong to $\partial\Omega$.

Indeed, suppose firstly that $u_{\max} = R > \frac{v_{\max}}{c}$ and take $\xi \in [0, T]$ is such that $u_{\max} = u(\xi)$. From the first equation of the system we obtain

$$\frac{\alpha(\xi)}{1+\beta(\xi)e^{nu(\xi-\tau_1)}} = \frac{\lambda(\xi)}{1+\mu(\xi)e^{mv(\xi-\tau_2)}} > \frac{\lambda(\xi)}{1+\mu(\xi)e^{mcR}}.$$

Moreover, observe that $u'(t) > -\lambda(t)$ for all t, so by periodicity we deduce that

$$u(\xi-\tau_1) - R \ge -\int_\xi^{kT+\xi-\tau_1} \lambda(t)\,dt \ge -\int_0^T \lambda(t)\,dt := -C_1$$

where k is the first natural number such that $kT > \tau_1$. It follows that

$$\alpha(\xi) > \lambda(\xi)\frac{1+\beta(\xi)e^{nu(\xi-\tau_1)}}{1+\mu(\xi)e^{mcR}} > \lambda(\xi)\frac{1+\beta(\xi)e^{n(R-C_1)}}{1+\mu(\xi)e^{mcR}}.$$

The right-hand side of this inequality tends uniformly to $+\infty$ as $R \to +\infty$. Now assume that $v_{\max} = cR \geq cu_{\max}$, then take $\eta \in [0,T]$ such that $v(\eta) = v_{\max}$ and deduce, from the second equation of the system:

$$\omega(\eta) = \frac{\lambda(\eta)e^{u(\eta)-v(\eta)}}{1+\mu(\eta)e^{mv(\eta-\tau_2)}} \leq \frac{\lambda(\eta)e^{(1-c)R}}{1+\mu(\eta)e^{mv(\eta-\tau_2)}}.$$

As before, from the inequality $v'(t) \geq -\omega(t)$ it is seen that

$$v(\eta-\tau_2) - cR \geq -\int_{\eta}^{lT+\eta-\tau_2} \omega(t)\,dt \geq -\int_0^T \omega(t)\,dt := -C_2,$$

where l is the first natural number such that $lT > \tau_2$. This implies

$$\omega(\eta) \leq \frac{\lambda(\eta)e^{(1-c)R}}{1+\mu(\eta)e^{m(cR-C_2)}} \to 0$$

uniformly as $R \to +\infty$. We conclude that $u_{\max}$ and $v_{\max}$ cannot be arbitrarily large.

Next, suppose that $u_{\min} = -R < v_{\min}$ and $\xi \in [0,T]$ be such that $u_{\min} = u(\xi)$. As before,

$$\frac{\alpha(\xi)}{1+\beta(\xi)e^{nu(\xi-\tau_1)}} = \frac{\lambda(\xi)}{1+\mu(\xi)e^{mv(\xi-\tau_2)}} < \frac{\lambda(\xi)}{1+\mu(\xi)e^{-mR}}$$

and hence

$$\alpha(\xi) < \lambda(\xi)\frac{1+\beta(\xi)e^{nu(\xi-\tau_1)}}{1+\mu(\xi)e^{-mR}}.$$

As $u(\xi-\tau_1) \leq -R + \int_{\xi-\tau_1}^{\xi} \lambda(t)\,dt$, the right-hand side of the last inequality tends uniformly to $\lambda(\xi)$ as $R \to +\infty$. In the same way, if $v(\eta) = v_{\min} = -R \leq u_{\min}$, then it is seen that

$$\omega(\eta) \geq \frac{\lambda(\eta)}{1+\mu(\eta)e^{mv(\eta-\tau_2)}} \to \lambda(\eta)$$

uniformly as $R \to +\infty$. As $\alpha(t) > \lambda(t) > \omega(t)$ for all t, we deduce that R cannot be arbitrarily large and the claim is proven. □

2.2. **Case 2: With pharmokinetic.**

Theorem 2.3. *Assume that $\alpha(t), \beta(t), \lambda(t), \mu(t), \omega(t), p(t)$ and $q(t)$ are positive and T-periodic. Furthermore, assume that:*

$$\alpha(t) - p(t) > \lambda(t) > \omega(t) + q(t)$$

for all t. Then system (1.6) with $\delta = 1$ admits at least one positive T-periodic solution.

Proof. We shall follow the general outline of the previous proof. As before, set $u(t) = \ln M(t)$ and $v(t) = \ln B(t)$, then the model with $\delta = 1$ reads

$$u'(t) = \frac{\alpha(t)}{1+\beta(t)e^{nu(t-\tau_1)}} - \frac{\lambda(t)}{1+\mu(t)e^{mv(t-\tau_2)}} - p(t) := \psi_1^{p,q}(u,v)(t),$$

$$v'(t) = -\omega(t) + \frac{\lambda(t)e^{u(t)-v(t)}}{1+\mu(t)e^{mv(t-\tau_2)}} - q(t) := \psi_2^{p,q}(u,v)(t).$$

For the first step, let us consider now $F^{p,q} : \mathbb{R}^2 \to \mathbb{R}^2$ given by

$$F^{p,q}(u,v) := F(u,v) - (\overline{p}, \overline{q})$$

with F as in the previous proof. First, assume that $|v| \le R$. Then

$$F_1^{p,q}(R,v) = \frac{1}{T}\int_0^T \frac{\alpha(t)}{1+\beta(t)e^{nR}} - \frac{\lambda(t)}{1+\mu(t)e^{mv}}\,dt - \overline{p} < 0$$

for $R \gg 0$. On the other hand,

$$\begin{aligned} F_1^{p,q}(-R,v) &= \frac{1}{T}\int_0^T \frac{\alpha(t)}{1+\beta(t)e^{-nR}} - \frac{\lambda(t)}{1+\mu(t)e^{mv}}\,dt - \overline{p} \\ &\ge \frac{1}{T}\int_0^T \frac{\alpha(t)}{1+\beta(t)e^{-nR}}\,dt - \overline{\lambda} - \overline{p}. \end{aligned}$$

The last term tends to $\overline{\alpha} - \overline{\lambda} - \overline{p}$ as $R \to +\infty$; thus, as $\alpha(t) > \lambda(t) + p(t)$ for all t, we deduce that $F_1^{p,q}(-R,v) < 0$ for $R \gg 0$.

Next, assume that $|u| \le R$ and compute

$$F_2^{p,q}(u,R) \le \int_0^T \frac{\lambda(t)}{1+\mu(t)e^{mR}}\,dt - \overline{\omega} - \overline{q} < 0$$

for $R \gg 0$ and

$$F_2^{p,q}(u,-R) \ge \frac{1}{T}\int_0^T \frac{\lambda(t)}{1+\mu(t)e^{-mR}}\,dt - \overline{\omega} - \overline{q}.$$

Here, the right-hand side term tends to $\overline{\lambda} - \overline{\omega} - \overline{q}$ as $R \to +\infty$. This quantity is positive since $\lambda(t) > \omega(t) + q(t)$ for all t; so we conclude that $F_2^{p,q}(u,R) < 0 < F_2^{p,q}(u,-R)$ for $R \gg 0$. As in the previous proof, we have $\deg(F^{p,q}, (-R,R)^2, 0) = 1$.

For the second step, set

$$\Omega := \{(u(t),v(t)) \in C_T \times C_T : \|u\|_\infty < R, \|v\|_\infty < R\}.$$

As before, we claim that if R is large enough then the T-periodic solutions of the system

$$\begin{aligned} u'(t) &= \sigma\psi_1^{p,q}(u,v)(t), \\ v'(t) &= \sigma\psi_2^{p,q}(u,v)(t) \end{aligned}$$

with $0 < \sigma \le 1$ do not belong to $\partial\Omega$. Indeed, suppose firstly that $u_{\max} = R > v_{\max}$, then take $\xi \in [0,T]$ is such that $u_{\max} = u(\xi)$ and from the first equation we obtain

$$\frac{\alpha(\xi)}{1+\beta(\xi)e^{nu(\xi-\tau_1)}} > \frac{\lambda(\xi)}{1+\mu(\xi)e^{mR}} + p(\xi).$$

As before, using now the fact that $u'(t) > -\lambda(t) - p(t)$ for all t we deduce that

$$u(\xi-\tau_1) - R \ge -\int_0^T [\lambda(t) + p(t)]\,dt := -C_1^{p,q}.$$

It follows that

$$\frac{\alpha(\xi)}{p(\xi)} > 1 + \beta(\xi)e^{nu(\xi-\tau_1)} \ge 1 + \beta(\xi)e^{n(R-C_1^{p,q})}$$

and hence R cannot be arbitrarily large. On the other hand, assume that $u_{\max} \le v_{\max} = R$, then take $\eta \in [0,T]$ such that $v(\eta) = v_{\max}$ and deduce, from the second equation of the system, that

$$\omega(\eta) + q(\eta) \le \frac{\lambda(\eta)}{1+\mu(\eta)e^{mv(\eta-\tau_2)}}$$

and, from the inequality $v'(t) \geq -\omega(t) - q(t)$, that

$$v(\eta - \tau_2) - R \geq -\int_0^T [\omega(t) + q(t)]\, dt := -C_2^{p,q}.$$

This implies

$$\omega(\eta) + q(\eta) \leq \frac{\lambda(\eta)}{1 + \mu(\eta)e^{m(R - C_2^{p,q})}} \to 0$$

uniformly as $R \to +\infty$. We conclude that $u_{\max}$ and $v_{\max}$ cannot be arbitrarily large.

Next, suppose that $u_{\min} = -R < v_{\min}$ and $\xi \in [0, T]$ be such that $u_{\min} = u(\xi)$. As before, it follows that

$$\frac{\alpha(\xi)}{1 + \beta(\xi)e^{nu(\xi - \tau_1)}} < \frac{\lambda(\xi)}{1 + \mu(\xi)e^{-mR}} + p(\xi)$$

and hence

$$\alpha(\xi) < \Big(\frac{\lambda(\xi)}{1 + \mu(\xi)e^{-mR}} + p(\xi)\Big)\Big(1 + \beta(\xi)e^{nu(\xi - \tau_1)}\Big).$$

Thus, the right-hand side of the last inequality tends uniformly to $\lambda(\xi) + p(\xi)$ as $R \to +\infty$. In the same way, if $v(\eta) = v_{\min} = -R \leq u_{\min}$, then

$$\omega(\eta) + q(\eta) \geq \frac{\lambda(\eta)}{1 + \mu(\eta)e^{mv(\eta - \tau_2)}} \to \lambda(\eta)$$

uniformly as $R \to +\infty$. As $\alpha(t) - p(t) > \lambda(t) > \omega(t) + q(t)$ for all t, we deduce that R cannot be arbitrarily large and the proof is complete. □

3. Remarks about equilibrium points

In this section, we briefly discuss the uniqueness or multiplicity of positive equilibrium points for the autonomous case and make some comments on possible oscillation properties of the solutions.

With this aim, assume that all the parameters of (1.6) are constant, then the existence of at least one positive equilibrium (M_*, B_*) is easily shown, provided that

$$n > (1 - \delta)\frac{m}{m + 1}, \quad \alpha > \lambda - \delta p.$$

Indeed, consider the system

$$\begin{aligned} \frac{\alpha}{1 + \beta M^n} &= \frac{\lambda}{1 + \mu B^m} + \delta p, \\ (\omega + \delta q)B &= \frac{\lambda M}{1 + \mu B^m} \end{aligned} \tag{3.1}$$

and let

$$c(B) := \frac{B(1 + \mu B^m)(\omega + \delta q)}{\lambda}.$$

Then (3.1) has at least a positive solution if and only if the function $\varphi : [0, +\infty) \to \mathbb{R}$ given by

$$\varphi(B) := \frac{\alpha}{1 + \beta c(B)^n} - \frac{\lambda}{1 + \mu B^m} - \delta p$$

has at least a positive root. This is easily verified, since

$$\varphi(0) = \alpha - \lambda - \delta p > 0$$

and

$$\lim_{B\to+\infty}\varphi(B)=-\delta p.$$

Thus, the result follows for $\delta=1$. When $\delta=0$, condition $n>\frac{m}{m+1}$ implies $\varphi(B)<0$ for $B\gg 0$ and so completes the proof.

It is worth noticing that the number of equilibria depends on the parameters of the system. Although more precise computations are possible, we shall not pursue a detailed analysis here and restrict ourselves to some elementary comments. Consider, for instance, the case $\delta=0$, then

$$B_*=\frac{\alpha M}{\omega(1+\beta M^n)}.$$

Calling $z=1+\beta M^n$, we obtain the following equation for z:

$$z=\frac{\alpha}{\lambda}+r\Big[\frac{\sqrt[n]{z-1}}{z}\Big]^m:=\psi(z),$$

where $r=\frac{\alpha^{m+1}\mu}{\omega^m\beta^{m/n}\lambda}$. The function $z-\psi(z)$ is negative for $z=1$ and, as $n>\frac{m}{m+1}$, tends to $+\infty$ as $z\to+\infty$. Next, we compute

$$\psi'(z)=\frac{rm(z-1)^{\frac{m-n}{n}}}{nz^{m+1}}[n-(n-1)z],$$
$$\psi''(z)=\frac{rm(z-1)^{\frac{m-2n}{n}}}{nz^{m+2}}[az^2+bz+c],$$

where

$$a=\frac{n-1}{n}[n+m(n-1)],\quad b=-2[n+m(n-1)],\quad c=(m+1)n.$$

In particular, ψ vanishes at most twice in $(1,+\infty)$, which implies that the system cannot have more than 3 positive equilibrium points.

When $n\neq 1$, the quadratic az^2+bz+c has two different real roots, namely

$$R_\pm=\frac{n}{n-1}\Big(1\pm\frac{1}{\sqrt{n+m(n-1)}}\Big).$$

Let us prove, in the first place, that the positive equilibrium is unique when $m\le n$. This is immediate for $m<n$, since the function $z-\psi(z)$ is strictly decreasing near 1, and ψ'' vanish at most once in $(1,+\infty)$. When $m=n$, there are two cases:

- If $n\le 1$, then ψ'' does not vanish in $(1,+\infty)$.
- If $n>1$, then direct computation shows that the equation $\psi'(z)=1$ has at most one solution in $(1,+\infty)$.

In both cases, the function $z-\psi(z)$ has at most one critical point in $(1,+\infty)$ and the claim follows.

The situation is different when $m>n$: for instance, if r is large enough then there are 3 positive equilibria, provided that $\frac{\alpha}{\lambda}$ is sufficiently close to 1. Indeed, we may set, for example, $R>1$ as the largest root of the quadratic function az^2+bz+c, namely

$$R=\begin{cases}\frac{m+1}{2} & \text{if } n=1,\\ R_- & \text{if } n<1,\\ R_+ & \text{if } n>1,\end{cases}$$

with $R_\pm$ as before. Next, consider the function $g(z) = z - \psi(z) + \frac{\alpha}{\lambda} - 1$ and fix r such that $r > \frac{R^m}{(R-1)^{\frac{m-n}{n}}}$. Then $g(R) < 0$ and, as $g(1) = 0$ and $g'(1) = 1$, it is seen that g has exactly one zero in $(1, R)$ and another one in $(R, +\infty)$. Now let

$$\varepsilon = \max_{1 \le z \le R} g(z),$$

then the function $z - \psi(z)$ has 3 zeros when $\frac{\alpha}{\lambda} < 1 + \varepsilon$.

In view of the previous example, a natural question arises: is it possible to find a sharp set of sufficient conditions for the uniqueness of the positive equilibrium when $m > n$? For example, a sufficient condition when $n \le 1$ is

$$\frac{\alpha}{\lambda} \ge R$$

with R as before: indeed, in this case $\psi'(z) > 0$ in $(1, +\infty)$, so $\psi(z) > z$ in $[1, R]$ and ψ'' does not vanish after R, so the equation $\psi'(z) = 1$ has at most one solution in $(R, +\infty)$.

When $n > 1$, a sufficient condition for uniqueness of the positive equilibrium is:

$$\frac{\alpha}{\lambda} \ge \frac{n}{n-1}.$$

Indeed, in this case ψ strictly increases up to $z = \frac{n}{n-1}$ and strictly decreases after that point. As $\psi(z) > z$ on $(1, \frac{n}{n-1})$ it follows that the equation $\psi(z) = z$ has exactly one solution. Observe that $R > \frac{n}{n-1}$, so the previous condition is sharper than the condition $\alpha/\lambda \ge R$.

Also, it is worth noticing that, in all cases, if r is small then the equilibrium is unique. More precisely, for $n \le 1$ the function ψ' is positive and achieves its absolute maximum at $z = R$; thus, a sufficient condition for uniqueness is:

$$\psi'(R) < 1. \tag{3.2}$$

For $n > 1$, the function ψ' achieves its absolute maximum at $z = R_- > 1$. This yields the sufficient condition

$$\psi'(R_-) < 1. \tag{3.3}$$

Conditions (3.2) and (3.3) are obviously satisfied when r is small.

The presence of delays yields also an interesting matter about the oscillation properties of the autonomous model. This is an interesting field of research that can be the object of a future work; here, we shall only prove some behavior that might indicate the presence of oscillation.

In more precise terms, we set a positive equilibrium (M_*, B_*) as the center of coordinates and denote by Q_j the j-th quadrant, namely

$$\begin{aligned}
Q_1 &:= \{(M, B) : M > M_*, B > B_*\},\\
Q_2 &:= \{(M, B) : M < M_*, B > B_*\},\\
Q_3 &:= \{(M, B) : M < M_*, B < B_*\},\\
Q_4 &:= \{(M, B) : M > M_*, B < B_*\}.
\end{aligned}$$

We shall prove that, under appropriate conditions, if a non-constant positive solution starts in $\overline{Q}_2$ or $\overline{Q}_4$ then it cannot remain there for all t.

Proposition 3.1. *Let $\tau_1 > (1 + \beta M_*^n)^2/(n\alpha\beta M_*^n)$ and assume that there are no equilibrium points in Q_4. Then there exists a sequence $t_n \to +\infty$ such that, for all n, $M(t_n) < M_*$ or $B(t_n) > B_*$.*

Proposition 3.2. *Let $\tau_1 > \frac{(1+\beta M_*^n)^2}{n\alpha\beta M_*^n}$ and assume that there are no equilibrium points in Q_2. Then there exists a sequence $t_n \to +\infty$ such that, for all n, $M(t_n) > M_*$ or $B(t_n) < B_*$.*

In other words, a non-constant positive solution starting at $\overline{Q}_2$ or $\overline{Q}_4$ might abandon the respective quadrant and never return, or it might eventually come back but then it leaves the quadrant again and so on. A proof of Proposition 3.1 is given below; the proof of Proposition 3.2 is similar so we omit it.

Lemma 3.3. *Assume that $R(t_1-\tau_1) \geq R(t_2-\tau_1)$ and $B(t_1-\tau_2) \leq B(t_2-\tau_2)$. If $R(t_1) \geq R(t_2)$ and $B(t_1) \leq B(t_2)$, at least one of the inequalities being strict, then $R'(t_1) < R'(t_2)$ and $B'(t_1) > B'(t_2)$.*

Proof. It suffices to observe that the right hand side of the first equation of (1.7) is strictly decreasing in the variables $R(t-\tau_1)$ and strictly increasing in the variable $B(t-\tau_2)$, and the right hand side of the second equation of (1.7) is strictly increasing in the variable $R(t)$ and strictly decreasing in the variables $B(t)$ and $B(t-\tau_2)$. Then $R'(t_1) < R'(t_2)$ and $B'(t_1) > B'(t_2)$. □

Remark 3.4. As in Lemma 3.3, it is easily seen that if $R(t) > R_* := \ln(M_*)$ for $t \in [t_0-\tau_1, t_1)$ and $B(t) < B_*$ for all $t \in [t_0-\tau_2, t_1)$ then $R'(t) < 0 < B'(t)$ for all $t \in [t_0, t_1]$. If $R(t_1) = R_*$ or $B(t_1) = B_*$, then there exists $\eta > 0$ such that $(R(t), B(t)) \notin \overline{Q}_4$ for $t \in (t_1, t_1+\eta)$. On the other hand, if $R(t) > R_*$ for all $t \geq t_0-\tau_1$ and $B(t) < B_*$ for all $t \geq t_0-\tau_2$ then $R'(t) < 0 < B'(t)$ for all $t \geq t_0$ and, if there are no equilibrium points in Q_4, then $R(t) \to R_*$ and $B(t) \to B_*$.

Proof of Proposition 3.1. Suppose that $M(t) > M_*$ for all $t \geq t_0-\tau_1$ and $B(t) < B_*$ for all $t \geq t_0-\tau_2$. A simple computation shows that

$$R'(t) = -A(R(t-\tau_1) - R_*) - C(B_* - B(t-\tau_2)),$$

with

$$A = A(R(t), R(t-\tau_1)) := \frac{\alpha\beta(e^{nR_*} - e^{nR(t-\tau_1)})}{(1+\beta e^{nR(t-\tau_1)})(1+\beta e^{nR_*})(R_* - R(t-\tau_1))} > 0,$$

$$C = C(B(t), B(t-\tau_2)) := \frac{\lambda\mu(B_*^m - B^m(t-\tau_2))}{(1+\mu B_*^m)(1+\mu B^m(t-\tau_2))(B_* - B(t-\tau_2))} > 0,$$

$$A(R(t), R(t-\tau_1)) \to \frac{n\alpha\beta e^{nR_*}}{(1+\beta e^{nR_*})^2} \quad \text{as } t \to +\infty,$$

$$C(B(t), B(t-\tau_2)) \to \frac{\lambda\mu m B_*^{m-1}}{(1+\mu B_*^m)^2} \quad \text{as } t \to +\infty.$$

Moreover,

$$R(t-\tau_1) - R_* = R(t-\tau_1) - R(t) + R(t) - R_* = -\tau_1 R'(\theta) + R(t) - R_*$$

for some mean value $\theta \in (t-\tau_1, t)$. From Lemma 3.3 with $t_1 = \theta$ and $t_2 = t$, it follows that $R'(\theta) < R'(t)$. Thus,

$$R'(t) < -A(R(t) - R_*) - C(B_* - B(t-\tau_2)) + \tau_1 A R'(t).$$

Observe that the hypothesis says that $\tau_1 > \frac{(1+\beta e^{nR_*})^2}{n\alpha\beta e^{nR_*}}$. Without loss of generality, we may assume that t_0 is large enough so that $\tau_1 A(R(t), R(t-\tau_1)) > 1$, then

$$(\tau_1 A - 1)R'(t) > A(R(t) - R_*) + C(B_* - B(t-\tau_2)) > 0,$$

a contradiction. □

Open Problems. We outline some problems that might be of interest for scientists who plan to start future research in this field.

(1) Use Lyapunov-like functionals to find sufficient conditions for the global stability of a non-trivial equilibrium of the autonomous model.

(2) Prove or disprove that for a new model the complete recovery is possible for sufficiently high drug dosage; examine permanence, persistence and extinction of the solutions.

(3) Define what is the required type, frequency and intensity of the cancer treatment that switch unfavorable oscillatory dynamics of a system to a non-oscillatory state.

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