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Abstract

The main purpose of this paper is to study the existence of periodic solutions for a nonautonomous differential-difference system describing the dynamics of hematopoietic stem cell (HSC) population under some external periodic regulatory factors at the cellular cycle level. The starting model is a nonautonomous system of two age-structured partial differential equations describing the HSC population in quiescent (G_0) and proliferating (G_1, S, G_2 and M) phase. We are interested in the effects of periodically time varying coefficients due for example to circadian rhythms or to the periodic use of certain drugs, on the dynamics of HSC population. The method of characteristics reduces the age-structured model to a nonautonomous differential-difference system. We prove under appropriate conditions on the parameters of the system, using topological degree techniques and fixed point methods, the existence of periodic solutions of our model.

Keywords: Hematopoietic stem cells; Delay differential-difference nonautonomous equations; Periodic solutions; Topological degree and fixed point methods.

AMS Math. Subj. Classification: 34K13, 37C25, 37B55, 39A23

1 Introduction

1.1 Biological motivation

The process that leads to the production and regulation of blood cells (red blood cells, white cells and platelets) to maintain homeostasis (metabolic equilibrium) is called hematopoiesis. The different blood cells have a short life span of one day to several weeks. The hematopoiesis process must provide daily renewal with very high output (approximately 10^{11}-10^{12} new blood cells are produced each day [18]). It consists of mechanisms triggering differentiation and maturation of hematopoietic stem cells (HSCs). Located in the bone marrow, HSCs are undifferentiated cells with unique capacities of differentiation (the ability to produce cells committed to one of blood cell types) and self-renewal (the ability to produce identical cells with the same properties) [29]. Cell biologists classify HSCs, [7], as proliferating (cells in the cell cycle: G_1-S-G_2-M-phase) and quiescent (cells that are withdrawn from the cell cycle and cannot divide: G_0-phase). Quiescent cells are also called resting cells. The vast majority of HSCs are in quiescent phase [7, 29]. Provided they do not die, they eventually enter the proliferating phase. In the proliferating phase, if they do not die by apoptosis, the cells are committed to divide a certain time after their entrance in this phase. Then, they give birth to two daughter cells which, either enter directly into the quiescent phase (long-term proliferation) or return immediately to the proliferating phase (short-term proliferation) to divide again [10, 28, 29].

The first mathematical model for the dynamics of HSCs was proposed by Mackey in 1978 [19]. He proposed a system of delay differential equations for the two types of HSCs, proliferating and quiescent cells. Several improvements to this model have been made by many authors. In many of these works, it is assumed that after mitosis, all daughter cells go to the quiescent state. In a recent work by M. Adimy, A. Chekroun, and T.M. Touaoula [1], a model was proposed that takes into account the fact that only a fraction of daughter cells enter the quiescent phase (long-term proliferation) and the other fraction of cells return immediately to the proliferating phase to divide again (short-term proliferation). This assumption leads to an important difference in the mathematical treatment of the model: it can no longer be posed as a system of delay differential equations. The system of equations has a different mathematical nature. An extra variable is introduced whose dynamics are ruled by a difference equation (no derivative involved).

Several hematological diseases are due to some abnormalities in the feedback loops between different compartments of hematopoietic populations [11]. In many cases, this results in the appearance of periodic oscillations in blood cells, as in chronic myelogenous leukemia [2, 8, 12, 24, 25], cyclical neutropenia [9, 16, 17], periodic auto-immune hemolytic anemia [20, 22], and cyclical thrombocytopenia [3, 27]. In some of these diseases, oscillations occur in all mature blood cells with the same period; in others, the oscillations appear in only one or two cell types. The existence of oscillations in more than one cell line seems to be due to their appearance in HSC compartment. That is why the dynamics of HSC have attracted attention of modelers for more than thirty years now (see the review of C. Foley and M.C. Mackey [11]). On another side, as for most human cells, the circadian rhythm orchestrates the daily rhythms of HSCs. It consists of a set of events that regulates DNA synthesis and mitotic activity [4, 5, 23, 26], and on a genetic level, tumor suppression [13], and DNA damage control [14]. Molecular mechanisms underlying circadian control on apoptosis and cell cycle phases through proteins such as p53 and the cyclin-dependent kinase inhibitor p21 are currently being unveiled [13, 21]. The circadian fluctuations create periodic effects on the dynamics of cell population which promote certain times of cell division. This phenomenon contributes to the emergence of cells with specific cell cycle durations which could play a role in promoting tumor development and at the same time, allowed the establishment of strategies for the treatment of cancer. The assumption of the periodicity of the parameters in the system incorporates the periodicity of the extracellular factors (extracellular proteins and various constituent components of the temporally oscillatory environment). For this reason, the assumption of periodicity is an approximation of the fluctuation of environmental factors.

We will consider some of the key aspects of our model and briefly review the results obtained in [1]. In particular, we shall focus on the existence of equilibria and their stability properties. In this paper, a further generalization is considered, in order to take into account some external periodic regulatory factors at the cellular cycle level, by allowing some of the constants of the model, δ, K and γ, to be time T-periodic functions. This introduces further mathematical complexity since now the system of equations is nonautonomous. Some of the results of [1] can be emulated in a straightforward manner but others, like the equilibria under different regimes of parameters, change to other kind of structures in the nonautonomous setting. More specifically, the results in [1] guarantee the existence of a non-trivial equilibrium under appropriate conditions; using topological techniques, we shall show that a nonautonomous version of these conditions is sufficient to prove the existence of periodic solutions for our extended model.

1.2 Autonomous mathematical model of HSC dynamics

Let us present the model introduced in [1]. Denote by $q(t,a)$ and $p(t,a)$ the population density of quiescent HSCs and proliferating HSCs respectively, at time $t \geq 0$ and age $a \geq 0$. The age represents the time spent by a cell in its current state. Quiescent cells can either be lost randomly at a rate $\delta \geq 0$, which takes into account the cellular differentiation, or enter into the proliferating phase at a rate $\beta \geq 0$. A cell can stay its entire life in the quiescent phase, therefore its age a ranges from 0 to $+\infty$. In the proliferating phase, cells stay a time $\tau \geq 0$, necessary to perform a series of processes, G_1, S, G_2 and M, leading to division at mitosis. Meanwhile they can be lost by apoptosis (programmed cell death) at a rate $\gamma \geq 0$. At the end of proliferating phase, that is, when cells have spent a time $a = \tau$, each cell divides in two daughter cells. A part $K \in (0,1)$ of daughter cells returns immediately to the proliferating phase to go over a new cell cycle while the other part $(1-K)$ enters directly the resting phase. This dynamic is depicted in Figure 1. Consider $Q(t) = \int_0^{+\infty} q(t,a)da$

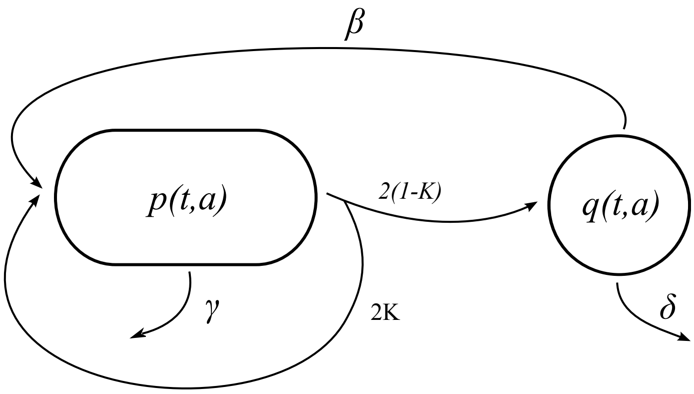

Figure 1: Dynamic of HSCs (see, [1])

and $P(t) = \int_0^\tau p(t,a)da$ the total populations at a given time $t \geq 0$, and $u(t) := p(t,0)$ the number of cells entering the proliferating state at a given time $t \geq 0$. The rate β depends on $Q(t)$ in a nonlinear way, by a Hill function (see [19]),

$$\beta(Q) := \frac{\beta_0}{1+Q^r}, \qquad \beta_0 > 0, \; r > 1.$$

The partial differential equations for this age-structured model read, for $t \geq 0$,

$$\begin{cases} q_t + q_a &= -(\delta + \beta(Q(t)))q, & a \in [0, +\infty), \\ p_t + p_a &= -\gamma p, & a \in [0, \tau], \\ q(t,0) &= 2(1-K)p(t,\tau), \\ p(t,0) &= \beta(Q(t))Q(t) + 2Kp(t,\tau), \end{cases} \tag{1}$$

with initial conditions

$$\begin{cases} q(0,a) = q_0(a), & a \in [0, +\infty), \\ p(0,a) = p_0(a), & a \in [0, \tau], \end{cases} \tag{2}$$

and the following natural condition

$$\lim_{a \to +\infty} q(t,a) = 0.$$

Using the method of characteristics (see [1]), we get for $t > \tau$

$$p(t,\tau) = e^{-\gamma\tau} p(t-\tau, 0).$$

Integrating the system (1) with respect to the age a and putting

$$u(t) = \varphi(t) := e^{-\gamma t} p_0(-t), \quad t \in [-\tau, 0],$$

yields the following system, for $t > 0$,

$$\begin{cases} Q'(t) = -(\delta + \beta(Q(t)))Q(t) + 2(1-K)e^{-\gamma\tau}u(t-\tau), & (3) \\ P'(t) = -\gamma P(t) + \beta(Q(t))Q(t) - (1-2K)e^{-\gamma\tau}u(t-\tau), & (4) \\ u(t) = \beta(Q(t))Q(t) + 2Ke^{-\gamma\tau}u(t-\tau), & (5) \end{cases}$$

with initial conditions

$$Q(0) = Q_0 := \int_0^{+\infty} q_0(a)da, \quad P(0) = P_0 := \int_0^{\tau} p_0(a)da$$

and

$$u(t) = \varphi(t), \quad t \in [-\tau, 0].$$

Remark that P can be recovered from u, namely,

$$P(t) = \int_0^{\tau} e^{-\gamma a} u(t-a)da, \quad t \geq 0.$$

On the other hand, the two equations satisfied by Q and u are independent of P. So, it suffices to analyze the reduced system for Q and u only. It should be noted that the equation for u is not differential. This fact poses a difficulty in using some of the standard topological methods, because the right inverse of the linear operator associated to the equation of u is not compact. The reduced system reads

$$\begin{cases} Q'(t) = -(\delta + \beta(Q(t)))Q(t) + 2(1-K)e^{-\gamma\tau}u(t-\tau), & (6) \\ u(t) = \beta(Q(t))Q(t) + 2Ke^{-\gamma\tau}u(t-\tau). & (7) \end{cases}$$

The following set of hypotheses can be regarded as "natural" in the context of the model.

(h0) δ, K and γ are positive parameters, $0 < K < 1$ and $\beta(Q) := \dfrac{\beta_0}{1+Q^r}$, with $\beta_0 > 0$ and $r > 1$.

In order to express our conditions for existence of solutions in an accurate way, let us define the following quantities:

$$h_1 := 2(1-K)e^{-\gamma\tau}, \quad h_2 := 2Ke^{-\gamma\tau}, \quad \alpha := \frac{h_1}{1-h_2} - 1.$$

Also, for $Q > 0$ we define the function $\mathrm{j}(Q) := \beta(Q)Q$, which attains a global maximum $B := \max_{Q>0} \mathrm{j}(Q)$.

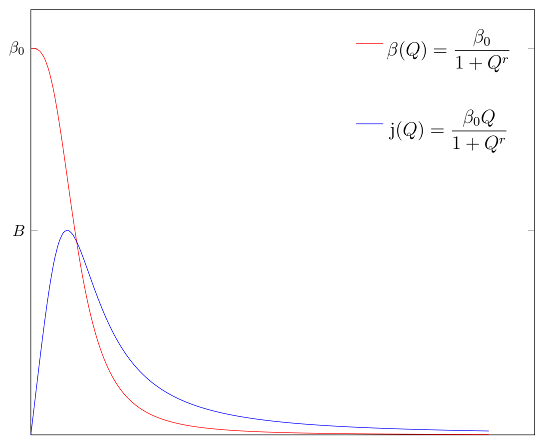

Figure 2. Graphs of β and j.

The following results were proven in [1].

Theorem 1. *System* (6)-(7) *has a nontrivial equilibrium* ($\underline{Q}$,$\underline{u}$) *iff*

(h1) $h_2 < 1$ *(whence* $\alpha < \infty$*),*

(h2) $\alpha > 0$*,*

(h3) $\delta < \alpha\beta_0$*.*

In that case, the nontrivial equilibrium is given by

$$(\underline{Q}, \underline{u}) = \left(\beta^{-1}\left(\frac{\delta}{\alpha}\right), \frac{\delta}{2e^{-\gamma\tau}}\beta^{-1}\left(\frac{\delta}{\alpha}\right)\right).$$

We remark that as the parameters δ and β_0 are positive, the assumption (h3) implies (h2). Furthermore, the assumptions (h1)-(h2) are equivalent to

$$\max\left\{\frac{1}{\gamma}\ln(2K), 0\right\} < \tau < \frac{1}{\gamma}\ln(2)$$

and the condition (h3) is equivalent to

$$\tau < \frac{1}{\gamma}\ln\left(\frac{2(\beta_0 + \delta K)}{\beta_0 + \delta}\right).$$

Theorem 2. *Assume that (h1)-(h2) and the following condition*

(h3') $\delta > \alpha\beta_0$*,*

are satisfied. Then, the trivial equilibrium is globally asymptotically stable.

We remark that the assumption (h3') is equivalent to

$$\tau > \frac{1}{\gamma}\ln\left(\frac{2(\beta_0 + \delta K)}{\beta_0 + \delta}\right).$$

1.3 Nonautonomous model of HSC dynamics

In this work, we shall consider a nonautonomous case, with K, γ and δ continuous T-periodic functions, that is for $t \in [0, +\infty)$,

$$\left\{\begin{array}{rcll} q_t + q_a &=& -(\delta(t) + \beta(Q(t)))q, & a \in [0, +\infty), \\ p_t + p_a &=& -\gamma(t)p, & a \in [0, \tau], \\ q(t,0) &=& 2(1 - K(t))p(t,\tau), & \\ p(t,0) &=& \beta(Q(t))Q(t) + 2K(t)p(t,\tau). & \end{array}\right. \quad (8)$$

Using again the method of characteristics, we obtain

$$p(t,\tau) = \exp\left(-\int_{t-\tau}^{t} \gamma(s)ds\right) p(t-\tau,0) \quad \text{for } \ t \geq \tau.$$

For convenience, set

$$\rho(t) = \int_{t-\tau}^{t} \gamma(s)ds \quad t \geq \tau,$$

which is also a T-periodic function. As for the system (1), the age-structured partial differential model (8) can be reduced to

$$\begin{cases} Q'(t) = -(\delta(t) + \beta(Q(t)))Q(t) + 2(1-K(t))e^{-\rho(t)}u(t-\tau), & (9) \\ u(t) = \beta(Q(t))Q(t) + 2K(t)e^{-\rho(t)}u(t-\tau). & (10) \end{cases}$$

For convenience, we define as before

$$h_1(t) := 2(1-K(t))e^{-\rho(t)}$$

and

$$h_2(t) := 2K(t)e^{-\rho(t)},$$

which turn out to be T-periodic functions. Also, we define the quantity

$$\alpha := \frac{\min(h_1)}{1-\min(h_2)} - 1.$$

Our basic hypothesis now reads as follows.

(H0) δ, γ and K are positive T-periodic functions, $\max(K) < 1$ and $\beta(Q) = \dfrac{\beta_0}{1+Q^r}$ with $\beta_0 > 0$ and $r > 1$.

1.4 Main results

Three results will be presented in this work. In the first place, we shall prove the existence of T-periodic solutions of (9)-(10) under appropriate conditions on the functions δ, γ and K.

Theorem 3. *Assume that (H0) holds and*

(H1) $h_2(t) < 1$*, for all* $t \in \mathbb{R}$*,*

(H2) $\alpha > 0$*,*

(H3) $\delta(t) < \alpha\beta_0$*, for all* $t \in \mathbb{R}$*.*

Then, (9)-(10) *has at least one positive* T*-periodic solution.*

The condition (H3) is equivalent to $\max(\delta) < \alpha\beta_0$. To give a biological interpretation of this last inequality, let us firstly notice that

$$\alpha = \frac{\min h_1 + \min(h_2) - 1}{1 - \min(h_2)}$$

where, regarded as functions of τ, the numerator is decreasing and the denominator is increasing. It is seen that α becomes negative for τ large enough, because $\lim_{\tau\to\infty} \alpha = -1$. According to condition (H1), it is natural to assume that $\min(K) < \frac{1}{2}$; moreover, suppose that the amplitude of the function K is such that

$$\max(K) - \min(K) < \frac{1}{2}. \tag{11}$$

Then, for $\tau = 0$,

$$\alpha = \frac{1 - 2(\max(K) - \min(K))}{1 - 2\min(K)} > 0.$$

If the condition (11) is not satisfied, then $\alpha \leq 0$ for all $\tau \geq 0$: in this case, it is expected that the cell population will not survive. On the other hand, when (11) is assumed, the value of α decreases until it reaches 0 for some τ^* and $\alpha < 0$ for $\tau > \tau^*$. However, the condition (11) alone does not guarantee that the cell population will not disappear for $\tau < \tau^*$. We also have to choose the mortality rate δ (this takes into account the differentiation) small such that

$$\max(\delta) < \frac{\beta_0\,(1 - 2(\max(K) - \min(K)))}{1 - 2\min(K)}. \tag{12}$$

Therefore, there is a threshold $\tau_{\max} > 0$ for the duration of the cell cycle, such that the condition (H3) is satisfied for $\tau \in [0, \tau_{\max})$ and not for $\tau \geq \tau_{\max}$. In order to ensure the existence of periodic solutions for the cell population, in addition to the conditions (11)-(12), the cell cycle duration τ has to be less than a threshold $\tau_{\max}$.

For a proof of Theorem 3, we shall rewrite the system (9)-(10) as a single equation for Q. Thus, solutions can be obtained as the zeros of a conveniently defined operator over the Banach space of continuous T-periodic functions. We guarantee the existence of at least one nontrivial zero by means of the Leray-Schauder degree theory. We remark that, in contrast with other methods (*i.e.* using the contraction mapping theorem), the Leray-Schauder continuation method gives no information about the uniqueness of such periodic solution or its amplitude.

In the second place, we shall study small perturbations of the autonomous system. In more precise terms, assume the conditions of Theorem 1 are satisfied and consider small T-periodic perturbations of the parameters. It would be natural to expect that the nontrivial equilibrium is then perturbed into a T-periodic solution of small amplitude oscillating close to such equilibrium. In order to formalize such intuition, consider the continuous T-periodic vector function $\Lambda = (\delta, K, \gamma) \in C_T^3$, with $C_T^3 := (C_T)^3$ the Banach space of continuous T-periodic functions. Thus, (9)-(10) can be thought as a parametric system of equations with parameters defined in C_T^3. For convenience, the subset of constant functions in C_T^3 shall be identified with $\mathbb{R}^3$. This setting includes both the autonomous and nonautonomous systems and allows to introduce our second result as follows.

Theorem 4. *Assume that a constant parameter* $\underline{\Lambda} \in \mathbb{R}^3$ *and the delay* τ *satisfy appropriate conditions (to be specified), then there exist open subsets* $U \subset C_T^3$ *with* $\underline{\Lambda} \in U$ *and* $V \subset C_T$*, and a continuous map* $I : U \to V$ *such that* $I(\Lambda)$ *is a* T*-periodic solution of the system* (9)-(10) *with continuous* T*-periodic vector function* Λ*. Moreover,* $I(\Lambda)$ *is unique in* V*.*

The preceding theorem gives also a way to obtain periodic solutions; in some sense, it provides a better characterization of such solutions. We remark, however, that the sufficient conditions for existence are explicit in the first result and not in the second one.

Finally, our last result extends Theorem 2 to the nonautonomous case.

Theorem 5. *Assume that (H1)-(H2) and the following condition*

(H3') $\delta(t) > \alpha(t)\beta_0$ *for all* $t \in \mathbb{R}$*,*

are satisfied, where α *is the function defined by*

$$\alpha(t) := \frac{h_1(t)}{1 - h_2(t)} - 1.$$

Then, the trivial equilibrium is locally asymptotically stable.

As for (H3), we can give a biological interpretation of the inequality (H3'). Indeed, in order to guarantee the condition (H3'), we may take a sufficiently large mortality rate δ, or the duration of the cell cycle bigger than a certain threshold. In this case, the population will go to extinction.

It is worth mentioning that the latter theorem is local and, consequently, it does not imply that nontrivial periodic solutions cannot exist. However, if such solutions exist, then they are necessarily "large". An explicit subset of the basin of attraction of the trivial equilibrium shall be characterized in the proof.

2 Existence of T-periodic solutions

2.1 Sketch of the proof

For the reader's convenience, let us firstly sketch the idea of the proof of Theorem 3. The details shall be given in the subsequent subsections.

Due to the above mentioned lack of compactness, we shall reduce the problem to a scalar equation in the following way. Set C_T as the Banach space of continuous T-periodic functions and $\mathcal{C} \subset C_T$ the cone of nonnegative functions.

Given $Q \in \mathcal{C}$, we shall prove the existence of a unique solution $\mathbf{u}(Q)$ of (10) and, furthermore, that the mapping $\mathbf{u} : \mathcal{C} \mapsto C_T$ is continuous. Thus, finding a T-periodic solution of the system is equivalent to solve the problem

$$Q' = N(Q) := \mathbf{N}(Q, \mathbf{u}(Q)), \tag{13}$$

in $\mathcal{C}$, where $\mathbf{N}(Q, u)$ is the Nemytskii operator associated to the right-hand side of the equation (9). Once a T-periodic solution Q of (13) is found, the pair $(Q, \mathbf{u}(Q))$ is a T-periodic solution for the system (9)-(10).

For the scalar equation (13), we shall apply the continuation method over a bounded open set of the form $\Omega_{\epsilon,R} = \{Q \in C_T : \epsilon < Q(t) < R\}$, with $R > \epsilon > 0$ chosen in such a way that $\Omega_{\epsilon,R}$ satisfies the hypotheses of Mawhin's continuation Theorem (see [6]). For convenience, the ideas behind this result (degree theory, Lyapunov-Schmidt reduction) shall be briefly discussed in the next section.

2.2 Mawhin's continuation Theorem

For the sake of completeness, let us recall the basic facts concerning degree theory that shall be employed in our proof. The Leray-Schauder degree is an infinite dimensional extension of the Brouwer degree $\mathrm{d_B}$ of a continuous function. The Leray-Schauder degree $\mathrm{d_{LS}}$ is defined for operators on a Banach space B that are compact perturbations of the identity. In more precise terms, $\mathrm{d_{LS}}$ is defined for $\mathcal{F} : \overline{\Omega} \to B$ given by $\mathcal{F} = Id - \mathcal{C}$, where $\Omega \subset B$ is open and bounded and $\mathcal{C}$ is compact, with $\mathcal{C}(Q) \neq Q$ for $Q \in \partial\Omega$. The degree is simply defined as the Brouwer degree of $I - \mathcal{C}_{\mathbb{V}}$ restricted to $\Omega \cap \mathbb{V}$, where $\mathbb{V}$ is a suitable finite-dimensional subspace of B and $\mathcal{C}_{\mathbb{V}} : \overline{\Omega} \to \mathbb{V}$ is an ε-approximation of $\mathcal{C}$ for some ε sufficiently small. It can be proven that the definition does not depend on the choice of $\mathcal{C}_{\mathbb{V}}$ (see Theorem 9.4, page 60 of [6]). Let us give a brief summary of the properties that shall be used in this work (for more details on the degree theory see [6]).

Proposition 1. *If* $\mathrm{d_{LS}}(\mathcal{F}, \Omega, 0) \neq 0$ *then* $\mathcal{F}$ *has a zero in* Ω.

Definition 1. *We say that the family of operators* $\{\mathcal{F}_\lambda\}_{0\le\lambda\le1}$ *is an admissible homotopy over a bounded open set* Ω *if and only if*

- $\mathcal{F}_\lambda = Id - \mathcal{C}_\lambda$, *with* $\mathcal{C}_\lambda = \mathcal{C}(\cdot, \lambda)$ *and* $\mathcal{C} : \overline{\Omega} \times [0, 1] \to B$ *compact.*
- $\mathcal{F}_\lambda(Q) \neq 0$, *for all* $Q \in \partial\Omega$ *and for all* $\lambda \in [0, 1]$.

Proposition 2. *Let* $\{\mathcal{F}_\lambda\}_{0\le\lambda\le1}$ *be an admissible homotopy over a bounded open set* Ω. *Then* $\mathrm{d_{LS}}(\mathcal{F}_\lambda, \Omega, 0)$ *is constant with respect to* λ.

Proposition 3. *Let* $f : [a, b] \to \mathbb{R}$ *be continuous such that* $f(a), f(b) \neq 0$. *Then*

$$\mathrm{d_B}(f, \Omega, 0) = \frac{sgn(f(b)) - sgn(f(a))}{2}.$$

In our setting, let $C^1_T = C^1 \cap C_T$, and let

$$\overline{Q} = \frac{1}{T}\int_0^T Q(t)dt$$

denote the average of a function Q. The set of constant functions shall be identified with $\mathbb{R}$. The following result by J. Mawhin (see [6]), adapted for our purposes, sums up the technique that shall be used to prove the existence theorem.

Lemma 1. *Assume $N : C_T \to C_T$ is a continuous nonlinear operator and $\Omega \subset C_T$ is an open bounded set and consider the equation*

$$Q' = N(Q). \tag{14}$$

For a constant function $Q \equiv q$, define $f(q) := \overline{N(Q)}$ and assume that the following conditions hold:

1. *$Q' = \lambda N(Q)$ has no solutions on $\partial\Omega$, for $\lambda \in (0, 1)$;*
2. *$f(q) \neq 0$, for $q \in \partial\Omega \cap \mathbb{R}$;*
3. *$\mathrm{d_B}(f, \partial\Omega \cap \mathbb{R}, 0) \neq 0$.*

Then, there exists a T-periodic solution of the equation (14) *with range in $\overline{\Omega}$.*

2.3 The mapping $\mathbf{u}(Q)$

Let us recall that our method consists in reducing the system (9)-(10) to a scalar equation for Q, for which Lemma 1 can be applied. In order to do so, it needs to be shown that, for given $Q \in C_T$, there exists a unique $\mathbf{u}(Q)$ solution of (10). This shall define a mapping $\mathbf{u} : C_T \mapsto C_T$. The following lemma proves that such mapping exists and is continuous. Further, it also gives estimates on the image of some set of the form

$$\Omega_{\epsilon,R} = \{Q \in C_T : \epsilon < Q(t) < R\},$$

that will be employed in the continuation Lemma.

Lemma 2. *Assume that the hypothesis (H1) of Theorem 3 holds. Then, given $Q \in C_T$, there exists a unique solution $\mathbf{u}(Q)$ of* (10)*. The mapping $\mathbf{u} : C_T \mapsto C_T$ is continuous. Moreover, if $0 < \epsilon < R$ are such that $\mathrm{j}(\epsilon) < \mathrm{j}(R)$, then*

$$\mathbf{u}(\Omega_{\epsilon,R}) \subset \mathcal{U}_\epsilon := \left\{ u \in C_T : \frac{\beta(\epsilon)\epsilon}{1 - \min(h_2)} \leq u \leq \frac{B}{1 - \max(h_2)} \right\}.$$

Proof. Define $S(u)(t) := u(t) - h_2(t)u(t - \tau)$. Then, the equation (10) can be written as

$$S(u) = \mathrm{j} \circ Q.$$

The norm of $(Id - S)(u)(t) = h_2(t)u(t - \tau)$ in the space $\mathcal{L}(C_T)$ of linear operators on C_T is computed from the inequality

$$|(Id - S)(u)(t)| = |h_2(t)u(t - \tau)| \leq \max(h_2)\ |u(t - \tau)| \leq \max(h_2)\|u\|_{C_T},$$

which implies

$$\|Id - S\| \leq \max(h_2) < 1.$$

As a consequence, S is invertible with continuous inverse. Hence, the mapping $\mathbf{u}(Q) = S^{-1}(\mathrm{j} \circ Q)$ is well defined and continuous.

In order to find estimates for $\mathbf{u}(Q)$ in terms of the estimates on Q, we will follow a roundabout way. Given a fixed $Q \in C_T$, let us define $S_Q(u)(t) = \mathrm{j}(Q(t)) + h_2(t)u(t-\tau)$. Solving the equation (10) for Q, is equivalent to find a fixed point of S_Q. Next observe that, given any $Q \in C_T$, the mapping S_Q is a contraction. So, by the Banach Fixed Point Theorem it has a unique fixed point, which is necessarily equal to $\mathbf{u}(Q)$. This gives us another way to characterize $\mathbf{u}(Q)$.

Now, let $Q \in \Omega_{\epsilon,R}$. If we could find an invariant set $\mathcal{U}$ for S_Q then, by Banach's Theorem, the (unique) fixed point $\mathbf{u}(Q)$ will belong to $\mathcal{U}$. With this idea in mind, consider sets of the form $\mathcal{U}_{a,b} := \{u \in C_T : a \leq u \leq b\}$. It follows from the hypothesis that the minimum value of j in $[\epsilon, R]$ is attained at ϵ. Suppose that $Q \in \Omega_{\epsilon,R}$, then given $u \in \mathcal{U}_{a,b}$, we have

$$\mathrm{j}(\epsilon) + a \ \min(h_2) \leq \mathrm{j}(Q(t)) + h_2(t)u(t-\tau) \leq B + b \ \max(h_2).$$

Hence, taking $a = \dfrac{\mathrm{j}(\epsilon)}{1 - \min(h_2)}$ and $b = \dfrac{B}{1 - \max(h_2)}$ we deduce that $S_Q(\mathcal{U}_{a,b}) \subseteq \mathcal{U}_{a,b}$. So, for $Q \in \Omega_{\epsilon,R}$, $\mathbf{u}(Q) \in \mathcal{U}_\epsilon$. This means that $\mathbf{u}(\Omega_{\epsilon,R}) \subset \mathcal{U}_\epsilon$. □

2.4 Proof of Theorem 3

We are now in condition of proving our existence theorem. To this end, we shall show that (H1), (H2) and (H3) allow to find ϵ and R such that the assumptions of Lemma 1 are satisfied for $\Omega_{\epsilon,R}$.

Since $\beta(R) \to 0$ and $\frac{1}{R}\frac{B\max(h_1)}{1-\max(h_2)} \to 0$ as $R \to +\infty$, we may choose R large enough such that $\min(\delta) > -\beta(R) + \frac{1}{R}\frac{B\max(h_1)}{1-\max(h_2)}$. Once R is chosen, using (H3) and the fact that $\mathrm{j}(\epsilon) \to 0$ as $\epsilon \to 0$, we may choose ϵ small enough such that $1 + \epsilon^r < \dfrac{\beta_0\alpha}{\max(\delta)}$ and also $\mathrm{j}(\epsilon) < \mathrm{j}(R)$. Summarizing, our choice of ϵ and R yields:

(C0) $0 < \epsilon < R$ and $\mathrm{j}(\epsilon) < \mathrm{j}(R)$,

(C1) $1 + \epsilon^r < \dfrac{\beta_0\alpha}{\max(\delta)}$,

(C2) $\min(\delta) > -\beta(R) + \dfrac{1}{R}\dfrac{B\max(h_1)}{1 - \max(h_2)}$.

Let us check now that for such ϵ and R, the first condition in Lemma 1 is satisfied.

Let $\lambda \in (0,1)$ and suppose there exists $Q \in \partial\Omega_{\epsilon,R}$ such that $Q' = \lambda N(Q)$. The fact that $Q \in \partial\Omega_{\epsilon,R}$ implies the existence of $t_0 \in [0,T]$ such that $Q(t_0) = \epsilon$, or such that $Q(t_0) = R$. If $Q(t_0) = \epsilon$, then, Q reaches its minimum value at t_0 and hence $0 = Q'(t_0) = \lambda N(Q(t_0))$. That is,

$$\begin{aligned} 0 &= -(\delta(t_0) + \beta(\epsilon))\epsilon + h_1(t_0) u_Q(t_0 - \tau), \\ \delta(t_0)\epsilon &= -\beta(\epsilon)\epsilon + h_1(t_0)\mathbf{u}(Q)(t_0 - \tau). \end{aligned}$$

Using (C0) and the fact that $Q \in \Omega_{\epsilon,R}$, we may apply Lemma 2 in order to get

$$\delta(t_0)\epsilon \geq -\beta(\epsilon)\epsilon + \min(h_1)\frac{\beta(\epsilon)\epsilon}{1 - \min(h_2)}.$$

Thus,

$$\delta(t_0) \geq \beta(\epsilon)\left\{\frac{\min(h_1)}{1 - \min(h_2)} - 1\right\} = \frac{\beta_0\alpha}{1 + \epsilon^r}. \tag{15}$$

This contradicts (C1).

Now suppose there exists t_0 such that $Q(t_0) = R$. Then, by (C0) and Lemma 2, we obtain

$$\begin{aligned} \delta(t_0)R &= -\beta(R)R + h_1(t_0)\mathbf{u}(Q)(t_0 - \tau), \\ &\leq -\beta(R)R + \frac{B\max(h_1)}{1 - \max(h_2)}. \end{aligned}$$

This contradicts (C2) and the first condition of Lemma 1 is thus proven.

Next, we shall verify the second condition. In the first place, notice that $\Omega_{\epsilon,R} \cap \mathbb{R} = [\epsilon, R]$. Now, suppose $f(q) = \overline{N(Q)} = 0$, for some $Q \equiv q \in \partial\Omega_{\epsilon,R} \cap \mathbb{R} = \{\epsilon, R\}$. Then, $Q \equiv \epsilon$ or $Q \equiv R$. In the first case, the fact that $\overline{N(\epsilon)} = 0$ implies

$$\begin{aligned} 0 &= -\overline{(\delta(t) + \beta(\epsilon))\epsilon + h_1(t)\mathbf{u}(Q)(t - \tau)}, \\ \overline{\delta} &= -\beta(\epsilon) + \frac{1}{\epsilon}\overline{h_1(t)\mathbf{u}(Q)(t - \tau)} \geq \frac{\beta_0\alpha}{1 + \epsilon^r}. \end{aligned}$$

But, $\max(\delta) \geq \overline{\delta} \geq \dfrac{C\alpha}{1 + \epsilon^r}$ contradicts (H1). On the other hand, if $Q \equiv R$ then $\overline{N(Q)} = 0$ implies

$$\overline{\delta} = -\beta(R) + \frac{1}{R}\overline{h_1(t)\mathbf{u}(Q)(t - \tau)} \leq -\beta(R) + \frac{1}{R}\frac{B\max(h_1)}{1 - \max(h_2)}.$$

This contradicts (H2).

It remains to show that the last condition in Lemma 1 is satisfied. By Proposition 3, the inequalities

$$f(\epsilon) > -(\max(\delta))\epsilon + \beta(\epsilon)\epsilon\alpha = \epsilon\left(\frac{\beta_0\alpha}{1 + \epsilon^r} - \max(\delta)\right) > 0$$

and

$$f(R) < -\overline{\delta}R - \beta(R)R + R\frac{B\max(h_1)}{1 - \max(h_2)} < 0,$$

imply that $d_B(f, [\epsilon, R], 0) = -1$.

Finally, using Lemma 1, we conclude the existence of T-periodic solution to equation (13), which, in turn, gives us a T-periodic solution of system (9)-(10).

3 Small perturbations of the autonomous problem

3.1 Preliminaries

Consider the operator $\mathcal{F} : C_T \times C_T^3 \to C_T$ given by

$$\mathcal{F}(Q, \Lambda) := Q - \overline{Q} + \overline{N(Q, \Lambda)} + \mathcal{K}(N(Q, \Lambda) - \overline{N(Q, \Lambda)}). \tag{16}$$

In other words, for each fixed $\Lambda \in C_T^3$, the mapping $\mathcal{F}(\cdot, \Lambda)$ is the operator defined in the proof of Lemma 1. We already know that for any constant $\underline{\Lambda} = (\underline{\delta}, \underline{K}, \underline{\gamma})$ satisfying the assumptions of Theorem 1, there exists a (unique) stationary solution $\underline{Q}$. That is, under the previous identification of $\mathbb{R}$ with the set of constant functions, we have a pair $(\underline{Q}, \underline{\Lambda})$ such that $\mathcal{F}(\underline{Q}, \underline{\Lambda}) = 0$. We shall obtain a (locally unique) branch of solutions $Q(\lambda)$ when λ is close to $\underline{\lambda}$ with the help of the Implicit Function Theorem, namely:

Theorem 6. *Let X, Y and Z be Banach spaces and let U be an open subset of $X \times Y$. Let $\mathcal{F}$ be a continuously differentiable map from U to Z. If $(\underline{x}, \underline{y}) \in U$ is a point such that $\mathcal{F}(\underline{x}, \underline{y}) = 0$ and $D_x\mathcal{F}(\underline{x}, \underline{y})$ is a bounded, invertible, linear map from X to Z, then there exist open neighborhoods G and H of $\underline{y}$ and $\underline{x}$, respectively, and a unique C^1 function $\varphi : G \to H$ such that $\varphi(\underline{y}) = \underline{x}$ and $\mathcal{F}(\varphi(y), y) = 0$, for all $y \in G$.*

In more precise terms, if the Fréchet derivative of $\mathcal{F}$ with respect to Q at the point $(\underline{Q}, \underline{\Lambda})$ is an isomorphism, then, for all $\Lambda \in C_T^3$ in a neighbourhood of $\underline{\Lambda}$ there exists a (locally unique) associated T-periodic function Q and the mapping $\Lambda \mapsto Q$ is continuous. This shows there is a continuity between the equilibrium provided by Theorem 1 and the periodic solutions $(Q, \mathbf{u}(Q))$ associated to small periodic perturbations of $\underline{\Lambda}$. In particular, these periodic solutions shrink to a point in the (Q, u) plane, as the amplitude of the oscillations of Λ goes to zero.

With this in mind, let us firstly recall that for any continuous linear operator $\mathcal{T} : C_T \times C_T^3 \to C_T$ one has

$$(D_Q\mathcal{T})(Q, \Lambda)\psi = \mathcal{T}\psi, \qquad \text{for all } \psi.$$

Moreover, for an arbitrary operator H we may write $\overline{H} = P \circ H$. So, by the chain rule we have

$$D_Q(\overline{H}) = D_Q(P \circ H) = P \circ D_Q H = \overline{D_Q H}.$$

Let us compute $(D_Q\mathcal{F})(Q, \Lambda)$:

$$(D_Q\mathcal{F})(Q, \Lambda)\psi = \psi - \overline{\psi} + \overline{(D_Q N)(Q, \Lambda)\psi} + K\big((D_Q N)(Q, \Lambda)\psi - \overline{(D_Q N)(Q, \Lambda)\psi}\big). \tag{17}$$

Proposition 4. *If $\mathcal{C} : X \to Y$ is a compact (nonlinear) operator differentiable at x_0, then $D_x\mathcal{C}(x_0)$ is a compact linear operator.*

Proof. See Theorem 14.1, page 96 of [6]. $\square$

From the previous computation and the last proposition we conclude that $(D_Q\mathcal{F})(Q,\Lambda)$ is a compact perturbation of the identity (namely, a Fredholm operator of the type $I + \mathcal{C}$). Thus, in order to prove that it is an isomorphism, we only have to check its injectivity. To this end, observe that having an element ψ in the kernel, means

$$\psi' = (D_Q N)(\underline{Q},\underline{\Lambda})\psi. \tag{18}$$

Next, recall that

$$N(Q,\Lambda) = -(\delta + \beta(Q))Q + h_2(\Lambda)R_\tau \mathbf{u}(Q,\Lambda), \tag{19}$$

where $R_\tau(\psi)(t) = \psi(t-\tau)$. Thus,

$$(D_Q N)(Q,\Lambda)\psi = -(\delta + \mathrm{j}'(Q))\psi + h_2(\Lambda)R_\tau(D_Q\mathbf{u})(Q,\Lambda)\psi. \tag{20}$$

In order to compute the differential of $\mathbf{u}$, let us firstly clarify its definition. As shown before, given a fixed function Λ satisfying (H1), it is possible to define an invertible operator S. This definition shall be now extended as follows. Let $\Lambda \subset C_T^3$ the subset of Λ satisfying (H1), then

$$S : C_T \times C_T^3 \to C_T, \quad S(u,\Lambda) = u + h_2(\Lambda)R_\tau u. \tag{21}$$

For each fixed Λ, the operator $S_\Lambda(u) := S(u,\Lambda)$ is invertible and $\mathbf{u}(Q,\Lambda) = S_\Lambda^{-1}(\mathrm{j}(Q))$ is continuous in (Q,Λ) and differentiable in Q, with

$$(D_Q\mathbf{u})(Q,\Lambda)\psi = S_\Lambda^{-1}(\mathrm{j}'(Q)\psi) = \mathrm{j}'(Q)S_\Lambda^{-1}(\psi). \tag{22}$$

So, the equation (18) reads

$$\begin{aligned} \psi' &= -\underline{\delta}\psi - \mathrm{j}'(\underline{Q})\psi + h_1(\underline{\Lambda})\mathrm{j}'(\underline{Q})R_\tau S_{\underline{\Lambda}}^{-1}(\psi), \\ \psi' + (\underline{\delta} + \mathrm{j}'(\underline{Q}))\psi &= h_1(\underline{\Lambda})\mathrm{j}'(\underline{Q})R_\tau S_{\underline{\Lambda}}^{-1}(\psi). \end{aligned}$$

We shall apply $S_{\underline{\Lambda}}R_\tau^{-1}$ at both sides of the last equality. Because $(R_\tau^{-1}\psi)(t) = \psi(t+\tau)$, we obtain

$$\begin{aligned} S_{\underline{\Lambda}}R_\tau^{-1}\big(\psi' + (\underline{\delta} + \mathrm{j}'(\underline{Q}))\psi\big) &= h_1(\underline{\Lambda})\mathrm{j}'(\underline{Q})\psi, \\ S_{\underline{\Lambda}}\big(\psi'(t+\tau) + (\underline{\delta} + \mathrm{j}'(\underline{Q}))\psi(t+\tau)\big) &= h_1(\underline{\Lambda})\mathrm{j}'(\underline{Q})\psi. \end{aligned}$$

Expanding the definitions of $S_{\underline{\Lambda}}$, we get an expression in terms of $\psi(t)$, $\psi'(t)$, $\psi(t+\tau)$ and $\psi'(t+\tau)$. The resulting equation is of the form

$$A\psi'(t+\tau) + B\psi(t+\tau) = a\psi'(t) + b\psi(t), \tag{23}$$

with

$$\begin{aligned} A &= 1, & B &= \underline{\delta} + \mathrm{j}'(\underline{Q}), \\ a &= h_2(\underline{\Lambda}), & b &= 2e^{-\underline{\gamma}\tau}(\underline{K}\,\underline{\delta} + \mathrm{j}'(\underline{Q})). \end{aligned} \tag{24}$$

From now on, the arguments Q and $\underline{\Lambda}$ shall be omitted to simplify notations. In summary, the kernel of $(D_Q\overline{\mathcal{F}})(Q, \underline{\Lambda})$ is non-trivial if and only if the equation (23) has a non-trivial solution in C_T. Let us take a generic function $\psi \in C_T$, and expand it in complex Fourier series, with $\omega = \frac{1}{T}$. We get

$$\psi(t) = \sum_{k\in\mathbb{Z}} a_k e^{ik\omega t}, \qquad \psi'(t) = \sum_{k\in\mathbb{Z}} a_k ik\omega e^{ik\omega t}, \tag{25}$$

$$\psi(t-\tau) = \sum_{k\in\mathbb{Z}} a_k e^{ik\omega\tau} e^{ik\omega t}, \qquad \psi'(t-\tau) = \sum_{k\in\mathbb{Z}} a_k ik\omega e^{ik\omega\tau} e^{ik\omega t}. \tag{26}$$

By replacing in the equation (23) and comparing coefficients, we obtain

$$a_k\big(e^{ik\omega\tau}(Aik\omega + B) - (aik\omega + b)\big) = 0. \tag{27}$$

In order to have a non-trivial periodic solution, we need that at least for some $k \in \mathbb{Z}$, the following identity is satisfied:

$$e^{ik\omega\tau} = \frac{aik\omega + b}{Aik\omega + B}. \tag{28}$$

Let's call this equation the characteristic equation. For fixed values of $\underline{\Lambda}$, τ and T, this equation may or may not have integer solutions k.

Lemma 3. *For fixed $\underline{\Lambda}$ and T, there exists a set $E \subset \mathbb{R}$ such that for $\tau \in \mathbb{R} \setminus E$ the equation (28) has no integer solutions. E is empty for almost all values of $\underline{\Lambda}$ and T, and countable for the remaining ones.*

Proof. Consider the homography $\mathcal{H}(z) = \frac{aiz+b}{Aiz+B}$. The image of the real line under $\mathcal{H}$ is either a circle or a straight line in $\mathbb{C}$. In order to decide which is the case, it suffices to compute the value of the function at three points on the real line.

$$\mathcal{H}(0) = \frac{b}{B}, \quad \mathcal{H}(1) = \frac{ai+b}{Ai+B}, \quad \mathcal{H}(-1) = \frac{-ai+b}{-Ai+B} \quad \text{and} \quad \mathcal{H}(\infty) = \frac{a}{A}.$$

Thus, $\mathcal{H}(\mathbb{R})$ is a circle centered on the real axis and intersecting this axis at $\mathcal{H}(0)$ and $\mathcal{H}(\infty)$. Hence $\mathcal{H}(\mathbb{R}_{>0})$ is a semicircle and the possible scenarios are the following:

1. If $\mathcal{H}(\mathbb{R}_{>0}) \cap S^1 = \emptyset$, then the equation (28) has no solutions, for any $\tau \in \mathbb{R}$. Hence, $E_T = \emptyset$.
2. If $\mathcal{H}(\mathbb{R}_{>0}) \cap S^1 \neq \emptyset$, then there exists $r \in \mathbb{R}_{>0}$ and $\eta \in \mathbb{R}$ such that

$$e^{i\eta} = \mathcal{H}(r).$$

   (a) If T is such that $r = k_0\omega$ for some $k_0 \in \mathbb{Z}$, then the equation (28) has solutions for $\tau = \frac{\eta+2l\pi}{k_0\omega}$, with $l \in \mathbb{Z}$. That is: $E_T = \{\frac{\eta+2l\pi}{k_0\omega} \mid l \in \mathbb{Z}\}$.
   (b) If $r \neq k\omega$ for all $k \in \mathbb{Z}$, then the equation (28) has no solution independently of τ. Hence, $E_T = \emptyset$.

□

Remark 1. *Given that $\mathcal{H}(\infty) = h_2 < 1$ (hypothesis (h1)), a more detailed analysis of the value of $\mathcal{H}(0)$ indicates that option 1 is impossible under assumptions (h0)-(h3).*

Theorem 7. *Assume (h1) holds for some constant $\underline{\Lambda}$. Then, for each period T (except at most countably many), there exist open U, V with $\underline{\Lambda} \in U \subset C_T^3$ and $V \subset C_T$ and a continuous map $I : U \to V$ such that $I(\Lambda)$ is a T-periodic solution to the system (9)-(10) with parameter Λ. Moreover, $I(\Lambda)$ is unique in V.*

In [1], the authors focused on autonomous periodic oscillations arising as consequences of a destabilization of the system through a Hopf bifurcation. In particular, they proved that the possible cause of the appearance of periodic oscillations is the increase in the duration of the cell cycle (the delay τ). In the extended model (9)-(10), the situation is different. We are interested in the effects of periodically time varying coefficients on the dynamics of HSC population (even for small delay). This new aspect has never been investigated for HSC dynamics in the context of differential-difference systems. Our investigation improves the model in [1], both biologically and mathematically. In particular, this new model may be helpful to understand the appearance of periodic oscillations in HSC dynamics due to time fluctuation of factors, exterior to the process of hematopoiesis. In our model, we assumed that all cells divide at the same age τ; however, it is believed (see [2]) that τ is distributed with a density f supported on an interval $[0, \bar{\tau}]$ with $\bar{\tau} > 0$. In addition, we did not consider in our model the case when τ is time dependent. In both cases, the resulting model is a differential-difference system with distributed or time dependent delay, whose analysis is more complicated. This is one of the limitations of our model, that will be investigated in a future work.

4 Local stability of the trivial solution

In this section, we shall prove that if the condition (H3) of Theorem 3 is replaced by the condition

(H3') $\delta(t) > \beta_0 \alpha(t)$ for all $t \in \mathbb{R}$,

then the solutions of the nonautonomous system (9)-(10), with small positive initial conditions, are bounded from above by the solutions of the autonomous system

$$\begin{cases} Q'(t) = -(\delta^* + \beta(Q(t))Q(t) + h_1^* u(t-\tau), & (29) \\ u(t) = \beta(Q(t))Q(t) + h_2^* u(t-\tau), & (30) \end{cases}$$

with the same initial conditions, and

$$\delta^* = \min(\delta) - \epsilon, \quad h_i^* = \max(h_i) + \epsilon, \quad \text{for some } \epsilon \ll 1.$$

This, in turn, implies the local stability of the trivial solution because, as we shall see, the system (29)-(30) is globally asymptotically stable at the origin.

The proof of stability for the autonomous system (taken from [1]), is based on a Lyapunov functional argument. An adaptation of this argument for the nonautonomous system seems to be elusive. For this reason, we shall employ a different approach, which consists in using the solutions of the autonomous problem as bounds for the nonautonomous one.

First we recall some definitions.

Definition 2. *Consider a system described by the coupled differential-functional equations*

$$\begin{cases} Q'(t) = f(t, Q(t), u_t), & (31) \\ u(t) = g(t, Q(t), u_t) & (32) \end{cases}$$

where $u_t \in C[-\tau, 0]$ *is defined by* $u_t(s) := u(t+s)$. *The function* g *or the subsystem* (32) *defined by* g *is said to be uniformly input to state stable if there exist:*

1. *A function* $\xi : \mathbb{R}_{\geq 0} \times \mathbb{R}_{\geq 0} \to \mathbb{R}_{\geq 0}$ *such that* $\xi(a,t)$ *is continuous, strictly increasing with respect to* a*, strictly decreasing with respect to* t*,* $\xi(0,t) = 0$*, and* $\lim_{t\to\infty} \xi(a,t) = 0$.
2. *A function* $\nu : \mathbb{R}_{\geq 0} \to \mathbb{R}_{\geq 0}$ *continuous, strictly increasing, with* $\nu(0) = 0$*,*

such that the solution $u_t(t_0, \varphi, Q)$ *corresponding to the initial condition* $u_{t_0} = \varphi$ *and input function* $Q(t)$ *satisfies*

$$\|u_t(t_0, \varphi, Q)\| \leq \xi(\|\varphi\|, t - t_0) + \nu(\|Q\big|_{[t_0,t)}\|).$$

Theorem 8. *Suppose that* f *and* g *map* $\mathbb{R} \times$ (*bounded sets in* $\mathbb{R}^m \times C[0,1]$) *into bounded sets of* $\mathbb{R}^m$ *and* $\mathbb{R}^n$ *respectively, and* g *is uniformly input to state stable;* $v_1, v_2, w : \mathbb{R}_{\geq 0} \to \mathbb{R}_{\geq 0}$ *are continuous nondecreasing functions, where additionally* $v_i(s)$ *are positive for* $s > 0$*, and* $v_i(0) = 0$*. If there exists a functional*

$$V : \mathbb{R} \times \mathbb{R}^m \times C[0,1] \to \mathbb{R},$$

such that

$$v_1(|Q|) \leq V(t, Q, \varphi) \leq v_2(\|(Q, \varphi)\|)$$

and

$$\dot{V}(s, Q(s), u_s) := \frac{d}{dt} V(t, Q(t), u_t)\bigg|_{t=s} \leq -w(|Q(s)|),$$

then, the trivial solution of the coupled differential-functional equations (31)-(32) *is uniformly stable. If* $w(s) > 0$ *for* $s > 0$*, then it is uniformly asymptotically stable. If, in addition,* $\lim_{s\to\infty} v_1(s) = \infty$ *, then it is globally uniformly asymptotically stable.*

Proof. The proof can be found in [15]. □

Theorem 9. *If the conditions (h0),(h1) and (h3') hold, then the trivial equilibrium of the autonomous system* (29)-(30) *is globally asymptotically stable.*

Proof. For $t \in [0, \tau]$, we have

$$u(t) \leq C\|Q\big|_{[0,t)}\| + h_2^*\varphi(t-\tau).$$

If we define $n(t) := \min\{n \in \mathbb{N} : n > \frac{t}{\tau}\}$ then by induction

$$u(t) \leq C\left(\frac{1-(h_2^*)^{n(t)}}{1-h_2^*}\right)\|Q\big|_{[0,t)}\| + (h_2^*)^{n(t)}\|\varphi\|.$$

In consequence,

$$u(t) \leq C\left(\frac{1}{1-h_2^*}\right)\|Q\big|_{[0,t)}\| + (h_2^*)^{t/\tau}\|\varphi\|.$$

This implies that $\xi(a,t) = (h_2^*)^{t/\tau}a$ and $\nu(a) = C\left(\frac{1}{1-h_2^*}\right)a$ satisfy the conditions for uniformly input to state stability.

Next, define

$$V(t, Q, \varphi) := |Q| + \frac{h_1^*}{1-h_2^*}\int_{-\tau}^{0}|\varphi(\theta)|d\theta.$$

It is immediate to verify that

$$|Q| \leq V(t, Q, \varphi) \leq |Q| + \frac{h_1^*}{1-h_2^*}\tau\|\varphi\| \leq \left(1 + \frac{h_1^*}{1-h_2^*}\tau\right)\|(Q, \varphi)\| \tag{33}$$

and, over trajectories of positive solutions,

$$\dot{V}(t, Q(t), u_t) = Q'(t) + \frac{h_1^*}{1-h_2^*}(u(t) - u(t-\tau)), \tag{34}$$

$$= -\delta^*Q(t) - \beta(Q)Q + h_1^*u(t-\tau) + \frac{h_1^*}{1-h_2^*}\left(\beta(Q)Q + h_2^*u(t-\tau) - u(t-\tau)\right), \tag{35}$$

$$= -\delta^*Q(t) + \beta(Q)Q\left(\frac{h_1^*}{1-h_2^*} - 1\right) + u(t-\tau)\left(\frac{h_1^*h_2^*}{1-h_2^*} + h_1^* - \frac{h_1^*}{1-h_2^*}\right), \tag{36}$$

$$= -\left(\delta^* - \beta(Q)\left(\frac{h_1^*}{1-h_2^*} - 1\right)\right)Q. \tag{37}$$

This implies that V is a Lyapunov functional for the system, with $v_1(s) = s$, $v_2(s) = \left(1 + \frac{h_1^*}{1-h_2^*}\tau\right)s$ and $w(s) = \delta^* - \beta(s)\left(\frac{h_1^*}{1-h_2^*} - 1\right) > 0$. We remark that the quantities δ^* and h_i^* were defined in order to guarantee that the latter inequality is strict. □

Lemma 4. *Let $\bar{r} > 0$ be the value where* j *reaches its maximum. If $\|(Q_0, \varphi)\|$ is small enough then $Q(t) < \bar{r}$ for all $t \geq 0$.*

Proof. Take

$$\|(Q_0, \varphi)\| \leq \frac{\bar{r}}{1 + \dfrac{h_1^*}{1 - h_2^*}\tau}.$$

Then, by (33) we have

$$V(0, Q_0, \varphi) \leq \bar{r}.$$

Also, because of (34),

$$\dot{V}(t, Q(t), u_t) \leq 0, \quad \text{for all } t \geq 0,$$

and again by (33), this implies $|Q(t)| \leq \bar{r}$, for all $t \geq 0$. □

Remark that for the Hill function $\beta(Q) := \dfrac{\beta_0}{1 + Q^r}$, $\beta_0 > 0$, $r > 1$, we have

$$\bar{r} = \left(\frac{1}{r - 1}\right)^{\frac{1}{r}}.$$

The following result shall provide a comparison between the solutions (Q, u) and $(\overline{Q}, \overline{u})$, the solutions to the nonautonomous and the autonomous case respectively, for given initial conditions (Q_0, φ).

Theorem 10. *Assume the initial conditions satisfy*

$$\|(Q_0, \varphi)\| \leq \frac{\bar{r}}{1 + \dfrac{h_1^*}{1 - h_2^*}\tau}.$$

Then, $Q(t) \leq \overline{Q}(t)$ *and* $u(t) \leq \overline{u}(t)$*, for all* $t \geq 0$.

Proof. The proof will proceed by the method of steps. Let $t \in [0, \tau]$, then

$$\begin{aligned}(Q - \overline{Q})'(t) &\leq -\delta(t)Q(t) - \mathrm{j}(Q(t)) + \delta^*\overline{Q}(t) + \mathrm{j}(\overline{Q}(t)) + h_1(t)u(t - \tau) - h_1^*\overline{u}(t - \tau),\\ &< -\delta^*(Q - \overline{Q})(t) - (\mathrm{j}(Q(t)) - \mathrm{j}(\overline{Q}(t))) + h_1^*(u - \overline{u})(t - \tau).\end{aligned}$$

Now, because $u(t - \tau) = \overline{u}(t - \tau) = \varphi(t - \tau)$, we get

$$(Q - \overline{Q})'(t) < -\delta^*(Q - \overline{Q})(t) - (\mathrm{j}(Q(t)) - \mathrm{j}(\overline{Q}(t))).$$

As $(Q - \overline{Q})(0) = 0$ and $(Q - \overline{Q})'(0) < 0$, so $(Q - \overline{Q})$ starts negative. Suppose there exists $t_0 \in [0, \tau]$ such that $Q(t_0) = \overline{Q}(t_0) = 0$ and $Q(t_0) < \overline{Q}(t_0)$ for $0 \leq t < t_0$. Then, $(Q - \overline{Q})'(t_0) < 0$, which is a contradiction. So, $Q(t) < \overline{Q}(t)$ for all $t \in [0, \tau]$. In particular, $Q(t) < \bar{r}$ for all $t \in [0, \tau]$. So, given that j is increasing in $[0, \bar{r}]$, $\mathrm{j}(Q) - \mathrm{j}(\overline{Q}) < 0$. For the second equation in $[0, \tau]$,

$$(u - \overline{u})(t) < \mathrm{j}(Q) - \mathrm{j}(\overline{Q}) < 0.$$

Now, for $t \in [\tau, 2\tau]$, $t - \tau \in [0, \tau]$. So, $(u - \overline{u})(t - \tau) < 0$ and then

$$\begin{aligned}(Q - \overline{Q})'(t) &< -\delta^*(Q - \overline{Q})(t) - (\mathrm{j}(Q) - \mathrm{j}(\overline{Q})) + h_1^*(u - \overline{u})(t - \tau),\\ &< -\delta^*(Q - \overline{Q})(t) - (\mathrm{j}(Q) - \mathrm{j}(\overline{Q})).\end{aligned}$$

Given $(Q - \overline{Q})(\tau) < 0$ and $(Q - \overline{Q})'(\tau) < 0$, by a similar argument as before,

$$Q(t) < \overline{Q}(t) < \bar{r}, \quad \text{for all } t \in [\tau, 2\tau].$$

Similarly, for the second equation,

$$(u - \overline{u})'(t) < \mathrm{j}(Q(t)) - \mathrm{j}(\overline{Q}(t)) + h_1^*(u - \overline{u})(t - \tau) < 0.$$

The result follows inductively. □

Corollary 10.1. *Suppose that*

$$\|(Q_0, \varphi)\| \leq \frac{\bar{r}}{1 + \dfrac{h_1^*}{1 - h_2^*}\tau}.$$

Then, the solutions of the original system tend asymptotically to zero. That is, the trivial solution is locally asymptotically stable.

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