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Targeting the quiescent cells in cancer chemotherapy treatment: Is it enough?

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ABSTRACT

In this work, we develop a mathematical model to study the effect of drug on the development of cancer including the quiescent compartment. The model is governed by a system of delay differential equations where the delay represents the time that the cancer cell take to proliferate. Our analytical study of the stability shows that by considering the time delay as a parameter of bifurcation, it is possible to have stability switch and oscillations through a Hopf bifurcation. Moreover, by introducing the drug intervention term, the critical delay value increases. This indicates that the system can tolerate a longer delay before oscillations start. In the end, we present some numerical simulations illustrating our theoretical results.

1. Introduction and background

Cancer is one of the most dangerous illnesses which causes many deaths every year. A study done by the National Cancer Institute (NCI) shows that there is approximately a 40% chance for average individuals to develop cancer in their lifetime [1]. According to the most recent report on cancer in USA, cancer incidence decreased for men by 1.8% annually between 2007 and 2011. Whoever this rate is stable for women between 1998 and 2011 [2]. To fight cancer, oncologists use three modes of treatment: surgery, radiotherapy, and chemotherapy.

Although chemotherapy has shown to be a possible strategy to control disseminated metastatic cancer, it is well known that it is not a safe strategy, since it kills cancerous cells as well as the normal cells. It would only be common sense to find a way for chemotherapy to kill only cancerous cells or at least to kill as few normal cells as possible [3]. In fact, this is possible with some drugs such as Cytarabine (Ara-C), 5-fluorouracil (5-FU), Prednisone Vincristine, Paclitaxel and Bleomycin [3–5]. The mechanism based on which these drugs work , is basically by blocking the cell from going to the normal cell cycle; as a result, the drugs stop the proliferation of the cell and permit the immune system to eliminate cancerous cells in a natural way [3,6].

These cell-cycle specific agents are most effective in divided doses mode or continuous pump infusion [7]. These divided doses can be in the form of one dose in multiple days, or at time points such as multiple doses per day [7].

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Other chemotherapy agents are non-phase specific (chemotherapy agents are able to kill a cell during any phase of the cycle). Some examples of such drugs are Alkylating agents (which break the DNA helix strand, interfering with DNA replication, and which are most active in the G_0 phase), and Antitumour Antibiotics (which bind to DNA and interfere with further replication of DNA and transcription of RNA).

These chemotherapy treatments are given in repeated doses in different forms: orally, intravenously, as an injection and intra-arterially [7]. Hence, the cancer cell does not die immediately, rather it undergoes several divisions before it dies.

In addition to the extensive clinical and experimental research that has been done to understand the effect of chemotherapy on cancer progression and to increase the efficacy of chemotherapy treatment (dosage and timing), mathematical modeling of cancer, has also contributed substantially to shedding some light on the complexity of the dynamics of this disease. These mathematical models are either multi-scale models, where multiple levels of the components (proteins, cells, etc.) of cancer are involved (see for example [8,9, 39–42]), or sample models that represent certain levels of the interaction. One of the advantages of this simple models is their ability to do deep mathematical analysis that contributes to our understanding of chemotherapy, beyond what can be done in an experimental research investigation. For example, one of the areas that the mathematical models are considering is the so called G_0 state. Although the cells are quiescent in this state, i.e.,there is no growth or division, they are able to go to the normal path and start the cell cycle in a certain period of time [10]. In order to treat cancer efficiently and eradicate the cancer, it is crucial to investigate this cell state with respect to chemotherapy.

In fact, since the first paper by Mackey [11], where quiescent cancer cells were considered in a simple mathematical model, several mathematical models have tried to improve this model or to build new models that study this type of cancer cells and the management of chemotherapy treatment. For example, the work by Webb [12], where chemotherapy was considered in *on-off* mode in a linear model of active phase and quiescent cancer cells, was extended to a nonlinear cell-kinetic model [13]. In a series of models, Panetta and Adam [14–17], using the *very optimistic* assumption that chemotherapy kills the cells immediately, showed, that there is a possibility to have optimal timing and dosage of treatment to kill the maximum number of cancer cells. Another study by Bertuzzi et al. [18] investigated the time course of diffusion and consumption of oxygen and the redistribution of cells between quiescent and proliferating cells under chemotherapy. In this study, the authors found a more effective way of timing the drug. In [3] Liu et al. studied a mathematical model of the M phase specific chemotherapy with the quiescent phase G_0 and the effect of delay of the adaptive immune response. Their mathematical analysis showed that when the delay reached a critical value, there was a Hopf bifurcation. Venkatasubramanian et al. [19] introduced a new mathematical model (coupled PDE, ODE and algebraic equations) that integrated cell-cycle progression with chemotherapy (5-FU and paclitaxel) and its cellular diffusion as well as intracellular metabolism. The simulation of this model showed that the quiescent cancer cells were more responsive than non quiescent cancer cells to chemotherapy. This indicated that the efficacy of treatment might depend on the quantification of proliferation of cancer cells.

In a recent work by Barbarossa et al. [20] an improved mathematical model of [3,6] for tumor cell growth based on the cell cycle was studied. The authors considered three compartment models of quiescent cells, interphase cells, which included states G_1, S and G_2, and mitotic cells, which are also called the M state. In addition to modeling these three types of cells, the immune response (Lymphoytes) and the drug treatment were also considered. The model was derived in a delay differential equation (DDE) from a partial differential equation (PDE) where the delay represented the length of the interphase. By assuming that all transition rates between different cells states were constant, the authors could not show the effect of this delay on the reoccurrence of cancer. Moreover, the drug treatment was considered only for the Mitotic stage. In fact, it is true that all existing drugs mainly affect the proliferating cells but also, to a certain extent, the quiescent cells. In fact, as it was mentioned in [21] recent findings suggested that a combination of drugs can increase the effect of chemotherapy against the non mitotic cells [22]. Moreover, recent in vivo experimental results identified therapeutic targets for quiescent cells in Human Acute Myeloid Leukemia [23]. More precisely, CD32 and CD25 are present in the cell cycle in quiescent form, and they are stably located on the surface of leukemia stem cells after chemotherapy [23].

In the light of these recent findings, the natural question to ask is: Is it possible to irradiate cancer if we have a chemotherapy that targets the proliferating cells as well as the quiescent cells? Also, do we only need to have this type of medication, or do we also need to have an efficient timing and dosage of the chemotherapy that takes into consideration the length of the interphase between G_0 and G_1?

In an attempt to answer these questions, we investigate a delay differential equation of a general type of interaction between the proliferating and quiescent cells with nonspecific phase chemotherapy. Our model is an extension of our previous work [24], by introducing the chemotherapy into the proliferating and quiescent cells. Our objective is to understand to what extent this type of combination drug can help cancer patients.

The outline of this paper is as follows: In Section 2, we present the extended model with non-specific chemotherapy. In Section 3, we study the model without drug intervention. We analyze stability and stability switch of the model without/with delay. The occurrence of a Hopf bifurcation will be also proved. In Section 4, we study the asymptotic behavior of the interior equilibrium in the presence of a drug intervention term (i.e., an initial dose). We prove that the delay and drug intervention term can affect the asymptotic behavior of the interior equilibrium. Existence of periodic oscillations is showed when the delay crosses some critical value. Section 5 is devoted the numerical analysis and interpretation. In the end, we present some discussion in Section 6.

2. Description of the mathematical model

First, we present the model on which we will base our extended model [24]. This model is nonlinear unstructured delayed differential equations with two types of cells, $P(t)$ the proliferating cancer cells and $Q(t)$ the quiescent cancer cells, defined as follows:

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

where $N(t)$: total cancerous cells (or cancer size) and τ is the time delay that the proliferating cells need to divide. The intrinsic rate of the proliferating cells is defined as follows $b = \beta - \mu_P > 0$, with $\beta > 0$ being the division rate of the proliferating cells and $\mu_P \geq 0$ is the death rate of cells of the proliferating cells, and $\mu_Q \geq 0$ is the death rate of the quiescent cells. $r_P(N)$ (resp. $r_Q(N)$) is the nonlinear transition rate from the proliferating class to the quiescent class (resp. from the quiescent class to the proliferating class). Similar to Gyllenberg and Webb [25], we assume that these two transition rates are Lipschitz continuous on bounded sets of N in $\mathbb{R}$, $r_P(N)$ is increasing, and $r_Q(N)$ is decreasing.

In this study, we extend model (1) by introducing the chemotherapy drug. The chemotherapy has an effect on both cells, proliferating and quiescent, by increasing their death rates. As described in [16,26,27] and others, the response functions to drugs can be expressed as $h(u) = a_i(1 - exp(-du))$, with a_i being response coefficient factor; the term $1 - exp(-du)$ describes the chemotherapy fractional cell control factor, the amount of the drug as function of time is u, and the constant d represents the intensity of the drug. The kinetics of the drug can be expressed as

$$\frac{du(t)}{dt} = v(t) - ku(t),$$

where $v(t)$ is a function of time which represents the drug intervention term, and k is the per capita decay rate.

This work will investigate two cases. First, we will consider the phase where the drug is no longer injected, $v(t) = 0$. In this case, u has the exponentially decaying behavior of $u(t) = u_0 exp(-kt)$ [26] with $u(0) = u_0$ being the initial concentration of the drug. Since the drug administration start with an impulsive drug dose, which means that we assume $u_0 > 0$.

In the second case, we will study the mode of the continuous injection of the drug $v(t) \neq 0$ is constant rate.

The full model is given as follows:

$$\begin{cases} \dfrac{dP(t)}{dt} = \underbrace{bP(t-\tau)}_{\text{exponential growth}} - \underbrace{r_P(N(t))P(t)}_{\text{to resting compartment}} + \underbrace{r_Q(N(t))Q(t)}_{\text{from resting compartment}} - \underbrace{a_1(1 - exp(-k_1u))P(t)}_{\text{destroyed by drug}} \\ \dfrac{dQ(t)}{dt} = \underbrace{r_P(N(t))P(t)}_{\text{from proliferating compartment}} - \underbrace{r_Q(N(t)Q(t)}_{\text{to proliferating compartment}} - \underbrace{\mu_Q Q(t)}_{\text{natural death}} - \underbrace{a_2(1 - exp(-k_2u))Q(t)}_{\text{destroyed by drug}} \\ \left[\dfrac{du}{dt}\right](t) = \underbrace{v(t)}_{\text{drug intervention term}} - \underbrace{ku(t)}_{\text{decay of drug}} \\ N(t) = \underbrace{P(t) + Q(t),}_{\text{total number of cancerous cells}} \end{cases} \tag{2}$$

with initial conditions

$$P(s) = \phi(s), \quad s \in [-\tau, 0], \quad Q(0) = Q_0, \quad u(0) = u_0.$$

3. Model without drug intervention term

At first, we consider the case where the drug is losing its strength exponentially, which corresponds, in model (2), to the case without the presence of drug intervention term (i.e., $v(t) = 0$). We start by determining the steady state of the following:

$$\begin{cases} \dfrac{dP(t)}{dt} = bP(t-\tau) - r_P(N(t))P(t) + r_Q(N(t))Q(t) - a_1(1 - exp(-k_1u))P(t) \\ \dfrac{dQ(t)}{dt} = r_P(N(t))P(t) - (\mu_Q + r_Q(N(t))Q(t) - a_2(1 - exp(-k_2u))Q(t) \\ \left[\dfrac{du}{dt}\right](t) = -ku(t) \\ N(t) = P(t) + Q(t). \end{cases} \tag{3}$$

At the equilibrium, we have $u = 0$ and

$$\begin{cases} bP - r_P(N)P + r_Q(N)Q = 0 \\ r_P(N)P - (\mu_Q + r_Q(N)Q = 0. \end{cases} \tag{4}$$

We consider the system (3), and define the functions f and g: $\mathbb{R}^+ \longrightarrow \mathbb{R}$ by

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

and

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

We also consider the following hypothesizes:

(A_1) $f(0) < 0$
(NA_1) $f(0) > 0$
(A_2) $f(+\infty) > 0$
(A_3) $g(x) < 0$ for all $x \geq 0$.

We have the following result, the proof of which is similar to a result given in our previous study [24]. Therefore, we will give this theorem without proof.

Theorem 3.1. *(i) Under the hypothesis* **(NA_1)**, $E_0 = (0, 0, 0)$ *is the unique equilibrium point of system (3).*
(ii) Under the hypotheses **(A_1)** *and* **(A_2)**, *system (3) has a positive non trivial equilibrium point* $E^* = (P^*, Q^*, 0)$ *and the trivial equilibrium point* $E_0 = (0, 0, 0)$, *where* P^* *is the unique solution of equation* $f((1 + \frac{b}{\mu_Q})x) = 0$ *and* $Q^* = \frac{b}{\mu_Q}P^*$.

In order to study the stability of our model and determine necessary and sufficient conditions that guarantee the stability of the cancer-free steady state E_0 and endemic steady state E^*, we consider, as the first step, the model (3) without delay (i.e., $\tau = 0$). We begin with the stability of the steady state E_0.

By linearizing system (3) around the trivial steady state E_0, we obtain the associated characteristic equation

$$\Delta = [(\lambda - b + r_P(0))(\lambda + \mu_Q + r_Q(0)) + r_P(0)r_Q(0)](\lambda + k) = \left[\lambda^2 - \lambda g(0) + f(0) + 2r_P(0)r_Q(0)\right](\lambda + k). \tag{5}$$

Then the associated eigenvalues are given as follows:

$$\lambda_{1,2} = \frac{1}{2}(g(0) \pm \sqrt{g(0)^2 - 4f(0) - 8r_P(0)r_Q(0)}), \qquad \lambda_3 = -k.$$

It is easy to see that $r_P(0) > b$ implies $f(0) + r_P(0)r_Q(0) > 0$, which guarantees $\lambda_{1,2} < 0$ under the hypothesis **(A_3)**.

The condition of the local stability of cancer-free steady state E_0 shows that if the proliferation rate cancer cells b is smaller than the transition rates r_P, then the cancer will vanish.

For the stability of $E^* = (P^*, Q^*, 0)$, the corresponding characteristic equation is given by

$$(\lambda + k)(\lambda^2 + \lambda(-M - b + \mu_Q + L) - M\mu_Q - b(\mu_Q + L)) = 0,$$

where

$$M = -r_P(N^*) - r'_P(N^*)P^* + r'_Q(N^*)Q^* \tag{6}$$

and

$$L = r_Q(N^*) - r'_P(N^*)P^* + r'_Q(N^*)Q^*. \tag{7}$$

Since

$$-M - b + \mu_Q + L = -b + \mu_Q + r_P(N^*) + r_Q(N^*)$$

and

$$-\mu_Q M - b(\mu_Q + L) = (\mu_Q + b)(r'_P(N^*)P^* - r'_Q(N^*)Q^*) \quad (\text{because } f(N^*) = 0).$$

We deduce the corresponding eigenvalues as follows:

$$\lambda_{1,2} = \frac{-H \pm \sqrt{H^2 - 4K}}{2}$$

$$\lambda_3 = -k < 0,$$

with

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

and

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

As r_P is an increasing function (i.e., $r_P'(N^*) > 0$), and r_Q is a decreasing function (i.e., $r_Q'(N^*) < 0$); therefore, from hypothesis **(A_3)**, we deduce that $K > 0$, $H > 0$ and $\lambda_{1,2} < 0$ and the positive steady state E^* is asymptotically stable for $\tau = 0$.

It is easy to see that condition $b > r_P(0)$ implies condition **(A_1)**, i.e., the more the proliferation rate increases above the threshold of the initial transition rate from cancer to quiescent cells, the steady state E_0 becomes unstable. Moreover, condition **(A_3)** holds if $b \leq \mu_Q$, and if $b > \mu_Q$ then **(A_3)** is equivalent to the following inequality:

$$\frac{b-\mu_Q}{r_P(x)+r_Q(x)} < 1, \quad \text{for all} \quad x \geq 0.$$

This means that, if the proliferation rate of cancer is higher than the death rate of the quiescent cells, then there is a high transition rate between proliferating and quiescent cells, compare to the difference between proliferation rate of the cancer cells and death rate of the quiescent cells. Which would lead to stability of the coexistence steady state.

Now, we consider the model (3) with the presence of time delay $\tau > 0$. Since our goal is to study the condition of existence of cancer and to find the possible scenarios that lead to the persistence of cancer under possible advanced chemotherapy, we focus only on the study of the stability of coexistence steady state E^* with respect to time delay. We will not study the stability of the cancer-free equilibrium because from a disease management point of view it is irrelevant.

By linearizing system (3) around the non trivial steady state E^*, we obtain the following characteristic equation:

$$\Delta_0(\lambda,\tau) = (\lambda+k)(\lambda^2+p\lambda+r+(s\lambda+q)e^{-\lambda\tau}) = 0, \tag{8}$$

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

$$p = \mu_Q + r_P(N^*) + r_Q(N^*) = \mu_Q - M + L,\ s = -b,\ r = \mu_Q(r_P(N^*) + r_P'(N^*)P^* - r_Q'(N^*)Q^*) = -\mu_Q M.$$

Since the last computation of M and L is correct, we can write r in function of M and the results are the same in Section 4, and

$$q = -b(\mu_Q + r_Q(N^*) - r_P'(N^*)P^* + r_Q'(N^*)Q^*) = -b(\mu_Q + L).$$

As $k > 0$, the stability of the coexistence steady state E^* depends on the eigenvalues of the study of the following characteristic equation:

$$\Delta_1(\lambda,\tau) = \lambda^2+p\lambda+r+(s\lambda+q)e^{-\lambda\tau} = 0. \tag{9}$$

With the hypothesis

(A_4) : $0 < \frac{\mu_Q}{b} < \Phi(x,y)$. for all x, $y > 0$,

where the function $\Phi : \mathbb{R}^{+2} \longrightarrow [0,1[$ is defined by

$$\Phi(x,y) = \frac{r_P'(x+y)x - r_Q'(x+y)y}{2r_P(x+y) + r_P'(x+y)x - r_Q'(x+y)y}.$$

The stability analysis of this steady is similar to the one studied in [24] for the model without chemotherapy. Therefore, we state the following stability and switch stability result without proof.

Theorem 3.2. *Assume hypotheses* **(A_1), (A_2), (A_3)**, *and* **(A_4)** *and functions r_P (increasing function) and r_Q (decreasing function) are of class $\mathcal{C}^1$, then there exists a critical value τ_0 of the time delay, such that the non trivial steady state E^* is asymptotically stable for $\tau \in [0, \tau_0[$ and unstable for $\tau > \tau_0$, where*

$$\tau_0 = \frac{1}{\zeta_+}\arccos\left\{\frac{q(\zeta_+^2 - r) - ps\zeta_+^2}{s^2\zeta_+^2 + q^2}\right\} \tag{10}$$

and

$$\zeta_+^2 = \frac{1}{2}(s^2 - p^2 + 2r) + \frac{1}{2}[(s^2-p^2+2r)^2 - 4(r^2-q^2)]^{\frac{1}{2}}. \tag{11}$$

After proving the existence of Hopf bifurcation at τ_0, it is normal to investigate the existence of bifurcating branch of periodic solutions. In fact, we have the following result:

Theorem 3.3. *Assume hypotheses* **(A_1), (A_2), (A_3)**, *and* **(A_4)** *and the functions r_P and r_Q are of class $\mathcal{C}^1$.*

Then periodic oscillations occur when τ passes through the critical value τ_0 where τ_0 and ζ_+ are given in Eqs. (10) and (11), respectively.

Proof. By the translation $X = (p, q, w) = (P, Q, u) - E^*$ system (3) is written as an FDE in $C := C([-\tau, 0], \mathbb{R}^3)$ as

$$\dot{X}(t) = L(\tau)X_t + H(\tau, X_t), \tag{12}$$

where $L(\tau) : C \longrightarrow \mathbb{R}^3$ is the linear term and $H(\tau, X_t) : C \times \mathbb{R}^+ \longrightarrow \mathbb{R}^3$ the nonlinear term and are given as follows:

$$L(\tau)(\varphi) = \begin{pmatrix} b\varphi_1(-\tau) + (-r_P(N^*) - r_P'(N^*)P^* + r_Q'(N^*)Q^*)\varphi_1(0) \\ \quad +(r_Q(N^*) - r_P'(N^*)P^* + r_Q'(N^*)Q^*)\varphi_2(0) - a_1k_1P^*\varphi_3(0) \\ (r_P(N^*) + r_P'(N^*)P^* - r_Q'(N^*)Q^*)\varphi_1(0) \\ \quad -(\mu_Q + r_Q(N^*) - r_P'(N^*)P^* + r_Q'(N^*)Q^*)\varphi_2(0) - a_2k_2Q^*\varphi_3(0) - k\varphi_3(0) \end{pmatrix}$$

$$H(\varphi, \tau) = \begin{pmatrix} bP^* - r_P(\varphi_1(0) + \varphi_2(0) + N^*)(\varphi_1(0) + P^*) + r_Q(\varphi_1(0) + \varphi_2(0) + N^*)(\varphi_2(0) + Q^*) \\ \quad -(-r_P(N^*) - r_P'(N^*)P^* + r_Q'(N^*)Q^*)\varphi_1(0) - (r_Q(N^*) - r_P'(N^*)P^* + r_Q'(N^*)Q^*)\varphi_2(0) \\ \quad +a_1k_1P^*\varphi_3(0) - a_1(1 - \exp(-k_1\varphi_3(0)))(\varphi_1(0) + P^*) \\ r_P(\varphi_1(0) + \varphi_2(0) + N^*)(\varphi_1(0) + P^*) - (\mu_Q + r_Q(\varphi_1(0) + \varphi_2(0) + N^*))(\varphi_2(0) + Q^*) \\ \quad -(r_P(N^*) + r_P'(N^*)P^* - r_Q'(N^*)Q^*)\varphi_1(0) \\ \quad +(\mu_Q + r_Q(N^*) - r_P'(N^*)P^* + r_Q'(N^*)Q^*)\varphi_2(0) + a_2Q^*\varphi_3(0) \\ \quad +a_2k_2Q^*\varphi_3(0) - a_2(1 - \exp(-k_2\varphi_3(0)))(\varphi_2(0) + Q^*) \\ 0 \end{pmatrix}$$

where $N^* = P^* + Q^*$ and $\varphi = (\varphi_1, \varphi_2, \varphi_3) \in C$.

From the expression of H, we have

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

Since the second term on the right hand side of the characteristic Eq. (8) is the same as in [24]. Then we obtain the transversality condition, that is: $Re(\lambda)'_{\tau=\tau_0} \neq 0$. Therefore, from the Hopf bifurcation theorem, we deduce the result. □

Our finding shows the possibility of the coexistence steady state losing its stability, hence cancer cells enter to an oscillation phase, when cancer cells have a considerable delay to proliferate. In fact, we showed that there exists a threshold value of the delay of proliferation τ_0 after which cancer cells will have periodic oscillations. This indicates that if the cancer cells have longer cycle of proliferation, the chemotherapy does not have any effect on the cancer, even when the chemotherapy is targeting the quiescent cells as well. Therefore, if the chemotherapy has a negative effect on the proliferation process of the cancer cells, then that can lead to an even worse case scenario and lead to a phenomenon that was observed clinically in some tumor cancer patients. This phenomenon is called **Jeff's phenomenon** or **self regression of tumor**, where the tumor size starts to oscillate in an unsynchronized mode with the chemotherapy treatment [26,28,29].

It is important to notice that the case where the chemotherapy has no effect on the quiescent cells ($a_2 = 0$), the results are the same. In fact, our stability analysis show that the term a_2 does not show up in any of the previous characteristic equations. Therefore, targeting the quiescent cells does not change the outcome of the chemotherapy.

Next, we will be investigating the effect of the drug intervention term on the role of the chemotherapy on the cancer dynamic.

4. Model with drug intervention term

In this section, we consider the model (2) with a constant drug intervention term $\nu(t) = \nu = cnst > 0$

$$\begin{cases} \dfrac{dP(t)}{dt} = bP(t-\tau) - r_P(N(t))P(t) + r_Q(N(t))Q(t) - a_1(1 - e^{-k_1u})P(t) \\ \dfrac{dQ(t)}{dt} = r_P(N(t))P(t) - (\mu_Q + r_Q(N(t))Q(t) - a_2(1 - e^{-k_2u})Q(t) \\ \left[\dfrac{du}{dt}\right](t) = \nu(t) - ku(t) \\ N(t) = P(t) + Q(t). \end{cases} \tag{13}$$

In comparison to the previous case, the drug concentration will eventually vanish, with the drug concentration is above or equal to $\dfrac{\nu}{k}$.

$$bP - r_P(N)P + r_Q(N)Q - a_1\left(1 - \exp\left(-k_1\frac{\nu}{k}\right)\right)P = 0 \tag{14}$$

$$r_P(N)P - (\mu_Q + r_Q(N))Q - a_2\left(1 - \exp\left(-k_2\frac{v}{k}\right)\right)Q = 0, \tag{15}$$

which imply that

$$BP - r_P(N)P + r_Q(N)Q = 0 \tag{16}$$

$$r_P(N)P - (U + r_Q(N))Q = 0, \tag{17}$$

where

$$B = b - a_1\left(1 - \exp\left(-k_1\frac{v}{k}\right)\right) \tag{18}$$

and

$$U = \mu_Q + a_2\left(1 - \exp\left(-k_2\frac{v}{k}\right)\right). \tag{19}$$

Let us define the following functions:

$$F(x) = Ur_P(x) - B(U + r_Q(x))$$

and

$$G(x) = B - U - r_P(x) - r_Q(x).$$

and consider the hypotheses

(B_1) $F(0) < 0$
(NB_1) $F(0) > 0$
(B_2) $F(+\infty) > 0$
(B_3) $G(x) < 0$ for all $x \geq 0$.

The following result gives the existence of equilibrium points.

Theorem 4.1.

(i) *If the hypothesis* **(NB_1)** *holds, then the cancer free steady state* $E_0 = (0, 0, \frac{v}{k})$ *is the unique steady state of (13).*
(ii) *If the hypotheses* **(B_1)** *and* **(B_2)** *hold, then system (13) has a positive non trivial coexistence steady state* $E_1 = (P_1, Q_1, \frac{v}{k})$ *and cancer free steady state* $E_0 = (0, 0, \frac{v}{k})$ *; where* P_1 *is the unique solution of equation* $F((1 + \frac{B}{U})x) = 0$ *and* $Q_1 = \frac{B}{U}P_1$.

Proof. The addition of Eqs. (16) and (17) result in

$$Q = \frac{B}{U}P,$$

and by replacing Q in Eq. (16), we obtain

$$BP - r_P\left(\left(1 + \frac{B}{U}\right)P\right)P + r_Q\left(\left(1 + \frac{B}{U}\right)P\right)\frac{B}{U}P = 0.$$

That implies that

$$Ur_P\left(\left(1 + \frac{B}{U}\right)P\right) - B\left(U + r_Q\left(\left(1 + \frac{B}{U}\right)P\right)\right) = 0.$$

Let $x = (1 + \frac{B}{U})P$, then we have $F(x) = Ur_P(x) - B(U + r_Q(x)) = 0$.

From the derivative of F we have

$$F'(x) = Ur_P'(x) - Br_Q'(x).$$

As r_P is an increasing function and r_Q is a decreasing function, we conclude that if $B > 0$, which is equivalent to $b > a_1(1 - exp(-k_1u_1))$, then F is an increasing function on $]0, +\infty[$.

Therefore, from the hypotheses **(B_1)** and **(B_2)**, F has only one positive zero solution $x_1 = (1 + \frac{B}{U})P_1$, and system (13) has two equilibrium points $E_0 = (0, 0, \frac{v}{k})$ and $E_1 = (P_1, Q_1, \frac{v}{k})$.

In the case of the hypothesis **(NB_1)**, system (13) has only the trivial equilibrium point $E_0 = (0, 0, \frac{v}{k})$.

Now, our goal is to examine the effect of the drug treatment on the persistence of cancer cells. For this purpose, we investigate the stability of our steady states in the absence of the delay. For this, let us now consider model (13) without the presence of the delay and study the stability of the two equilibrium points.

To study the stability of E_0, we linearize system (13) around the healthy steady state E_0, and we obtain the corresponding characteristic equation

$$\Delta_2 = (\lambda + k)[(\lambda - B + r_P(0))(\lambda + U + r_Q(0)) + r_P(0)r_Q(0)] = 0 \tag{20}$$

and the corresponding eigenvalue are given by

$$\lambda_1 = -k,\ \lambda_{2,3} = \frac{1}{2}(G(0) \pm \sqrt{G(0)^2 - 4F(0) - 8r_P(0)r_Q(0)}).$$

Since λ_1 and λ_3 are negative, then the stability of E_0 is deduced from the signs of λ_2. In fact, from (18) it is easy to see that $\lambda_2 < 0$ if $\frac{b}{a_1(1-\exp(-k_1\frac{v}{k}))} < r_P(0)$, which implies that E_0 is locally asymptotically stable.

It is worth to see that the condition $\frac{b-r_P(0)}{a_1(1-\exp(-k_1\frac{v}{k}))} < 1$ represents the possibility of the clearing of the infection as $\frac{v}{k}$ or drug intensity increases. Of course, this could be problematic because these values can lead to the toxicity and the intolerance of the patient to the drug if they are above the normal value defined by the chemotherapy treatment protocols.

Next, we study the stability of the coexistence steady state $E_1 = (P_1, Q_1, u_1 = \frac{v}{k})$, by linearizing system (13) around the steady state E_1, we obtain the following characteristic matrix:

$$\begin{pmatrix} B+M & L & -k_1a_1\exp(-k_1u_1)P_1 \\ -M & -(U+L) & -k_2a_2\exp(-k_2u_1)Q_1 \\ 0 & 0 & -k \end{pmatrix}$$

where M and L are given in Eqs. (6) and (7), respectively. The corresponding characteristic equation is similar to the characteristic equation obtained for E_1 in system (3) by replacing the quantity b by B and the quantity μ_Q by U.

In the case of non zero delay $\tau > 0$, where the system is defined as follows:

$$\begin{cases} \dfrac{dP(t)}{dt} = bP(t-\tau) - r_P(N(t))P(t) + r_Q(N(t))Q(t) - a_1(1-exp(-k_1u))P(t) \\ \dfrac{dQ(t)}{dt} = r_P(N(t))P(t) - (\mu_Q + r_Q(N(t))Q(t) - a_2(1-exp(-k_2u))Q(t) \\ \left[\dfrac{du}{dt}\right](t) = v(t) - ku(t) \\ N(t) = P(t) + Q(t). \end{cases} \tag{21}$$

By linearizing the system (21) around the coexistence steady state E_1, we obtain the following characteristic equation:

$$\Delta_3 = det\begin{pmatrix} \lambda - be^{-\lambda\tau} - (B-b) - M & -L & k_1a_1\exp(-k_1u_1)P_1 \\ M & \lambda+U+L & k_2a_2\exp(-k_2u_1)Q_1 \\ 0 & 0 & \lambda+k \end{pmatrix} = 0$$

which is

$$\Delta_3(\lambda,\tau) = (\lambda+k)(\lambda^2 + p_1\lambda + r_1 + (s_1\lambda + q_1)e^{-\lambda\tau}) = 0, \tag{22}$$

where p_1, s_1, r_1, and q_1 have the following expressions:

$$p_1 = U - (B-b) + r_P(N_1) + r_Q(N_1),\ s_1 = -b,\ q_1 = -b(U+L) \text{ and } r_1 = -(B-b)(U+L) - UM.$$

□

In this section, we consider the following notation as in the last section $p_1 = p$, $s_1 = s$, $q_1 = q$ and $r_1 = r$.

To obtain the switch of stability, one needs to find a purely imaginary root of the following equation:

$$\Delta_4(\lambda,\tau) = \lambda^2 + p\lambda + r + (s\lambda + q)e^{-\lambda\tau} = 0. \tag{23}$$

Let $\lambda = i\zeta$, replacing in Eq. (23) and separating the real and imaginary roots, we obtain

$$\begin{cases} -\zeta^2 + r = -q\cos(\tau\zeta) + s\zeta\sin(\tau\zeta) \\ \text{and} \\ p\zeta = -s\zeta\cos(\tau\zeta) - q\sin(\tau\zeta). \end{cases} \tag{24}$$

It follows that ζ satisfies

$$\zeta^4 - (s^2 - p^2 + 2r)\zeta^2 + (r^2 - q^2) = 0. \tag{25}$$

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

$$\zeta^2 = \frac{1}{2}(s^2 - p^2 + 2r) \pm \frac{1}{2}[(s^2 - p^2 + 2r)^2 - 4(r^2 - q^2)]^{\frac{1}{2}}. \tag{26}$$

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

From the expressions of r and q and the monotonicity property of the functions r_P and r_P, we have

$$r+q=(U+B)(r_P^{'}(N_1)P_1-r_Q^{'}(N_1)Q_1)>0.$$

Let us consider the following hypothesis:

($\mathbf{B_4}$) : $0<\frac{U}{B}<\Psi(x,y)$ for all $x,y>0$,

where the function $\Psi:\mathbb{R}^{+2}\longrightarrow[0,1[$ is defined by

$$\Psi(x,y)=\frac{r_P^{'}(x+y)x-r_Q^{'}(x+y)y}{2r_P(x+y)+r_P^{'}(x+y)x-r_Q^{'}(x+y)y}.$$

From the hypothesis **($\mathbf{B_4}$)**, we have

$$r-q=2Ur_P(N_1)+(U-B)(r_P^{'}(N_1)P_1-r_Q^{'}(N_1)Q_1)<0.$$

Then

$$r^2-q^2<0.$$

As $p+s>0$ and $q+r>0$, the unique solution of Eq. (23) has the following form:

$$\zeta_c^2=\frac{1}{2}(s^2-p^2+2r)+\frac{1}{2}[(s^2-p^2+2r)^2-4(r^2-q^2)]^{\frac{1}{2}} \tag{27}$$

and there exists a unique critical value of the time delay

$$\tau_c=\zeta_c^{-1}\arccos\left\{\frac{q(\zeta_c^2-r)-ps\zeta_c^2}{s^2\zeta_c^2+q^2}\right\}. \tag{28}$$

Then we have the following result of switch stability of the coexistence steady state E_1.

Theorem 4.2. *Assume the hypotheses* **($\mathbf{B_1}$), ($\mathbf{B_2}$), ($\mathbf{B_3}$)** *and* **($\mathbf{B_4}$)** *and the functions r_P (increasing function) and r_Q (decreasing function) are of class $\mathcal{C}^1$. Then there exists a critical value τ_c of the time delay, such that all roots of the characteristic equation (22) have negative real parts and the coexistence steady state E_1 is asymptotically stable for $\tau\in[0,\tau_c[$, when $\tau=\tau_c$ the characteristic equation (22) has a pair of purely imaginary roots $\pm i\zeta_c$, and when $\tau>\tau_c$ the characteristic equation (22) has at least one root with positive real part and the coexistence steady state E_1 is unstable, where ζ_c and τ_c are given in Eqs. (27) and (28), respectively.*

Remark 4.1. From hypothesis **($\mathbf{B_4}$)**, Ψ is a continuous function if and only if the transitions rates r_P and r_Q are of class $\mathcal{C}^1$. As the function r_P is increasing and r_Q is decreasing, then the function Ψ is a bounded function (i.e., $0<\Psi<1$), and hypothesis **($\mathbf{B_4}$)** is realistic because $0<U<B$ implies that $b>a_1(1-exp(-k_1u_1))+a_2(1-exp(-k_2u_1))+\mu_Q$, which means there is non extinction of the population of tumoral tissue but there is a decrease in death rates and the regression of the tumor size.

The following result gives the existence of the branch of periodic solutions bifurcating from the coexistence steady state E_1 of system (13).

Theorem 4.3. *Assume the hypotheses* **($\mathbf{B_1}$), ($\mathbf{B_2}$), ($\mathbf{B_3}$)** *and* **($\mathbf{B_4}$)** *and the functions r_P and r_Q are of class $\mathcal{C}^1$.*

Then system (21) has a Hopf bifurcation at $\tau=\tau_c$ (i.e., periodic oscillations may occur around the coexistence steady state E_1).

Proof. We prove this theorem using a very well known result of the formulation of the Hopf bifurcation theorem for retarded differential equations by Hale and Verduyn Lunel [30]. In fact, by the translation $z = (z_1, z_2, z_3) = (P, Q, u) - E_1$, system (2) is written as an FDE in $C := C([-\tau, 0], \mathbb{R}^3)$ as

$$\dot{z}(t) = L_1(\tau) z_t + H_1(\tau, z_t) \tag{29}$$

where $L_1(\tau) : C \longrightarrow \mathbb{R}^3$ is the linear part and $H_1(\tau, z_t) : C \times \mathbb{R}^+ \longrightarrow \mathbb{R}^3$ are given as follows:

$$L_1(\tau)(\varphi) = \begin{pmatrix} b\varphi_1(-\tau) + (-r_P(N_1) - r_P'(N_1)P_1 + r_Q'(N_1)Q_1)\varphi_1(0) \\ \quad +(r_Q(N_1) - r_P'(N_1)P_1 + r_Q'(N_1)Q_1)\varphi_2(0) - a_1k_1P_1\varphi_3(0) \\ \quad -a_1(1 - \exp(-k_1u_1))(\varphi_1(0) + P_1) \\ (r_P(N_1) + r_P'(N_1)P_1 - r_Q'(N_1)Q_1)\varphi_1(0) \\ \quad -(\mu_Q + r_Q(N_1) - r_P'(N_1)P_1 + r_Q'(N_1)Q_1)\varphi_2(0) - a_2k_2Q_1\varphi_3(0) \\ -a_2(1 - \exp(-k_2u_1))(\varphi_2(0) + Q_1) \\ \qquad -k\varphi_3(0) \end{pmatrix}$$

$$H_1(\varphi, \tau) = \begin{pmatrix} bP_1 - r_P(\varphi_1(0) + \varphi_2(0) + N_1)(\varphi_1(0) + P_1) \\ \quad +r_Q(\varphi_1(0) + \varphi_2(0) + N_1)(\varphi_2(0) + Q_1) - (-r_P(N_1) - r_P'(N_1)P_1 + r_Q'(N_1)Q_1)\varphi_1(0) \\ \quad -(r_Q(N_1) - r_P'(N_1)P_1 + r_Q'(N_1)Q_1)\varphi_2(0) + a_1k_1P_1\varphi_3(0) - a_1(1 - \exp(-k_1\varphi_3(0)))(\varphi_1(0) + P_1) \\ \quad +a_1(1 - \exp(-k_1u_1))(\varphi_1(0)+_1) \\ r_P(\varphi_1(0) + \varphi_2(0) + N_1)(\varphi_1(0) + P_1) - (\mu_Q + r_Q(\varphi_1(0) + \varphi_2(0) + N_1))(\varphi_2(0) + Q_1) \\ -(r_P(N_1) + r_P'(N_1)P_1 - r_Q'(N_1)Q_1)\varphi_1(0) + (\mu_Q + r_Q(N_1) - r_P'(N_1)P_1 + r_Q'(N_1)Q_1)\varphi_2(0) + a_2Q_1\varphi_3(0) \\ +a_2k_2Q_1\varphi_3(0) - a_2(1 - \exp(-k_2\varphi_3(0)))(\varphi_2(0) + Q_1) + a_2(1 - \exp(-k_2u_1))(\varphi_2(0) + Q^*) \\ \nu - ku_1 = 0 \end{pmatrix}$$

where $N^* = P^* + Q^*$ and $\varphi = (\varphi_1, \varphi_2, \varphi_3) \in C$. □

From the expression of H_1, we obtain

$$H_1(0, \tau) = 0 \qquad \text{and} \qquad \frac{\partial H_1(0, \tau)}{\partial \varphi} = 0, \text{ for all } \tau > 0.$$

Now, we need to verify the transversality condition.

From the continuity of the characteristic Eq. (22) and Theorem 4.2, we have

$$\Delta_3(\lambda(\tau), \tau) = 0, \text{ for } \tau \text{ in a neighborhood of } \tau_c$$

and

$$\lambda'(\tau) = -\frac{\partial \Delta_3(\lambda, \tau)/\partial \tau}{\partial \Delta_3(\lambda, \tau)/\partial \lambda}, \text{ for } \tau \text{ in a neighborhood of } \tau_c. \tag{30}$$

From the calculation of the real part of $\lambda'(\tau_c)$, we have

$$Re\lambda'(\tau_c) = \frac{p^2 + 2(\zeta_c^2 - r)}{(p - (\tau_c - 1)(\zeta_c^2 - r))^2 + (2\zeta_c + (\tau_c - 1)p\zeta_c)^2}.$$

From (27), we obtain

$$Re\lambda'(\tau_c) = \frac{s^2 + ((s^2 - p^2 + 2r)^2 - 4(r^2 - q^2))^{\frac{1}{2}}}{(p - (\tau_c - 1)(\zeta_c^2 - r))^2 + (2\zeta_c + (\tau_c - 1)p\zeta_c)^2} > 0.$$

In the previous case, where we considered the chemotherapy without the intervention term, we showed that regardless of the efficacy of the drug, there is a delay proliferation threshold of the cancer cells after which the model becomes unstable and the model goes to Hopf bifurcation and periodic orbits. This means that the high rate transition rate between the two cells type will not guarantee the stability of coexistence steady state if the drug has no effect on the cancer cell proliferation.

In this case, where the intervention term $\nu \neq 0$, the chemotherapy treatment has a direct effect on the possibility of having oscillatory behavior of our model. If fact, the critical value τ_c depends on the drug efficacy terms. This can be interpreted that the drug has a direct effect on the cancer cell proliferation and therefore on the control of the level of the newly cancerous cells. We also need to mention that the dependence of τ_c on the drug management is not clear cut and need more mathematical investigation.

5. Numerical simulation

In order to have numerical simulations of our results, we need to first estimate the parameters of our model. Although we are not modeling a specific cancer and our goal, in this study, is to investigate the possible effects and efficacy of a chemotherapy drug that would target both proliferating and quiescent cells for any type of cancer, we would like to illustrate the findings of our theoretical results by simulations using parameters of a specific cancer. The estimation of these parameters also has an uncertainty, depending on the person, stage of the cancer and other lurking variables.

Therefore, we made the choice to follow similar approach as [27] by using melanoma cancer data from the murine experimental studies [31] and the human clinical trials [32], as well as some parameters estimations using curve fitting from different papers [3,27,33–35]. On the other hand, due to of the lack of data, the parameter a_1 cannot be estimated. Therefore, we pick values to fit the conditions of our mathematical findings. The parameters estimations, with their units, are presented in the following table:

The choice of r_p and r_Q is made in a way to verify the conditions of our theoretical results. In fact, we suppose that r_P takes the form of Lotka–Volterra that is $r_P(x) = cx$ [36], and $r_Q(x)$ takes the form of the function of Hill that is $r_Q(x) = \frac{d}{1+x}$ [38].

First, using the parameters values cited in Table 1, with chemotherapy ($u \neq 0$) and without drug intervention term ($v = 0$), we show (see Fig. 1) the asymptotic stability of the coexistence steady state $E^* \simeq (1,\ 04 \times 10^8,\ 0.44 \times 10^8)$ for $\tau < \tau_0 = 0.52$ and becomes unstable for $\tau > \tau_0 = 0.52$. In Fig. 2, the existence of switch off stability for $\tau = \tau_0 = 0.52$ and this situation is not different in the case of without chemotherapy ($u = 0$). This shows the cancer is uncontrollable (to a steady state) if the delay of the proliferation of the cancer cells goes above the threshold τ_0. Moreover, we observe that without the drug intervention term the coexistence steady state and their stability conditions are the same as the case without treatment ($u = 0$), and there is no change in the total number of cancerous cells.

Table 1
Parameters estimation.

Parameters values	Values used	Unit	Source
b	4.31×10^{-1}	day^{-1}	[3,27]
τ	$0 - 2$	days	[3,27]
μ_Q	$0 - 1$	day^{-1}	[3,27]
k	$0.1 \times 10^{-2} - 1 \times 10^{-2}$	day^{-1}	[3,27]
v	$< v_{max} = 1$	mg/day	[34]
$a_{i=1,2}$	$0 - 1$	day^{-1}	[3,27]
c	6.41×10^{-11}	day^{-1}	[3,27,36]
d	$1.38 \times 10^8 - 0.5 \times 10^6$	cells kg^{-1}	[3]
$k_{i=1,2}$	$0.01 \times 10^{-2} - 1 \times 10^{-2}$	mg^{-1}	[3]
N_0	$3 \times 10^9 - 1 \times 10^{11}$	cells	[27]
u_0	$0.6 - 2.6$	gram	[3,11,37]
P_0	0.7×10^8	cells kg^{-1}	[37]
Q_0	2.87×10^8	cells kg^{-1}	[37]

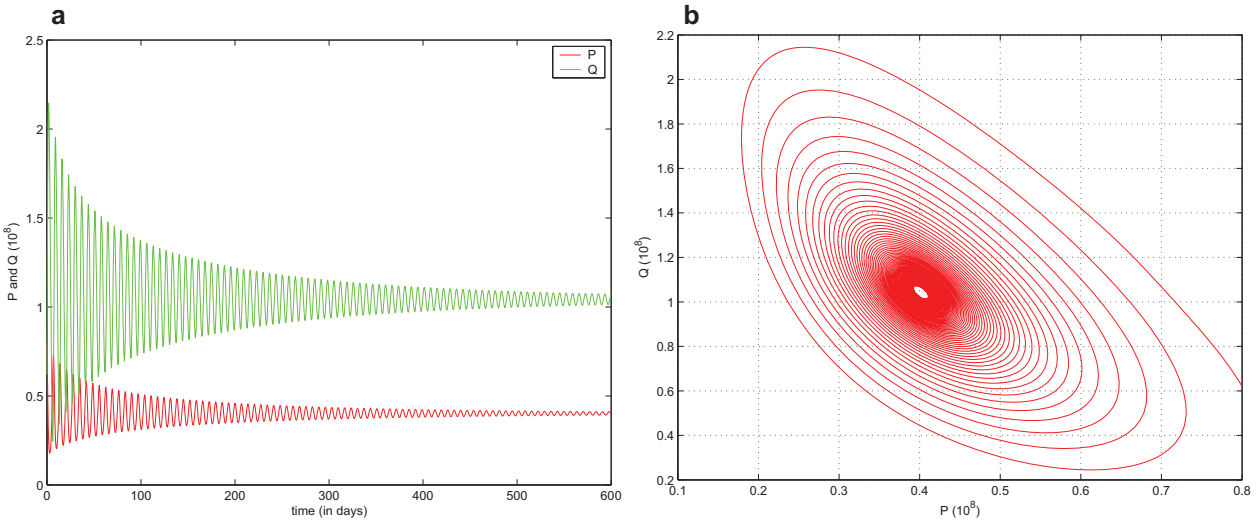

Fig. 1. Stability of the nontrivial steady state E^* for $\tau < \tau_0$, $v = 0$, we obtain the same phase portrait for $u = 0$ and $u \neq 0$.

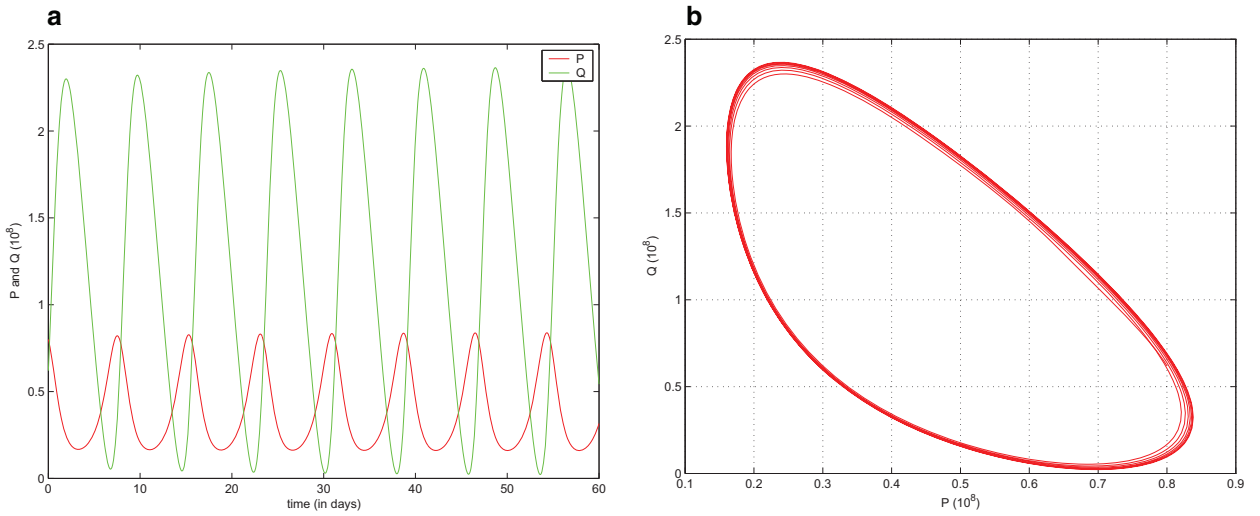

Fig. 2. The bifurcating periodic solution around the nontrivial steady state E^* for $\tau > \tau_0 = 0.52$, $\nu = 0$, we obtain the same phase portrait for $u = 0$ and $u \neq 0$.

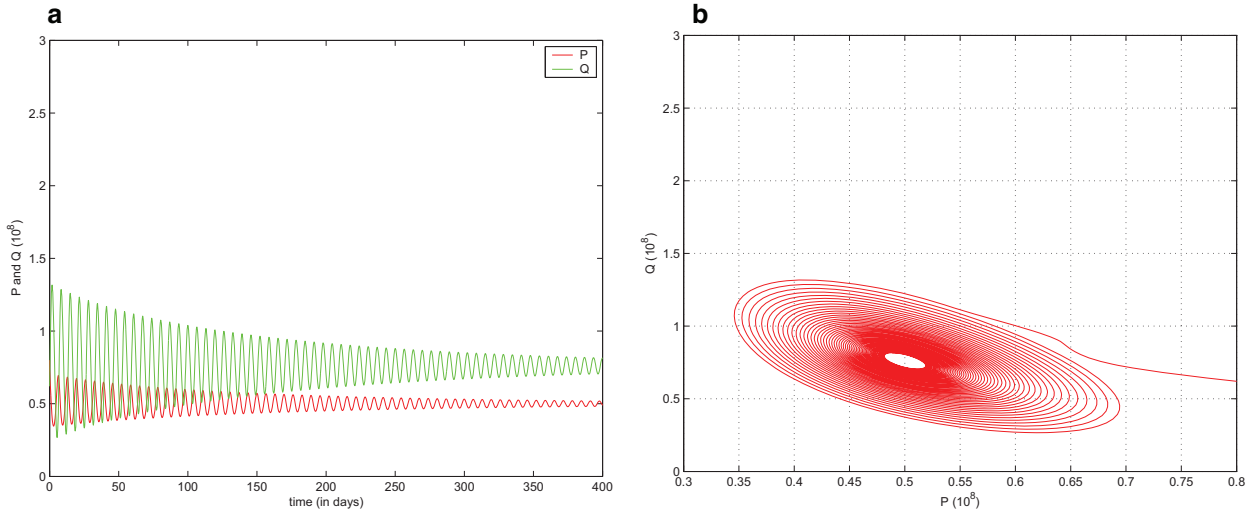

Fig. 3. The asymptotic stability of the nontrivial steady state E_1 for $\tau < \tau_c$, $\nu = 1$.

With drug intervention term with time delay ($\tau \neq 0$), there exists a unique steady state $E_1 \simeq (0.73 \times 10^8, 0.48 \times 10^8)$ that depends on the drug intervention term ν. This steady state is asymptotically stable for $\tau < \tau_c = 0.8$ (see, Fig. 3) (last remark of referee 2) and unstable for $\tau > \tau_c = 0.8$ and the existence of limit cycle at $\tau_c = 0.8$ (see, Figs. 4 and5) (last remark of referee 2). We observe that there is a decay in the total number of cancerous cells.

From this simulation, by introducing the intervention term, it becomes clear that the critical value of the delay is increased. This can be explained by a certain type of inverse dependence between the delay of the proliferation of cancer cells and the drug efficacy treatment.

By comparing the total size of cancer cells N in the cases with and without the drug intervention, as presented in Fig. 5, it becomes clear that the chemotherapy with intervention term helps to reduce N. More precisely, and as shown in Fig. 5(a), when we consider the model without drug intervention term, the total size of cancer cells is $N^* = 1.48 \times 10^8$ (red line) and the case when we consider the model with drug intervention term $N^* = 1.21 \times 10^8$ (green line) and there is a regression in the cancer.

On the other hand, the simulation showed that the oscillation occurs for $\nu = 0$ at $\tau_0 = 0.52$ (see Fig. 5(b) red line) and for $\nu \neq 0$ periodic oscillations occurs at $\tau_c = 0.8$ (green line, see Fig. 5(c)). Therefore, we claim that the increase of the intervention term can have a positive effect on the outcome of the cancer progress and can delay the occurrence of a situation such as the Jeff's phenomenon.

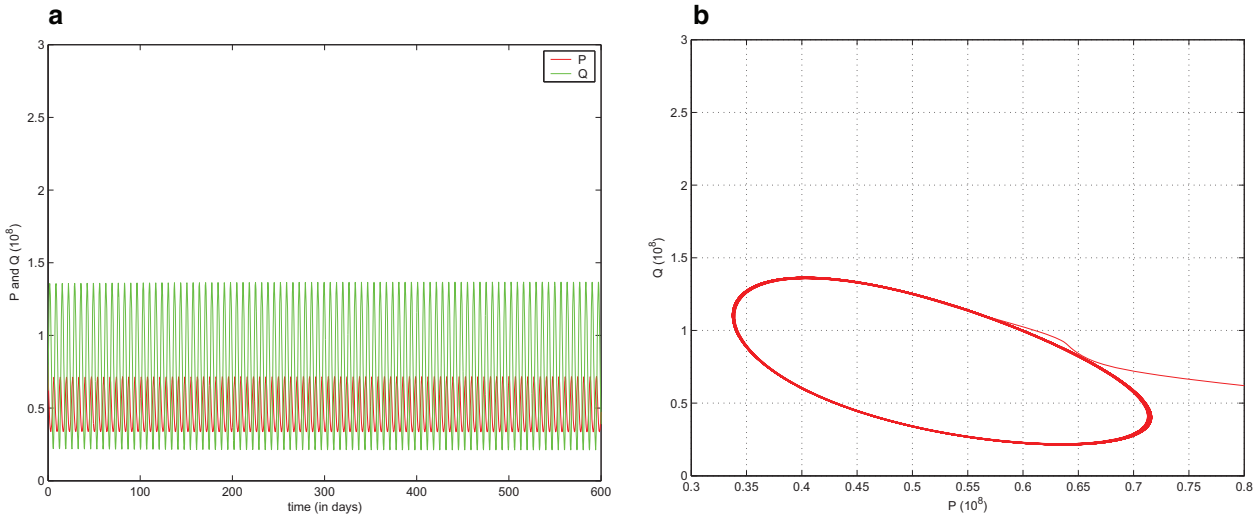

Fig. 4. Bifurcating periodic solution around the nontrivial steady state E_1 for $\tau > \tau_c = 0.8$, $\nu = 1$.

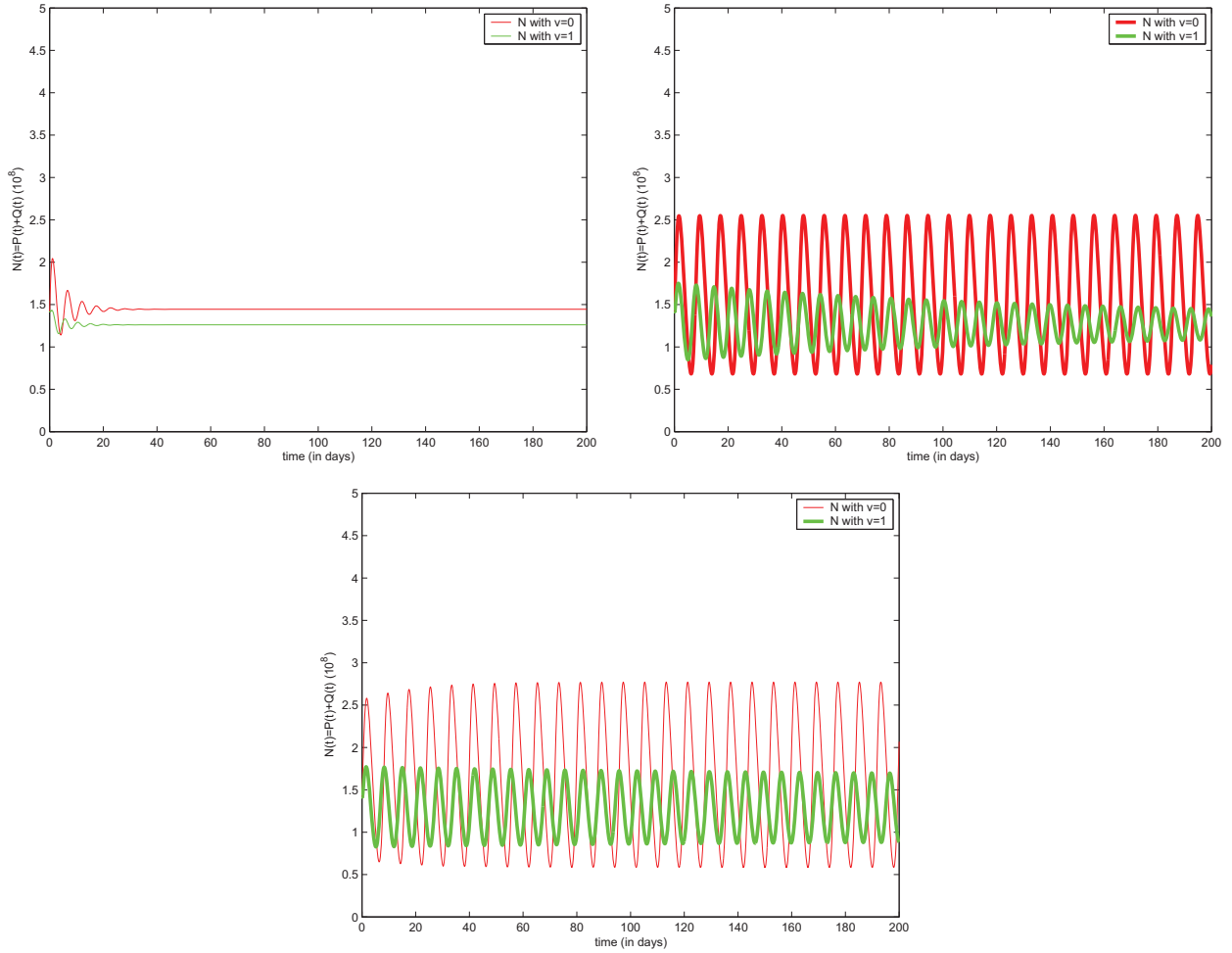

Fig. 5. Curves showing the stability and instability of steady states E^* and E_1 and periodic oscillations of the total number of cancerous cells $N(t)$ with and without intervention drug term. (For interpretation of the references to color in this figure text, the reader is referred to the web version of this article.)

6. Conclusion and discussions

In this work, we studied the possibility of having a chemotherapy treatment of a cancer that targets not only the proliferating cancer cells but also the quiescent cancer cells. This study is motivated by the possibility of the recurrence of the cancer after the chemotherapy treatment which is due to the transition from the quiescent stage to the proliferation stage and also by the recent findings of a new drug in Human acute myeloid leukemia that targets the quiescent cells [23] and the development of the new drugs combination that is effective also against the non mitotic cells [22].

Our model is an extension of our previous delay differential equations model presented in [24] by introducing the chemotherapy treatment in the two types of cancer cells and using a saturation term $1 - \exp(ku)$ that represents the drug fractional cell kill [27]. The dynamic of the chemotherapy treatment was introduced, with and without the intervention term, to examine the effect of the delay on the proliferation of the cancer cells. In difference to the work of Liu et al. [3] where the chemotherapy as assume to target the cells at M-phase and the immune response, our work did not consider the immune response instead, we focused on the possible effect of the chemotherapy on the G_0 phase.

The mathematical analysis of the model without the intervention term and without delay showed that the stability of the cancer free and coexistence steady states is similar to the case without treatment as it was presented in our work [24]. If the delay is none zero, the coexistence steady state is stable as far as the delay is below the critical value τ_0. At $\tau = \tau_0$ we showed that there is Hopf bifurcation and the system goes to the oscillatory behavior. It is worth to mention that the critical value τ_0 does not depend on the drug efficacy and the chemotherapy, in this case, is not beneficial to the patient regardless of which cell it is targeting.

When we introduced the intervention term in our model, the stability analysis of the model again showed the existence of Hopf bifurcation at $\tau = \tau_c$ and oscillation of the cancer and quiescent cells for $\tau > \tau_c$, but the critical delay value τ_c depended on the proportions of drugs which eliminate cancer cells. Our numerical simulation showed that $\tau_c > \tau_0$, which might indicate a possible indirect and negative effect of the chemotherapy on the proliferation of the cancer cells. We have to mention that the oscillation in the dynamic of cancer is a very well known aspect of the cancer treatment, and it is called Jeff's phenomenon, although it is not fully understood. There are no data that indicate the impact of this phenomenon of the dynamic of cancer, but our simulations showed the decay of the size of cancer in this case compare to the model without the drug intervention term. Therefore, it would be a normal step to study the critical delay value as function of the drug efficacy and find out the nature of this function. This study would shed some light on the clinical limitation (if any) in considering the chemotherapy that targets the quiescent cells.

One would be concerned with the level of toxicity for all types of cells including the immune cells, particularly the adaptive immune cells that play a crucial rule in eliminating the cancer cell. Liu et al. [3] had consider, in different context, the impact of the chemotherapy with the immune response . Hence, we should extend this model by including the adaptive immune cells. In addition, an optimal control study to achieve maximum efficacy and minimum toxicity would be needed.

Finally, it would be interesting to extend our work to the case where the chemotherapy is a pulse type function. This will help to consider the timing and dosage of the chemotherapy in a more realistic approach to the cancer treatment.

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