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STABILITY AND INSTABILITY INDUCED BY TIME DELAY IN AN ERYTHROPOIESIS MODEL

Mostafa Adimy and Fabien Crauste

Abstract. We study a mathematical model of erythropoiesis, that is the production of blood cells under the influence of the hormone erythropoietin. Our model consists in a system of two nonlinear delay differential equations, with the cell cycle duration as the delay. We study the local asymptotic stability of the equilibria by using the characteristic equation of the model and we show the existence of a local Hopf bifurcation.

Keywords: blood production system, erythropoietin, delay differential equation, local asymptotic stability, Hopf bifurcation.

AMS classification: 92B05, 34K99, 34K13.

§1. Introduction

Biological phenomena occurring in human body, such as breathing, glucose/insulin regulation, etc., involve complex behaviors (we refer to the book by Mackey and Glass [9] for further details). Amongst these behaviors, oscillations, bifurcations and chaos are often observed in biological processes.

Blood production system is one of the complex processes involved in the living. It takes place in the bone marrow where pluripotent stem cells, the more immature cells, give birth, throughout a series of division, to committed stem cells (white or red blood cells, platelets). These cells finally divide in mature blood cells which enter the bloodstream.

Blood production has been studied mathematically since the end of the seventies. Mackey [8], in 1978, proposed the first, to our knowledge, model of blood production. His model consists in a system of two delay differential equations, where the delay corresponds to the cell cycle duration. It has been studied more recently by Adimy and Pujo-Menjouet [3, 4], Adimy and Crauste [2] and Pujo-Menjouet et al [11, 12]. In [12], the authors showed the existence of a local Hopf bifurcation in the model of Mackey [8].

It is now well known that the production of blood cells is regulated by negative feedback controls, mediated by hormones. However, the exact nature of these regulatory processes is still not well known at this time. Amongst the hormones acting on blood production, some are of main importance. This is the case of erythropoietin, usually known as Epo, a glycoprotein hormone produced mainly in the kidney. What we call erythropoiesis is the production of blood

cells (especially red blood cells) under the action of the hormone Epo. Erythropoietin acts as a growth factor on blood cells. In fact, the concentration of Epo reacts to changes in oxygen concentration in bloodstream. For example, a decrease in the concentration of oxygen (which may be due to bleeding or moving to high altitudes) leads to a release of erythropoietin. The control of Epo on blood production system triggers the production of blood cells, by acting on pluripotent stem cells (see Adamson [1]). These cells divide and increase the production of mature blood cells. By the same way, when the concentration of blood cells is too high (which means that a lot of oxygen is carried by mature blood cells), then the negative feedback acts on the concentration of erythropoietin to decrease the production of the hormone.

A mathematical model of erythropoiesis has been proposed by Belair et al [5] in 1995 and studied by Mahaffy et al [10] in 1998. Their model consists in a system of partial differential equations which reduce to a system of two delay differential equations. Reaction to bleeding and stability of the equilibria of the model have been studied.

In this paper, we propose a new model of erythropoiesis. It consists in a system of two nonlinear delay differential equations, describing the production of blood stem cells in the bone marrow and the evolution of the Epo concentration (see Equations (2) and (3)). The stem cells production is modelled by a positive function of the population density and the Epo concentration, decreasing with respect to the cellular population and increasing with respect to the hormone concentration. The negative feedback control on Epo is given by a monotone decreasing function of the cellular population. In the next section, we present the model and we study the existence of equilibria. In Section 3, we study the local asymptotic stability of these equilibria. In particular, we show the existence of a local Hopf bifurcation, with the delay as the bifurcation parameter.

§2. The Model

Denote by $N(t)$ the total population density (cells/kg) of stem cells. In fact, stem cells can be either proliferating or quiescent [6], and $N(t)$ denotes the population of resting cells (also known as G_0 -cells). Proliferating cells are cells actually in the cell cycle: they divide a time τ after their entrance in two daughter cells. Contrary to proliferating cells, G_0 -cells are in a quiescent stage. They can differentiate in blood cells, which enter the bloodstream, or be introduced in the proliferating phase. We denote by $\delta \geq 0$ the rate of disappearance of G_0 -cells, which also includes the natural mortality. Resting cells represent the major part of the stem cell population (about 95% of the stem cell population) and their behavior influence the behavior of the entire population. This has already be noticed by Mackey [8], Pujo-Menjouet et al [11, 12] and Adimy and Crauste [2]. We refer to these works for further details.

Denote by $E(t)$ the erythropoietin concentration (mL/mU) at time t . The production rate of the hormone erythropoietin (Epo) is controlled by a negative feedback, induced by the stem cell population $N(t)$, denoted by f . Typically, the function f is a monotone decreasing Hill function,

$$f(N) = \frac{a}{1 + KN^r}, \quad (1)$$

often used in enzyme kinetics (see [5]). The parameters $a > 0$, $K > 0$ and $r > 0$ are deduced from experimental data.

The system we consider in this paper is

$$\frac{dN}{dt}(t) = -\delta N(t) + g(N(t-\tau), E(t-\tau))N(t-\tau), \quad (2)$$

$$\frac{dE}{dt}(t) = -kE(t) + f(N(t)), \quad (3)$$

where $\tau \geq 0$ is the cell cycle duration (or equivalently the length of the proliferating phase) and $k > 0$ is the disappearance rate of the hormone Epo. The term $g(N, E)$ controls the production of stem cells under the action of Epo. It is an increasing function of the Epo concentration E , because Epo acts as a growth factor on blood cell production, and a decreasing function of the cellular population N . This control is induced by concentration and populations a time τ earlier, that means, before stem cells entered the cell cycle.

The function $g(N, E)$ is assumed to be nonnegative, nonconstant and continuously differentiable. Moreover, it is supposed that

$$\lim_{N \rightarrow +\infty} g(N, E) = 0, \quad \text{for all } E \geq 0.$$

We are interested in the asymptotic stability of the equilibria of System (2)-(3). We say that (\bar{N}, \bar{E}) is an *equilibrium* of System (2)-(3) if (\bar{N}, \bar{E}) is a solution of $dN/dt = dE/dt = 0$, that is

$$\delta \bar{N} = g(\bar{N}, \bar{E})\bar{N}, \quad (4)$$

$$k\bar{E} = f(\bar{N}). \quad (5)$$

By using (5), Equation (4) becomes

$$\delta \bar{N} = g\left(\bar{N}, \frac{1}{k}f(\bar{N})\right)\bar{N}.$$

We deduce that either $\bar{N} = 0$ or \bar{N} is solution of

$$g\left(\bar{N}, \frac{1}{k}f(\bar{N})\right) = \delta. \quad (6)$$

Since the function f is decreasing, the function $\bar{N} \mapsto g\left(\bar{N}, \frac{1}{k}f(\bar{N})\right)$ is decreasing for $\bar{N} \geq 0$. Moreover,

$$g\left(0, \frac{1}{k}f(0)\right) > 0 \quad \text{and} \quad \lim_{\bar{N} \rightarrow +\infty} g\left(\bar{N}, \frac{1}{k}f(\bar{N})\right) = 0. \quad (7)$$

By using (5), (6) and (7), we can conclude to the existence of at most two equilibria for System (2)-(3). This is done in the next proposition.

Proposition 1. (i) If

$$g\left(0, \frac{1}{k}f(0)\right) \leq \delta \quad \text{or} \quad \delta = 0,$$

System (2)-(3) has a unique equilibrium $(0, f(0)/k)$.

(ii) If

$$0 < \delta < g\left(0, \frac{1}{k}f(0)\right), \quad (8)$$

System (2)-(3) has two distinct equilibria, $(0, f(0)/k)$ and (N^*, E^*) , where $N^* > 0$ is the unique solution of the equation

$$g\left(N^*, \frac{1}{k}f(N^*)\right) = \delta,$$

and

$$E^* = \frac{1}{k}f(N^*).$$

The equilibrium $(0, f(0)/k)$ of System (2)-(3) corresponds to a critical biological case: the population dies out and the concentration of erythropoietin is saturated, inhibiting the production of blood cells. We focus in the next section on the local stability of the equilibria given by Proposition 1.

§3. Local Asymptotic Stability

Denote by (\bar{N}, \bar{E}) one of the two equilibria of System (2)-(3), defined in Proposition 1. In order to study the local stability of the equilibrium (\bar{N}, \bar{E}) , we linearize System (2)-(3) around this equilibrium. We set $x(t) = N(t) - \bar{N}$ and $y(t) = E(t) - \bar{E}$, for $t \geq 0$. For the sake of simplicity, we still use the variables N and E instead of x and y . The linearized system of (2)-(3) is

$$\frac{dN}{dt}(t) = -\delta N(t) + AN(t - \tau) + BE(t - \tau), \quad (9)$$

$$\frac{dE}{dt}(t) = -kE(t) + f'(\bar{N})N(t), \quad (10)$$

where A and B are explicitly given by

$$A = g(\bar{N}, \bar{E}) + \bar{N} \frac{\partial g}{\partial N}(\bar{N}, \bar{E}) \quad \text{and} \quad B = \bar{N} \frac{\partial g}{\partial E}(\bar{N}, \bar{E}).$$

One can notice that $B \geq 0$. We write System (9)-(10) in the form

$$\begin{pmatrix} \frac{dN}{dt}(t) \\ \frac{dE}{dt}(t) \end{pmatrix} = \begin{pmatrix} -\delta & 0 \\ f'(\bar{N}) & -k \end{pmatrix} \begin{pmatrix} N(t) \\ E(t) \end{pmatrix} + \begin{pmatrix} A & B \\ 0 & 0 \end{pmatrix} \begin{pmatrix} N(t - \tau) \\ E(t - \tau) \end{pmatrix}.$$

So the characteristic equation is given by

$$(\lambda + k)(\lambda + \delta - Ae^{-\lambda\tau}) - Bf'(\bar{N})e^{-\lambda\tau} = 0. \quad (11)$$

We recall that the equilibrium (\bar{N}, \bar{E}) is locally asymptotically stable if all roots of (11) have negative real part. Therefore, we are going to investigate the sign of the real part of roots of (11).

First, we consider the case $\tau = 0$. When $\tau = 0$, the characteristic equation (11) reduces to a second degree polynomial

$$\lambda^2 + (k + \delta - A)\lambda + k(\delta - A) - Bf'(\bar{N}) = 0. \quad (12)$$

By applying the Routh-Hurwitz Criterion, we obtain the following lemma.

Lemma 2. *All roots of (12) have negative real parts if and only if $k + \delta > A$ and $k\delta > Ak + Bf'(\bar{N})$.*

We assume, in the sequel, that $k + \delta > A$ and $k\delta > Ak + Bf'(\bar{N})$. In this case, the equilibrium is locally asymptotically stable when $\tau = 0$. Hence, if instability occurs for a particular value of τ , a characteristic root of (11) must intersect the imaginary axis (see Rouché's Theorem [7, p.248]).

Suppose that (11) has a purely imaginary root $i\omega$, with $\omega \in \mathbb{R}$. Then, by separating real and imaginary parts in (11), we have

$$-\omega^2 + k\delta = (Ak + Bf'(\bar{N})) \cos(\omega\tau) + A\omega \sin(\omega\tau), \quad (13)$$

$$(k + \delta)\omega = A\omega \cos(\omega\tau) - (Ak + Bf'(\bar{N})) \sin(\omega\tau). \quad (14)$$

Note that if $i\omega$ is a characteristic root of (11), then $-i\omega$ is also a characteristic root. Moreover, since $k\delta > Ak + Bf'(\bar{N})$, $\omega = 0$ cannot be a solution of (13)-(14). Then, we can assume that $\omega > 0$.

Adding up the squares of Equations (13) and (14), we obtain

$$\omega^4 + \left[(k + \delta)^2 - A^2 - 2k\delta \right] \omega^2 + (k\delta)^2 - (Ak + Bf'(\bar{N}))^2 = 0. \quad (15)$$

We set

$$p = k^2 + \delta^2 - A^2, \quad q = (k\delta)^2 - (Ak + Bf'(\bar{N}))^2 \quad \text{and} \quad \xi = \omega^2.$$

Equation (15) becomes

$$h(\xi) := \xi^2 + p\xi + q = 0. \quad (16)$$

Lemma 3. *(i) If $q < 0$ or $q = 0$ and $p < 0$, Equation (16) has exactly one positive root. (ii) If $q > 0$, $p < 0$ and $p^2 > 4q$, Equation (16) has two positive roots. (iii) If $p < 0$ and $p^2 = 4q$, Equation (16) has only one root which is positive. (iv) If $q \geq 0$ and $p \geq 0$ or $p < 0$ and $p^2 < 4q$, Equation (16) has no real roots or nonpositive roots.*

We suppose that one of the conditions (i), (ii) or (iii) of Lemma 3 is satisfied. Let ξ_l ($l = 1, 2$ in case (ii) and $l = 1$ in cases (i) and (iii)) be the real positive roots of (16). We set $\omega_l = \sqrt{\xi_l} > 0$. Then ω_l are the only positive solutions of (15). By using Equations (13) and (14), we obtain, for $l = 1, 2$,

$$\cos(\phi(\omega_l) - \omega_l\tau) = \frac{-\omega_l^2 + k\delta}{\sqrt{(Ak + Bf'(\bar{N}))^2 + (A\omega_l)^2}},$$

and

$$\sin(\phi(\omega_l) - \omega_l\tau) = \frac{(k + \delta)\omega_l}{\sqrt{(Ak + Bf'(\bar{N}))^2 + (A\omega_l)^2}},$$

with

$$\phi(\omega_l) = \arcsin \left(\frac{A\omega_l}{\sqrt{(Ak + Bf'(\bar{N}))^2 + (A\omega_l)^2}} \right).$$

One can easily check, by using (15), that

$$\left| \frac{-\omega_l^2 + k\delta}{\sqrt{(Ak + Bf'(\bar{N}))^2 + (A\omega_l)^2}} \right| \leq 1 \quad \text{and} \quad \left| \frac{(k + \delta)\omega_l}{\sqrt{(Ak + Bf'(\bar{N}))^2 + (A\omega_l)^2}} \right| \leq 1.$$

We define the nonnegative sequences $\{\tau_{1,j}^l\}$ and $\{\tau_{2,j}^l\}$, for $j \in \mathbb{N} \setminus \{0\}$ and $l = 1, 2$, by

$$\tau_{1,j}^l = \frac{1}{\omega_l} \left[\phi(\omega_l) - \arcsin \left(\frac{(k + \delta)\omega_l}{\sqrt{(Ak + Bf'(\bar{N}))^2 + (A\omega_l)^2}} \right) + 2j\pi \right],$$

and

$$\tau_{2,j}^l = \frac{1}{\omega_l} \left[\phi(\omega_l) + \arcsin \left(\frac{(k + \delta)\omega_l}{\sqrt{(Ak + Bf'(\bar{N}))^2 + (A\omega_l)^2}} \right) + (2j - 1)\pi \right].$$

Set

$$\tau_0 = \tau_{\cdot, j_0}^{l_0} := \min_{l=1,2; j \in \mathbb{N} \setminus \{0\}} \{\tau_{1,j}^l, \tau_{2,j}^l\} \quad \text{and} \quad \omega_0 = \omega_{l_0}. \quad (17)$$

Lemma 4. *For $\tau = \tau_0$, $\pm i\omega_0$ is a pair of simple purely imaginary roots of (11). Moreover,*

$$\left. \frac{d\operatorname{Re}(\lambda)}{d\tau} \right|_{\tau=\tau_0} > 0 \quad \text{if and only if} \quad h'(\omega_0^2) > 0.$$

Proof. Consider the branch of characteristic roots $\lambda(\tau) = \nu(\tau) + i\omega(\tau)$, such that

$$\nu(\tau_0) = 0 \quad \text{and} \quad \omega(\tau_0) = \omega_0.$$

From (11), we have

$$\left[2\lambda + k + \delta + \left(\tau[A(\lambda + k) + Bf'(\bar{N})] - A \right) e^{-\lambda\tau} \right] \frac{d\lambda}{d\tau} = -\lambda[A(\lambda + k) + Bf'(\bar{N})]e^{-\lambda\tau}. \quad (18)$$

If we suppose, by contradiction, that $\lambda(\tau_0)$ is not a simple characteristic root of (11), we obtain

$$-i\omega_0[A(i\omega_0 + k) + Bf'(\bar{N})]e^{-i\omega_0\tau_0} = 0.$$

By separating real and imaginary parts, this leads to

$$\begin{aligned} A\omega_0^2 \cos(\omega_0\tau_0) - \omega_0(Ak + Bf'(\bar{N})) \sin(\omega_0\tau_0) &= 0, \\ \omega_0(Ak + Bf'(\bar{N})) \cos(\omega_0\tau_0) + A\omega_0^2 \sin(\omega_0\tau_0) &= 0. \end{aligned} \quad (19)$$

Since $\omega_0 > 0$, by using (13) and (14), (19) reduces to

$$\begin{aligned} k + \delta &= 0, \\ \omega_0^2 &= k\delta. \end{aligned}$$

On one hand, if $k + \delta \neq 0$ we obtain a contradiction. On the other hand, if $k + \delta = 0$, then

$$\omega_0^2 = -\delta^2 \leq 0.$$

Thus, $\omega_0 = 0$, which gives a contradiction. We conclude that $i\omega_0$ is always a simple root of (11).

From (18), we have

$$\begin{aligned} \left(\frac{d\lambda}{d\tau}\right)^{-1} &= \frac{2\lambda + k + \delta + \left(\tau[A(\lambda + k) + Bf'(\bar{N})] - A\right)e^{-\lambda\tau}}{-\lambda[A(\lambda + k) + Bf'(\bar{N})]e^{-\lambda\tau}}, \\ &= \frac{A - e^{\lambda\tau}(2\lambda + k + \delta)}{\lambda(A(\lambda + k) + Bf'(\bar{N}))} - \frac{\tau}{\lambda}. \end{aligned}$$

Moreover, Equation (11) implies that

$$e^{\lambda\tau} = \frac{A(\lambda + k) + Bf'(\bar{N})}{(\lambda + k)(\lambda + \delta)}.$$

Then,

$$\begin{aligned} \text{sign} \left\{ \frac{d\text{Re}(\lambda)}{d\tau} \right\} \Big|_{\tau=\tau_0} &= \text{sign} \left\{ \text{Re} \left(\frac{d\lambda}{d\tau} \right)^{-1} \right\} \Big|_{\tau=\tau_0}, \\ &= \text{sign} \left\{ \text{Re} \left(\frac{A - e^{\lambda\tau}(2\lambda + k + \delta)}{\lambda(A(\lambda + k) + Bf'(\bar{N}))} \right) \right\} \Big|_{\tau=\tau_0}, \\ &= \text{sign} \left\{ \text{Re} \left(\frac{A - e^{i\omega_0\tau_0}(2i\omega_0 + k + \delta)}{i\omega_0(A(i\omega_0 + k) + Bf'(N^*))} \right) \right\}, \\ &= \text{sign} \left\{ \frac{-A^2}{A^2\omega_0^2 + (Ak + Bf'(\bar{N}))^2} + \frac{(k + \delta)^2 + 2(\omega_0^2 - k\delta)}{(k + \delta)^2\omega_0^2 + (\omega_0^2 - k\delta)^2} \right\}. \end{aligned}$$

By using Equation (15), we obtain

$$(k + \delta)^2\omega_0^2 + (\omega_0^2 - k\delta)^2 = A^2\omega_0^2 + (Ak + Bf'(\bar{N}))^2.$$

Thus,

$$\begin{aligned} \text{sign} \left\{ \frac{d\text{Re}(\lambda)}{d\tau} \right\} \Big|_{\tau=\tau_0} &= \text{sign} \left\{ \frac{2(\omega_0^2 - k\delta) + (k + \delta)^2 - A^2}{A^2\omega_0^2 + (Ak + Bf'(\bar{N}))^2} \right\}, \\ &= \text{sign} \{2\omega_0^2 + p\}, \\ &= \text{sign} \{h'(\omega_0^2)\}. \end{aligned}$$

This concludes the proof. \square

This result, together with Lemmas 2 and 3, allows us to prove the main result of this paper, stated in the next theorem.

Theorem 5. Assume that $k + \delta > A$ and $k\delta > Ak + Bf'(\bar{N})$. If Condition (iv) in Lemma 3 is satisfied, the equilibrium (\bar{N}, \bar{E}) is locally asymptotically stable for all values of $\tau \geq 0$. If either Conditions (i) or (ii) of Lemma 3 hold, then there exists a critical value $\tau_0 > 0$, defined in (17), such that the equilibrium (\bar{N}, \bar{E}) is locally asymptotically stable when $\tau \in [0, \tau_0)$, and a Hopf bifurcation occurs at (\bar{N}, \bar{E}) when $\tau = \tau_0$.

Proof. From Lemma 2, all the characteristic roots of (11) have negative real parts when $\tau = 0$. If Condition (iv) of Lemma 3 is satisfied, then (11) has no purely imaginary root. Consequently, since all the characteristic roots of (11) have negative real part when $\tau = 0$, Rouché's Theorem [7, p.248] implies that all characteristic roots of (11) have negative real part for all $\tau \geq 0$.

Suppose now that either Condition (i) or (ii) of Lemma 3 holds. Rouché's Theorem [7, p.248] implies that all characteristic roots of (11) have negative real parts while $\tau < \tau_0$, where τ_0 is defined in (17). Consequently, (\bar{N}, \bar{E}) is locally asymptotically stable when $\tau \in [0, \tau_0)$. When $\tau = \tau_0$, Lemma 4 implies that (11) has a pair of simple purely imaginary roots $\pm i\omega_0$. Moreover, from Conditions (i) and (ii) of Lemma 3, we obtain $h'(\omega_0^2) \neq 0$. By contradiction, assume that

$$\frac{dRe(\lambda)}{d\tau}(\tau) < 0,$$

for $\tau < \tau_0$ and τ close to τ_0 . Then (11) has a characteristic root $\lambda(\tau) = \nu(\tau) + i\omega(\tau)$ with $\nu(\tau) > 0$. This contradicts the fact that all roots of (11) have negative real parts when $\tau < \tau_0$. Hence, we obtain that

$$\left. \frac{dRe(\lambda)}{d\tau} \right|_{\tau=\tau_0} > 0.$$

This yields to the existence of a Hopf bifurcation at (\bar{N}, \bar{E}) when $\tau = \tau_0$. This ends the proof. \square

Remark 1. When Condition (iii) of Lemma 3 holds, the equilibrium (\bar{N}, \bar{E}) is locally asymptotically stable while $\tau \in [0, \tau_0)$. However, when $\tau = \tau_0$, we cannot conclude to stability or instability of the equilibrium. In this case, $h'(\omega_0^2) = 0$ so, from Lemma 4, $(dRe(\lambda)/d\tau)(\tau = \tau_0) = 0$.

With values of the parameters satisfying (8), it is shown in Figure 1 that a Hopf bifurcation occurs at (N^*, E^*) for $\tau = 3.9$ days, with a period about 22 days. In Figure 2, the solutions are shown in the (N, E) -plan: one can see that the solutions reach a limit cycle.

The function g in computer simulations is a Hill function (see Mackey [8]),

$$g(N, E) = \beta_0 \frac{\theta^n E}{\theta^n + N^n},$$

where $\beta_0 > 0$, $\theta \geq 0$ and $n > 0$ are given by experimental data (see [8, 11, 12]). The function f is defined by (1).

Corollary 6. *The equilibrium $(0, f(0)/k)$ of System (2)-(3) is locally asymptotically stable for all $\tau \geq 0$ when*

$$g\left(0, \frac{1}{k}f(0)\right) < \delta. \quad (20)$$

Proof. Let $\bar{N} = 0$. Then $A = g(0, f(0)/k)$ and $B = 0$. Assume that (20) holds, that is $\delta > A$. Then $k + \delta > A$ and $k\delta > Ak = Ak + Bf'(0)$. Moreover, $q > 0$ and $p > 0$. Hence, Condition (iv) of Lemma 3 holds. Theorem 5 leads to the local asymptotic stability of $(0, f(0)/k)$ for all values of $\tau \geq 0$. \square

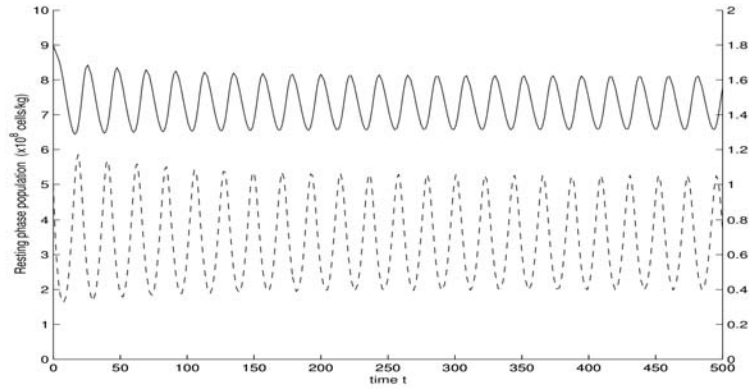


Figure 1: A Hopf bifurcation occurs at the equilibrium (N^*, E^*) for $\tau = 3.9$ days. The parameters values are $\delta = 0.05$, $\beta_0 = 6.5$, $\theta = 1.62 \times 10^8$, $n = 3$ (see [8, 11, 12]), $k = 0.28$, $a = 6570$, $K = 0.0382$ and $r = 6.96$ (see [5]). A periodic solution appears with a period close to 22 days. The solid line is for the resting phase population $N(t)$ and the dashed one is for the Epo concentration $E(t)$.

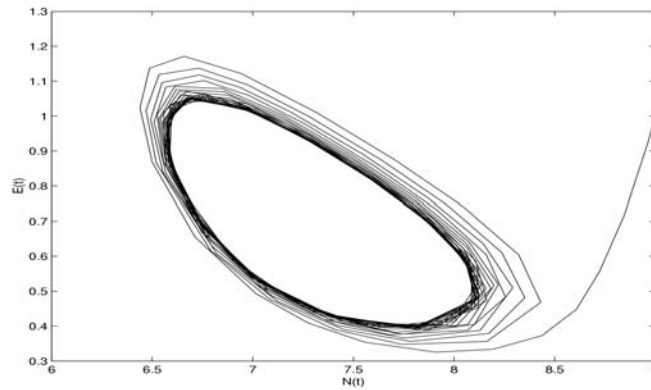


Figure 2: With the same parameters values than in Figure 1, the solutions are shown in the (N, E) -plane. The solutions reach a limit cycle.

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