DISCRETE AND CONTINUOUS
DYNAMICAL SYSTEMS SERIES B

doi:10.3934/dcdsb.2018259

OSCILLATIONS AND ASYMPTOTIC CONVERGENCE FOR A DELAY DIFFERENTIAL EQUATION MODELING PLATELET PRODUCTION

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(Communicated by Tomas Gedeon)

Abstract. We analyze the existence of oscillating solutions and the asymptotic convergence for a nonlinear delay differential equation arising from the modeling of platelet production. We consider four different cell compartments corresponding to different cell maturity levels: stem cells, megakaryocytic progenitors, megakaryocytes, and platelets compartments, and the quantity of circulating thrombopoietin (TPO), a platelet regulation cytokine.

Our initial model consists in a nonlinear age-structured partial differential equation system, where each equation describes the dynamics of a single compartment. This system is reduced to a single nonlinear delay differential equation describing the dynamics of the platelet population, in which the delay accounts for a differentiation time.

After introducing the model, we prove the existence of a unique steady state for the delay differential equation. Then we determine necessary and sufficient conditions for the existence of oscillating solutions. Next we set up conditions to get local asymptotic stability and asymptotic convergence of this steady state. Finally we present a short analysis of the influence of the conditions at $t < 0$ on the proof for asymptotic convergence.

2010 *Mathematics Subject Classification.* Primary: 34K11, 34K20; Secondary: 92D25.

Key words and phrases. Megakaryopoiesis, platelet, oscillations, stability, delay.

LB was supported by the LABEX MILYON (ANR-10-LABX-0070) of Université de Lyon, within the program "Investissements d'Avenir" (ANR-11-IDEX-0007) operated by the French National Research Agency (ANR). Also, LB is supported by a grant of Région Rhône-Alpes and benefited of the help of the France Canada Research Fund, of the NSERC and of a support from MITACS.

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1. **Introduction.** Megakaryopoiesis, also known as thrombopoiesis or thrombocytopoiesis, is the process of production and regulation of platelets, the blood elements in charge of hemostasis [35]. All platelets originate from hematopoietic stem cells (HSC), like other blood cells (white cells, red blood cells), and differentiate through successive divisions into progenitor cells, a large class of undifferentiated immature cells. Megakaryocytic progenitors differentiate then into megakaryocytic precursors, called megakaryocytes. They are considered as the last stage of differentiation before producing mature differentiated cells. Megakaryocytes are very large cells of about 40 to 100 μ m of diameter, which corresponds to approximately 10 to 15 times the size of an average red blood cell. This large size is due to the fact that they perform endomitosis (division of the nucleus *without* cell division) and become polyploid (with a nucleus containing multiple pairs of DNA), before finally producing platelets through a fragmentation process [8]. Each megakaryocyte produces, in average, between 2,000 and 5,000 platelets [27, 28].

Platelets, which are enucleated cells, enter the bloodstream after production. The platelet lifespan in circulating blood is about 7 to 10 days in humans, and 4 days in mice [30]. The density of platelets is stable in every individual (150–400 $\times 10^9$ cells.L^{-1} in the healthy human adult, compared to 1,000-1,500 $\times 10^9$ cells.L^{-1} in normal mice), but it may vary between individuals [16], in particular in clinically significant disorders. The two main ones are thrombocytopenia and thrombocytosis. Thrombocytosis, characterized in humans by platelet counts greater than 600×10^9 cells.L^{-1}, can increase the risk for thrombotic events, including stroke, peripheral ischemia, and myocardial infarction [28]. Thrombocytopenia, also known as thrombopenia, corresponds to platelet counts less than 150×10^9 cells.L^{-1}, and can lead to inadequate clot formation and increased risk of bleeding. Cyclical thrombocytopenia (CT), a rare form of thrombocytopenia, is a disease characterized by oscillations of platelet counts with periods between 20 and 40 days [32] in humans, whose origin is currently unknown.

Several cytokines regulate platelet production, at various stages of differentiation [7, 37]. The main cytokine involved in megakaryopoiesis is thrombopoietin, or TPO: it has been shown to stimulate HSC differentiation [7], megakaryocytic progenitor proliferation and differentiation into megakaryocytes [27], and megakaryocyte production [27], and to induce megakaryocyte endomitosis, cytoplasmic expansion, membrane maturation and platelet release [17, 28].

TPO is constitutively produced by the liver [31] (and partially by kidneys and bone marrow). This means that production of TPO is not directly controlled by the platelet count. Nevertheless, the level of circulating TPO depends on the platelet count: these latter fix TPO on their surface through the protein c-Mpl. Consequently, the more circulating platelets the less circulating TPO [16], implying a decrease in platelet production, resulting in less in circulating platelets.

Mathematical modeling of thrombopoiesis has not attracted so much attention so far. Over the past thirty years, to our knowledge, five attempts to model platelet dynamics can be found, mostly focused on the description of CT.

Following early works by Wichmann *et al.* [36] and Eller *et al.* [9], in 2000 Santillan *et al.* [29] proposed an age-structured model for the regulation of platelet production, which is compared to both normal and pathological platelet production. The model is based on previous works by Bélair *et al.* [2] on erythropoiesis, and considers explicitly ploidy classes for megakaryocytes: three different classes (low, average and high ploidy) are described, and the recruitment of megakaryocytes depends

linearly on the TPO concentration. Santillan *et al.* [29] investigated the existence of steady states and estimated parameters from data on thrombocytopenic sheep, healthy human adults, and mice. They studied, in particular, numerical description of CT, and showed that data can be reproduced for large platelet destruction rates.

In 2008, Apostu and Mackey [1], inspired by a model of hematopoiesis dynamics describing the three main hematopoietic lineages [4, 5], focused on the causes of CT. Parameters were estimated and comparison to data indicated that the platelet destruction rate, the effective growth rate of megakaryocytes, the minimal number of platelets released per megakaryocyte, and the megakaryocyte maturation time played key roles in the onset of oscillations in platelet production.

Most recently, Langlois *et al.* [21] investigated the normal and pathological dynamics of platelets in humans, observing the dynamics in the amounts of megakaryocytes, of platelets and of TPO, with an up-regulation by TPO of the proliferation rate of progenitors and of the growth rate of megakaryocytes. The result is a system of two differential equations with a distributed delay, for which they estimated parameter values using clinical data and model fits.

Similarly to Santillan *et al.* [29] and Apostu and Mackey [1], Langlois *et al.* [21] used numerical tools to find parameters associated with oscillatory behaviors, and generated simulations matching the oscillating platelet counts observed in CT patients. However, powerful analytical results can be found in the mathematical literature concerning the long term behavior of delay differential equations like the ones describing megakaryopoiesis. For example, results regarding oscillation properties of hematopoiesis models have been obtained. Gopalsamy *et al.* [10] found a sufficient condition for oscillating solutions for the Mackey-Glass equation [23]

$$\dot{x}(t) = -\gamma x(t) + \frac{B}{1 + [x(t-r)]^n}, \tag{1}$$

where $\gamma, B, r, n > 0$, as well as a criterion that makes it a necessary condition ; and Kulenovic and Ladas [20] found a necessary and sufficient condition for oscillating solutions for the Lasota-Wazewska model of the red blood cell supply in an animal [34]

$$x'(t) = -\gamma x(t) + \rho e^{-\mu x(t-r)}, \tag{2}$$

where $\mu, \rho, \gamma, r > 0$.

Results can also be found regarding global stability for the general case

$$x'(t) = F(t, x_t), \tag{3}$$

using so-called "Yorke functional" (see [26] for a review). A framework has also been built for a more restricted family of equations

$$x'(t) = f_1(x(t-r))g_2(x(t)) - f_2(x(t-r))g_1(x(t)). \tag{4}$$

In particular, Ivanov *et al.* [15] obtained two results on global stability, one delay-independent and the other delay-dependent. They successfully applied the second one to the two equations

$$x'(t) = -x(t)\phi(x(t-h)) + 1,$$

with ϕ increasing positive, and

$$x'(t) = -g(x(t)) + f(x(t-h)),$$

with g positive increasing and f positive.

In this paper, we explore the potential of such analytical tools by proposing a new age-structured model of megakaryopoiesis, focusing on the differentiation pathway (from HSC to progenitors to megakaryocytes) and including the role of TPO. Despite the various influences of TPO on the differentiation process, we will only consider in this work its influence on the initiation of the differentiation process (stimulation of HSC differentiation) and its termination (up-regulation of the amount of platelets obtained through fragmentation) in order to retain most of TPO influence on platelet production and to facilitate the model's analysis. Complexifications of the current model could be considered in further analyses. Under these assumptions the age-structured model reduces to a scalar nonlinear delay differential equation on the platelet count which can be expressed as

$$x'(t) = -\gamma x(t) + f(x(t))g(x(t-r)), \tag{5}$$

with $\gamma, r > 0$ and f, g two decreasing positive functions. We notice that (5) is a generalization of (1) and (2), which motivates the search for a new criterion for the existence of oscillating solutions that would encompass the pre-existing results on these two subcases. We also notice that (5) is a subcase of both (3) and (4), but neither the "Yorke functional" nor the condition given in the result from Ivanov *et al.* can be applied to (5).

Unlike Ivanov *et al.* [15], we decided to study the equilibrium as an attractor for solutions on $\mathbb{R}^+$ rather than on $\mathbb{R}$: this requires to introduce a limitation on the initial behavior of the solution that we named the low initial slope condition, which depends heavily on the conditions at $t = 0$. Therefore we focus on asymptotic convergence rather than on global asymptotic stability. Finally, while the existence of periodic solutions have been addressed both for generalizations [25] and subcases [3, 33] of (5), these questions are out of the scope of this paper.

The paper goes as follows. In Section 2, we present the new age-structured model. In Section 3 we reduce this model to a delay differential equation on the platelet count and prove that it has a unique steady state, which is locally asymptotically stable. We also give a result on the boundedness of the solutions. Section 4 is dedicated to determining a sufficient and necessary condition for the existence of oscillating solutions. We show that this condition is equivalent to those given in [10] and in [20]. In Section 5 we define what we mean by low initial slope and we give the proof for a new delay-dependent condition for asymptotic convergence. Finally, in Section 6, we return to the biological premises of our model used to obtain (5): using a simplified version of the age-structured model, we give sufficient conditions on the initial conditions implying the low initial slope needed for asymptotic convergence.

2. **An age-structured model of megakaryopoiesis.**

In order to model megakaryopoiesis, we consider 4 different cell populations: hematopoietic stem cells (HSC), megakaryocytic progenitors, megakaryocytes, and platelets, and the quantity of circulating thrombopoietin (TPO). They are represented in Figure 1.

Hematopoietic stem cells partly differentiate in megakaryocytic progenitors under the action of TPO [7]. Megakaryocytic progenitors differentiate through successive divisions, and produce megakaryocytes. Megakaryocytes no longer differentiate, they only mature, without dividing. They perform endomitosis, increase their size (the size of their nucleus as well as the size of their cytoplasm), and finally produce platelets through a particular process of fragmentation [8]. The production of platelets, through the fragmentation of megakaryocytes, is also positively mediated by TPO [37].

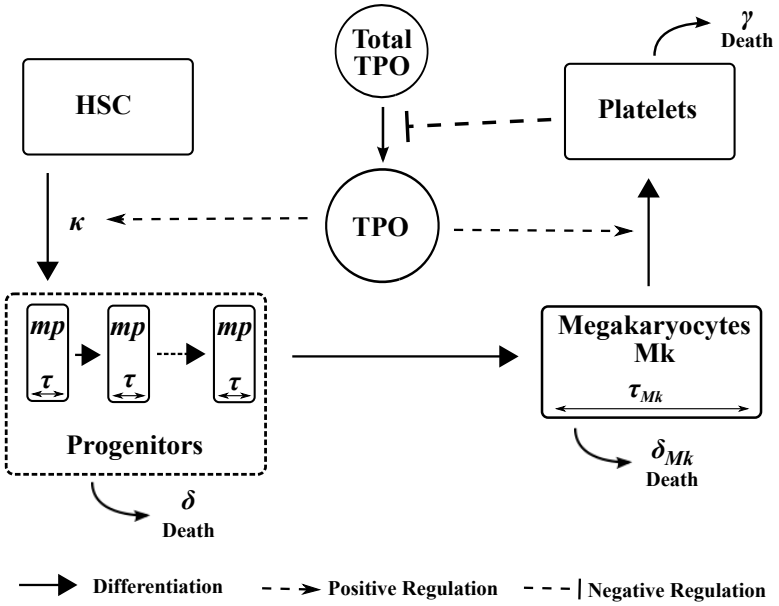

FIGURE 1. **Model of Megakaryopoiesis.** The linear differentiation process, starting from HSC and ending with platelets, is positively regulated by TPO. The quantity of TPO is in turn modulated by the number of platelets: the more platelets, the less circulating TPO.

TPO is constitutively produced by the liver [31]. However, the quantity of circulating TPO depends on the number of platelets which fix TPO on their surface and then negatively control the quantity of circulating TPO [16].

In order to model megakaryopoiesis and to analyze the resulting model, we give some biological assumptions, based on the above-mentioned remarks:

(H1) The number of HSC is constant over time, denoted by HSC;
(H2) The megakaryocytic progenitor cell cycle duration is assumed to be constant, equal to τ days;
(H3) The total quantity of TPO is constant, denoted by $TTPO$;
(H4) Circulating TPO positively mediates HSC differentiation in megakaryocytic progenitors, and fragmentation of megakaryocytes in platelets.

Assumption (H1) implies that we do not focus on HSC dynamics and regulation, we only consider that the platelet production process originates from the HSC compartment. Assumption (H4) allows us to focus on some specific roles of TPO in megakaryopoiesis.

In the following, we denote by $MP(t)$ the number of megakaryocytic progenitors, by $Mk(t)$ the number of megakaryocytes, by $P(t)$ the number of platelets in blood, and by $TPO(t)$ the quantity of circulating TPO, at time t.

2.1. **Megakaryocytic progenitor dynamics.** Let us focus on the progenitor cell population behavior. We suppose that megakaryocytic progenitors differentiate throughout n divisions, where $n \geq 1$ is fixed. We also assume that in each generation, progenitor cells either die with the same apoptosis rate $\delta > 0$, or divide after a

given fixed time $\tau > 0$. After division, progenitor cells immediately enter the next generation.

We denote by $mp_i(t,a)$ the number of megakaryocytic progenitors in the i-th generation, $1 \leq i \leq n$, with age $a \in [0,\tau]$ at time $t > 0$. Then, we assume that a TPO-dependent proportion $\kappa(TPO)$ of HSC differentiate in megakaryocytic progenitors and can be formulated as a standard feedback function as explained in [24]:

$$\kappa(TPO) = \frac{\alpha_\kappa TPO^{Q_\kappa}}{\theta_\kappa^{Q_\kappa} + TPO^{Q_\kappa}}, \tag{6}$$

such that $0 < \alpha_\kappa < 1$ is the maximum proportion of HSC differentiating in megakaryocytes, θ_κ the quantity of TPO needed to bring this proportion to $\alpha_\kappa/2$ and Q_κ a parameter controlling the sharpness of the change from low state to high state.

Hence, the following equations describe the megakaryocytic progenitor population dynamics:

$$\begin{cases} \dfrac{\partial}{\partial t}mp_i(t,a) + \dfrac{\partial}{\partial a}mp_i(t,a) &= -\delta mp_i(t,a), & \\ mp_1(t,0) &= \kappa(TPO(t))HSC, & \\ mp_i(t,0) &= 2mp_{i-1}(t,\tau), & 2 \leq i \leq n, \\ mp_i(0,a) &= I_{mp_i}(a), & 1 \leq i \leq n. \end{cases} \tag{7}$$

$I_{mp_i} : \mathbb{R}^+ \to \mathbb{R}^+$ is a continuous function representing the initial amount of progenitors of age a in the i-th generation. Denoting by $MP_i(t)$ the total number of megakaryocytic progenitors in the i-th generation, then

$$MP_i(t) := \int_0^\tau mp_i(t,a)da.$$

Integrating the age structured partial differential equations in (7) with respect to age, and using the method of characteristics (given here by the lines $a(t) = t + a_0$), one can easily obtain, for $1 \leq i \leq n$ and $t \geq n\tau$,

$$\begin{aligned} \frac{d}{dt}MP_i(t) =& -\delta MP_i(t) + \\ & 2^{i-1}e^{-\delta(i-1)\tau}\left[\kappa(TPO(t-(i-1)\tau)) - e^{-\delta\tau}\kappa(TPO(t-i\tau))\right]HSC, \end{aligned} \tag{8}$$

and $mp_i(t,\tau) = 2^{i-1}e^{-\delta i\tau}\kappa(TPO(t-i\tau))HSC$. In particular, the population of the last generation of progenitors at the end of its cycle is given by

$$mp_n(t,\tau) = 2^{n-1}e^{-\delta n\tau}\kappa(TPO(t-n\tau))HSC, \qquad t \geq n\tau. \tag{9}$$

This quantity is the cell population that leaves the progenitor compartment and reaches the megakaryocyte one. This population corresponds then to the boundary condition of the equation in the next section when age is equal to 0.

2.2. **Megakaryocyte dynamics.** Let us now focus on the dynamics of megakaryocytes. Contrary to progenitor cells, megakaryocytes only mature without dividing. We assume that this population dies with a rate δ_{Mk}. The maturation time is denoted by τ_{Mk} (days). The megakaryocyte population is supplied with progenitor cells from the n-th generation (see the previous section), that has differentiated in megakaryocytes.

Denote by $mk(t,a)$ the number of megakaryocytes with age $a \in [0, \tau_{Mk}]$ at time t. Then $mk(t,a)$ satisfies the following age-structured system,

$$\begin{cases} \dfrac{\partial}{\partial t}mk(t,a) + \dfrac{\partial}{\partial a}mk(t,a) &= -\delta_{Mk}mk(t,a), \\ mk(t,0) &= 2mp_n(t,\tau), \\ mk(0,a) &= I_{mk}(a). \end{cases} \tag{10}$$

$I_{mk} : \mathbb{R}^+ \to \mathbb{R}^+$ is a continuous function representing the initial amount of megakaryocytes of age a at $t = 0$. With the total number of megakaryocytes given by

$$Mk(t) := \int_0^{\tau_{Mk}} mk(t,a)da,$$

then using (9) and integrating (10) over the age variable a and using the method of characteristics, it is straightforward to get, for $t \geq \tau_{Mk} + n\tau$,

$$\begin{aligned} \frac{d}{dt}Mk(t) = &- \delta_{Mk}Mk(t) + 2^n e^{-\delta n\tau}\big[\kappa(TPO(t-n\tau)) \\ &- e^{-\delta_{Mk}\tau_{Mk}}\kappa(TPO(t-r_{Mk}-n\tau))\big]HSC, \end{aligned} \tag{11}$$

and

$$mk(t,\tau_{Mk}) = 2^n e^{-\delta n\tau}e^{-\delta_{Mk}\tau_{Mk}}\kappa(TPO(t-r_{Mk}-n\tau))HSC, \quad t \geq \tau_{Mk}+n\tau. \tag{12}$$

This last equality is used as the boundary condition for the next equation.

2.3. **Platelet dynamics.** Let us now concentrate on the platelet population. We denote by $p(t,a)$ the number of platelets of age $a \geq 0$ at time t, with the total number of platelets at time t given by

$$P(t) = \int_0^{+\infty} p(t,a)da.$$

We denote by γ the mortality rate of platelets. Then we assume that the TPO-dependent amplification factor describing the average number of platelets obtained from the fragmentation of a single megakaryocyte $A(TPO)$ can be formulated as a standard feedback function as explained in [24],

$$A(TPO) = \frac{\alpha_A TPO^{Q_A}}{\theta_A^{Q_A} + TPO^{Q_A}}, \tag{13}$$

such that α_A is the maximum amount of platelets that can be produced by a megakaryocyte, θ_A the quantity of TPO needed to bring this quantity to $\alpha_A/2$ and Q_A a sensitivity parameter.

Hence, we write the following system,

$$\begin{cases} \dfrac{\partial}{\partial t}p(t,a) + \dfrac{\partial}{\partial a}p(t,a) &= -\gamma p(t,a), \\ p(t,0) &= A(TPO(t))mk(t,\tau_{Mk}), \\ \lim_{a\to+\infty} p(t,a) &= 0, \\ p(0,a) &= I_p(a). \end{cases} \tag{14}$$

The function $I_p(a)$ represents the initial amount of platelets of age a. Using (12), this system reduces to an equation for $P(t)$, given for $t \geq \tau_{Mk} + n\tau$ by

$$\frac{d}{dt}P(t) = -\gamma P(t) + 2^n e^{-\delta n\tau}e^{-\delta_{Mk}\tau_{Mk}}\kappa(TPO(t-r_{Mk}-n\tau))A(TPO(t))HSC. \tag{15}$$

This platelet population is the one released in the blood stream that regulates the circulating TPO level. This is described in the next section.

2.4. **Circulating TPO regulation.** Finally, let us focus on the evolution of the quantity of TPO. The circulating TPO quantity, denoted by $TPO(t)$, is proportional to the total quantity of TPO, $TTPO$, and the proportionality coefficient depends on the total number of platelets $P(t)$: the more platelets, the less circulating TPO [16]. We define

$$TPO(t) = \alpha(P(t))TTPO, \tag{16}$$

where α is a decreasing function, that could be chosen as a Hill function, as a standard feedback function as explained in [24],

$$\alpha(P) = \frac{\theta_T^{Q_T}}{\theta_T^{Q_T} + P^{Q_T}}, \qquad \theta_T, Q_T > 0. \tag{17}$$

The TPO function can then be seen as a function of $P(t)$, and we write $TPO(t) = TPO(P(t))$.

Remark 1. In the following sections, we present simulations to illustrate analytical results. Hence, we use the formulations of $\kappa(TPO), A(TPO)$ and $\alpha(P)$ respectively given in Equations (6), (13) and (17). However, determining the correct parameters for these functions is not the object of this paper. We use biologically relevant parameters and plan to perform an estimation of these parameters in a later work.

The system formed with equations (7), (10), (14) and (16) is our age-structured system of thrombopoiesis dynamics. In the next section, we show that this system reduces to a delay differential equation describing evolution of the number of platelets $P(t)$, that it has a unique steady state. We also show that solutions are bounded.

3. **A delay differential equation describing platelet dynamics.** The age-structured system made of equations (7), (10), (14) and (16) is reduced to the nonlinear ordinary differential system of threshold-type made of equations (8), (11), (15) and (16), with initial conditions corresponding to the integration of the age-structured system on the corresponding time interval. Using (16) in Equation (15), the system of equations (8), (11), (15) and (16) is in turn equivalent, for $t \geq r := \tau_{Mk} + n\tau$, to the following delay differential equation,

$$\frac{d}{dt}x(t) = -\gamma x(t) + f(x(t))g(x(t-r)), \tag{18}$$

where

$$f := A \circ TPO \quad \text{and} \quad g := 2^n e^{-\delta n\tau} e^{-\delta_{Mk}\tau_{Mk}} HSC\kappa \circ TPO. \tag{19}$$

Functions $TPO \mapsto \kappa(TPO)$ and $TPO \mapsto A(TPO)$ are supposed to be increasing, since a lack of TPO decreases the differentiation of HSC in megakaryocytic progenitors as well as the production of platelets by megakaryocyte fragmentation. The function TPO is supposed to be a decreasing function of the amount of platelets, see (16) and (17). Consequently, functions f and g are assumed to be positive decreasing functions.

Equation (18) is a nonlinear delay differential equation, existence and uniqueness of solutions are straightforwardly obtained from Hale and Verduyn Lunel [14] under classical smoothness assumptions on the functions f and g. In addition, for every

nonnegative initial condition φ defined on $[0, r]$, the associated solution $x(\varphi, t)$ is nonnegative. Indeed, this result can be proven using the non-negativity of f and g.

We denote by x^* a steady state of (18), which is a solution satisfying $dx^*/dt = 0$. Then x^* satisfies

$$\chi(x^*) = 0, \qquad \text{with } \chi(x) = g(x)f(x) - \gamma x. \tag{20}$$

Since f and g are non-negative and decreasing continuously differentiable functions, then χ is decreasing, with

$$\chi'(x) = g'(x)f(x) + g(x)f'(x) - \gamma < 0.$$

Moreover,

$$\chi(0) = g(0)f(0) > 0 \qquad \text{and} \qquad \lim_{x\to+\infty} \chi(x) = -\infty.$$

Consequently, there exists a unique $x^* > 0$ solution of (20) and we can claim the following result.

Proposition 1. *Equation (18) has a unique steady state, denoted by x^*, positive, and satisfying*

$$g(x^*)f(x^*) = \gamma x^*. \tag{21}$$

In order to study the local asymptotic stability of x^*, Equation (18) is linearized about its unique steady state x^*, leading to

$$\frac{dx}{dt}(t) = [g(x^*)f'(x^*) - \gamma]x(t) + g'(x^*)f(x^*)x(t-r).$$

Thus, the associated characteristic equation is

$$\lambda + \gamma - g(x^*)f'(x^*) - g'(x^*)f(x^*)e^{-\lambda r} = 0. \tag{22}$$

Proposition 2. *If*

$$r < \frac{1}{-g'(x^*)f(x^*)}, \tag{23}$$

then the steady state x^* of (18) is locally asymptotically stable.

Proof. Equation (22) can be written as

$$\lambda + A + Be^{-r\lambda} = 0,$$

where

$$\begin{cases} A = \gamma - g(x^*)f'(x^*) > 0, \\ B = -g'(x^*)f(x^*) > 0. \end{cases}$$

If $B > A$, (23) implies

$$r < \frac{1}{B} < \frac{\pi/2}{B} < \frac{\arccos(-A/B)}{\sqrt{B^2 - A^2}}.$$

Therefore, condition (23) implies that either $A > B$ or

$$B > A \text{ and } r < \frac{\arccos(-A/B)}{\sqrt{B^2 - A^2}},$$

We use Theorem 8.6 of [6] to conclude the local stability of x^*. □

Boundedness of the solutions of Equation (18) is straightforwardly obtained, we mention it in the next proposition.

Proposition 3. *The solutions of (18) are eventually bounded by $x_{\max} = f(0)g(0)/\gamma$.*

The result of Proposition 3, establishing the boundedness of solutions of (18), together with the local asymptotic stability of the unique steady state of (18) given by proposition 2, indicate that under reasonable assumptions on the parameters of (18), asymptotic convergence should be obtained. Before that, we investigate the existence of oscillating solutions.

4. **Oscillating solutions.** Our aim in this part is to show that under appropriate hypotheses every positive solution of Equation (18) oscillates about its positive steady state x^*, with damped oscillations. Recall that a solution x of (18) is said to oscillate (or to be oscillatory) about x^* if $t \mapsto x(t) - x^*$ has arbitrarily large zeros. That is, for every $t > r$ there exists $s > t$ such that $x(s) = x^*$. Otherwise, x is called non-oscillatory about x^*. As mentioned in the introduction, oscillations of platelet counts can sometimes be associated to hematological diseases, such as cyclical thrombocytopenia, and therefore existence of oscillations in platelet numbers are biologically relevant. We establish a link between the oscillatory character of (18) and that of its associated linearized equation about the steady state x^*

$$\frac{d}{dt}u(t) + (\gamma + p)u(t) + qu(t-r) = 0, \tag{24}$$

where

$$\begin{cases} p &= -f'(x^*)\, g(x^*) &> 0, \\ q &= -f(x^*)\, g'(x^*) &> 0. \end{cases} \tag{25}$$

The characteristic equation associated to (24) is

$$\Delta(\lambda) := \lambda + (\gamma + p) + qe^{-\lambda r} = 0. \tag{26}$$

We begin with a basic result on the existence of oscillations of the linear delay differential equation (24).

Proposition 4. *Every solution of Equation (24) oscillates if and only if*

$$rqe^{(\gamma+p)r} > \frac{1}{e}. \tag{27}$$

Proof. In the theory of oscillations of linear delay differential equations with constant coefficients (see [12]), every solution of (24) oscillates if and only if the characteristic equation (26) has no real root. Consider $\Delta : \mathbb{R} \to \mathbb{R}$ as a real function. Then, we have

$$\frac{d}{d\lambda}\Delta(\lambda) = 1 - rqe^{-\lambda r} \quad \text{and} \quad \lim_{\lambda \to \pm\infty} \Delta(\lambda) = +\infty.$$

Then, the minimum of Δ is given by

$$\Delta\left(\frac{1}{r}\ln(rq)\right) = \frac{1}{r}\left(\ln(rq) + r(\gamma + p) + 1\right).$$

Hence

$$\frac{1}{r}\left(\ln(rq) + r(\gamma + p) + 1\right) > 0$$

is a necessary and sufficient condition for the oscillation of all solutions of Equation (24), and it is equivalent to (27). □

Now we can state and prove the next result.

Theorem 4.1. *Assume that*

$$rqe^{(\gamma+p)r} > \frac{1}{e}. \tag{28}$$

Then, every positive solution of Equation (18) oscillates about the steady state x^*.

Proof. Suppose by contradiction that Equation (18) has a non-oscillatory solution x. Then, there exists $T > 0$ such that $x(t) > x^*$ (or $x(t) < x^*$), for all $t \geq T$. See in the proof of Theorem 5.1 that x is decreasing (or x is increasing) and $\lim_{t\to+\infty} x(t) = x^*$. We focus on the case $x(t) > x^*$. The proof in the case $x(t) < x^*$ is similar. We set

$$y(t) = x(t) - x^*.$$

Then, the function y is positive and decreasing on $[T, +\infty)$ with $\lim\limits_{t\to+\infty} y(t) = 0$. On the other hand, y satisfies the delay differential equation

$$\begin{aligned}\frac{d}{dt}y(t) &= -\gamma(y(t)+x^*) + f\left(y(t)+x^*\right) g\left(y(t-r)+x^*\right), \\ &= -\gamma y(t) + \left[f\left(y(t)+x^*\right) - f\left(x^*\right)\right] g\left(y(t-r)+x^*\right) \\ &\quad + f\left(x^*\right)\left[g\left(y(t-r)+x^*\right) - g\left(x^*\right)\right].\end{aligned}$$

Remark that

$$\lim_{t\to+\infty}\left[\frac{f\left(y(t)+x^*\right)-f\left(x^*\right)}{y(t)}\right] g\left(y(t-r)+x^*\right) = f'\left(x^*\right) g\left(x^*\right) < 0,$$

and

$$\lim_{t\to+\infty}\frac{g\left(y(t-r)+x^*\right)-g\left(x^*\right)}{y(t-r)} = g'\left(x^*\right) < 0.$$

Let $\varepsilon \in (0,1)$. We have

$$\left\{\begin{array}{rcccl} f'\left(x^*\right) g\left(x^*\right) & < & (1-\varepsilon) f'\left(x^*\right) g\left(x^*\right) & < & 0, \\ g'\left(x^*\right) & < & (1-\varepsilon) g'\left(x^*\right) & < & 0. \end{array}\right.$$

The function y is positive, then there exists $t_\varepsilon > T + r$ such that, for $t \geq t_\varepsilon$,

$$\left\{\begin{array}{rcl} \left[f\left(y(t)+x^*\right) - f\left(x^*\right)\right] g\left(y(t-r)+x^*\right) & \leq & (1-\varepsilon) f'\left(x^*\right) g\left(x^*\right) y(t), \\ \left[g\left(y(t-r)+x^*\right) - g\left(x^*\right)\right] & \leq & (1-\varepsilon) g'\left(x^*\right) y(t-r). \end{array}\right.$$

Summing these inequalities we obtain for $t \geq t_\varepsilon$,

$$\begin{aligned}&\left[f\left(y(t)+x^*\right) - f\left(x^*\right)\right] g\left(y(t-r)+x^*\right) + f\left(x^*\right)\left[g\left(y(t-r)+x^*\right) - g\left(x^*\right)\right] \\ &\leq (1-\varepsilon)\left[f'\left(x^*\right) g\left(x^*\right) y(t) + f\left(x^*\right) g'\left(x^*\right) y(t-r)\right].\end{aligned}$$

We conclude that y is a positive solution of the following delay differential inequality

$$y'(t) + (\gamma + (1-\varepsilon)\, p)\, y(t) + (1-\varepsilon)\, q y(t-r) \leq 0, \quad t \geq t_\varepsilon,$$

where p and q are given by (25).

We use the transformation

$$z(t) = e^{\gamma t} y(t),$$

to obtain

$$z'(t) + (1-\varepsilon)\left[p z(t) + e^{\gamma r} q z(t-r)\right] \leq 0, \quad t \geq t_\varepsilon. \tag{29}$$

From [12], we know that the delay differential inequality (29) has positive solution if and only if the delay differential equation

$$u'(t) + p u(t) + e^{\gamma r} q u(t-r) = 0, \quad t \geq t_\varepsilon, \tag{30}$$

has a positive solution.

We use the transformation

$$v(t) = e^{pt} u(t),$$

to write Equation (30) in the following form

$$v'(t) + e^{(\gamma+p)r} q v(t-r) = 0, \quad t \geq t_\varepsilon. \tag{31}$$

From [12] (Theorem 2.2.3), we know that there exists positive solutions of Equation (31) if and only if $re^{(\gamma+p)r}q \leq 1/e$. Therefore if (28) is verified, none of the solutions of (30), neither of (31), are positive, hence (29) has no positive solution: y is not positive. By contradiction, it implies that x is oscillatory. □

Using the formulations of f and g as given in Equation (19), we present in Figure 2 an example of the onset of oscillations as the value $rqe^{r(\gamma+p)} - \frac{1}{e}$ goes from negative to positive along with a change in parameters.

To prove that condition (28) is a necessary condition for the oscillation of every positive solution of (18), we add the following assumption: There exists $\eta > 0$ such that

$$\begin{cases} f(x^*+h) - f(x^*) & \geq & f'(x^*)h, & \text{for } 0 < h \leq \eta, \\ g(x^*+h) - g(x^*) & \geq & g'(x^*)h, & \text{for } 0 < h \leq \eta, \\ f(x^*+h) - f(x^*) & \leq & f'(x^*)h, & \text{for } -\eta \leq h < 0, \\ g(x^*+h) - g(x^*) & \leq & g'(x^*)h, & \text{for } -\eta \leq h < 0. \end{cases} \tag{32}$$

We need the following comparison results for positive solutions of delay differential inequalities.

Lemma 4.2. [12] *Let $a_i \geq 0$, $b_i \geq 0$, $c_i \geq 0$, $r_i \geq 0$ for $i = 1, ..., n$, and $0 \leq t_0 < T \leq +\infty$. Suppose that*

$$a_i \geq b_i \geq c_i, \quad i = 1, ..., n.$$

Assume that $x(t)$, $y(t)$, and $z(t)$ are solutions of

$$\begin{cases} x'(t) + \sum_{i=1}^{n} a_i x(t - r_i) \leq 0, & t_0 \leq t < T, \\ x(t) > 0, & t_0 \leq t < T, \\ y'(t) + \sum_{i=1}^{n} b_i y(t - r_i) = 0, & t_0 \leq t < T, \\ z'(t) + \sum_{i=1}^{n} c_i z(t - r_i) \geq 0, & t_0 \leq t < T, \end{cases}$$

with initial conditions on $[t_0 - r, t_0]$ such that

$$\begin{cases} z(t_0) \geq y(t_0) \geq x(t_0), \\ \dfrac{x(t)}{x(t_0)} \geq \dfrac{y(t)}{y(t_0)} \geq \dfrac{z(t)}{z(t_0)} \geq 0, \quad t_0 - r \leq t \leq t_0. \end{cases}$$

Then,

$$z(t) \geq y(t) \geq x(t), \quad t_0 \leq t < T.$$

Proposition 5. *Assume that (32) is satisfied. Then, every positive solution of Equation (18) oscillates about the steady state x^* if and only if*

$$rqe^{r(\gamma+p)} > \frac{1}{e}.$$

Proof. We need to prove that if $rqe^{r(\gamma+p)} \leq \frac{1}{e}$ then (18) has a non-oscillatory solution. Proposition 4 implies that if $rqe^{r(\gamma+p)} \leq \frac{1}{e}$ then the linearized Equation (24) has a non-oscillatory solution. It means that it is enough to prove that if (24) has a non-oscillatory solution then (18) has a non-oscillatory positive solution. Suppose that Equation (24) has a positive solution $t \mapsto u(t)$ for $t \geq T$ (the proof for a negative solution follows the same steps). Then, u is decreasing for $t \geq T$ and $\lim_{t \to +\infty} u(t) = 0$. This means that there exists $t_0 \geq T$ such that $0 < u(t) < \eta$, $t \geq t_0$.

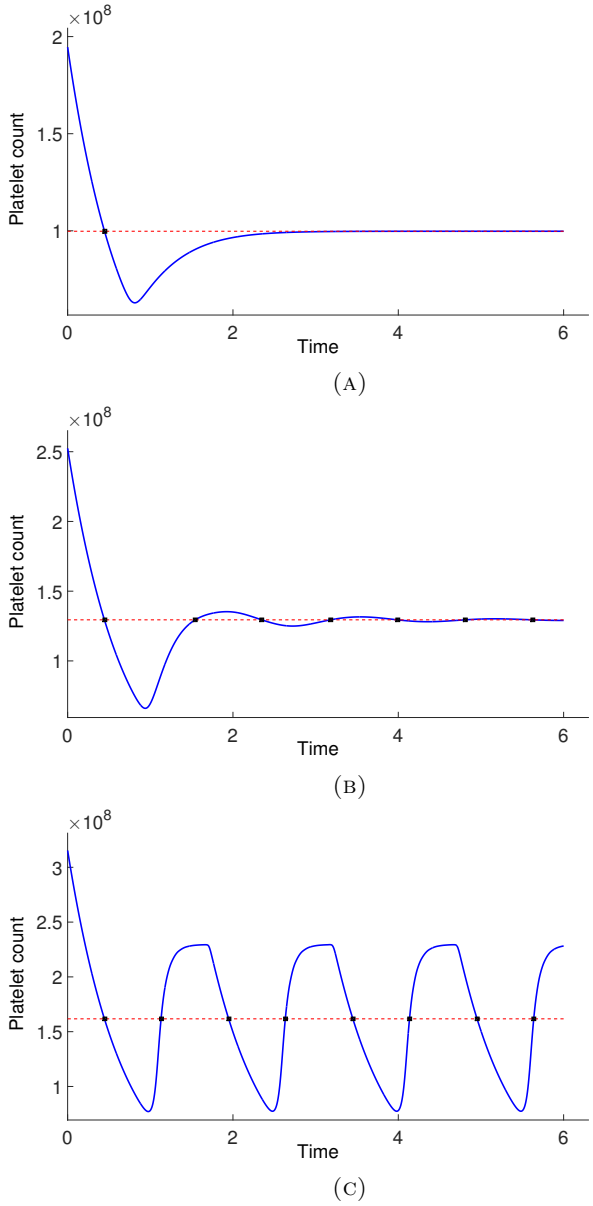

FIGURE 2. **Oscillations appear when α_A increases.** As α_A (the maximum number of platelets that a megakaryocyte can shed, see Equation (6)) increases, $R = rqe^{r(\gamma+p)} - \frac{1}{e}$ becomes positive and x (blue) starts to oscillate around x^* (dashed red). Black marks are placed where $x(t)$ goes through x^*. (A) $\alpha_A = 5000, R = -0.0492$ and there are no oscillations. (C) $\alpha_A = 10000, R = 7.6863$ and there are oscillations. (B) $\alpha_A = 20000, R = 83$ and there are oscillations.

Let x be the solution of (18) with initial condition equal to $t \mapsto u(t) + x^*$ for $t_0 - r \leq t \leq t_0$. We introduce $t \mapsto y(t) := x(t) - x^*$, and we notice that for $t \geq t_0$ we have

$$\begin{aligned} 0 = y'(t) - x'(t) &= y'(t) + \gamma x(t) - f(x(t))g(x(t-r)) \\ &= y'(t) + \gamma(y(t) + x^*) - f(y(t) + x^*)g(y(t-r) + x^*) \\ &= y'(t) + \gamma y(t) + f(x^*)g(x^*) - f(y(t) + x^*)g(y(t-r) + x^*). \end{aligned}$$

Then, the function y is the solution of

$$\begin{cases} 0 &= y'(t) + \gamma y(t) + f(x^*)g(x^*) - f(y(t) + x^*)g(y(t-r) + x^*), \quad \text{for } t \geq t_0, \\ y(t) &= u(t), \quad t_0 - r \leq t \leq t_0, \end{cases}$$

with

$$0 < y(t) = u(t) < \eta, \ t_0 - r \leq t \leq t_0.$$

Assumption (32) implies

$$f(x^* + h)\, g(x^* + h) \geq \big(f'(x^*)\, h + f(x^*)\big)\big(g'(x^*) + g(x^*)\big), \quad \text{for } 0 < h \leq \eta,$$

such that

$$\begin{aligned} & f(x^*)g(x^*) - f(y(t) + x^*)f(y(t-r) + x^*) \\ \leq & f(x^*)g(x^*) - \big[g'(x^*)y(t) + f(x^*)\big]\big[g'(x^*)y(t-r) + g(x^*)\big] \\ \leq & - f'(x^*)g'(x^*)y(t-r)y(t) - f'(x^*)g(x^*)y(t) - f(x^*)g'(x^*)y(t-r) \\ \leq & e^{\delta r}\big(py(t) + qy(t-r)\big). \end{aligned}$$

It means that for $t < t_0 + \varepsilon$,

$$y'(t) + (\gamma + p)\, y(t) + qy(t-r) \geq y'(t) + \gamma y(t) + f(x^*)g(x^*) - f(y(t) + x^*)g(y(t-r) + x^*),$$

implying

$$y'(t) + (\gamma + p)\, y(t) + qy(t-r) \geq 0,$$

with

$$0 < y(t) = u(t) < \eta, \ t_0 - r \leq t \leq t_0.$$

Thanks to Lemma 4.2,

$$0 < u(t) \leq y(t) < \eta, \ \text{for } t_0 \leq t < t_0 + \varepsilon.$$

As f and g are decreasing, y is also decreasing on $[t_0, t_0 + \varepsilon)$. So,

$$0 < u(t + \varepsilon) \leq y(t_0 + \varepsilon) < \eta.$$

By steps, we conclude that

$$0 < y(t) < \eta, \ \text{for all } t \geq t_0.$$

It follows from Lemma 4.2, that

$$0 < u(t) \leq y(t) < \eta, \ \text{for } t \geq t_0.$$

Therefore, x is a non-oscillatory positive solution of Equation (18) and the proof is complete. □

Remark 2. We apply Theorem 4.1 to the Mackey-Glass equation [10]

$$\dot{x}(t) = -\gamma x(t) + \frac{B}{1 + [x(t-r)]^n}, \tag{33}$$

which is a specific case of (18) with the functions $x \mapsto f(x) = 1$ and $x \mapsto g(x) = B/(1 + x^n)$. The fixed point x^* is the solution of $B/(1 + x^{*n}) = \gamma x^*$, and satisfies

$$g'(x^*) = -(nBx^{*n-1})/((1 + x^{*n})^2) = -(\gamma^2 x^{*n+1} n)/B.$$

From (25)

$$p = 0 \quad \text{and} \quad q = \frac{\gamma^2 x^{*n+1} n}{B},$$

such that the sufficient condition for the oscillation of every positive solution of (33) is

$$\tau \frac{\gamma^2 x^{*n+1} n}{B} e^{\tau\gamma} > \frac{1}{e},$$

that is

$$x^* > \Big(\frac{B}{e\gamma^2 n\tau e^{\gamma\tau}}\Big)^{1/(n+1)}.$$

Furthermore, condition (32) for $h > 0$ can be written

$$\frac{B}{1+(x^*+h)^n} - \frac{B}{1+x^{*n}} \geq -h\frac{nBx^{*n-1}}{(1+x^{*n})^2},$$

which is equivalent to

$$\sigma(h) := \big((x^*+h)^n - x^{*n}\big)\big(1+x^{*n}\big) - \big(1+(x^*+h)^n\big)\big(nhx^{*n-1}\big) \leq 0.$$

Notice that $\sigma(0) = 0$ and

$$\sigma'(h) = n(x^*+h)^{n-1} - [n(x^*+h)^{n-1} nhx^{*n-1} + (1+(x^*+h)^n) nx^{*n-1}],$$

hence $\sigma'(0) = nx^{*n-1}(1-x^{*n})$ for $h = 0$. If $x^* > 1$, $\sigma'(0)$ is negative, which implies that there exists $\eta > 0$ such that (2) is satisfied for $0 < h < \eta$. The same result can be found for the condition (32) for $h < 0$. Therefore, from Theorem 4.1, if $x^* > \Big(B/(e\gamma^2 n\tau e^{\gamma\tau})\Big)^{1/(n+1)}$ then every solution of (33) oscillates about its positive equilibrium x^*, and from Proposition 5 $x^* > 1$ implies that this condition is necessary.

Consequently, in the case of the Mackey-Glass equation (33), Theorem 4.1 and Proposition 5 are equivalent to Theorems 2.1 (a) and 2.1 (b) of Gopalsamy *et al.* [10].

Remark 3. We apply Theorem 4.1 to the Lasota-Wazewska equation [20]

$$x'(t) = -\gamma x(t) + \rho e^{-\mu x(t-r)}, \tag{34}$$

which is a specific case of (18) with $x \mapsto f(x) = 1$ and $x \mapsto g(x) = \rho e^{-\mu x}$ such that

$$g'(N^*) = -\mu\rho e^{-\mu N^*} = -\gamma\mu N^*,$$

where $N^* = \frac{\rho}{\gamma} e^{-\mu N^*}$. From (25),

$$p = 0 \quad \text{and} \quad q = \gamma\mu N^*,$$

such that the sufficient condition for the oscillation of every positive solution of (34) is

$$rqe^{(\gamma+p)r} = \mu r\gamma N^* e^{\gamma r} > \frac{1}{e}.$$

Furthermore, condition (32) for $h > 0$ can be written

$$\rho e^{-\mu(N^*+h)} - \rho e^{-\mu N^*} \geq -\mu\rho e^{-\mu N^*} h, \tag{35}$$

which is equivalent to

$$e^{-\mu h} - 1 \geq -\mu h.$$

Using Taylor expansion of e^x for $x > 0$ near 0, we find that there exists η such that (35) is satisfied for $0 < h < \eta$. The same way we can show that condition (32) for

$h < 0$ is verified. Therefore, from Theorem 4.1 and Proposition 5, the solution N(t) of (34) oscillates about N^* if and only if $\mu r \gamma N^* e^{\gamma r} > \frac{1}{e}$.

Consequently, in the case of the Lasota-Wazewska model, Theorem 4.1 and Proposition 5 are equivalent to Theorem 3 of Kulenovic and Ladas [20].

Condition (28) needed for solutions to oscillate holds for large values of r and γ. This means that oscillating solutions are obtained for large immature cell mortality rates and/or with short (resp. long) differentiation times. Furthermore, tedious computations reveal that parameters from the function describing the interaction between TPO and platelets have an impact on this sufficient condition: sufficiently increasing q (representing the strength of the feedback on TPO from platelets), decreasing TTPO (the total amount of TPO in the blood) or decreasing θ (a sensitivity parameter) will lead to condition (28). Similarly, as shown in Figure 2, there exists a set of parameters for which the condition $rqe^{(\gamma+p)r} > 1/e$ can be reached simply by increasing α_A, a parameter from the fragmentation function A representing the maximum number of platelets that can be shed by one megakaryocyte.

In the next section we will obtain a sufficient condition for asymptotic convergence.

5. Asymptotic convergence.

In order to study the asymptotic convergence of the unique steady state x^* of (18), it is worthwhile to discuss whether solutions of (18) are oscillatory or not.

Theorem 5.1. *If x is non-oscillatory about x^* then, $\lim_{t\to+\infty} x(t) = x^*$.*

Proof. Let x be a non-oscillatory solution of Equation (18). Then, there exists $t_0 \geq r$ such that $x(t) - x^*$ is either negative or positive for all $t \geq t_0$. These two cases can be treated in the same manner, then we study only one case.

Assume that there exists $t_0 \geq r$ such that $0 \leq x(t) \leq x^*$, for every $t \geq t_0$. Let $t \geq t_0 + r$. Then,

$$0 \leq x(t-r) \leq x^* \quad \text{and} \quad 0 \leq x(t) \leq x^*.$$

The functions f and g are decreasing, then for $t \geq t_0 + r$,

$$g(x^*) \leq g(x(t-r)), \quad f(x^*) \leq f(x(t)) \quad \text{and} \quad -\gamma x^* \leq -\gamma x(t).$$

So, from (21)

$$x'(t) \geq -\gamma x^* + f(x^*)\, g(x^*) = 0, \quad \text{for } t \geq t_0 + r.$$

Consequently, the solution x is increasing for $t \geq t_0 + r$. As x is bounded (Proposition 3), we get

$$\lim_{t\to+\infty} x(t) = x^*.$$

□

The next theorem deals with the asymptotic convergence of the unique steady state x^* of (18) in the case of oscillating initial conditions.

Definition 5.2. Let $x(t), t > 0$, be a solution of Equation (18) such that there exists a first time $t_0 > 0$ such that $x(t_0) = x^*$. Then we will say that $x(t)$ has a low initial slope if $t_0 \geq r$.

Figure 3 represents solutions of the same equation with different initial values, one with low initial slope, the other without low initial slope.

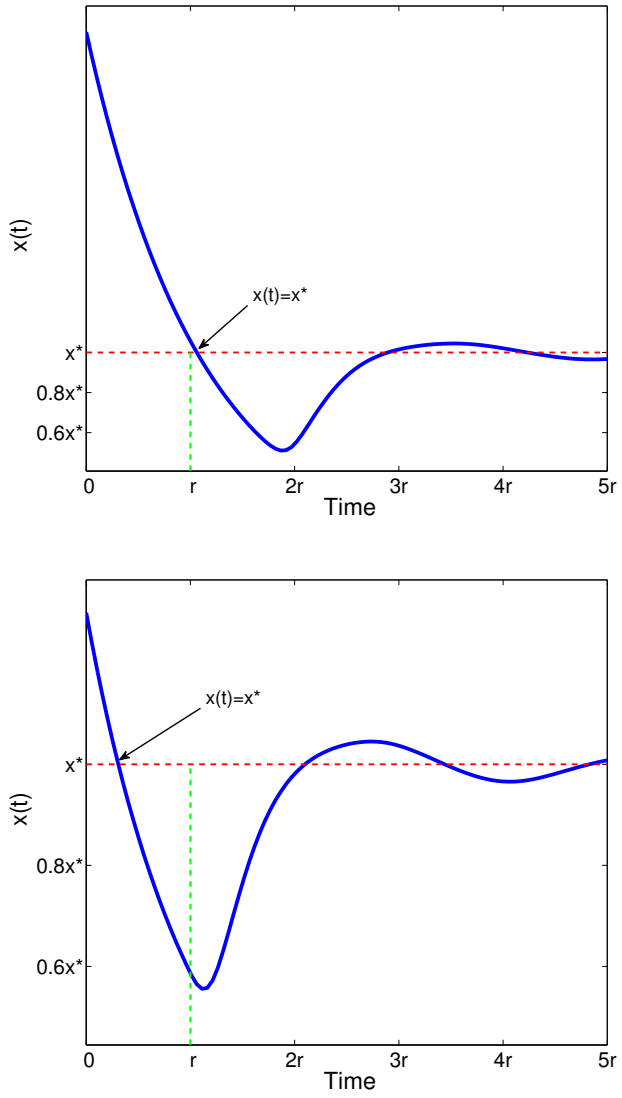

FIGURE 3. **Solutions of (18) with or without low initial slope.** (Top) The solution goes through $x(t) = x^*$ after $t = r$, it meets the low initial slope criterion. (Bottom) The solution goes through $x(t) = x^*$ before $t = r$, it does not meet the low initial slope criterion.

Theorem 5.3. *Let assume that*

$$\gamma r \leq 1 \quad \text{and} \quad r f(x^*) \sup_{x \in \mathbb{R}^+} |g'(x)| < 1. \tag{36}$$

Let x be a solution of system (18) on $\mathbb{R}^+$. If x oscillates about x^* and satisfies the low initial slope condition, then $\lim_{t \to +\infty} x(t) = x^*$.

Proof. Let x be an oscillatory solution of Equation (18) about x^*. Then, there exists a sequence $(t_n)_{n\in\mathbb{N}}$, $t_0 < t_1 < ... < t_n < ...$, $\lim_{n\to+\infty} t_n = +\infty$, such that $x(t_n) = x^*$ for all $n \in \mathbb{N}$. Suppose indeed that $t_0 \geq 0$ is the first point such that $x(t_0) = x^*$ and $x(t) > x^*$, for $t \in (t_0, t_1)$. Then there exists $t_0^* \in (t_0, t_1)$ such that the function x reaches its maximum at $t = t_0^*$, *i.e.* $x'(t_0^*) = 0$.

Because of the low initial slope hypothesis and as $t_0^* > t_0$, we know that $t_0^* > r$, hence we can apply the differential equation (18):

$$-\gamma x(t_0^*) + f\left(x(t_0^*)\right) g\left(x(t_0^* - r)\right) = 0.$$

Consequently,

$$g\left(x(t_0^* - r)\right) = \frac{\gamma x(t_0^*)}{f\left(x(t_0^*)\right)}. \tag{37}$$

Note that, since f is decreasing, the function $x \mapsto \gamma x / f(x)$ is increasing. Moreover, $x(t_0^*) > x^*$. Then, from (21) and (37),

$$g\left(x(t_0^* - r)\right) > \frac{\gamma x^*}{f(x^*)} = g(x^*).$$

The function g being decreasing, this yields $x(t_0^* - r) < x^* = x(t_0)$, and consequently

$$t_0^* - r < t_0 < t_0^*.$$

On the other hand, $x(t_1) = x^*$ and $x'(t_1) \leq 0$, so from (18),

$$-\gamma x^* + f(x^*)\, g\left(x(t_1 - r)\right) \leq 0.$$

Similarly, we get

$$t_1 - r \geq t_0.$$

We then obtain

$$t_0^* - t_0 < r \leq t_1 - t_0.$$

Using the same arguments, we prove

$$t_n^* - t_n < r \leq t_{n+1} - t_n, \quad \text{for all } n \in \mathbb{N}, \tag{38}$$

with $t_n^* \in (t_n, t_{n+1})$ defined by $x'(t_n^*) = 0$.

Next, we build a sequence $(x_n)_{n\in\mathbb{N}}$ from which we extract two subsequences $(y_n)_{n\in\mathbb{N}}$ and $(z_n)_{n\in\mathbb{N}}$ converging towards x^* with

$$y_n \leq x(t_{2n+1}^*) < x^* < x(t_{2n}^*) \leq z_n, \quad \text{for } n \in \mathbb{N}.$$

Because of the low initial slope hypothesis, we can integrate Equation (18) from t_0 to t_0^*, such that we obtain

$$x(t_0^*) \leq x^* - \gamma \int_{t_0}^{t_0^*} x(s)ds + g(0) \int_{t_0}^{t_0^*} f\left(x(s)\right) ds.$$

For $s \in (t_0, t_0^*]$, $x(s) > x^*$. Then, as the function f is decreasing and from (21) and the above inequality, we get

$$x^* < x(t_0^*) \leq x_1 := x^* + r f(x^*) \left[g(0) - g(x^*)\right]. \tag{39}$$

Let $s \in (t_1, t_1^*]$. Then $0 \leq x(s) < x^*$, and thanks to (38), we obtain $s - r \in (t_1 - r, t_1^* - r] \subseteq (t_0, t_1)$, so $x(s - r) \leq x(t_0^*) \leq x_1$. Therefore, by integrating (18) from t_1 to t_1^*, we get

$$x(t_1^*) \geq x^* - \gamma \int_{t_1}^{t_1^*} x(s)ds + g(x_1) \int_{t_1}^{t_1^*} f\left(x(s)\right) ds.$$

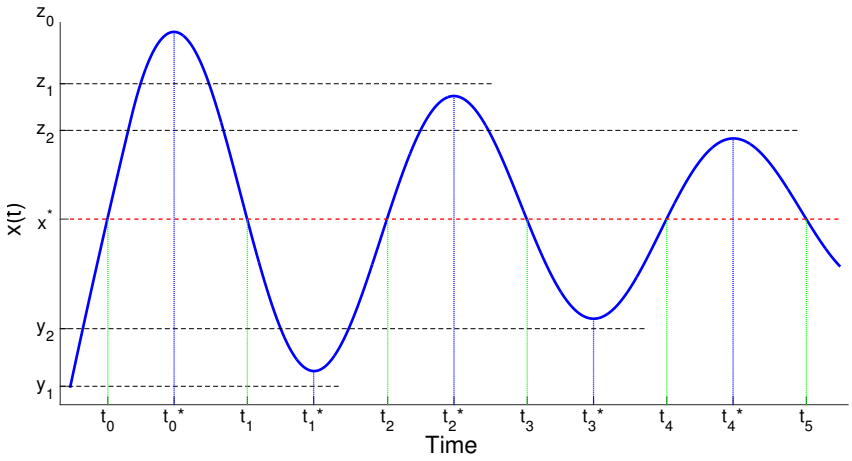

FIGURE 4. **An example of sequences** $(y_n)_{n\in\mathbb{N}}$ **and** $(z_n)_{n\in\mathbb{N}}$. The decreasing (resp. increasing) sequence $(z_n)_{n\in\mathbb{N}}$ (resp. $(y_n)_{n\in\mathbb{N}}$) bounds $x(t)$ for $t > t^*_{2n}$ (resp. for $t > t_{2n-1}$).

It follows that

$$x^* > x(t_1^*) \geq x_2 := x^* + rf\left(x^*\right)\left[g\left(x_1\right) - g\left(x^*\right)\right]. \tag{40}$$

Then, we build a sequence $(x_n)_{n\in\mathbb{N}}$ defined by

$$\left\{\begin{array}{lcl} x_{n+1} & = & x^* + rf\left(x^*\right)\left[g\left(x_n\right) - g\left(x^*\right)\right], \\ x_0 & = & 0. \end{array}\right.$$

Consider the function K defined, for $x \geq 0$, by

$$K(x) = x^* + rf\left(x^*\right)\left[g\left(x\right) - g\left(x^*\right)\right].$$

We need to prove that $K([0,+\infty)) \subseteq [0,+\infty)$ in order to build a positive sequence $(x_n)_{n\in\mathbb{N}}$. From (21), it follows that, for $x \geq 0$

$$K(x) = (1 - r\gamma)\, x^* + rf\left(x^*\right) g\left(x\right).$$

Then, the positivity of $K(x)$, for $x \geq 0$, is equivalent to

$$rf\left(x^*\right) g\left(x\right) \geq (r\gamma - 1)\, x^*. \tag{41}$$

As we assumed $r\gamma \leq 1$, then (41) is satisfied. On the other hand, from (39), (40) and (41), one can prove by induction that

$$0 \leq x_{2n+2} \leq x(t^*_{2n+1}) < x^* < x(t^*_{2n}) \leq x_{n+1}.$$

Let now define the following two subsequences of $(x_n)_{n\in\mathbb{N}}$,

$$\left\{\begin{array}{lcl} y_n & = & x_{2n}, \\ y_0 & = & 0, \end{array}\right. \quad \text{and} \quad \left\{\begin{array}{lcl} z_n & = & x_{2n+1}, \\ z_0 & = & K(0). \end{array}\right.$$

These sequences are illustrated in Figure 4. In fact, we have

$$y_{n+1} = H(y_n), \quad z_{n+1} = H(z_n) \quad \text{with} \quad y_0 = 0, \quad z_0 = K(0),$$

where H is the function defined for $x \geq 0$ by $H(x) = K^2(x) := K(K(x))$.

Now, using

$$K(x) = x^* + rf(x^*)[g(x) - g(x^*)],$$

the second inequality of (36) implies

$$|K'(x)| = rf(x^*)|g'(x)| < 1.$$

Then, $|H'(x)| = |K'(K(x))K'(x)| < 1$ so x^* is the unique fixed point of H: both y_n and z_n converge to x^*. Since y_n and z_n are respectively lower bound of x_{2n} and upper bound of x_{2n+1}, we proved that

$$\lim_{n\to+\infty} x(t^*_{2n}) = \lim_{n\to+\infty} x(t^*_{2n+1}) = x^*.$$

Then, $\lim_{t\to+\infty} x(t) = x^*$. □

While the condition (28) for oscillating solutions holds for large values of γ and r, condition (36) for asymptotic convergence holds for small values of $r\gamma$. This means that asymptotic convergence is obtained for large (resp. small) immature cell mortality rates associated with short (resp. long) differentiation times, or, of course, for small mortality rates associated with short differentiation times.

If (36) is not satisfied, that is if r is too big in comparison with the average cell lifespan or the inertia of the differentiation feedback $1/|g'(x)|$, our theorem can not guarantee asymptotic convergence, which in the case of an oscillatory solution could imply the existence of sustained oscillations or even periodic solution. The body of work currently existing on the existence of periodic solutions [3, 25, 33] could serve as a basis to complete our description with results on periodic behavior. On the other hand, in the case where $t_0 < r$ we would need to take into account the influence of the initial condition on the dynamics for $t > r$ which is out of the scope of this paper. However, we can study the influence of the conditions at $t = 0$ on the behavior of the solution for $0 < t < r$: in the next section, we study the effect of the initial conditions $I_{mp_i}(a), I_{mk}(a), a > 0$ and $P(0)$ from the model of megakaryopoiesis on the initial slope of the solution.

6. Influence of initial conditions on the onset of fast initial oscillations.

As explained in Section 5, the result for asymptotic convergence is restricted to solutions that satisfy the low initial slope criterion, given in Definition 5.2.

Because this feature concerns $P(t)$ for $0 < t < r$, it can not be assessed using only Equation (18): it depends heavily on the initial conditions given for $t < 0$, and we use the model for megakaryopoiesis presented in Section 2 as an example to give a description of this dependence.

6.1. A simplified model to study P for $t \in [0, r]$.

If we use the original model with n compartments where $mp_i(t, a)$ describes the number of progenitors in the i-th generation and $I_{mp_i}(a) = mp_i(0, a)$ represents the initial amount of progenitors at age a in the i-th generation, the method of characteristics gives the following results for $t \in [0, r]$ and $i = 1, 2$:

$$mp_1(t,\tau) = \begin{cases} e^{-\delta\tau}\kappa(TPO(t-r))HSC, & t \geq \tau, \\ I_{mp_1}(\tau - t)e^{-\delta t}, & 0 < t < \tau, \end{cases}$$

$$mp_2(t,\tau) = \begin{cases} 2e^{-\delta 2\tau}\kappa(TPO(t-2\tau))HSC, & t \geq 2\tau, \\ e^{-\delta\tau} I_{mp_1}(2\tau - t)e^{-\delta(t-r)}, & \tau \leq t \leq 2\tau, \\ I_{mp_2}(\tau - t)e^{-\delta t}, & 0 < t < \tau. \end{cases} \tag{42}$$

From Equation (42) we can guess that the final expression of $P'(t), 0 < t < r$ is defined differently on each interval $[0, \tau]$, $[\tau, 2\tau]$, ..., $[(n-1)\tau, n\tau]$: for the sake of simplicity, in this section we then use a simplified version of the original model

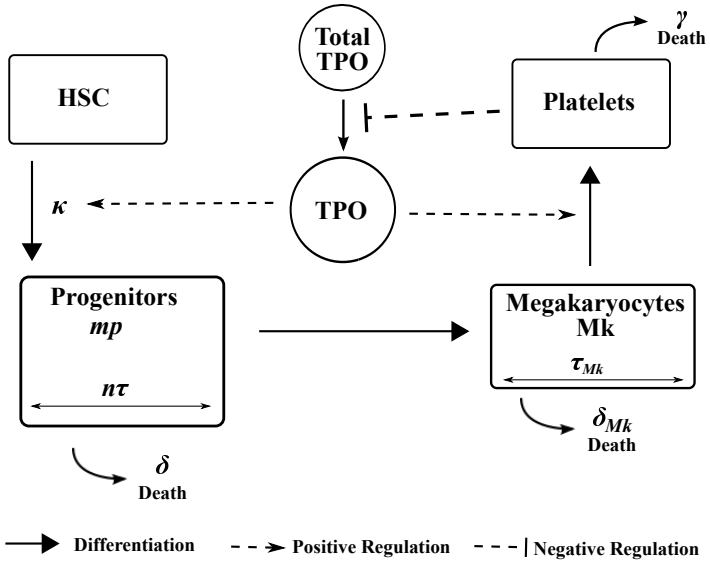

FIGURE 5. **Simplified model of Megakaryopoiesis**.

with only one equality for $t \in [0, n\tau]$. In this model, megakaryocytic progenitors are represented with a single compartment supplied by HSC, and release 2^{n-1} megakaryocytes after a time $n\tau$ (see Figure 5).

This hypothesis transforms the system (7) into the following one:

$$\begin{cases} \dfrac{\partial}{\partial t}mp(t,a) + \dfrac{\partial}{\partial a}mp(t,a) &= -\delta mp(t,a), & 0 < a < \tau n, t > 0, \\ mp(t,0) &= 2^{n-1}\kappa(TPO(t))HSC, & t > 0, \\ mp(0,a) &= I_{mp}(a), & 0 < a < \tau n. \end{cases} \tag{43}$$

Therefore, applying the method of characteristics on the new set of equations (43), (10), (14) allows us to obtain a differential equation for the total number of platelets $P'(t)$ when $t \leq r$, divided into two parts:

$$\begin{cases} P'(t) &= \begin{cases} -\gamma P(t) + 2^n e^{-\delta t} I_{mp}(r-t) f(P(t)), & \tau_{Mk} \leq t \leq r, \\ -\gamma P(t) + e^{-\delta t} I_{mk}(\tau_{mk} - t) f(P(t)), & 0 < t \leq \tau_{Mk}, \end{cases} \\ P(0) &= P_0, \end{cases} \tag{44}$$

with notations $r = n\tau + \tau_{Mk}$ and $f(.) = A \circ TPO(.)$ which is a decreasing function.

6.2. **Sufficient conditions for low initial slope.** We want to monitor the sign of $P(t) - P^*$ for $t \in [0, r]$ with regards to the sign of $P(0) - P^*$. Using Equation (44) and a variation of constant formula, we obtain, for $t \in [0, \tau_{Mk}]$,

$$P(t) = e^{-\gamma t}\Big[\int_0^t e^{(\gamma-\delta)s} I_{mk}(\tau_{mk} - s) f(P(s))\,\mathrm{d}s + P(0)\Big],$$

and for $t \in [\tau_{Mk}, r]$,

$$P(t) = e^{-\gamma t}\Big[\int_{\tau_{mk}}^{t} 2^n e^{(\gamma-\delta)s} I_{mp}(r-s) f(P(s))\,\mathrm{d}s + \int_0^{\tau_{mk}} e^{(\gamma-\delta)s} I_{mk}(\tau_{mk}-s) f(P(s))\,\mathrm{d}s + P(0)\Big].$$

We write $\overline{I_{mk}} = \max I_{mk}$, $\underline{I_{mk}} = \min I_{mk}$, $\overline{I_{mp}} = \max I_{mp}$.

It implies that for $0 < t \leq \tau_{Mk}$,

$$e^{-\gamma\tau_{Mk}} P(0) < P(t) < \overline{I_{mk}} f(0) \frac{e^{(\gamma-\delta)\tau_{Mk}} - 1}{\gamma - \delta} + P(0), \tag{45}$$

and for $\tau_{Mk} \leq t \leq r$,

$$\begin{aligned} & e^{-\gamma r}\Big(\underline{I_{mk}} f\big(\frac{\overline{I_{mk}} f(0)}{\gamma}\big) \frac{e^{(\gamma-\delta)\tau_{Mk}} - 1}{\gamma - \delta} + P(0)\Big) \\ <& P(t) < f(0) \frac{2^n e^{(\gamma-\delta)\tau_{Mk}} \overline{I_{mp}} (e^{(\gamma-\delta)n\tau} - 1) + \overline{I_{mk}} (e^{(\gamma-\delta)\tau_{Mk}} - 1)}{\gamma - \delta} + P(0). \end{aligned} \tag{46}$$

Hence, we can deduce the following proposition:

Proposition 6. *If $P(0) > P^*$, then*

$$P(0) > \max(m_0, m_{mk}),$$

where $m_0 := e^{\gamma\tau_{Mk}} P^*$ and $m_{mk} := e^{\gamma r} P^* - \underline{I_{mk}} f\big(\frac{\overline{I_{mk}} f(0)}{\gamma}\big) \frac{e^{(\gamma-\delta)\tau_{Mk}} - 1}{\gamma - \delta}$, is a sufficient condition to obtain a low initial slope.

If $P(0) < P^*$, then

$$P(0) < \min(M_0, M_{mk})$$

where $M_0 := P^* - \overline{I_{mk}} f(0) \frac{e^{(\gamma-\delta)\tau_{Mk}} - 1}{\gamma - \delta}$ and

$$M_{mk} := P^* - \frac{f(0)}{\gamma - \delta}\Big(2^n e^{(\gamma-\delta)\tau_{Mk}} \overline{I_{mp}} (e^{(\gamma-\delta)n\tau} - 1) + \overline{I_{mk}} (e^{(\gamma-\delta)\tau_{Mk}} - 1)\Big),$$

is a sufficient condition to obtain a low initial slope.

In Figure 6 we give an example of how to go from $t_0 < \tau$ (Figure 6 (a)) to $t_0 > \tau$ (Figure 6 (b-c)) and then to $t_0 > r$ (*i.e.*, low initial slope, Figure 6 (d)) by increasing $P(0)$ respectively above m_0 and m_{mk}.

Such a result can have serious implications, because it tells us that if conditions (36) are satisfied and platelet count ever goes above a certain $m = \max(m_0, m_{mk})$, then oscillations always fade out: oscillations on platelet count might be treated by an injection of the appropriate amount of platelets (a common procedure).

7. **Conclusion.** In order to study its dynamics (short and long term), a model of megakaryopoiesis has been built using the framework of population dynamics. Considering the interactions between stem cells, progenitors cells, mature megakaryocytes, platelets and thrombopoietin, we combined age-structured modeling and the method of characteristic to obtain a single delay differential equation. Particular features of this equation, like linear decay rate or a negative feedback with respect to current state, involve the development of new tools to study its dynamics.

We first obtained sufficient and necessary conditions for solutions to oscillate. Then we found that when solutions have a low initial slope, we can build two enclosing sequences converging toward the steady state by restricting the delay r:

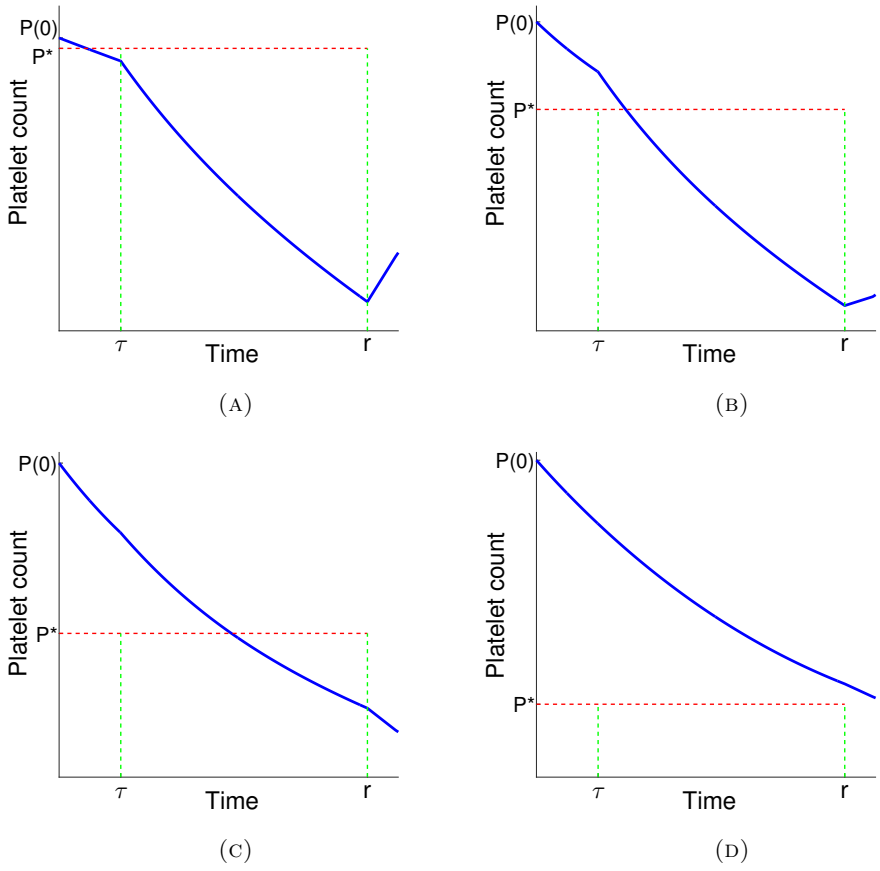

FIGURE 6. **Initial slope and initial conditions.** Four solutions of the equation (44) (blue) where different initial conditions lead to different relative position for τ, r (dashed green) and the time t_0 when $P(t)$ crosses P^* (dashed red).
(A) $P(0) = 0.95e^{\gamma\tau}P^*$ such that $t_0 < \tau$. (B) $P(0) = 1.1e^{\gamma\tau}P^*$ such that $t_0 > \tau$ (as implied by (45)). (C) $P(0) = 0.6M_{mk}$ such that $t_0 > \tau$. (D) $P(0) = 1.1M_{mk}$ such that $t_0 > r$ (as implied by (46)).

this gives a sufficient condition for the asymptotic convergence of the steady state. We emphasize the influence of initial conditions as the behavior of the solution before $t = r$ is critical for the proof. The history of the system might be inconsequential in some applications, but in medicine it is crucial as dynamics can change after a component is either removed, destroyed or injected. We provided such an example in Section 6.

From these two results we can extract preliminary insights regarding the biological system. On one hand, the stationary state can be made asymptotically stable by accelerating the differentiation process of progenitors $(1/\tau)$ or decreasing the number of divisions before maturity (n), in order to decrease $r = (n+1)\tau$, or by increasing the resistance of platelets $(1/\gamma)$ and either decreasing the sensitivity of the differentiation feedback $|g'(x)|$ or the strength of the expansion feedback at the

steady state $f(x^*)$. On the other hand, oscillations appear if r or γ are increased to a certain threshold, but also if parameters from the feedback functions like q (the strength of the feedback on TPO from platelets) or α_A (the maximum number of platelets that can be shed by one megakaryocyte) are modified.

It is straightforward to extend our results from megakaryopoiesis to any system presenting a linear decay term and a feedback expressed as the product of two decreasing functions of current state and delay state, like in populations with a constant death rate and a feedback assured by an input rate decreasing with current and/or past population. Indeed we have shown that classical physiology equations like the Mackey-Glass equation and the Lasota-Wazewska equation can be represented by the equation we are studying: the sufficient condition for oscillations that we obtained is a generalization of the previously existing results for these two equations [10, 20].

Finally, the analytic work on initial conditions that we presented in Section 6 could be replicated on other systems in order to obtain stability results: delay-dependent conditions for stability are likely to be relying on specific initial behavior, and we used a simplified version of our model to give an example of the dependency between this initial behavior and the initial conditions of the system.

Note that the asymptotic stability of a general family of DDE on $\mathbb{R}$ has been explored by Ivanov *et al.* in 2003 [15], whose results can be adapted to our context of solutions on $\mathbb{R}^+$ by adding the low initial slope condition introduced in Definition 5.2. However, a simple computation (not shown here) proves that both delay-independent and delay-dependent results in [15] lead to more complex assumptions than those given in Theorem 5.3. With regard to the two equations on which Ivanov *et al.* successfully applied their results, it seems that the problem is caused by the remaining non-linearity $f(x(t))g(x(t-r))$ in the positive term of the equation, or at least by the fact that this non-linearity involves two decreasing functions. A result on an even more general family of DDE also exists using the so-called York condition [26], which neither can be applied to our case due to the linear decay rate. Furthermore, it can be shown that this criterion can not be used for any equation of the form

$$x'(t) = f_1(x(t-r))g_2(x(t)) - f_2(x(t-r))g_1(x(t)) \tag{47}$$

with f_i, g_i positive, f_2, g_1 increasing and convex, and g_2, f_1 decreasing. Thus it is tempting to think that by a reasoning similar to ours, one could find a stability result for such equations, or at least for such equations with $f_2(x) = 1$. Also, successive improvements have been made regarding the condition for global asymptotic stability in more specific cases of (18) (for Mackey-Glass equation see [3, 11, 18, 22]), and future work will be dedicated to explore a potential extension of these works onto our equation.

Nevertheless, papers mentioning the oscillatory behaviors of specific cases [3, 13, 38] did not improve the results obtained in the aforementioned papers [10, 20]. The interest in the community has shifted towards other versions of the Mackey-Glass equation [19], equations with periodic coefficients or other types of equations (second- or third-order, neutral or impulsive). Similarly to the results on asymptotic convergence, we think that further work should be dedicated to the oscillatory behavior of equations of the general form (47), or at least for such equations with $f_2(x) = 1$.

Finally, in this work we linked these different dynamics (oscillations and asymptotic convergence) to mechanistic parameters of megakaryopoiesis, but to reach full

potential these results would need to be tested against actual medical data. On one hand, we would assess the strength of our biological hypothesis. For example, this work is focused on the impact of TPO only on platelet regulation, while it is known that other cytokines, like SDF-1 for instance, play important roles in megakaryopoiesis. Although its action is mainly unknown [16], it has been shown that SDF-1 stimulates megakaryopoiesis via TPO-independent CXCR4 receptor pathways by enhancing the chemotactic activity of their progenitors [27]. Because of the lack of biological information about their role into megakaryocyte population dynamics, it is likely that they would have a limited role, and we restricted our study to the role played by TPO considered as the main stimulating factor in megakaryopoiesis lineage. Comparing our results with clinical data through parameter estimation will lead us to a clear idea of the different protagonists of this process in normal and pathological cases. On the other hand, once we are able to reproduce the dynamics that can be found both in normal and pathological cases, we have the possibility to assess the strength of our mathematical results and possibly gain insights on possible therapeutic strategies.

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Received July 2017; 1st revision February 2018; 2nd revision April 2018.

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