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Periodic Chemotherapy in Nonspecific Phase of a Hematopoietic Stem Cells Model with one Delay

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Abstract

We consider a model describing the dynamics of hematopoietic stem cells with periodic chemotherapy. The model is governed by a system of two nonautonomous ordinary differential equations with one delay. Its dynamics are studied in terms of local stability of the trivial steady state by using the Floquet theory. We illustrate our result by some numerical simulations. The existence of a periodic solution at a critical value of the delay is obtained numerically for some functional examples of periodic chemotherapy.

AMS Subject Classifications: 34K18, 34K60.
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1 Introduction

The population of hematopoietic stem cells (HSC) give rise to all of the differentiated elements of the blood: the white blood cells, red blood cells, and platelets, which may be either actively proliferating or in a resting phase. After entering the proliferating phase,

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a cell is committed to undergo cell division at a fixed later time τ. The generation time τ is assumed to consist of four phases, G_1 the pre-synthesis phase, S the DNA synthesis phase, G_2 the post-synthesis phase and M the mitotic phase. Just after the division, both daughter cells go into the resting phase called the G_0-phase. Once in this phase, they can either return to the proliferating phase and complete the cycle or die before ending the cycle. The (HSC) model that we consider is a classical G_0 model, see [15] and references therein. The full model for this situation consists of a pair of (age structured) reaction convection evolution equations with their associated boundary and initial conditions [10]. Using the method of characteristics [19], these equations can be transformed into a pair of nonlinear first-order differential delay equations, see [10, 12] and references cited therein,

$$\begin{cases} \dfrac{dN}{dt} = -\delta N - \beta(N)N + 2e^{-\gamma\tau}\beta(N_\tau)N_\tau, \\ \dfrac{dP}{dt} = -\gamma P + \beta(N)N - e^{-\gamma\tau}\beta(N_\tau)N_\tau, \end{cases} \tag{1.1}$$

where β is a monotone decreasing function of N which has the explicit form of a Hill function (see [10]) $\beta(N) = \beta_0 \dfrac{\theta^n}{\theta^n + N^n}$. The symbols in equation (1.1) have the following interpretation: N is the number of cells in nonproliferative phase, $N_\tau = N(t-\tau)$, P the number of cycling proliferating cells, γ the rate of cells loss from proliferative phase, δ the rate of cells loss from nonproliferative phase, τ the time spent in the proliferative phase, β the feedback function, rate of recruitment from nonproliferative phase, $\beta_0 > 0$ the maximal rate of reentry in the proliferating phase, $\theta \geq 0$ is the number of resting cells at which β has its maximum rate of change with respect to the resting phase population, $n > 0$ describes the sensitivity of reintroduction rate with changes in the population, and $e^{-\gamma\tau}$ accounts for the attenuation due to apoptosis (programmed cell death) at rate γ. The model (1.1) was intensively studied by many authors, see for example [10]. For numerical study, typical values of the parameters for humans are given by Mackey (1978) [10] as $\delta = 0.05d^{-1}$, $\beta_0 = 1.77d^{-1}$, $\tau = 2.2d$, and $n = 3$. The value of θ is 1.62×10^8 cells Kg^{-1}, but this is immaterial for dynamic considerations. For values of γ in the range $0.2d^{-1}$, the consequent steady state is unstable and there is a periodic solution whose period T at the bifurcation ranges from 20 to 40 days, see (Fowler and Mackey, 2002) [5]. In [10] the author proves that the stability of the non trivial steady state depend on the value of γ. When $\gamma = 0$, this steady state cannot be destabilized to produce dynamics characteristic of periodic hematopoiesis. On the other hand, for $\gamma > 0$, increase in γ lead to a decrease in the (HSC) numbers and a consequent decrease in the cellular efflux (given by δN) into the differentiated cell lines. This diminished efflux becomes unstable when a critical value of γ is reached, $\gamma = \gamma_1$, at which a supercritical Hopf bifurcation occurs. For all values of γ satisfying $\gamma_1 < \gamma < \gamma_2$, there is a periodic solution of the above model whose period is in good agreement with that seen in periodic hematopoiesis. At $\gamma = \gamma_2$, a reverse bifurcation occurs and greatly diminished (HSC) numbers as well as cellular efflux again become unstable. In [13],

authors numerically investigate the influence of each parameter (τ, δ, γ, β_0 and n) on the oscillation characteristics. In [12], authors consider the limiting case ($n = +\infty$) of the above model in order to compute an explicit solution, give an exact form of the period and the amplitude of oscillations. They illustrate these results numerically and show that the main parameters controlling the period are (τ, δ, γ, β_0 and n) mainly influence the amplitude. These authors consider $n = 12$ as a good approximation of high Hill coefficient for their numerical simulations. The Hill coefficient n is often regarded as a cooperativity coefficient, describing the number of agents (molecules, proteins or complexes) required to activate or deactivate a given process. If n is interpreted to be the number of ligand molecules required to active or deactivate a receptor site, then values of $n = 12$ or larger would not be biologically realistic. However, there are other situations in which cascade effects are known to create switch like phenomena [4]. In these circumstances, both experimental data and theoretical modelling suggest that the large values of n considered are quite realistic [12].

It is generally believed that normal and malignant cell population have different cell cycle times (Andersen and Mackey (2000) [1], Baserga (1981) [2]), and thus they will be described by different parameters in the above model. In particular, in untreated leukemic cells the apoptotic rate γ is significantly smaller than in normal cells (Palucka et al., (1999) [11]; Fukuma et al., (2000) [6]; Jones et al., (2000) [9]; Rasool et al., (2000) [14]), and the time τ spent in the proliferating phase is longer relative to normal cells in the bone morrow, see also (Andersen and Mackey 2001) [1].

In this paper, we consider model (1.1) with periodic chemotherapy, see [1]. The chemotherapy increases the apoptotic rate of cells in the proliferating phase P: that means $\gamma_1(t) = \gamma + \gamma_c(t)$. The parameter $\gamma_c(t)$ is the loss rate due to the chemotherapy with period w. To derive the system of model equation that includes the effect of non phase specific chemotherapy, note that the number of cells recruited from the non proliferating phase N and back into the cell cycle will, until division, obey

$$\frac{dN}{dt}(t) = -(\gamma + \gamma_c(t))N(t)$$

and integrating between $t - \tau$ and t the solution to this equation is given by

$$N(t) = N(t-\tau)\exp\left(-\gamma\tau - \int_{t-\tau}^{t} \gamma_c(s)ds\right). \tag{1.2}$$

The integral of γ_c represents the fact that all proliferative cells are affected by the history of γ_c from $t - \tau$ to time t. We consider the case when the delay is proportional to the period of chemotherapy and the case when the delay is very close to the proportional value of chemotherapy. Thus, when chemotherapy acts non specifically throughout the cell cycle (duration τ) the system of governing equations is given by (see [1]):

$$\begin{cases} \dfrac{dN}{dt} = -\delta N - \beta(N)N + 2e^{-\gamma\tau - \int_{t-\tau}^{t} \gamma_c(s)ds}\beta(N_\tau)N_\tau, \\ \dfrac{dP}{dt} = -\gamma_1(t)P + \beta(N)N - e^{-\gamma\tau - \int_{t-\tau}^{t} \gamma_c(s)ds}\beta(N_\tau)N_\tau. \end{cases} \tag{1.3}$$

The paper is organized as follows. In Section 2, we recall some results on Floquet multipliers. Section 3 is devoted to the stability analysis of the trivial steady state. In Section 4, we illustrate our results by numerical simulations. The existence of a periodic solution is obtained numerically for some functional examples of periodic chemotherapy, when the delay crosses some critical value of the delay. We end with a conclusion.

2 Preliminaries [8]

Consider the system

$$\frac{dx(t)}{dt} + \sum_{j=1}^{m} B_j x(t - k_j w) = 0, \tag{2.1}$$

where $B_j(t+w) = B_j(t)$ and $k_j \in \mathbb{N}$. One has that $\mu = e^{\lambda t}$ is a characteristic multiplier of equation (2.1) if, and only if, there is a nonzero n-vector $v(t) = v(t + w)$ such that $x(t) = v(t)e^{\lambda t}$ satisfies equation (2.1). Therefore,

$$\begin{cases} \dfrac{dv(t)}{dt} + \left(\lambda I + \displaystyle\sum_{j=1}^{m} B_j e^{-k_j w \lambda}\right) v(t) = 0, \\ v(t + w) = v(t). \end{cases} \tag{2.2}$$

If $V(t, \lambda)$ with $V(0, \lambda) = I$ is the principal matrix (see [8]) solution of equation $(2.2)_1$, then $v(t) = v(t, \lambda)v(0)$ and the initial value $v(0) \neq 0$ must be chosen in such a way that equation $(2.2)_2$ is satisfied. Because $v(0) \neq 0$ exists if, and only if, λ satisfies the characteristic equation

$$\det(V(w, \lambda) - I) = 0, \tag{2.3}$$

if all roots of the characteristic equation (2.3) have negative real parts, then the zero solution $x = 0$ of equation (2.1) is uniformly asymptotically stable.

3 Stability Analysis

Consider now the model (1.3) and the total size of stem cells $T(t) = N(t) + P(t)$. By addition of the two equations of system (1.3), we have

$$\begin{cases} \dfrac{dN}{dt} = -\delta N - \beta(N)N + 2e^{-\int_{t-\tau}^{t} \gamma_1(s)ds} \beta(N_\tau)N_\tau, \\ \dfrac{dT}{dt} = -\gamma_1(t)P(t) - \delta N(t) + e^{-\int_{t-\tau}^{t} \gamma_1(s)ds} \beta(N_\tau)N_\tau, \end{cases} \tag{3.1}$$

where $\gamma_1(t)P(t) + \delta N(t)$ is the total death rate. We consider that $\gamma_1(t)P(t) + \delta N(t) = \gamma_2(t)T(t)$ and $\gamma_2(t)$ is w-periodic. System (3.1) is written as follows:

$$\begin{cases} \dfrac{dN}{dt} = -\delta N - \beta(N)N + 2e^{-\int_{t-\tau}^{t}\gamma_1(s)ds}\beta(N_\tau)N_\tau, \\ \dfrac{dT}{dt} = -\gamma_2(t)T(t) + e^{-\int_{t-\tau}^{t}\gamma_1(s)ds}\beta(N_\tau)N_\tau. \end{cases} \tag{3.2}$$

Proposition 3.1. *Each solution of system* (3.2)*, with nonnegative initial conditions, is nonnegative.*

Proof. We follow the proof given in [3] for the autonomous case. Assume that there exists t_1 such that $N(t_1) = 0$ and $N(t) > 0$ for $t < t_1$. From equation $(3.2)_1$, we have

$$\frac{dN}{dt}(t_1) = 2e^{-\int_{t_1-\tau}^{t_1}\gamma_1(s)ds}\beta\left(N(t_1-\tau)\right)N(t_1-\tau) > 0.$$

Then $N(t) > 0$ for $t > 0$. Suppose that there exists $t_2 > 0$ such that $T(t_2) = 0$ and $T(t) > 0$ for $t < t_2$. From equation $(3.2)_2$, we have

$$\frac{dT}{dt}(t_2) = e^{-\int_{t_2-\tau}^{t_2}\gamma_1(s)ds}\beta(N(t_2-\tau))N(t_2-\tau) > 0.$$

We deduce that $T(t) > 0$ for $t > 0$. □

Proposition 3.2. *For every solution* $(N(t), T(t))$ *of* (3.2) *such that* $\lim_{t\to+\infty} N(t) = 0$*, we have* $\lim_{t\to+\infty} T(t) = 0$.

Proof. Let

$$m_1 = \inf_{t\in[0,w]} \gamma_1(t) \text{ and } M_1 = \sup_{t\in[0,w]} \gamma_1(t)$$

and

$$m_2 = \inf_{t\in[0,w]} \gamma_2(t) \text{ and } M_2 = \sup_{t\in[0,w]} \gamma_2(t).$$

As $\lim_{t\to+\infty} N(t) = 0$, there exists T_1 such that $N(t) < \varepsilon\dfrac{m_2 e^{m_1\tau}}{2\beta_0}$ for $t \geq T_1$. Using the variation of constant formula in equation $(3.2)_2$, we have

$$T(t) = e^{-\int_0^t \gamma_2(\sigma)d\sigma}T(0) + \int_0^t e^{-\int_s^t \gamma_2(\sigma)d\sigma}e^{-\int_{s-\tau}^{s}\gamma_1(\sigma)d\sigma}\beta(N(s-\tau))N(s-\tau)ds.$$

By boundedness, we have:

$$\begin{aligned} T(t) &\leq e^{-m_2 t}T(0) + e^{-m_1\tau}\int_0^t e^{-m_2(t-s)}\beta(N(s-\tau))N(s-\tau)ds \\ &\leq e^{-m_2 t}\left(T(0) + e^{-m_1\tau}\int_0^t e^{m_2 s}\beta(N(s-\tau))N(s-\tau)ds\right). \end{aligned}$$

Setting $\alpha = s - \tau$, we get:

$$T(t) \leq e^{-m_2 t}\left(T(0) + e^{(m_2-m_1)\tau}\int_{-\tau}^{t-\tau} e^{m_2\alpha}\beta(N(\alpha))N(\alpha)d\alpha\right).$$

For $t - \tau > T_1$,

$$T(t) \leq e^{-m_2 t}\left(T(0) + e^{(m_2-m_1)\tau}\int_{-\tau}^{T_1} e^{m_2\alpha}\beta(N(\alpha))N(\alpha)d\alpha\right) + e^{-m_2 t}e^{(m_2-m_1)\tau}\int_{T_1}^{t-\tau} e^{m_2\alpha}\beta(N(\alpha))N(\alpha)d\alpha.$$

As $T(t) > 0$ for $t > 0$ and β is bounded by β_0, we deduce that

$$\begin{aligned} T(t) &\leq e^{-m_2 t}\left(T(0) + e^{(m_2-m_1)\tau}\int_{-\tau}^{T_1} e^{m_2\alpha}\beta(N(\alpha))N(\alpha)d\alpha\right) \\ &\quad + \varepsilon\frac{m_2 e^{m_1\tau}}{2}e^{(m_2-m_1)\tau}e^{-m_2 t}\int_{T_1}^{t-\tau} e^{m_2\alpha}d\alpha \\ &\leq e^{-m_2 t}\left(T(0) + e^{(m_2-m_1)\tau}\int_{-\tau}^{T_1} e^{m_2\alpha}\beta(N(\alpha))N(\alpha)d\alpha\right) \\ &\quad + \varepsilon\frac{e^{m_1\tau}}{2}e^{(m_2-m_1)\tau}\left(e^{-m_2\tau} - e^{m_2(T_1-t)}\right) \\ &\leq e^{-m_2 t}\left(T(0) + e^{(m_2-m_1)\tau}\int_{-\tau}^{T_1} e^{m_2\alpha}\beta(N(\alpha))N(\alpha)d\alpha\right) + \frac{\varepsilon}{2}. \end{aligned}$$

Let $T_2 > 0$ such that

$$e^{-m_2 t}\left(T(0) + e^{(m_2-m_1)\tau}\int_{-\tau}^{T_1} e^{m_2\alpha}\beta(N(\alpha))N(\alpha)d\alpha\right) < \frac{\varepsilon}{2} \quad \text{for } t > T_2.$$

Then, for $t > \max(T_2, T_1 + \tau)$, we deduce that $T(t) < \varepsilon$ and

$$\lim_{t\to+\infty} T(t) = 0.$$

This concludes the proof. □

Corollary 3.3. *For every solution* $(N(t), P(t))$ *of* (1.3) *such that* $\lim_{t\to+\infty} N(t) = 0$*, we have* $\lim_{t\to+\infty} P(t) = 0$.

Proof. As $P(t) = T(t) - N(t)$, the proof follows from the last propositions. □

Remark 3.4. The stability of the trivial equilibrium point $(0, 0)$ of system (1.3) is deduced from the equation modelling the cells in the resting phase N.

Considering the model without treatment (1.1), by linearizing around the zero solution, the characteristic matrix is given by

$$\Delta(\lambda) = (\lambda + \gamma)(\lambda + \delta + \beta_0 - 2\beta_0 e^{-\gamma\tau - \lambda\tau}). \tag{3.3}$$

The trivial equilibrium of (1.1) is asymptotically stable if there are no solutions of $\Delta(\lambda) = 0$ with $Re(\lambda) \geq 0$ and this happens if, and only if, $2\beta_0 e^{-\gamma\tau} < \delta + \beta_0$.

Consider now the system $(1.3)_1$. The linearized equation around the zero solution is given by

$$\frac{dN}{dt} = -\delta N - \beta_0 N + 2\beta_0 e^{-\gamma\tau} f(t) N_\tau, \tag{3.4}$$

where $f(t) = e^{-\int_{t-\tau}^{t} \gamma_c(s)ds}$ is w-periodic. Suppose also that, for some $k \in \mathbb{N} - \{0\}$, $\tau = kw$. Then equation (3.4) is written as follows:

$$\frac{dN(t)}{dt} = B_0(t)N(t) + B_1(t)N(t - kw), \tag{3.5}$$

where $B_0 = -\delta - \beta_0$ and $B_1 = 2\beta_0 e^{-kw\gamma} f(t)$. To study the stability of the zero solution $(0, 0)$, let $N(t) = e^{\lambda t} v(t)$ with $v(t + w) = v(t)$, $\forall t \geq 0$. Then equation (3.5) becomes

$$\frac{dv(t)}{dt} = (-\lambda + B_0(t) + B_1(t)e^{-kw\lambda})v(t) \tag{3.6}$$

and the solution of equation (3.6) is given by

$$v(t) = e^{-\int_0^t (-\lambda + B_0(s) + B_1(s)e^{-kw\lambda})ds} v(0), \tag{3.7}$$

where $v(0) \neq 0$ is the initial value. The principal matrix is as follows:

$$V(t, \lambda) = e^{-\int_0^t (-\lambda + B_0(s) + B_1(s)e^{-kw\lambda})ds}$$

such that

$$V(0, \lambda) = I.$$

Then the characteristic equation is

$$\det(V(w, \lambda) - I) = 0. \tag{3.8}$$

To localize the characteristic exponents, one needs to solve the following equation:

$$\triangle = \lambda + \delta + \beta_0 - 2\beta_0 e^{-kw\gamma} e^{-kw\lambda} \frac{1}{w} \int_0^w f(s)ds = 0. \tag{3.9}$$

The following result states the uniform stability of the zero solution $(0, 0)$.

Theorem 3.5. *If*

$$\delta + \beta_0 > 2\beta_0 e^{-kw\gamma}\frac{1}{w}\int_0^t f(s)ds, \tag{H_1}$$

then the zero solution of (1.3) *is uniformly asymptotically stable.*

Proof. From equation (3.4) and [16–18], all roots of the characteristic equation (3.9) have negative real parts if, and only if, $\delta + \beta_0 > 2\beta_0 e^{-\gamma\tau}\frac{1}{w}\int_0^t f(s)ds$. Then the characteristic multipliers of equation (3.4) have modulus < 1. This implies that the zero solution of (1.3) is uniformly asymptotically stable. □

In what follows, we consider that $\tau > kw$ and $\tau - kw = r \ll \varepsilon$ is small enough. As before, let $N(t) = e^{\lambda t}v(t)$ with $v(t+w) = v(t)$, $\forall t \geq 0$. Then equation (3.4) becomes

$$\frac{dv_1(t)}{dt} = (-\lambda - \delta - \beta_0)\, v_1(t) + 2\beta_0 e^{-\gamma\tau}e^{-\lambda\tau}f(t)v_1(t-r). \tag{3.10}$$

As v is a continuous solution, by Taylor expansion we have $v(t-r) = v(t) + o(r)$. By neglecting the term $o(r)$, equation (3.10) is written as follows:

$$\frac{dv(t)}{dt} = \left(-\lambda - \delta - \beta_0 + 2\beta_0 e^{-\gamma\tau}e^{-\lambda\tau}f(t)\right)(t). \tag{3.11}$$

The monodromy matrix [7] is given by

$$A = e^{\int_0^w (-\lambda-\delta-\beta_0+2\beta_0 e^{-\gamma\tau}e^{-\lambda\tau}f(t))dt}.$$

The characteristic exponents are determined from the following equation:

$$\lambda + \delta + \beta_0 - 2\beta_0 e^{-\gamma\tau}e^{-\lambda\tau}\frac{1}{w}\int_0^w f(t)dt = 0. \tag{3.12}$$

Then, all roots of equation (3.12) have negative real part if, and only if,

$$\delta + \beta_0 - 2\beta_0 e^{-\gamma\tau}\frac{1}{w}\int_0^w f(t)dt > 0.$$

We have $\mid e^{\lambda} \mid < 1$ and we deduce that all roots of the monodromy matrix have modulus < 1 and we deduce that the zero solution $(0,0)$ of equation (3.11) is uniformly asymptotically stable and the same for equations (3.10) and (1.3) for the time delay $\tau \approx kw$. We deduce the following result.

Proposition 3.6. *If $\tau > kw$ and $\tau - kw = r \ll \varepsilon$ is small enough, then the zero solution* $(0,0)$ *of equation* (1.3) *is uniformly asymptotically stable if, and only if,*

$$\delta + \beta_0 - 2\beta_0 e^{-\gamma\tau}\frac{1}{w}\int_0^w f(t)dt > 0. \tag{H_2}$$

To obtain the switch of stability, one needs to find a purely imaginary root of equation (3.12). Replacing $\lambda = i\eta$ in equation (3.12) and by separating the real and imaginary parts, we have

$$\begin{cases} M - N(\tau)\cos(\eta\tau) = 0, \\ \eta + N(\tau)\sin(\eta\tau) = 0, \end{cases} \tag{3.13}$$

where $M = \delta + \beta_0$ and $N(\tau) = 2\beta_0 e^{-\gamma\tau}\dfrac{1}{w}\displaystyle\int_0^w f(t)dt$:

$$\begin{cases} \tau = \dfrac{1}{\eta}\arccos\left(-\dfrac{M}{N(\tau)}\right) \in (0,\pi) \quad \text{for } 0 \le \left|\dfrac{M}{N(\tau)}\right| \le 1, \\ \eta = \sqrt{N^2(\tau) - M^2} \quad \text{for } 0 \le \left|\dfrac{M}{N(\tau)}\right| < 1. \end{cases} \tag{3.14}$$

Then, we can deduce the following result of switched stability.

Corollary 3.7. *i) If* (H_2) *is satisfied and there is no purely imaginary root of equation* (3.12)*, then the zero solution* $(0,0)$ *of equation* (1.3) *is uniformly asymptotically stable for all* $\tau - kw = r \ll \varepsilon$ *small enough. ii) If* (H_2) *is not satisfied, then there exists a* τ_0 *for which the zero solutions* $(0,0)$ *of equation* (1.3) *loses the uniform asymptotic stability, where* τ_0 *is obtained by solving the following equations:* $\tau = \dfrac{1}{\eta}\arccos\left(-\dfrac{M}{N(\tau)}\right)$ *and* $\eta = \sqrt{N^2(\tau) - M^2}$.

4 Numerical Simulations

If (H_2) is not satisfied, then equation (3.12) has a purely imaginary root. In this case there exists a characteristic multiplier with modulus equal to 1 and one can look for the occurrence of the Neimarck–Sacker bifurcation. Here we prove the existence of a periodic solution at a critical value of the delay numerically, for a functional example of periodic chemotherapy. A theoretical analysis of the Neimarck–Sacker bifurcation is our aim in a forthcoming paper. With the parameters defined in the Introduction and by using the Matlab software (DDE Solver) and $\gamma_c(t) = \cos(t)$ 2π-periodic, we obtain the numerical results of Figures 4.1–4.3.

5 Conclusion

In 2001, Andersen and Mackey studied the system (1.1) which models the growth of normal and malignant cells by taking into account the resting phase G_0 [1]. In the same paper [1], the authors propose the model (1.3) describing the effect of periodic chemotherapy, proving that periodic chemotherapy can induce resonance under high cell kill rate. In our paper, we consider the same model with periodic chemotherapy. Under

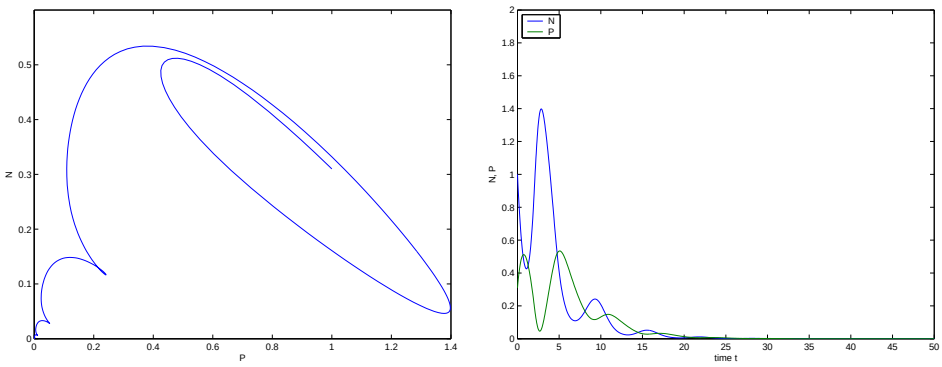

Figure 4.1: Stability of of the trivial equilibrium point $(0, 0)$ for $\tau = 2\pi$.

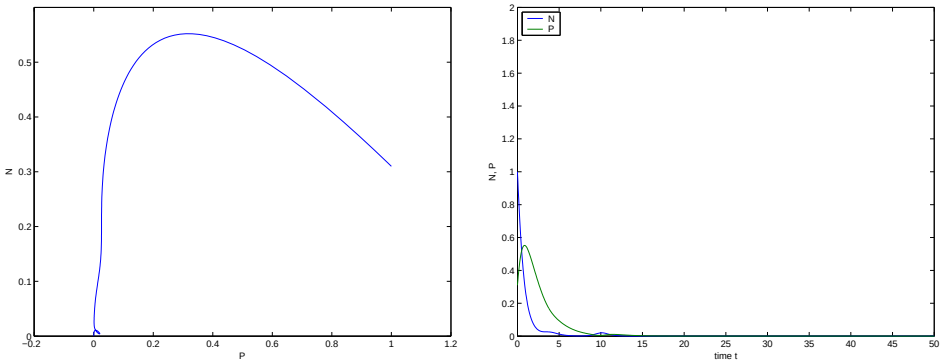

Figure 4.2: Stability of of the trivial equilibrium point $(0, 0)$ for $\tau - 2\pi = r = 0.05$.

certain conditions on the parameters values, we prove that the zero solution is uniformly asymptotically stable when the delay is proportional to the period of chemotherapy and when the delay is very close to the proportional value of period of chemotherapy. That implies that there is a decay of tumor size in the presence of chemotherapy and after some time the tumor disappears. By choosing the same parameter values introduced in [1], we give some numerical simulations of our result. For some functional example of periodic chemotherapy, we simulate numerically the existence of a periodic solution, which is called in biology Jeff's phenomenon, for some critical value of the delay.

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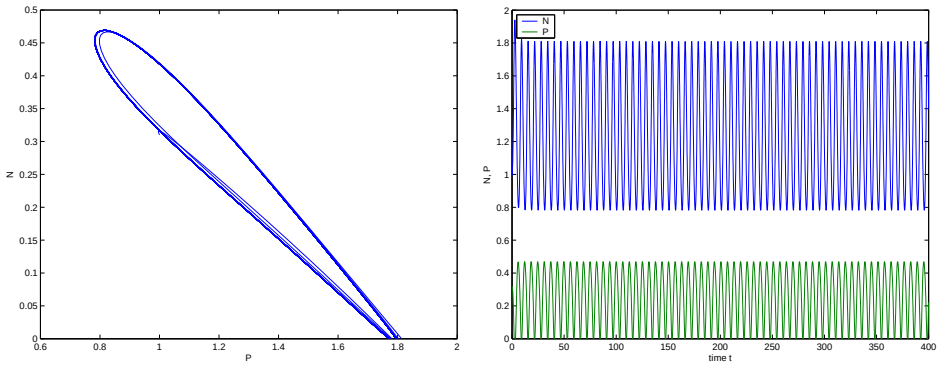

Figure 4.3: Periodic oscillations (Neimarck–Sacker bifurcation) for $\tau = \tau_0$.

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