

MATHEMATICAL ANALYSIS AND GLOBAL DYNAMICS FOR A TIME-DELAYED CHRONIC MYELOID LEUKEMIA MODEL WITH TREATMENT

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Abstract. In this paper, we investigate a time-delayed model describing the dynamics of the hematopoietic stem cell population with treatment. First, we give some property results of the solutions. Second, we analyze the asymptotic behavior of the model, and study the local asymptotic stability of each equilibrium: trivial and positive ones. Next, a necessary and sufficient condition is given for the trivial steady state to be globally asymptotically stable. Moreover, the uniform persistence is obtained in the case of instability. Finally, we prove that this system can exhibit periodic solutions around the positive equilibrium through a Hopf bifurcation.

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1. INTRODUCTION

Chronic myeloid leukemia (CML) is a chronic myeloproliferative neoplasms (MPN) found in the neutrophil granulopoiesis, it is a chronic clonal hemopathy due to the initial involvement of the hematopoietic stem cell. Like all MPN, CML is due to an excessive overproduction of mature blood cells: there is no maturation blocking unlike acute leukemia [22]. Mathematical modeling can help to make decisions and define control and prevention strategies in the case of diseases. In the case of our work, we try to show what are the factors (model parameters) that can influence the onset of the disease or its reduction or even eradication. Mathematical models are widely used to better understand complex biological processes. They facilitate the development of new hypotheses, allow us to test hypotheses, improve our understanding of biological interactions, interpreting experimental data. Mathematical models are commonly used to interrogate a variety of processes related to research on different types of leukemia, including: [4, 16, 35, 47, 49] for Leukemia models with ordinary differential equations (ODE), and [5, 10, 26, 39] for models with partial differential equations (PDE). Recently, numerous papers are dealing with optimal therapy modeling as in [37, 38, 40, 44]. The stochastic and impulsive differential equations are also used to describe the dynamics of leukemia stem cells as in [12, 17]. We can also find competition models of healthy and leukemic (stem) cells as in [8, 11, 48]. For more interesting models for leukemia, we can also see

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[14, 25, 29, 42]. Mathematical models provide a convenient and inexpensive mechanism for studying biological processes and interventions for which experimental data may be scarce or expensive. Cancer research is among the disciplines that have begun to use mathematical modeling to analyze several processes related to cancer diseases, including immunity and treatment, as in [6, 9, 46].

Along this paper, based on the model of Radulescu *et al.* [41], we will analyze a mathematical model on chronic myeloid leukemia with treatment called imatinib, the latter was already introduced in the literature, we cite as an example [13]. The sensitivity of leukemic stem cells to treatment with imatinib is the subject of various speculations, which is why additional studies are necessary to make this phenomenon more clear (see [15, 23, 24, 43]). The effect of imatinib on stem cells, even if it is very weak, is taken into consideration, this effect is observed on the reduction of the proliferation of leukemic stem cells (see [18, 32–36]).

We will present some results about existence and uniqueness of solutions of stem cell dynamics model. In our work we show the stability of the positive steady state by establishing Hopf bifurcation which is also used in [3, 27, 30, 31].

The paper is organized as follows. In Section 2, we develop the mathematical model to be studied and we discuss basic properties of solutions, including their existence, uniqueness, boundedness, and positivity. In Section 3, steady state solutions will be given. In Section 4, we investigate local and global stability of the trivial steady state. Section 5 is devoted to the uniform persistence of the model. Stability of the positive equilibrium and Hopf bifurcation with illustrative numerical simulations are provided in Section 6. In the last Section, we give some conclusions.

2. THE MODEL

Let $Q(t)$ denotes the density of leukemic stem cell population. In the proposed model, the cell is divided into two daughter cells, either by a symmetrical division with the fraction $\eta_1 > 0$, or by an asymmetrical division with the fraction $\eta_2 > 0$. The others, are supposed to renew with the fraction $(1 - \eta_1 - \eta_2)$. The parameter τ describes the duration of the cell division, which is supposed to be the same for all types of division. For a more clear understanding of different types of cell division, we give a schematic representation in Figure 1.

$D(t)$ denotes the amount of the drug that reaches the bloodstream, and $P(t)$ denotes the amount of drug in the plasmatic compartment.

The evolution of the population is described by the following system, for $t > 0$,

$$\begin{cases} \dot{Q}(t) &= -\gamma Q(t) - k_0\eta_1 Q(t) - k_0\eta_2 Q(t) - (1 - \eta_1 - \eta_2)\beta(Q(t))Q(t) \\ &\quad + 2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(Q(t-\tau))Q(t-\tau) \\ &\quad + k_0\eta_1 e^{-\gamma\tau}Q(t-\tau) - r(P(t))Q(t), \\ \dot{D}(t) &= -\kappa D(t) + K, \\ \dot{P}(t) &= -vP(t) + \kappa D(t). \end{cases} \quad (2.1)$$

The system (2.1) is completed by the following initial conditions,

$$Q(t) = \varphi(t) \geq 0, \quad t \in [-\tau, 0], \quad D(0) = D_0 \geq 0 \quad \text{and} \quad P(0) = P_0 \geq 0. \quad (2.2)$$

In this model, $\beta(Q)$ is a positive and decreasing function of Q . It denotes the rate of self-renewal. As example, β can be considered as a Hill function

$$\beta(Q) = \beta_0 \frac{\theta^n}{\theta^n + Q^n}, \quad n > 1.$$

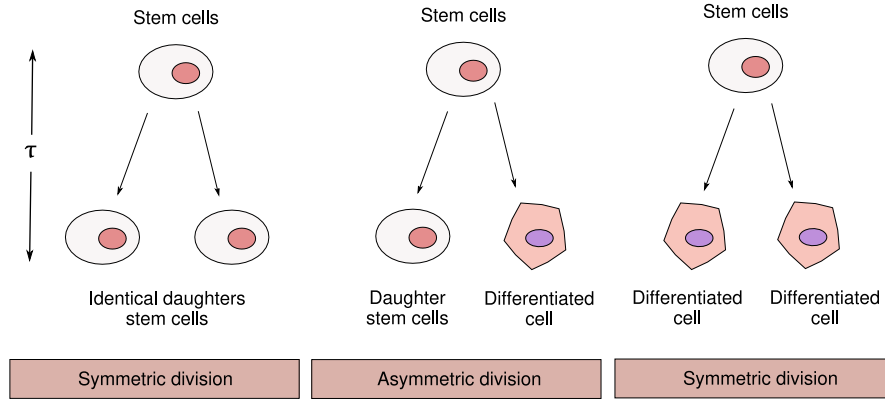


FIGURE 1. A schematic representation for different types of cell division.

TABLE 1. Parameter values of the model (2.1).

Parameters	Interpretation (units)
η_1	The fraction value of asymmetric division (none)
η_2	The fraction value of symmetric division (none)
β	The rate of self renewal (day^{-1})
γ	The mortality rate (day^{-1})
k_0	The rate of differentiation and of asymmetric division (day^{-1})
τ	The duration of the cell division(day)
K	The constant dose of administrated drug (mg/day)
κ	The first order absorption rate (day^{-1})
v	Clearance ratio, volume of drug distribution (hour^{-1})
β_0	Maximal self renewal rate (day^{-1})
θ	The value for which the function $\beta(Q)$ attains half of its maximum value (cells.kg^{-1})
m	A Hil coefficient (none)
P_0	The half of the maximum activity concentration
x_0	The number of infected cells (cells.kg^{-1})
R_0	The number of cells resistant to treatment (cells.kg^{-1})

The function $r(P)$ is supposed to be increasing and bounded. It describes the treatment's effect, which represents the reduction rate of leukemic stem cell proliferation. For instance, $r(P)$ is given by

$$r(P) = \frac{P^m}{P^m + P_0^m} \frac{x_0 - R_0}{x_0}.$$

Both β and r are supposed to be continuously differentiable. All the parameters are nonnegative constants and they are described in the Table 1. Let $C := C([-\tau, 0], \mathbb{R})$ be the space of continuous functions on $[-\tau, 0]$ and $C^+ := C([-\tau, 0], \mathbb{R}^+)$ be the space of nonnegative continuous functions on $[-\tau, 0]$. Throughout this paper, we assume that $(\varphi, D_0, P_0) \in C^+ \times \mathbb{R}^+ \times \mathbb{R}^+$. The existence and uniqueness of nonnegative solutions of (2.1)-(2.2) can be obtained by using the theory of functional differential equations as in [21] (see also [20] and [28]).

Proposition 2.1. *All solutions of system (2.1) with nonnegative initial conditions are nonnegative.*

Proof. Let (Q, D, P) be a solution of (2.1) associated to the initial condition $(\varphi, D_0, P_0) \in C^+ \times \mathbb{R}^+ \times \mathbb{R}^+$. We prove the nonnegativity on the interval $[0, \tau]$, and we apply the same reasoning by steps on each interval $[k\tau, (k+1)\tau]$, for $k = 1, 2, \dots$. For $t \in [0, \tau]$, we have $t - \tau \in [-\tau, 0]$. Then, the system (2.1) transforms to

$$\begin{cases} \dot{Q}(t) = -\gamma Q(t) - k_0\eta_1 Q(t) - k_0\eta_2 Q(t) - (1 - \eta_1 - \eta_2)\beta(Q(t))Q(t) \\ \quad + 2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(\varphi(t - \tau))\varphi(t - \tau) \\ \quad + k_0\eta_1 e^{-\gamma\tau}\varphi(t - \tau) - r(P(t))Q(t), \\ \dot{D}(t) = -\kappa D(t) + K, \\ \dot{P}(t) = -vP(t) + \kappa D(t). \end{cases} \quad (2.3)$$

The idea is to extend the analogous result known for ODE to the delay differential equations (DDE) as established in the Theorem 3.4 in [45]. More precisely, the positivity of DDE follows also as ODE with the classical sufficient conditions on the nonlinearity. We have the following implications

$$Q(t) = 0 \Rightarrow Q'(t) = 2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(\varphi(t - \tau))\varphi(t - \tau) + k_0\eta_1 e^{-\gamma\tau}\varphi(t - \tau) \geq 0,$$

$$D(t) = 0 \Rightarrow D'(t) = K \geq 0,$$

and

$$P(t) = 0 \Rightarrow P'(t) = \kappa D(t) \geq 0.$$

This yields $Q(t) \geq 0$, $D(t) \geq 0$ and $P(t) \geq 0$ for $t \in [0, \tau]$. One can just repeat the argument by steps on $[k\tau, (k+1)\tau]$, $k \in \mathbb{N}$. We conclude that Q , D and P are nonnegative on $[0, +\infty)$. \square

Next, we show the boundedness of solutions of (2.1).

Proposition 2.2. *All solutions of system (2.1) are bounded.*

Proof. Let (Q, D, P) be the solution of (2.1) associated to the initial condition $(\varphi, D_0, P_0) \in C^+ \times \mathbb{R}^+ \times \mathbb{R}^+$. First, we focus on the components D and P . From the differential equation of D we have, for $t > 0$,

$$D(t) = D(0)e^{-\kappa t} + \frac{K}{\kappa}(1 - e^{-\kappa t}).$$

Then, D never blows up in finite time since $\limsup_{t \rightarrow +\infty} D(t) < +\infty$. We set $\sup_{t \geq 0} D(t) = M$. Then, for $t > 0$,

$$\dot{P}(t) \leq -vP(t) + \kappa M.$$

This implies that for $t > 0$, we have

$$P(t) \leq P(0)e^{-vt} + \frac{\kappa M}{v} < +\infty.$$

Focus now on the component Q , and assume that

$$2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(0) > \gamma + k_0(\eta_1 + \eta_2) - k_0\eta_1 e^{-\gamma\tau}.$$

Since β is a decreasing function and $\lim_{x \rightarrow +\infty} \beta(x) = 0$, there exists a unique $Q_0 > 0$ such that

$$2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(Q_0) = \gamma + k_0(\eta_1 + \eta_2) - k_0\eta_1e^{-\gamma\tau},$$

and

$$2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(Q) \leq \gamma + k_0(\eta_1 + \eta_2) - k_0\eta_1e^{-\gamma\tau}, \quad \text{for } Q \geq Q_0. \quad (2.4)$$

If $2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(0) \leq \gamma + k_0(\eta_1 + \eta_2) - k_0\eta_1e^{-\gamma\tau}$, then (2.4) holds with $Q_0 = 0$. Let

$$Q_1 = 2(1 - \eta_1 - \eta_2)e^{-\gamma\tau} \frac{\beta(0)Q_0}{\gamma + k_0(\eta_1 + \eta_2) - k_0\eta_1e^{-\gamma\tau}} \geq 0.$$

We can check that

$$2(1 - \eta_1 - \eta_2)e^{-\gamma\tau} \max_{0 \leq y \leq Q} (\beta(y)y) \leq (\gamma + k_0(\eta_1 + \eta_2) - k_0\eta_1e^{-\gamma\tau})Q, \quad \text{for } Q \geq Q_1. \quad (2.5)$$

In fact, let $y \in [0, Q]$. We distinguish two cases. If $y \leq Q_0$, then

$$\begin{aligned} 2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(y)y &\leq 2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(0)Q_0, \\ &= (\gamma + k_0(\eta_1 + \eta_2) - k_0\eta_1e^{-\gamma\tau})Q_1, \\ &\leq (\gamma + k_0(\eta_1 + \eta_2) - k_0\eta_1e^{-\gamma\tau})Q. \end{aligned}$$

If $y > Q_0$, then

$$\begin{aligned} 2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(y)y &\leq (\gamma + k_0(\eta_1 + \eta_2) - k_0\eta_1e^{-\gamma\tau})y, \\ &\leq (\gamma + k_0(\eta_1 + \eta_2) - k_0\eta_1e^{-\gamma\tau})Q. \end{aligned}$$

Hence, (2.5) holds for all $y \in [0, Q]$. Assume, by contradiction, that $\limsup_{t \rightarrow +\infty} Q(t) = +\infty$, where $Q(t)$ is a solution of (2.1). Then, there exists $\tilde{t} > \tau$ such that

$$Q(t) \leq Q(\tilde{t}), \quad \text{for } t \in [\tilde{t} - \tau, \tilde{t}] \quad \text{and} \quad Q(\tilde{t}) > Q_1.$$

From (2.1), we have

$$\begin{aligned} \dot{Q}(\tilde{t}) &= -\gamma Q(\tilde{t}) - k_0\eta_1 Q(\tilde{t}) - k_0\eta_2 Q(\tilde{t}) - (1 - \eta_1 - \eta_2)\beta(Q(\tilde{t}))Q(\tilde{t}), \\ &\quad + 2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(Q(\tilde{t} - \tau))Q(\tilde{t} - \tau) \\ &\quad + k_0\eta_1e^{-\gamma\tau}Q(\tilde{t} - \tau) - r(P(\tilde{t}))Q(\tilde{t}), \\ &\leq -\gamma Q(\tilde{t}) - k_0\eta_1 Q(\tilde{t}) - k_0\eta_2 Q(\tilde{t}) - (1 - \eta_1 - \eta_2)\beta(Q(\tilde{t}))Q(\tilde{t}), \\ &\quad + 2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(Q(\tilde{t} - \tau))Q(\tilde{t} - \tau) + k_0\eta_1e^{-\gamma\tau}Q(\tilde{t} - \tau), \\ &\leq -[\gamma + k_0(\eta_1 + \eta_2) - k_0\eta_1e^{-\gamma\tau}]Q(\tilde{t}), \\ &\quad + 2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(Q(\tilde{t} - \tau))Q(\tilde{t} - \tau) - (1 - \eta_1 - \eta_2)\beta(Q(\tilde{t}))Q(\tilde{t}). \end{aligned}$$

From (2.5), we obtain that

$$2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(Q(\tilde{t} - \tau))Q(\tilde{t} - \tau) \leq [\gamma + k_0(\eta_1 + \eta_2) - k_0\eta_1e^{-\gamma\tau}]Q(\tilde{t}).$$

Consequently, we get

$$\dot{Q}(t) \leq -(1 - \eta_1 - \eta_2)\beta(Q(\tilde{t}))Q(\tilde{t}) < 0.$$

This leads to a contradiction. As a consequence, $\limsup_{t \rightarrow +\infty} Q(t) < +\infty$, that is Q is bounded. \square

3. EXISTENCE OF STEADY STATES

In this section, we focus on the existence of steady states for system (2.1). Let (Q^*, D^*, P^*) be a steady state of (2.1). Then, it satisfies

$$\begin{aligned} & -[\gamma + k_0(\eta_1 + \eta_2)]Q^* - (1 - \eta_1 - \eta_2)\beta(Q^*)Q^* \\ & + 2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(Q^*)Q^* + k_0\eta_1e^{-\gamma\tau}Q^* - r(P^*)Q^* = 0, \end{aligned} \quad (3.1)$$

$$\kappa D^* = K, \quad \text{and} \quad vP^* = \kappa D^*. \quad (3.2)$$

From (3.2), we get

$$D^* = \frac{K}{\kappa} \quad \text{and} \quad P^* = \frac{K}{v}.$$

The equation (3.1) becomes

$$\begin{aligned} & -[\gamma + k_0(\eta_1 + \eta_2)]Q^* - (1 - \eta_1 - \eta_2)\beta(Q^*)Q^* \\ & + 2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(Q^*)Q^* + k_0\eta_1e^{-\gamma\tau}Q^* - r(P^*)Q^* = 0. \end{aligned}$$

As a result, we have either $Q^* = 0$ or

$$\beta(Q^*) = \frac{\gamma + k_0(\eta_1 + \eta_2) - k_0\eta_1e^{-\gamma\tau} + r(P^*)}{(1 - \eta_1 - \eta_2)(2e^{-\gamma\tau} - 1)}.$$

The point $(0, D^*, P^*)$ is always an equilibrium of (2.1). In another side, since β is a decreasing function on $[0, +\infty[$, then the existence of a positive steady state Q^* is equivalent to

$$(2e^{-\gamma\tau} - 1) > 0 \quad \text{and} \quad \frac{\gamma + k_0(\eta_1 + \eta_2) - k_0\eta_1e^{-\gamma\tau} + r(P^*)}{(1 - \eta_1 - \eta_2)(2e^{-\gamma\tau} - 1)} < \beta(0).$$

This condition is satisfied for

$$0 \leq \tau < \tau_{\max}, \quad (3.3)$$

where

$$\tau_{\max} := \frac{1}{\gamma} \ln \left(\frac{2\beta(0)(1 - \eta_1 - \eta_2) + k_0\eta_1}{\gamma + k_0(\eta_1 + \eta_2) + r(P^*) + \beta(0)(1 - \eta_1 - \eta_2)} \right) < \frac{1}{\gamma} \ln(2). \quad (3.4)$$

In fact, we have

$$\begin{aligned} & \frac{2\beta(0)(1-\eta_1-\eta_2)+k_0\eta_1}{\gamma+k_0(\eta_1+\eta_2)+r(P^*)+\beta(0)(1-\eta_1-\eta_2)} - 2 \\ &= \frac{-2(\gamma+k_0\eta_2+r(P^*)) - k_0\eta_1}{\gamma+k_0(\eta_1+\eta_2)+r(P^*)+\beta(0)(1-\eta_1-\eta_2)} < 0. \end{aligned}$$

The following result summarizes the existence of the steady states.

Proposition 3.1. *If $0 \leq \tau < \tau_{max}$, then the system (2.1) has two distinct steady states: $E_0 := (0, D^*, P^*)$ and $E_1 := (Q^*, D^*, P^*)$, with $Q^* > 0$ such that*

$$Q^* = \beta^{-1} \left(\frac{\gamma + k_0(\eta_1 + \eta_2) - k_0\eta_1 e^{-\gamma\tau} + r(P^*)}{(1 - \eta_1 - \eta_2)(2e^{-\gamma\tau} - 1)} \right), \quad D^* = \frac{K}{\kappa} \quad \text{and} \quad P^* = \frac{K}{v}.$$

Otherwise, if $\tau \geq \tau_{max}$, then $(0, D^*, P^*)$ is the only steady state for the system (2.1).

4. STABILITY OF THE TRIVIAL STEADY STATE

In this section, we focus on the local stability and the global stability of the trivial steady state. We will show that the solution of the first component of (2.1) disappears when the trivial equilibrium is the only steady state.

4.1. Local asymptotic stability

The purpose of this part is to show the local asymptotic stability by studying the characteristic equation of the linearized system of (2.1).

Theorem 4.1. *If $\tau > \tau_{max}$, then the unique trivial steady state of system (2.1) is locally asymptotically stable. If $\tau < \tau_{max}$, then it is unstable.*

Proof. The linearization of (2.1) corresponding to $(0, D^*, P^*)$ is given by

$$\begin{cases} \dot{Q}(t) &= -(\gamma + k_0(\eta_1 + \eta_2) + r(P^*))Q(t) - (1 - \eta_1 - \eta_2)\beta(0)Q(t) \\ &\quad + (2(1 - \eta_1 - \eta_2)\beta(0) + k_0\eta_1)e^{-\gamma\tau}Q(t - \tau), \\ \dot{D}(t) &= -\kappa D(t), \\ \dot{P}(t) &= -vP(t) + \kappa D(t). \end{cases}$$

The characteristic equation is given by the following formula

$$\Delta_0(\lambda, \tau) = \det(\lambda I - M - e^{-\lambda\tau}N) = 0, \quad (4.1)$$

with

$$M = \begin{pmatrix} -\gamma - k_0(\eta_1 + \eta_2) - r(P^*) - (1 - \eta_1 - \eta_2)\beta(0) & 0 & 0 \\ 0 & -\kappa & 0 \\ 0 & \kappa & -v \end{pmatrix},$$

and

$$N = \begin{pmatrix} e^{-\gamma\tau}[2(1 - \eta_1 - \eta_2)\beta(0) + k_0\eta_1] & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

Thus, (4.1) becomes

$$(\lambda + \kappa)(\lambda + v)D_0(\lambda, \tau) = 0, \quad (4.2)$$

with

$$\begin{aligned} D_0(\lambda, \tau) &:= \lambda + \gamma + k_0(\eta_1 + \eta_2) + r(P^*) \\ &\quad + (1 - \eta_1 - \eta_2)\beta(0) - e^{-\gamma\tau}(2(1 - \eta_1 - \eta_2)\beta(0) + k_0\eta_1)e^{-\lambda\tau}. \end{aligned}$$

Since $\kappa > 0$ and $v > 0$, the stability is determined by the sign of the real part of $\lambda \in \mathbb{C}$ satisfying $D_0(\lambda, \tau) = 0$. If we consider D_0 as a real function, the derivative of $D_0(\lambda, \tau)$, with respect to λ , is

$$\frac{\partial D_0}{\partial \lambda}(\lambda, \tau) = 1 + \tau e^{-\gamma\tau}(2(1 - \eta_1 - \eta_2)\beta(0) + k_0\eta_1)e^{-\lambda\tau} > 0.$$

Consequently, $D_0(\lambda, \tau)$ is an increasing function with respect to λ , and satisfies

$$\lim_{\lambda \rightarrow -\infty} D_0(\lambda, \tau) = -\infty \quad \text{and} \quad \lim_{\lambda \rightarrow +\infty} D_0(\lambda, \tau) = +\infty.$$

Then, there exists λ_0 a unique real solution of the equation $D_0(\lambda, \tau) = 0$. Moreover, we have

$$\begin{aligned} D_0(0, \tau) &= \gamma + k_0(\eta_1 + \eta_2) + r(P^*) \\ &\quad + (1 - \eta_1 - \eta_2)\beta(0) - e^{-\gamma\tau}(2(1 - \eta_1 - \eta_2)\beta(0) + k_0\eta_1). \end{aligned}$$

If $\tau < \tau_{\max}$, then we can check that $D_0(0, \tau) < 0$, which implies that $\lambda_0 > 0$. Hence, the trivial steady state is unstable.

We suppose now that $\tau > \tau_{\max}$. Then, $D_0(0, \tau) > 0$ and $\lambda_0 < 0$. Let $\lambda = \mu + i\omega$, be a zero of $D_0(\lambda, \tau)$ given in (4.2), such that $\mu \geq \lambda_0$. We have

$$\begin{aligned} \mu + i\omega + \gamma + k_0(\eta_1 + \eta_2) + r(P^*) \\ + (1 - \eta_1 - \eta_2)\beta(0) - e^{-\gamma\tau}(2(1 - \eta_1 - \eta_2)\beta(0) + k_0\eta_1)e^{-(\mu+i\omega)\tau} = 0. \end{aligned}$$

The real part of this equation satisfies

$$\begin{aligned} \mu = -\gamma - k_0(\eta_1 + \eta_2) - r(P^*) - (1 - \eta_1 - \eta_2)\beta(0) \\ + e^{-\gamma\tau}(2(1 - \eta_1 - \eta_2)\beta(0) - k_0\eta_1)e^{-\mu\tau} \cos(\omega\tau). \end{aligned} \quad (4.3)$$

We have also

$$\begin{aligned} \lambda_0 = -\gamma - k_0(\eta_1 + \eta_2) - r(P^*) - (1 - \eta_1 - \eta_2)\beta(0) \\ + e^{-\gamma\tau}(2(1 - \eta_1 - \eta_2)\beta(0) - k_0\eta_1)e^{-\lambda_0\tau}. \end{aligned} \quad (4.4)$$

From (4.3) and (4.4), we get

$$\begin{aligned} \mu - \lambda_0 &= [e^{-\mu\tau} \cos(\omega\tau) - e^{-\lambda_0\tau}]e^{-\gamma\tau}(2(1 - \eta_1 - \eta_2)\beta(0) - k_0\eta_1), \\ &< e^{-\lambda_0\tau}(\cos(\omega\tau) - 1)e^{-\gamma\tau}(2(1 - \eta_1 - \eta_2)\beta(0) - k_0\eta_1) \leq 0. \end{aligned}$$

This leads to a contradiction. Then, necessarily $\mu < \lambda_0 < 0$. We conclude that the trivial steady state is locally asymptotically stable. \square

4.2. Global asymptotic stability of the trivial steady state

In this section, we investigate the global asymptotic stability of the trivial steady state. First, we focus on the subsystem of (2.1)

$$\begin{cases} \dot{D}(t) = -\kappa D(t) + K \\ \dot{P}(t) = -vP(t) + \kappa D(t). \end{cases} \quad (4.5)$$

All the parameters of (4.5) are positive. The set of the initial conditions is included in $\Omega := \{(D, P) \in \mathbb{R}_+^2, D \geq 0, P \geq 0\}$. By the resolution of the subsystem (4.5) we obtain

$$\begin{cases} D(t) = D(0)e^{-\kappa t} + \frac{K}{\kappa}(1 - e^{-\kappa t}) \\ P(t) = P(0)e^{-vt} + \frac{\kappa K}{\kappa v} = P(0)e^{-vt} + \frac{K}{v}. \end{cases} \quad (4.6)$$

Since $\lim_{t \rightarrow +\infty} e^{-\kappa t} = \lim_{t \rightarrow +\infty} e^{-vt} = 0$, the solution of the system (4.5) tends towards the unique equilibrium of the model $(K/\kappa, K/v)$. Then we conclude that the unique steady state (D^*, P^*) of system (4.5) is globally asymptotically stable.

Next, we use the global convergence of D, P to D^*, P^* , respectively, to obtain the global asymptotic stability of the equilibrium $(0, D^*, P^*)$ of system (2.1). In fact, with the choice of $\epsilon > 0$ small enough, there exists a sufficiently large $T_\epsilon > 0$, such that $P(t) \geq P^* - \epsilon$ for all $t \geq T_\epsilon$. Since $s \mapsto r(s)$ is an increasing function, then for all $t \geq T_\epsilon$ we have

$$\begin{aligned} \dot{Q}(t) &\leq -\gamma Q(t) - k_0(\eta_1 + \eta_2)Q(t) - (1 - \eta_1 - \eta_2)\beta(Q(t))Q(t) \\ &\quad + 2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(Q(t - \tau))Q(t - \tau) \\ &\quad + k_0\eta_1 e^{-\gamma\tau}Q(t - \tau) - r(P^* - \epsilon)Q(t). \end{aligned} \quad (4.7)$$

We will use a comparison principle. Then, we consider the following problem

$$\begin{cases} \dot{Q}^\epsilon(t) = -\gamma Q^\epsilon(t) - k_0(\eta_1 + \eta_2)Q^\epsilon(t) - (1 - \eta_1 - \eta_2)\beta(Q^\epsilon(t))Q^\epsilon(t) \\ \quad + 2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(Q^\epsilon(t - \tau))Q^\epsilon(t - \tau) \\ \quad + k_0\eta_1 e^{-\gamma\tau}Q^\epsilon(t - \tau) - r(P^* - \epsilon)Q^\epsilon(t), \quad t \geq T_\epsilon \\ Q^\epsilon(t) = Q(t), \quad t \in [T_\epsilon - \tau, T_\epsilon]. \end{cases} \quad (4.8)$$

Without loss of generality, we can assume that the system (4.8) holds for all $t \geq 0$ by taking $\tilde{\varphi}(\delta) = Q(T_\epsilon + \delta)$ with $\delta \in [-\tau, 0]$. We note that zero is also a steady state for the system (4.8). The global stability of this equilibrium is given in the following result.

Theorem 4.2. *Assume that*

$$\tau > \frac{1}{\gamma} \ln \left(\frac{k_0 \eta_1 + 2(1 - \eta_1 - \eta_2) \beta(0)}{(1 - \eta_1 - \eta_2) \beta(0) + \gamma + k_0(\eta_1 + \eta_2) + r(P^* - \epsilon)} \right). \quad (4.9)$$

Then, the zero equilibrium of (4.8) is globally asymptotically stable.

Proof. Consider the following continuous function

$$\begin{aligned} V: C([- \tau, 0], \mathbb{R}^+) &\rightarrow \mathbb{R}^+, \\ \phi &\mapsto V(\phi), \end{aligned}$$

defined by

$$V(\phi) = \phi(0) + 2(1 - \eta_1 - \eta_2) e^{-\gamma \tau} \int_{-\tau}^0 \beta(\phi(\theta)) \phi(\theta) d\theta + k_0 \eta_1 e^{-\gamma \tau} \int_{-\tau}^0 \phi(\theta) d\theta.$$

The derivative of V along the solution trajectory $t \mapsto Q^\epsilon(t)$ of (4.8) is calculated as follows

$$\begin{aligned} \dot{V}(Q_t^\epsilon) &= \dot{Q}^\epsilon(t) + 2(1 - \eta_1 - \eta_2) e^{-\gamma \tau} [\beta(Q^\epsilon(t)) Q^\epsilon(t) - \beta(Q^\epsilon(t - \tau)) Q^\epsilon(t - \tau)] \\ &\quad + k_0 \eta_1 e^{-\gamma \tau} [Q^\epsilon(t) - Q^\epsilon(t - \tau)], \\ &= -\gamma Q^\epsilon(t) - k_0(\eta_1 + \eta_2) Q^\epsilon(t) - (1 - \eta_1 - \eta_2) \beta(Q^\epsilon(t)) Q^\epsilon(t) \\ &\quad + 2(1 - \eta_1 - \eta_2) e^{-\gamma \tau} \beta(Q^\epsilon(t - \tau)) Q^\epsilon(t - \tau) + k_0 \eta_1 e^{-\gamma \tau} Q^\epsilon(t - \tau) \\ &\quad - r(P^* - \epsilon) Q^\epsilon(t) + 2(1 - \eta_1 - \eta_2) e^{-\gamma \tau} [\beta(Q^\epsilon(t)) Q^\epsilon(t) - \beta(Q^\epsilon(t - \tau)) Q^\epsilon(t - \tau)] \\ &\quad + k_0 \eta_1 e^{-\gamma \tau} [Q^\epsilon(t) - Q^\epsilon(t - \tau)], \\ &= [-(1 - \eta_1 - \eta_2) + 2(1 - \eta_1 - \eta_2) e^{-\gamma \tau}] \beta(Q^\epsilon(t)) Q^\epsilon(t) \\ &\quad + [2(1 - \eta_1 - \eta_2) e^{-\gamma \tau} - 2(1 - \eta_1 - \eta_2) e^{-\gamma \tau}] \beta(Q^\epsilon(t - \tau)) Q^\epsilon(t - \tau) \\ &\quad - [\gamma + k_0 \eta_1 + k_0 \eta_2 + r(P^* - \epsilon) - k_0 \eta_1 e^{-\gamma \tau}] Q^\epsilon(t) + [k_0 \eta_1 e^{-\gamma \tau} - k_0 \eta_1 e^{-\gamma \tau}] Q^\epsilon(t - \tau), \\ &= (2e^{-\gamma \tau} - 1)(1 - \eta_1 - \eta_2) \beta(Q^\epsilon(t)) Q^\epsilon(t) \\ &\quad - [\gamma + k_0 \eta_2 + r(P^* - \epsilon) - k_0 \eta_1 (e^{-\gamma \tau} - 1)] Q^\epsilon(t), \\ &= -[(1 - 2e^{-\gamma \tau})(1 - \eta_1 - \eta_2) \beta(Q^\epsilon(t)) + \gamma + k_0 \eta_2 + r(P^* - \epsilon) + k_0 \eta_1 (1 - e^{-\gamma \tau})] Q^\epsilon(t). \end{aligned}$$

Note that β is a decreasing function. If $1 - 2e^{-\gamma \tau} \geq 0$, then we have

$$\dot{V}(Q_t^\epsilon) \leq -[\gamma + k_0 \eta_2 + r(P^* - \epsilon)] Q^\epsilon(t).$$

If $1 - 2e^{-\gamma \tau} < 0$, then we have

$$\begin{aligned} \dot{V}(Q_t^\epsilon) &\leq -[(1 - 2e^{-\gamma \tau})(1 - \eta_1 - \eta_2) \beta(0) + \gamma + k_0 \eta_2 \\ &\quad + r(P^* - \epsilon) + k_0 \eta_1 (1 - e^{-\gamma \tau})] Q^\epsilon(t) =: -\nu(\epsilon) Q^\epsilon(t). \end{aligned}$$

From our hypothesis, we can observe easily that $\nu(\epsilon)$ is positive. Consequently, the both situations imply that the trivial steady state of (4.8) is globally asymptotically stable. \square

In the next theorem, we give a necessary and sufficient conditions for the trivial equilibrium to be globally asymptotically stable (see Fig. 2).

Theorem 4.3. *If $\tau > \tau_{max}$, where τ_{max} is given by (3.4), then the unique trivial equilibrium of (2.1) is globally asymptotically stable.*

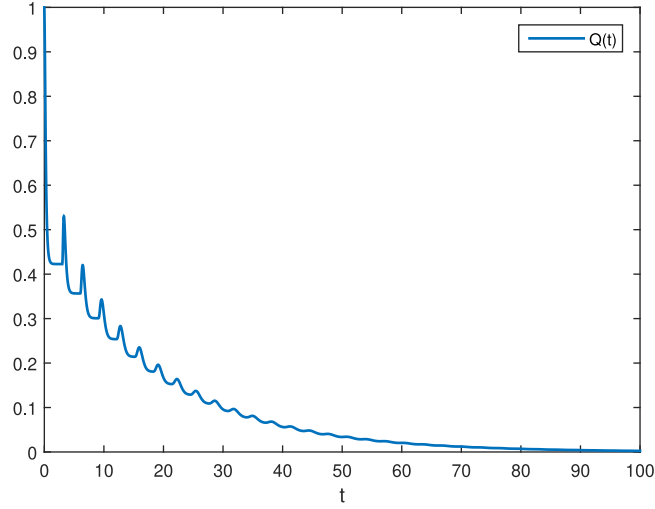


FIGURE 2. The solution is drawn when the trivial steady state is globally asymptotically stable, with $\tau = 3$, $n = 5$, $\theta = 1$, $\gamma = 0.2$, $\beta_0 = 4$, $k_0 = 1.5$, $\eta_1 = 0.01$, $\eta_2 = 0.01$, $v = 0.0412$, $K = 200$, $x_0 = 2.5 \times 10^4$, $R_0 = x_0/25$, $P_0 = 0.5$, $m = 3$, $\tau_{\max} = 2.1498$ and the initial conditions are $D(0) = 0.9$, $P(0) = 0.9$, $Q(t) = 1$ for $t \in [-\tau, 0]$.

Proof. From Theorem 4.2 and under the condition (4.9), we get the attractivity of the only trivial steady state of (4.8). Then,

$$\lim_{t \rightarrow +\infty} Q^\epsilon(t) = 0.$$

From (4.7), (4.8) and by the comparison principle, for all $t > 0$ we have

$$0 \leq Q(t) \leq Q^\epsilon(t). \quad (4.10)$$

Moreover, we can observe that if we suppose the condition (3.3), then there exists a small $\epsilon > 0$ such that (4.9) holds. This allows us to say that under (3.3) and using (4.10) the state $Q(t)$ converges to zero. Recalling that $(0, D^*, P^*)$ is locally asymptotically stable. Then, it is globally asymptotically stable. This completes the proof. \square

5. UNIFORM PERSISTENCE

Persistence of the solutions of system (2.1) ensures survival of the leukemic cells since solutions do not converge towards the trivial steady state.

Theorem 5.1. *Assume (3.3) holds. Then, for any initial condition $(\varphi, D_0, P_0) \in C^+ \times \mathbb{R}^+ \times \mathbb{R}^+$, there exists a constant $\epsilon > 0$ such that*

$$\limsup_{t \rightarrow +\infty} |Q(t)| \geq \epsilon, \quad \lim_{t \rightarrow +\infty} |D(t)| = \frac{K}{\kappa} > 0 \quad \text{and} \quad \lim_{t \rightarrow +\infty} |P(t)| = \frac{K}{v} > 0. \quad (5.1)$$

Proof. From (4.6) the solution of the second and third equation of the system (2.1) are given explicitly by

$$\begin{cases} D(t) = D(0)e^{-\kappa t} + \frac{K}{\kappa}(1 - e^{-\kappa t}), \\ P(t) = P(0)e^{-vt} + \frac{\kappa K}{\kappa v} = P(0)e^{-vt} + \frac{K}{v}, \end{cases}$$

for all $t > 0$. Consequently,

$$\lim_{t \rightarrow +\infty} D(t) = \frac{K}{\kappa},$$

and

$$\lim_{t \rightarrow +\infty} P(t) = \frac{K}{v}.$$

Now, we state the persistence of the component Q . First, it is clear that we can choose $\tilde{\epsilon} > 0$ small enough and a large $T_{\tilde{\epsilon}} > 0$ such that $P(t) < P^* + \tilde{\epsilon}$, for any $t \geq T_{\tilde{\epsilon}}$.

Since (3.3) holds, there exist sufficiently small $\epsilon > 0$ and a small $\lambda > 0$ such that $g(\epsilon, \tilde{\epsilon}, \lambda) < 0$ with

$$\begin{aligned} g(\epsilon, \tilde{\epsilon}, \lambda) &:= \lambda + \gamma + k_0(\eta_1 + \eta_2) + (1 - \eta_1 - \eta_2)\beta(0) + r(P^* + \tilde{\epsilon}) \\ &\quad - (2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(\epsilon) + k_0\eta_1e^{-\gamma\tau})e^{-\lambda\tau}. \end{aligned}$$

With this choice of ϵ , we are going to show that (5.1) holds true. On the contrary, suppose that (5.1) does not hold. Then, there exists a sufficiently large $T_{\epsilon, \tilde{\epsilon}} > T_{\tilde{\epsilon}}$ such that $Q(t) \leq \epsilon$ for all $t \geq T_{\epsilon, \tilde{\epsilon}}$. From (2.1), for $t \geq T_{\epsilon, \tilde{\epsilon}}$ we have

$$\begin{aligned} \dot{Q}(t) &\geq -[\gamma + k_0(\eta_1 + \eta_2) + (1 - \eta_1 - \eta_2)\beta(0) + r(P^* + \tilde{\epsilon})]Q(t), \\ &\quad + e^{-\gamma\tau} [2(1 - \eta_1 - \eta_2)\beta(Q(t - \tau)) + k_0\eta_1] Q(t - \tau). \end{aligned} \tag{5.2}$$

We notice that

$$\int_s^{+\infty} e^{-\lambda t} \frac{dQ(t)}{dt} dt = -e^{-\lambda s} Q(s) + \lambda \int_s^{+\infty} e^{-\lambda t} Q(t) dt. \tag{5.3}$$

Multiplying (5.2) by $e^{-\lambda t}$ and integrating from $t = T_{\epsilon, \tilde{\epsilon}}$ to $t = +\infty$, we obtain

$$\begin{aligned} &\int_{T_{\epsilon, \tilde{\epsilon}}}^{+\infty} e^{-\lambda t} \dot{Q}(t) dt \\ &\geq -[\gamma + k_0(\eta_1 + \eta_2) + (1 - \eta_1 - \eta_2)\beta(0) + r(P^* + \tilde{\epsilon})] \int_{T_{\epsilon, \tilde{\epsilon}}}^{+\infty} e^{-\lambda t} Q(t) dt \\ &\quad + 2(1 - \eta_1 - \eta_2)e^{-\gamma\tau} \int_{T_{\epsilon, \tilde{\epsilon}}}^{+\infty} e^{-\lambda t} \beta(Q(t - \tau)) Q(t - \tau) dt \\ &\quad + k_0\eta_1 e^{-\gamma\tau} \int_{T_{\epsilon, \tilde{\epsilon}}}^{+\infty} e^{-\lambda t} Q(t - \tau) dt. \end{aligned} \tag{5.4}$$

We have again that, for $t \geq T_{\epsilon, \tilde{\epsilon}}$,

$$\begin{aligned}
 & \int_{T_{\epsilon, \tilde{\epsilon}}}^{+\infty} e^{-\lambda t} \dot{Q}(t) dt \\
 & \geq -[\gamma + k_0(\eta_1 + \eta_2) + (1 - \eta_1 - \eta_2)\beta(0) + r(P^* + \tilde{\epsilon})] \int_{T_{\epsilon, \tilde{\epsilon}}}^{+\infty} e^{-\lambda t} Q(t) dt \\
 & \quad + 2(1 - \eta_1 - \eta_2)e^{-\gamma\tau} \int_{T_{\epsilon, \tilde{\epsilon}-\tau}}^{+\infty} e^{-\lambda(s+\tau)} \beta(Q(s))Q(s) ds \\
 & \quad + k_0\eta_1 e^{-\gamma\tau} \int_{T_{\epsilon, \tilde{\epsilon}-\tau}}^{+\infty} e^{-\lambda(s+\tau)} Q(s) ds, \\
 & \geq -[\gamma + k_0(\eta_1 + \eta_2) + (1 - \eta_1 - \eta_2)\beta(0) + r(P^* + \tilde{\epsilon})] \int_{T_{\epsilon, \tilde{\epsilon}}}^{+\infty} e^{-\lambda t} Q(t) dt \\
 & \quad + 2(1 - \eta_1 - \eta_2)e^{-\gamma\tau} \int_{T_{\epsilon, \tilde{\epsilon}}}^{+\infty} e^{-\lambda(s+\tau)} \beta(Q(s))Q(s) ds \\
 & \quad + k_0\eta_1 e^{-\gamma\tau} \int_{T_{\epsilon, \tilde{\epsilon}}}^{+\infty} e^{-\lambda(s+\tau)} Q(s) ds.
 \end{aligned}$$

Since, $Q(t) \leq \epsilon$, for any $t \geq T_{\epsilon, \tilde{\epsilon}}$, and β is an decreasing function, we have

$$\begin{aligned}
 & \int_{T_{\epsilon, \tilde{\epsilon}}}^{+\infty} e^{-\lambda t} \dot{Q}(t) dt \\
 & \geq -[\gamma + k_0(\eta_1 + \eta_2) + (1 - \eta_1 - \eta_2)\beta(0) + r(P^* + \tilde{\epsilon})] \int_{T_{\epsilon, \tilde{\epsilon}}}^{+\infty} e^{-\lambda t} Q(t) dt, \\
 & \quad + [2(1 - \eta_1 - \eta_2)e^{-\gamma\tau} \beta(\epsilon) + k_0\eta_1 e^{-\gamma\tau}] e^{-\lambda\tau} \int_{T_{\epsilon, \tilde{\epsilon}}}^{+\infty} e^{-\lambda s} Q(s) ds, \\
 & \geq -[\gamma + k_0(\eta_1 + \eta_2) + (1 - \eta_1 - \eta_2)\beta(0) + r(P^* + \tilde{\epsilon})] \\
 & \quad - (2(1 - \eta_1 - \eta_2)e^{-\gamma\tau} \beta(\epsilon) + k_0\eta_1 e^{-\gamma\tau}) e^{-\lambda\tau} \int_{T_{\epsilon, \tilde{\epsilon}}}^{+\infty} e^{-\lambda s} Q(s) ds.
 \end{aligned}$$

Hence, from (5.3) and (5.4) we have

$$\begin{aligned}
 & -e^{-\lambda T_{\epsilon, \tilde{\epsilon}}} Q(T_{\epsilon, \tilde{\epsilon}}) + \lambda \int_{T_{\epsilon, \tilde{\epsilon}}}^{+\infty} e^{-\lambda t} Q(t) dt \\
 & \geq -[\gamma + k_0(\eta_1 + \eta_2) + (1 - \eta_1 - \eta_2)\beta(0) + r(P^* + \tilde{\epsilon})] \\
 & \quad - (2(1 - \eta_1 - \eta_2)e^{-\gamma\tau} \beta(\epsilon) + k_0\eta_1 e^{-\gamma\tau}) e^{-\lambda\tau} \int_{T_{\epsilon, \tilde{\epsilon}}}^{+\infty} e^{-\lambda s} Q(s) ds.
 \end{aligned}$$

Then, for $t \geq T_{\epsilon, \tilde{\epsilon}}$

$$\begin{aligned} & -e^{-\lambda T_{\epsilon, \tilde{\epsilon}}} Q(T_{\epsilon, \tilde{\epsilon}}) \\ & \geq -[\lambda + \gamma + k_0(\eta_1 + \eta_2) + (1 - \eta_1 - \eta_2)\beta(0) + r(P^* + \tilde{\epsilon}) \\ & - (2(1 - \eta_1 - \eta_2)e^{-\gamma\tau}\beta(\epsilon) + k_0\eta_1 e^{-\gamma\tau}) e^{-\lambda\tau}] \int_{T_{\epsilon, \tilde{\epsilon}}}^{+\infty} e^{-\lambda s} Q(s) ds. \end{aligned}$$

The conclusion is that

$$0 > -e^{-\lambda T_{\epsilon, \tilde{\epsilon}}} Q(T_{\epsilon, \tilde{\epsilon}}) \geq -g(\epsilon, \tilde{\epsilon}, \lambda) \int_{T_{\epsilon, \tilde{\epsilon}}}^{+\infty} e^{-\lambda s} Q(s) ds > 0.$$

This leads to a contradiction. \square

The Theorem 5.1 shows the persistence of solution but not the strong one. The uniform (strong) persistence means that there exists a positive constant $\epsilon_1 > 0$ such that

$$\liminf_{t \rightarrow +\infty} |Q(t)| \geq \epsilon_1.$$

The Theorem 5.1 shows only that $\limsup_{t \rightarrow +\infty} |Q(t)| \geq \epsilon$ for some small $\epsilon > 0$ (weak persistence). Based on the theory in ([19], Thm. 11), it follows in our case that the uniform weak persistence implies the uniform (strong) persistence (see also [1, 2] for a same corresponding proof). Then, for any positive initial condition, there exists a positive constant $\epsilon_1 > 0$ such that

$$\liminf_{t \rightarrow +\infty} |Q(t)| \geq \epsilon_1, \quad \lim_{t \rightarrow +\infty} |D(t)| = \frac{K}{\kappa} > 0 \quad \text{and} \quad \lim_{t \rightarrow +\infty} |P(t)| = \frac{K}{v} > 0.$$

From above, we see that the condition (3.3), associated to the existence of the unique positive steady state or not, implies that it plays the role of a threshold not only for the eradication but also for the persistence of cells.

6. LOCAL ASYMPTOTIC STABILITY AND HOPF BIFURCATION

We focus now on the positive steady state of (2.1). In order to study the local asymptotic stability of the positive steady state, we write the characteristic equation given by the following formula

$$\Delta(\lambda, \tau) = \det(\lambda I - M_1 - e^{-\lambda\tau} N_1) = 0,$$

with

$$M_1 = \begin{pmatrix} -\gamma - k_0(\eta_1 + \eta_2) - r(P^*) - (1 - \eta_1 - \eta_2)(\beta(Q^*) + \beta'(Q^*)Q^*) & 0 & -r'(P^*)Q^* \\ 0 & -\kappa & 0 \\ 0 & \kappa & -v \end{pmatrix},$$

and

$$N_1 = \begin{pmatrix} e^{-\gamma\tau}[2(1 - \eta_1 - \eta_2)(\beta(Q^*) + \beta'(Q^*)Q^*) + k_0\eta_1] & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

Then, the characteristic equation becomes

$$\begin{aligned} \Delta(\lambda, \tau) = & (\lambda + \kappa)(\lambda + v) (\lambda + \gamma + k_0(\eta_1 + \eta_2) + \bar{\alpha}(\tau) \\ & + r(P^*) - e^{-\lambda\tau} e^{-\gamma\tau} (k_0\eta_1 + 2\bar{\alpha}(\tau))) = 0 \end{aligned} \quad ,$$

with

$$\bar{\alpha}(\tau) := (1 - \eta_1 - \eta_2)(\beta(Q^*) + \beta'(Q^*)Q^*).$$

We recall that a steady state is locally asymptotically stable if all roots of the associated characteristic equation have negative real parts, and unstable if at least one root with positive real part exists. Since κ and v are positive, we will consider the equation

$$D(\lambda, \tau) = \lambda + \gamma + k_0(\eta_1 + \eta_2) + \bar{\alpha}(\tau) + r(P^*) - e^{-\lambda\tau} e^{-\gamma\tau} (k_0\eta_1 + 2\bar{\alpha}(\tau)) = 0. \quad (6.1)$$

First, we will check that $\lambda = 0$ is not a root of $D(\lambda, \tau)$.

Proposition 6.1. $\lambda = 0$ is not a root of $D(\lambda, \tau)$.

Proof. Assume that $\lambda = 0$ is a root of the characteristic equation. Then, we obtain

$$D(0, \tau) = \gamma + k_0(\eta_1 + \eta_2) + \bar{\alpha}(\tau) + r(P^*) - e^{-\gamma\tau} (k_0\eta_1 + 2\bar{\alpha}(\tau)).$$

thus

$$\begin{aligned} D(0, \tau) &= \gamma + k_0\eta_1(1 - e^{-\gamma\tau}) + k_0\eta_2 + r(P^*) + \bar{\alpha}(\tau)(1 - 2e^{-\gamma\tau}), \\ &= \gamma + r(P^*) + k_0\eta_1(1 - e^{-\gamma\tau}) + k_0\eta_2, \\ &\quad + (1 - 2e^{-\gamma\tau})(1 - \eta_1 - \eta_2)\beta'(Q^*)Q^* \\ &\quad + (1 - 2e^{-\gamma\tau})(1 - \eta_1 - \eta_2) \left[\frac{\gamma + k_0(\eta_1 + \eta_2) - k_0\eta_1 e^{-\gamma\tau} + r(P^*)}{(2e^{-\gamma\tau} - 1)(1 - \eta_1 - \eta_2)} \right], \\ &= (1 - 2e^{-\gamma\tau})(1 - \eta_1 - \eta_2)\beta'(Q^*)Q^* > 0. \end{aligned}$$

In fact, the existence of the positive steady state implies that $1 - 2e^{-\gamma\tau} < 0$ and β is a decreasing function. This completes the proof. \square

Now, we study the sign of the root of $D(\lambda, \tau)$, given by (6.1). In the next lemma, we show the stability at $\tau = 0$.

Lemma 6.2. For $\tau = 0$, the steady state (Q^*, D^*, P^*) is locally asymptotically stable.

Proof. Assume that $\tau = 0$. Then, we have

$$\begin{aligned} D(\lambda, 0) &= \lambda + \gamma + k_0(\eta_1 + \eta_2) + \bar{\alpha}(0) + r(P^*) - (k_0\eta_1 + 2\bar{\alpha}(0)), \\ &= \lambda + \gamma + k_0\eta_2 + r(P^*) - \bar{\alpha}(0). \end{aligned}$$

The only solution of the equation $D(\lambda, 0) = 0$ is given explicitly by,

$$\begin{aligned} \lambda &= -(\gamma + k_0\eta_2 + r(P^*) - \bar{\alpha}(0)), \\ &= -[\gamma + k_0\eta_2 + r(P^*) - (1 - \eta_1 - \eta_2)\beta'(Q^*)Q^* - \gamma - k_0(\eta_1 + \eta_2) + k_0\eta_1 - r(P^*)], \\ &= (1 - \eta_1 - \eta_2)\beta'(Q^*)Q^* < 0. \end{aligned}$$

We conclude that the positive steady state is locally asymptotically stable for $\tau = 0$. \square

This lemma implies that there exists $\widehat{\tau} \in (0, \tau_{\max})$, for which (Q^*, D^*, P^*) is locally asymptotically stable for all $\tau \in [0, \widehat{\tau})$. Next, we will look for the existence of a purely imaginary roots $i\omega$, with $\omega > 0$. Then, the characteristic equation (6.1) becomes

$$i\omega + \gamma + k_0(\eta_1 + \eta_2) + \bar{\alpha}(\tau) + r(P^*) - e^{-i\omega\tau} e^{-\gamma\tau} (k_0\eta_1 + 2\bar{\alpha}(\tau)) = 0. \quad (6.2)$$

By separating the real and the imaginary parts in (6.2), we obtain

$$\begin{cases} e^{-\gamma\tau} \cos(\omega\tau) (2\bar{\alpha}(\tau) + k_0\eta_1) = \gamma + k_0(\eta_1 + \eta_2) + \bar{\alpha}(\tau) + r(P^*), \\ e^{-\gamma\tau} \sin(\omega\tau) (2\bar{\alpha}(\tau) + k_0\eta_1) = -\omega. \end{cases}$$

This yields to

$$\begin{cases} \cos(\omega\tau) = \frac{\gamma + k_0(\eta_1 + \eta_2) + \bar{\alpha}(\tau) + r(P^*)}{e^{-\gamma\tau} (2\bar{\alpha}(\tau) + k_0\eta_1)}, \\ \sin(\omega\tau) = \frac{-\omega}{e^{-\gamma\tau} (2\bar{\alpha}(\tau) + k_0\eta_1)}. \end{cases} \quad (6.3)$$

Remark 6.3. If $\tau = 0$, then the second equation of (6.3) can not be satisfied and no purely imaginary roots $i\omega$, with $\omega > 0$, exist.

From (6.3), by adding the square of the both equation, we obtain,

$$\begin{aligned} \omega^2 &= e^{-2\gamma\tau} (2\bar{\alpha}(\tau) + k_0\eta_1)^2 - (\gamma + k_0(\eta_1 + \eta_2) + \bar{\alpha}(\tau) + r(P^*))^2, \\ &= [e^{-\gamma\tau} (2\bar{\alpha}(\tau) + k_0\eta_1) - (\gamma + k_0(\eta_1 + \eta_2) + \bar{\alpha}(\tau) + r(P^*))] \\ &\quad [e^{-\gamma\tau} (2\bar{\alpha}(\tau) + k_0\eta_1) + (\gamma + k_0(\eta_1 + \eta_2) + \bar{\alpha}(\tau) + r(P^*))], \\ &= [\bar{\alpha}(\tau)(2e^{-\gamma\tau} - 1) + k_0\eta_1(e^{-\gamma\tau} - 1) - (\gamma + k_0\eta_2 + r(P^*))] \\ &\quad [\bar{\alpha}(\tau)(2e^{-\gamma\tau} + 1) + k_0\eta_1(e^{-\gamma\tau} + 1) + (\gamma + k_0\eta_2 + r(P^*))], \\ &= [(1 - \eta_1 - \eta_1)(2e^{-\gamma\tau} - 1)\beta'(Q^*)Q^* + \gamma + k_0(\eta_1 + \eta_2) - k_0\eta_1 e^{-\gamma\tau} \\ &\quad + r(P^*) + k_0\eta_1(e^{-\gamma\tau} - 1) - (\gamma + k_0\eta_2 + r(P^*))] \\ &\quad [\bar{\alpha}(\tau)(2e^{-\gamma\tau} + 1) + k_0\eta_1(e^{-\gamma\tau} + 1) + (\gamma + k_0\eta_2 + r(P^*))], \\ &= [(1 - \eta_1 - \eta_1)(2e^{-\gamma\tau} - 1)\beta'(Q^*)Q^*] \\ &\quad [\bar{\alpha}(\tau)(2e^{-\gamma\tau} + 1) + k_0\eta_1(e^{-\gamma\tau} + 1) + (\gamma + k_0\eta_2 + r(P^*))]. \end{aligned}$$

Observe that the condition $2e^{-\gamma\tau} - 1 > 0$ implies that

$$(1 - \eta_1 - \eta_1)(2e^{-\gamma\tau} - 1)\beta'(Q^*)Q^* < 0.$$

As a result, for the existence of $w > 0$, it is necessary to have

$$k_0\eta_1(e^{-\gamma\tau} + 1) + (\gamma + k_0\eta_2 + r(P^*)) < -\bar{\alpha}(\tau)(2e^{-\gamma\tau} + 1), \quad (6.4)$$

The following lemma is a straightforward consequence of the above arguments.

Lemma 6.4. *If (6.4) is not satisfied for all $\tau \in [0, \tau_{\max})$, then all the roots of (6.1) have a negative real part and the equilibrium (Q^*, D^*, P^*) is locally asymptotically stable for all $\tau \in [0, \tau_{\max})$.*

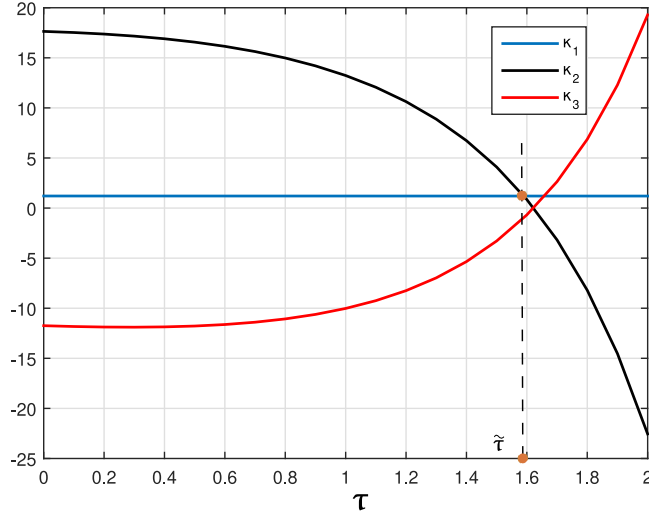


FIGURE 3. Functions $K_1(\tau) = k_0\eta_1(e^{-\gamma\tau} + 1) + (\gamma + k_0\eta_2 + r(P^*))$, $K_2(\tau) = -\bar{\alpha}(\tau)(2e^{-\gamma\tau} + 1)$ and $K_3(\tau) = 2\bar{\alpha}(\tau) + k_0\eta_1$ are drawn in $[0, 2]$, with $n = 5$, $\theta = 1$, $\gamma = 0.2$, $\beta_0 = 3$, $k_0 = 1.5$, $\eta_1 = 0.01$, $\eta_2 = 0.01$, $v = 0.0412$, $K = 200$, $x_0 = 2.5 \times 10^4$, $R_0 = x_0/25$, $P_0 = 0.5$, $m = 3$. The intersection of $K_1(\tau)$ and $K_2(\tau)$ is at $\tilde{\tau} = 1.58$.

Now, suppose that there exists $\tilde{\tau} \in (0, \tau_{\max})$, such that, for all $\tau \in (0, \tilde{\tau})$,

$$\begin{cases} k_0\eta_1(e^{-\gamma\tau} + 1) + (\gamma + k_0\eta_2 + r(P^*)) < -\bar{\alpha}(\tau)(2e^{-\gamma\tau} + 1), \\ 2\bar{\alpha}(\tau) + k_0\eta_1 < 0. \end{cases} \quad (6.5)$$

The threshold $\tilde{\tau}$ can be chosen such that one of the inequalities in (6.5) holds with equality as in Figure 3. Let's consider the function $\tilde{\omega} : (0, \tilde{\tau}) \rightarrow (0, +\infty)$ defined by

$$\tilde{\omega}(\tau) := \left(e^{-2\gamma\tau} (2\bar{\alpha}(\tau) + k_0\eta_1)^2 - (\gamma + k_0(\eta_1 + \eta_2) + \bar{\alpha}(\tau) + r(P^*))^2 \right)^{\frac{1}{2}}. \quad (6.6)$$

We notice that, for $\tau \in (0, \tilde{\tau})$,

$$\sin(\omega\tau) = \frac{-\tilde{\omega}}{e^{-\gamma\tau} (2\bar{\alpha}(\tau) + k_0\eta_1)} > 0. \quad (6.7)$$

From (6.3) and (6.7), for each $\tau \in [0, \tilde{\tau})$, there exists a unique $\Theta(\tau) \in [0, 2\pi[$ solution of system,

$$\begin{cases} \cos(\Theta(\tau)) = \frac{\gamma + k_0(\eta_1 + \eta_2) + \bar{\alpha}(\tau) + r(P^*)}{e^{-\gamma\tau} (2\bar{\alpha}(\tau) + k_0\eta_1)}, \\ \sin(\Theta(\tau)) = \frac{-\tilde{\omega}(\tau)}{e^{-\gamma\tau} (2\bar{\alpha}(\tau) + k_0\eta_1)}. \end{cases} \quad (6.8)$$

Consequently, $\Theta(\tau) \in]0, \pi[$ and it is given by

$$\Theta(\tau) = \arccos \left(\frac{\gamma + k_0(\eta_1 + \eta_2) + \bar{\alpha}(\tau) + r(P^*)}{e^{-\gamma\tau} (2\bar{\alpha}(\tau) + k_0\eta_1)} \right).$$

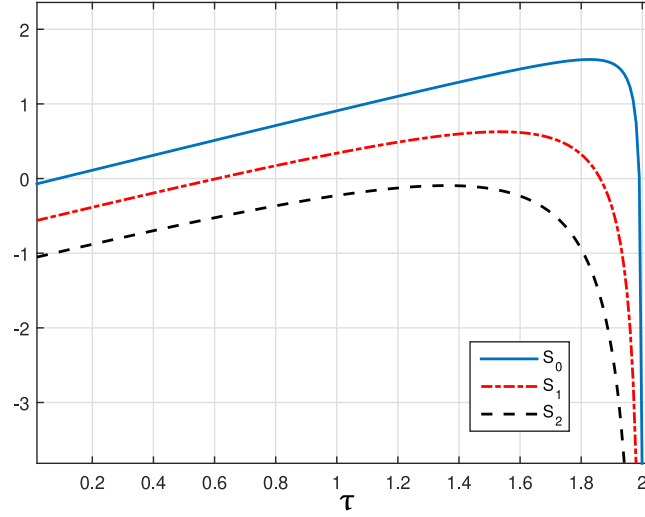


FIGURE 4. Functions S_0 , S_1 and S_2 are drawn. The parameters are given by $n = 5$, $\theta = 1$, $\gamma = 0.2$, $\beta_0 = 4$, $k_0 = 1.5$, $\eta_1 = 0.01$, $\eta_2 = 0.01$, $v = 0.0412$, $K = 200$, $x_0 = 2.5 \times 10^4$, $R_0 = x_0/25$, $P_0 = 0.5$, $m = 3$. We can observe that four roots exist at $\tau_1 = 0.089$, $\tau_2 = 0.6$, $\tau_3 = 1.86$ and $\tau_4 = 1.98$.

Now, the resolution of the system (6.8) is equivalent to find $\tau \in [0, \tilde{\tau})$ such that

$$\tau \tilde{\omega}(\tau) = \Theta(\tau) + 2k\pi, \quad k \in \mathbb{N} \quad (6.9)$$

where $\tilde{\omega}$ is given by (6.6). The resolution of the equation (6.9) is equivalent to solve the following equation

$$S_k(\tau) := \tau - \frac{1}{\tilde{\omega}(\tau)}(\Theta(\tau) + 2k\pi) = 0, \quad k \in \mathbb{N}, \quad \tau \in [0, \tilde{\tau}). \quad (6.10)$$

We can discuss the existence of roots of S_k according to its properties. We have the following result (See Fig. 4).

Lemma 6.5. *The functions S_k given by (6.10) satisfy, for all $k \in \mathbb{N}$ and $\tau \in [0, \tilde{\tau})$,*

$$S_k(0) < 0, \quad S_{k+1} < S_k \quad \text{and} \quad \lim_{\tau \rightarrow +\tilde{\tau}} S_k(\tau) = -\infty.$$

Therefore, provided that no root of S_k is a local extremum, the number of the positive of S_k , for $k \in \mathbb{N}$, on the interval $\tau \in [0, \tilde{\tau})$ is even. From the previous lemma, we conclude that if a fixed S_k has no root on $[0, \tilde{\tau})$, then all functions S_j , with $j > k$, also have no roots on $[0, \tilde{\tau})$. Consequently, we have the following proposition.

Proposition 6.6. *Assume that there exists $\tilde{\tau} \in (0, \tau_{max})$ such that (6.4) is satisfied on $[0, \tilde{\tau})$. If the function S_0 , given by (6.10), has no root on the interval $[0, \tilde{\tau})$, then the positive steady state (Q^*, D^*, P^*) of the system (2.1) is locally asymptotically stable for all $\tau \in [0, \tau_{max})$.*

Now, let suppose that S_0 has at least one positive root, on the interval $[0, \tilde{\tau})$. We denote by $\bar{\tau} \in (0, \tilde{\tau})$ the smallest root of S_0 . Then, (Q^*, D^*, P^*) is locally asymptotically stable for all $\tau \in [0, \bar{\tau})$ and loses its stability when $\tau = \bar{\tau}$. A finite number of stability switch may occurs as τ increases and passes through roots of the functions S_k (See Fig. 4).

Next, we will prove that (Q^*, D^*, P^*) can be destabilized through a Hopf bifurcation as τ increases. We need to

guarantee the transversality condition of the Hopf bifurcation theorem. We start by proving that if an imaginary characteristic root $i\omega$ exists, then it is simple.

Lemma 6.7. *If $\lambda = i\omega$, with $\omega > 0$, is an eigenvalue of (6.1), then it is simple.*

Proof. Suppose by contradiction that $\lambda = i\omega$ is not a simple root for the characteristic equation (6.1). Then, $\lambda = i\omega$ is a solution of

$$D(\lambda, \tau) = 0 \quad \text{and} \quad \frac{\partial D}{\partial \lambda}(\lambda, \tau) = 0.$$

Then,

$$\begin{cases} \lambda + \gamma + k_0(\eta_1 + \eta_2) + \bar{\alpha}(\tau) + r(P^*) - e^{-\lambda\tau}e^{-\gamma\tau}(\eta_1 k_0 + 2\bar{\alpha}(\tau)) = 0, \\ 1 + \tau e^{-\lambda\tau}e^{-\gamma\tau}(\eta_1 k_0 + 2\bar{\alpha}(\tau)) = 0. \end{cases} \quad (6.11)$$

Both equations of system (6.11) yield to

$$\tau\lambda + [\gamma + k_0(\eta_1 + \eta_2) + \bar{\alpha}(\tau) + r(P^*)]\tau + 1 = 0.$$

Consequently, for $\tau > 0$,

$$\lambda = -\frac{[\gamma + k_0(\eta_1 + \eta_2) + \bar{\alpha}(\tau) + r(P^*)]\tau + 1}{\tau} \in \mathbb{R}.$$

Since λ is a purely imaginary root, we lead to a contradiction. \square

As $\bar{\tau}$ is the smallest root of S_0 , then, from the definition of S_0 , the characteristic equation has purely imaginary roots $\pm i\tilde{\omega}(\bar{\tau})$, where $\tilde{\omega}$ is defined by (6.6). The stability of the positive steady state switches from stable to unstable as τ passes through $\bar{\tau}$. As in [7], we rewrite the characteristic equation (6.1) in the following form

$$D(\lambda, \tau) := A(\lambda, \tau) + B(\lambda, \tau)e^{-\lambda\tau} = 0.$$

We define the polynomial function

$$H(\omega, \tau) = |A(i\omega, \tau)|^2 - |B(i\omega, \tau)|^2.$$

Thus,

$$H(\omega, \tau) = \omega^2 + (\gamma + k_0(\eta_1 + \eta_2) + \bar{\alpha}(\tau) + r(P^*))^2 - e^{-2\gamma\tau}(k_0\eta_1 + 2\bar{\alpha}(\tau))^2.$$

Let $\lambda(\tau)$ be a root of the equation (6.1) such that $\lambda(\bar{\tau}) = i\omega(\bar{\tau})$. The Hopf bifurcation theorem says that a Hopf bifurcation occurs at the steady state (Q^*, D^*, P^*) when $\tau = \bar{\tau}$ if

$$\text{sign} \left[\left(\frac{d\text{Re}(\lambda(\tau))}{d\tau} \right)_{\tau=\bar{\tau}} \right] > 0. \quad (6.12)$$

We define the function h which is given explicitly by the following formula,

$$h(\omega^2, \tau) = H(\omega, \tau).$$

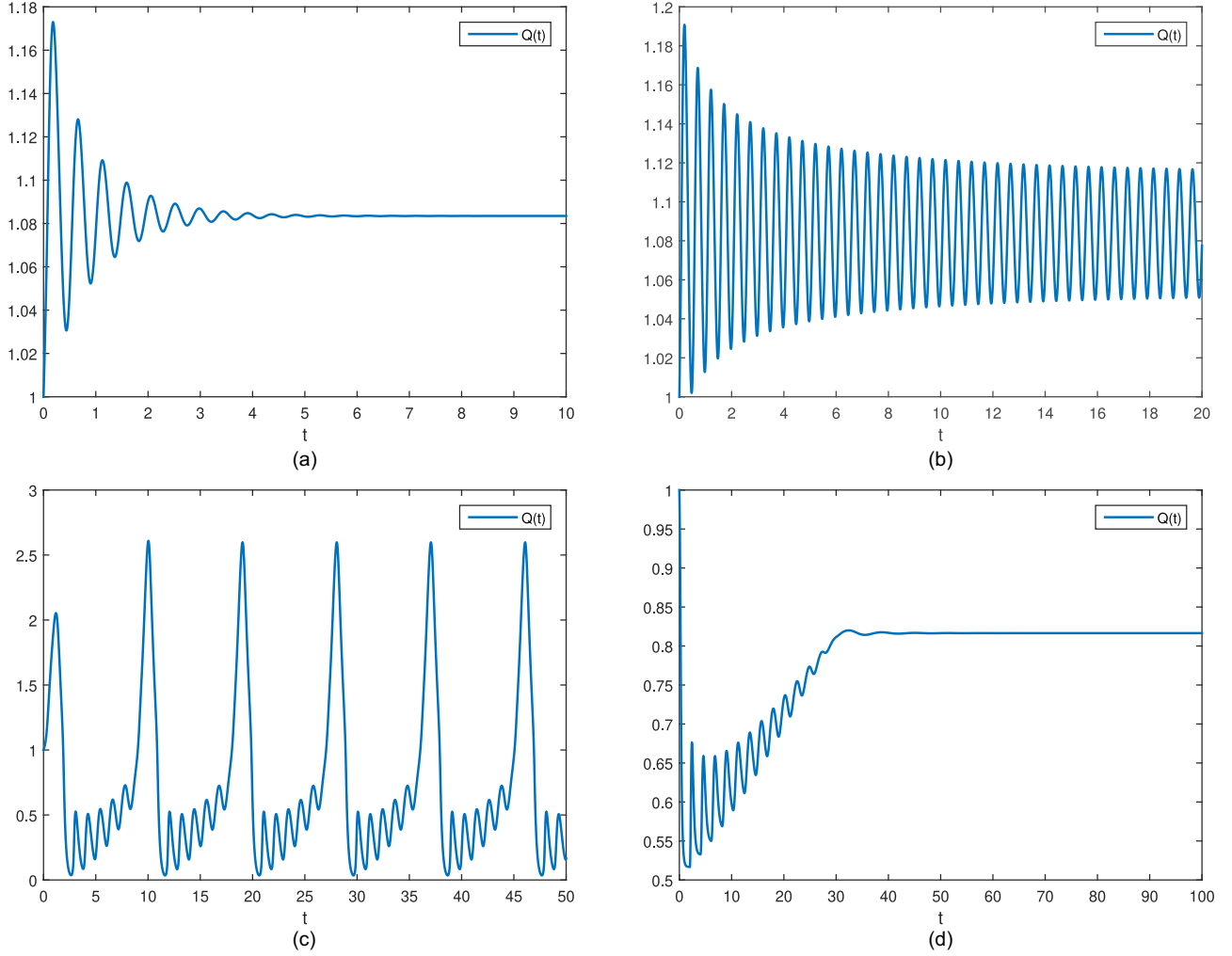


FIGURE 5. The solution is drawn for the stability and instability of the positive steady state, with $n = 5$, $\theta = 1$, $\gamma = 0.2$, $\beta_0 = 4$, $k_0 = 1.5$, $\eta_1 = 0.01$, $\eta_2 = 0.01$, $v = 0.0412$, $K = 200$, $x_0 = 2.5 \times 10^4$, $r_0 = x_0/25$, $P_0 = 0.5$, $m = 3$ and the initial conditions $D(0) = 0.9$, $P(0) = 0.9$, $Q(t) = 1$ for $t \in [-\tau, 0]$. In Fig. (a) (resp. (b), (c) and (d)), we take $\tau = 1.98$ (resp. 1.86, 0.6 and 0.089).

For $z = \omega^2$, we obtain

$$h(z, \tau) = z + (\gamma + k_0(\eta_1 + \eta_2) + \bar{\alpha}(\tau) + r(P^*))^2 - e^{-2\gamma\tau}(k_0\eta_1 + 2\bar{\alpha}(\tau))^2.$$

From [7], we have the following result.

Proposition 6.8. *The transversality condition is reduced to*

$$\text{sign} \left[\left(\frac{d\text{Re}(\lambda(\tau))}{d\tau} \right)_{\tau=\bar{\tau}} \right] = \text{sign} \left(\frac{dS_0(\bar{\tau})}{d\tau} \right).$$

Proof. Since $\frac{\partial h}{\partial z}(z(\bar{\tau}), \bar{\tau}) = 1$, then it follows from [7] that

$$\text{sign} \left[\left(\frac{d \text{Re}(\lambda(\tau))}{d\tau} \right)_{\tau=\bar{\tau}} \right] = \text{sign} \left(\frac{\partial h}{\partial z}(z(\bar{\tau}), \bar{\tau}) \right) \text{sign} \left(\frac{dS_0(\bar{\tau})}{d\tau} \right) = \text{sign} \left(\frac{dS_0(\bar{\tau})}{d\tau} \right).$$

□

The following theorem states the stability of the positive equilibrium and the existence of periodic solutions through the Hopf bifurcation.

Proposition 6.9. *Assume that (3.3) and (6.5) hold true. If $S_0(\tau)$ has at least one positive root on the interval $(0, \bar{\tau})$, then the positive steady state (Q^*, D^*, P^*) is locally asymptotically stable for $\tau \in [0, \bar{\tau})$, where $\bar{\tau}$ is the smallest root of $S_0(\tau)$ on $(0, \bar{\tau})$, and (Q^*, D^*, P^*) loses its stability when $\tau = \bar{\tau}$. A finite number of stability switch may occur as τ passes through the roots of the functions S_k . Moreover, if*

$$\frac{dS_0(\bar{\tau})}{d\tau} > 0,$$

then a Hopf bifurcation occurs at (Q^, D^*, P^*) for $\tau = \bar{\tau}$.*

The following theorem summarizes the result dealing with the asymptotic stability of the positive steady state (Q^*, D^*, P^*) of the system (2.1) (See Fig. 5).

Theorem 6.10. *Assume that the condition (3.3) holds true.*

1. *If (6.4) is not satisfied for all $\tau \in [0, \tau_{max})$, then the positive steady state (Q^*, D^*, P^*) is locally asymptotically stable for all $\tau \in [0, \tau_{max})$.*
2. *Assume there exists $\tilde{\tau} \in (0, \tau_{max})$ such that (6.4) (or equivalently, assume (6.5)) holds true for each $\tau \in [0, \tilde{\tau})$, then the following statements are satisfied:*
 - * *If $S_0(\tau)$, given by (6.10), has no root on the interval $[0, \tilde{\tau})$, then the positive steady state of the system (2.1) is locally asymptotically stable for all $\tau \in [0, \tau_{max})$.*
 - ** *If $S_0(\tau)$ has at least one root on the interval $[0, \tilde{\tau})$, then (Q^*, D^*, P^*) is locally asymptotically stable for $\tau \in [0, \bar{\tau})$, we denote by $\bar{\tau}$ the smallest root of $S_0(\tau)$ on $(0, \tilde{\tau})$ and a Hopf bifurcation occurs at the positive steady state for $\tau = \bar{\tau}$ if and only if*

$$\frac{dS_0(\bar{\tau})}{d\tau} > 0.$$

7. CONCLUSIONS

In this work we have considered a model of chronic myeloid leukemia under medical treatment. A mathematical analysis is proposed to draw conclusions.

The study of the existence of equilibria makes it possible to distinguish two stationary solutions, the trivial equilibrium corresponding to the extinction of the called stem cells which exists for any value of the cell cycle τ , and the nontrivial equilibrium which exists only for $\tau \in (0, \tau_{max})$.

The study of stability allows to conclude that under certain conditions on the parameters of the model, we can deduce the stability of the nontrivial equilibrium when it exists with the instability of the trivial equilibrium, and when the trivial is alone it is even overall stable. This involves the disappearance of the leukemic cells.

More precisely, from the results obtained in this work, in particular from Proposition 3.1 and Theorem 4.1, the amplitude τ of the cell cycle, which can be compared to a certain value τ_{max} , which depends on the parameters of the model, influences either the onset and viability of the disease for $\tau < \tau_{max}$ corresponding to the existence and stability of the nontrivial equilibrium E_1 , or the reduction of the disease in the case where $\tau < \tau_{max}$. From

(3.4), we see that τ_{max} depends on the parameter of medical treatment $r(P^*)$, then one could do the choice of the medical control protocol to move from a situation of the installation of the disease (for $\tau < \tau_{max}$) to a situation of control and significant reduction of the disease (for $\tau > \tau_{max}$).

Otherwise, other questions which were not considered in this work, can be raised and discussed in future works, for example considering leukemic progenitor cells in addition to stem cells or/and resistance to treatment.

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