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A MODEL FOR MEGAKARYOPOIESIS WITH STATE-DEPENDENT DELAY*

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Abstract. We analyze the stability of a system of differential equations with a threshold-defined delay arising from a model for platelet production. We consider a maturity-structured population of megakaryocyte progenitors and an age-structured population of platelets, where the cytokine thrombopoietin (TPO) increases the maturation rate of progenitors. Using the quasi-steady-state approximation for TPO dynamics and the method of characteristics, partial differential equations are reduced to a system of two differential equations with a state-dependent delay accounting for the variable maturation rate. We start by introducing the model and proving the positivity and boundedness of the solutions. Then we use a change of variables to obtain an equivalent system of two differential equations with a constant delay, from which we prove existence and uniqueness of the solution. As linearization around the unique positive steady state yields a transcendental characteristic equation of third degree, we introduce the main result, a new framework for stability analysis on models with fixed delays. This framework is then used to describe the stability of the megakaryopoiesis with respect to its parameters. Finally, with parameters being obtained and estimated from data, we give an example in which oscillations appear when the death rate of progenitors is increased 10-fold.

Key words. megakaryopoiesis, platelet, oscillations, stability, state-dependent delay, transcendental equation

AMS subject classifications. 34K13, 34K18, 92D25

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1. Introduction.

1.1. Objectives. The aim of this work is to study the stability of a new system of two delay differential equations with state-dependent delays. We use a change of variable introduced by Smith [51] to obtain an equivalent system of delay differential equations with a distributed delay. Then we analyze the stability of this system using an adaptation of the framework proposed by Beretta and Kuang [6]. Meanwhile, a new model of platelet production is formulated relying solely on the regulation of the maturation process of progenitor cells. The stability analysis presented before is then applied to explore the potential sources of oscillations in platelet count.

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1.2. Biological background.

Platelets, megakaryocytes, and disorders. Platelets are the blood cells in charge of preserving the structural integrity of the blood vessels. Among the smallest cells in the human body (2–3 μm), they originate from the hematopoietic stem cells (HSCs) located in the bone marrow. It is well known that HSCs also generate other blood cells like white blood cells (10–30 μm) and red blood cells (6–8 μm). Although platelets lack a nucleus, like red blood cells, the generating process of platelets is different as it cannot be traced back to a cell which excluded its nucleus. Instead, large differentiated HSCs called megakaryocytes undergo endomitosis, that is, multiple divisions of the nucleus without division of the cytoplasm. This process increases the ploidy of the cell (the number of DNA copies it contains) and modifies the structure of its cytoplasm, and platelets result from the fragmentation of this modified cytoplasm. Platelet counts are usually between 150,000 and $450,000$ per μL of blood, and platelet counts whose distance to this norm is clinically significant exhibit two kinds of pathologies: thrombocytopenia (below $150,000$ platelets per μL) and thrombocytosis (above $500,000/\mu$L) [22]. Both of these disorders may lead to severe complications. On one hand, aggravated thrombocytopenia ($< 50,000/\mu$L) may be associated with morbidity and complications in medical management of patients with conditions such as cancer, liver disease, or chronic hepatitis C virus infection [1]. On the other hand, aggravated thrombocytosis may induce thrombotic complications and (counterintuitively) bleeding associated with illness and death [46]. These two disorders may also be involved in a condition known as cyclic thrombocytopenia (CT) [52], where platelet count oscillates between very low ($1 \times 10^3/\mu$L) to normal or very high levels ($2000 \times 10^3/\mu$L) with a period usually between 20 and 40 days. Although the pathogenesis of CT is not clear, most cases are thought to belong to one of the following two categories. Autoimmune CT corresponds to patients with a high level of platelet-specific antibodies such that the destruction rate of platelet is increased although megakaryocyte levels are normal; amegakaryocytic CT corresponds to patients with the presence of specific antibodies targeting either mature megakaryocytes or megakaryocyte progenitors (MkPs), i.e., with an increased megakaryocyte destruction rate. Both involve autoimmune antibodies, resembling immune thrombocytopenia purpura: this often causes misdiagnosis, leading patients with CT to receive risky medical treatments (corticosteroids and splenectomy, i.e., removal of the spleen) with no result [26].

Figure 1.1 depicts a clinical case of cyclic oscillations in platelet count, where the patient was found to be positive for antibodies targeting MkPs and mature megakaryocytes [58].

Platelet regulation: role of the thrombopoietin. Since the discovery of platelets, megakaryopoiesis has been thought to be regulated by a similar mechanism as in erythropoiesis (production process of red blood cells). It has been believed indeed that low cell count was stimulating the release of a cytokine enhancing platelet production. But while such a cytokine, called thrombopoietin (TPO), was identified with certainty in the 1990s [33], it was later found that TPO level regulation was carried out by TPO receptors on the surface of platelets and other megakaryocytic cells [15, 47]. Similarly, many attempts were carried out to pinpoint the exact phase point where TPO would act on the megakaryocytic cell line. Results ranged from stem cell expansion [50] and reduced apoptosis in megakaryocytes [57] to an amplification of the endomitosis phase, where a bigger nucleus would imply more platelets per megakaryocyte [9]. But regarding this last hypothesis, several studies posed the question of the

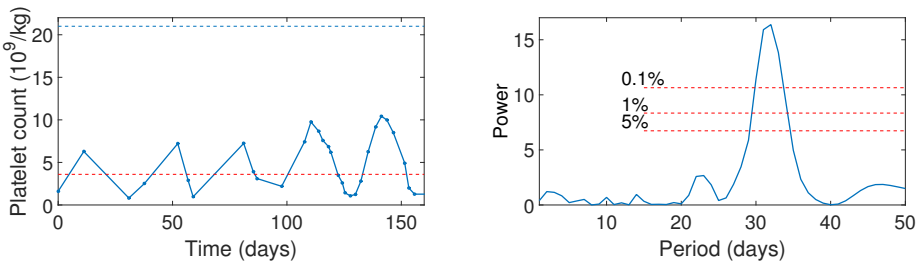

FIG. 1.1. (a) *Cyclical oscillations of platelet counts over* 160 *days, as they appear in the case report by Zent et al.* [58]. *The blue dashed line represents the average platelet level* $20.3 \times 10^9/kg$ *(that is,* $284 \times 10^3/\mu L$*), and the red dashed line represents the limit for aggravated thrombocytopenia* $3.8 \times 10^9/kg$ *(that is,* $50 \times 10^3/\mu L$*).* (b) *The corresponding normalized Lomb periodogram associates potential periods* T *with a score* $P(T)$ *(blue line). Using* $p = Ne^{P(T)}$ *(red dotted lines), where* N *is the number of data points as an approximation of the significance level* [23]*, we see that a period* $30 \leq T \leq 33$ *days is significant* ($p \leq 0.001$).

potency of TPO levels to control platelet production through endomitosis enhancement. First, Zimmet et al. explored the in vivo effect of the overexpression of cyclin D3 [59]. Their measurements showed that despite the increasing ploidy of transgenic mice, the difference between platelet counts was not significant. Later, two studies by Ng et al. [41] and Meyer et al. [40] were conducted to assess the potency of MkPs to be fully responsible for the increased production of platelets if needed. Disabling TPO interaction with mature megakaryocytes and platelets (through altering, respectively, the production of c-Mpl receptors [41] and the expression of the kinase Jak2 [40]), both teams observed a significant increase in platelet production. Therefore, whether the action of TPO on endomitosis might is dispensable is an open question.

Previous mathematical modeling approaches. The progress made regarding biological knowledge is nicely paralleled with the evolution of mathematical models for thrombopoiesis, starting in 1979 with Wichmann et al. [56]. Using three compartments corresponding to HSCs, megakaryocytes (whose proliferation is upregulated by TPO) and assuming a platelet-regulated TPO production, these authors successfully reproduced the overshoot that is observed following platelet depletion induced by exchange transfusion. The same authors later introduced an age-structure in their model via the McKendrick–von Foerster partial differential equation, although they focused only on platelet survival [55]. This idea was extended six years later by Eller et al. [21] where the McKendrick–von Foerster equation was also used to describe the dynamics of HSCs and of megakaryocytes: these authors proved existence and uniqueness of solutions, but stability results remained limited [27]. From 2000 onward two tendencies arose. The first was dedicated to obtaining results on the effect of chemotherapy and irradiations in medical treatment on megakaryopoiesis. Building upon previous successes reproducing the dynamics of granulopoiesis under heavy and/or repetitive stress [48], Scholz et al. [49] developed a model of megakaryopoiesis under chemotherapy with successful simulations of both cell count and TPO levels [49]. Results of the same quality were obtained later by Wentz et al. [54] with a model of megakaryopoiesis under radiations. Unfortunately, these last models seem, to the best of our knowledge, unfit for an extensive analytical work due the tendency to use successive compartments. The second tendency focused on oscillatory dynamics once TPO was purified, allowing measurements of TPO level [29]. Indeed, preliminary works [10, 53] involving delay differential equations were updated by Santillan et al., leading to a

model where transition dynamics from different levels of ploidy is upregulated by TPO [45]. Authors reproduced both stable and oscillating platelet counts, but no analytic account was given of this change of stability. Modeling of megakaryocyte growth was later changed from discrete ploidy classes to continuous megakaryocyte volume in a paper by Apostu and Mackey integrating each of the three hematopoietic lineages [2]. Exploring the effect of changes of the accelerated peripheral destruction of platelets on stability, the hypothesis of a Hopf bifurcation as the source of oscillations was formulated but not verified. This gap was filled nine years later when the same group managed to fit a refined model to both stable and oscillating platelets count from clinical data [34]: stability analysis revealed that there was indeed a Hopf bifurcation occurring along the parameter changes, inducing oscillations.

However, according to the experimental work presented above, these models might be more complicated than needed. In this paper, our aim is to answer the following question: is a TPO-induced increase in progenitor growth sufficient to produce a model with the ability to produce oscillatory behaviors consistent with CT pathogenesis? Considering this single feedback leads to a simpler model, implying that a more extensive stability analysis can be performed. We build a framework to explore the impact that different changes in parameters have on the onset of oscillations.

Our paper is organized as follows. We start with a description of the dynamics of progenitors, platelets, and TPO with nonlinear differential equations (section 2) that we reduce to a system of threshold-delay differential equations using the quasi-steady state approximation. We then prove the well-posedness of our model as well as the boundedness and positivity of the solution (section 3). Next, we transform this system into a standard functional differential equation system using the change of variable described by Smith [51] and use this new formulation to prove existence and uniqueness of solutions (section 4). This is followed by the main result, a new framework for stability analysis on models with a fixed delay, adapted from Beretta and Kuang [6], with more specific results for a special kind of third-order characteristic equation (section 5). Finally, we apply this framework to our model of megakaryopoiesis to show that an increase in the death rate of MkPs induces oscillations in the amount of platelets (section 6).

2. A maturity-structured model for megakaryopoiesis. In our model we consider three quantities.

- The MkP count: upon commitment, HSCs are assumed to enter the progenitors compartment with a constant rate and mature with a speed upregulated by the TPO blood level; hence, we use a maturity-structured model. The total amount of progenitors is written M (cells/kg).
- The platelet count: the platelets are only affected with a random decay, not by TPO level; hence we use an age-structured model. The total amount of platelets is written P (cells/kg).
- And finally, TPO blood level, which is considered quasi-stationary with regards to the two other quantities. The concentration of TPO in the blood is written T (pg/mL).

2.1. MkP dynamics.

2.1.1. Progenitors as a maturity-structured population. MkPs appear when the division of an HSC gives birth to two committed cells. We represent them with a maturity structure, assuming that they divide again once they reach maturity $x = 1$. The maturity x increases with a speed $V(T(t), M(t), P(t))$ as the cells progress in the maturation process, depending on the current state of the system. We give a

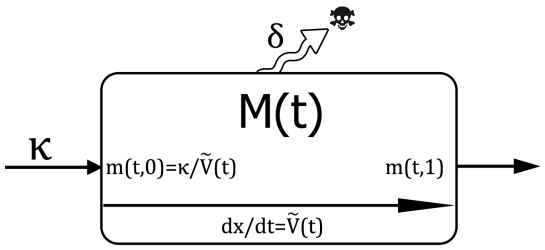

FIG. 2.1. *The maturity-structured model for megakaryopoiesis as presented in section* 2.1.1*: as detailed in system* (2.1)*, progenitors arrive from the pool of HSCs, they die randomly with a rate* δ*, and they mature with a rate* $\tilde{V}(t)$ *until they reach maturity* 1*, where they release platelets and disappear.*

formulation of $V(.)$ in section 2.3, but until then we write $\tilde{V}(t) = V(T(t), M(t), P(t))$ for a lighter reading. Readers should nevertheless keep in mind that our model remains autonomous.

This maturity-structured population is described by the following equation:

$$\begin{cases} \dfrac{\partial}{\partial t}m(t,x) + \dfrac{\partial}{\partial x}(\tilde{V}(t)m(t,x)) = -\delta m(t,x), & 0 < x \leq 1, t > 0, \\ m(t,0) = \kappa/\tilde{V}(t), & t > 0, \\ m(0,x) = m_0(x), & 0 \leq x \leq 1. \end{cases} \tag{2.1}$$

Here, $m(t,x)$ represents the number of MkPs of maturity x at time t, such that when an MkP reaches maturity $x = 1$ it releases its platelets and is removed from the MkP population. $\delta > 0$ is the constant death rate of progenitors, $\kappa > 0$ is the constant arrival rate of HSCs into the progenitor compartment, $V : \mathbb{R}^3_+ \to \mathbb{R}^*_+$ is a strictly positive, continuous increasing function representing the TPO-dependent maturation speed of progenitors (we recall that we write $\tilde{V}(t) = V(T(t), M(t), P(t))$ for a lighter reading), and $m_0 \in C^0([0,1])$ is the distribution of progenitors at time $t = 0$. This system is represented in Figure 2.1. For details on the derivation of the boundary condition, see Craig, Humphries, and Mackey [16, section 3.3].

2.1.2. A differential equation for progenitors count: method of characteristics. We introduce $t_1 > 0$ the solution of $\int_0^t \tilde{V}(y)\,\mathrm{d}y = 1$, and for all $t \geq t_1$ we define $\tau(t) > 0$ as the solution of

$$\int_{t-\tau(t)}^{t} \tilde{V}(y)dy = 1.$$

At a time t, $\tau(t)$ represents the time that MkPs that are maturing at time t have spent maturing; that is, if an MkP is of maturity 1 at time t, then it entered the MkP compartment at time $t - \tau(t)$.

The method of characteristics on system (2.1) then implies that for $t \geq t_1$, we have

$$m(t,1) = m(t - \tau(t), 0)e^{-\delta\tau(t)}. \tag{2.2}$$

The total number of progenitors is $\int_0^1 m(t,x)dx$ and denoted by $M(t)$. When we differentiate this integral, we combine the first two equations of system (2.1) with (2.2) to obtain the following differential equation on $M(t)$ for $t \geq t_1$:

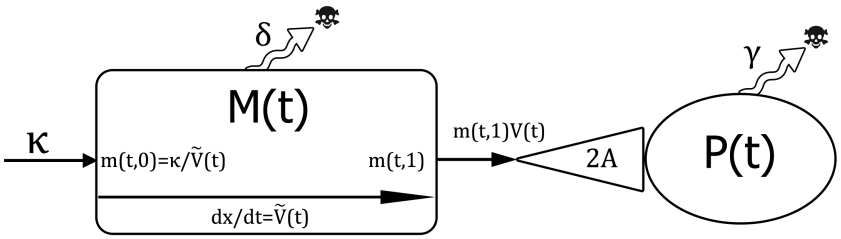

FIG. 2.2. *Model of megakaryopoiesis, where $M(t)$ and $P(t)$ are the total amount of MkPs and platelets, respectively.*

$$M'(t) = -\delta M(t) + \kappa\big[1 - \tilde{V}(t)e^{-\delta\tau(t)}/\tilde{V}(t-\tau(t))\big]. \tag{2.3}$$

While the method of characteristics also yields an expression for $0 \le t \le t_1$ of $M'(t)$, it is out of the scope of this paper which focuses on long-term dynamics.

2.2. An age-structured population of platelets. Progenitors undergo successive divisions until they become megakaryocytes. But the number of these divisions is currently unknown, and we believe that one TPO-induced division might already capture detailed dynamics. Therefore, we consider that when it reaches maturity, the progenitor divides itself into two mature megakaryocytes which immediately shed a constant quantity of A platelets each. This implies that this quantity A needs to be increased above the standard interval $[1000, 3000]$ [28] for the platelet count to reach its real order of magnitude, accounting for the missing divisions.

We assume that platelets are age-structured with decay $\gamma > 0$ such that $p(t,a)$ represents the amount of platelets of age a at time t. We obtain the following equations for $t > t_1$:

$$\begin{cases} \dfrac{\partial}{\partial t}p(t,a) + \dfrac{\partial}{\partial a}p(t,a) = -\gamma p(t,a), \\ p(t,0) = 2A\kappa\dfrac{\tilde{V}(t)}{\tilde{V}(t-\tau(t))}e^{-\delta\tau(t)}, \\ p(t,\infty) = 0 \text{ and } p(0,a) = p_0(a). \end{cases}$$

This system is represented in Figure 2.2.

Here the link between the incoming flux of platelets and flux of maturing MkPs is straightforward for $t \ge t_1$:

$$p(t,0) = 2A.m(t,1)\tilde{V}(t) = 2A.e^{-\delta\tau(t)}m(t-\tau(t),0)\tilde{V}(t) = 2A\kappa\frac{\tilde{V}(t)}{\tilde{V}(t-\tau(t))}e^{-\delta\tau(t)}.$$

Now if we account for the total population of platelets $P(t) = \int_0^{+\infty} p(t,a)da$, we get the following differential equation for $t > t_1$:

$$\frac{d}{dt}P(t) = -\gamma P(t) + 2A\kappa\frac{\tilde{V}(t)}{\tilde{V}(t-\tau(t))}e^{-\delta\tau(t)}. \tag{2.4}$$

2.3. The cytokine TPO upregulates the maturation process. As stated previously, the platelet production increases with TPO, and it has been observed that the acceleration of the division dynamics is a sufficient mechanism to obtain a complete feedback mechanism [40, 41]. As announced in section 2.1.1, we now fully denote the speed of maturity given by $\tilde{V}(t) = V(T(t), M(t), P(t))$. As $T(t)$ the quantity of TPO is "perceived" by progenitors through their c-Mpl receptors, we assume that

maturation rate is a function of the TPO available through this mechanism, leading to the following for $t \geq 0$:

$$V(T(t)) = \alpha \frac{T^n(t)}{K_T^n + T^n(t)} + \beta. \tag{2.5}$$

We use a saturating function of $T(t)$, representing the binding dynamics of the c-Mpl and TPO complex (see (2.6)). We add a fix coefficient β to account for the observations that megakaryopoiesis is still happening without an effective TPO feedback (10% of the normal count [17], possibly due to stimulation by other cytokines).

TPO itself is produced constitutively by the liver, stable in plasma [35], and cleared through binding to c-Mpl receptors on circulating platelets and progenitors [18, 35]. We formulate the binding dynamics with a Hill function and obtain the following differential equation for $t \geq 0$:

$$\frac{d}{dt}T(t) = T_{\text{prod}} - \alpha_T(\alpha_M M(t) + \alpha_P P(t)) \frac{T(t)^n}{K_T^n + T(t)^n}. \tag{2.6}$$

Similarly to Colijn and Mackey [14, equation (10)] or earlier Bernard, Belair, and Mackey [7, Appendix A], we assume that the process of TPO binding to c-Mpl is much faster than changes in the number of progenitors and platelets, implying that dynamics equilibrium is reached at any time for TPO, i.e., $\frac{dT}{dt}(t) \approx 0$ for all t. This is called the quasi-steady-state approximation, and it leads to

$$0 = T_{\text{prod}} - \alpha_T(\alpha_M M(t) + \alpha_P P(t)) \frac{T(t)^n}{K_T^n + T(t)^n} \tag{2.7}$$

such that if $\alpha_T(\alpha_M M(t) + \alpha_P P(t)) > T_{\text{prod}}$ we have

$$\frac{T(t)^n}{K_T^n + T(t)^n} = \frac{T_{\text{prod}}/\alpha_T}{\alpha_M M(t) + \alpha_P P(t)}.$$

What we see here is that if $\alpha_T(\alpha_M M(t) + \alpha_P P(t))$ is less than T_{prod}, there is no T such that $dT/dt = 0$. This implies that if $\alpha_T(\alpha_M M(t) + \alpha_P P(t))$ get closer to T_{prod}, T virtually goes to infinity.

Using this expression, (2.5) gives $\mathcal{V}$ the maturation rate as a function of $M(t)$ and $P(t)$, $t \geq 0$:

$$V(T(t)) = \mathcal{V}(\alpha_M M(t) + \alpha_P P(t)) := \alpha \frac{T_{\text{prod}}/\alpha_T}{\alpha_M M(t) + \alpha_P P(t)} + \beta. \tag{2.8}$$

The system formed with (2.3), (2.4), and (2.8) is our age and maturity-structured system of thrombopoiesis dynamics, as shown in Figure 2.3. In the next section, we formulate it as a system of threshold-defined delay differential equations. We also show that the solutions are positive and bounded.

3. A system of threshold-defined delay differential equations for megakaryopoiesis. Using (2.8) in (2.3) and (2.4), we obtain the following system for $t > t_1$:

$$\begin{cases} \frac{d}{dt}M(t) = -\delta M(t) + \kappa \left[1 - \dfrac{\mathcal{V}(\alpha_M M(t) + \alpha_P P(t))}{\mathcal{V}(\alpha_M M(t-\tau(t)) + \alpha_P P(t-\tau(t)))} e^{-\delta\tau(t)}\right], \\ \frac{d}{dt}P(t) = -\gamma P(t) + 2A\kappa \dfrac{\mathcal{V}(\alpha_M M(t) + \alpha_P P(t))}{\mathcal{V}(\alpha_M M(t-\tau(t)) + \alpha_P P(t-\tau(t)))} e^{-\delta\tau(t)}, \end{cases} \tag{3.1}$$

where $\tau(t)$ is such that $\int_{t-\tau(t)}^{t} \mathcal{V}(\alpha_M M(s) + \alpha_P P(s))ds = 1$ from (2.2).

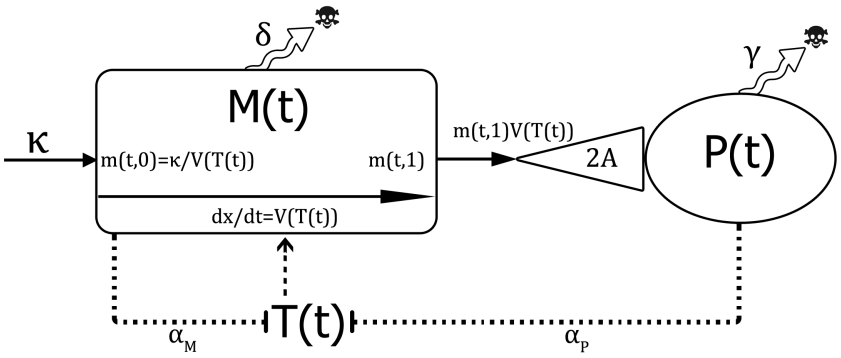

FIG. 2.3. *The quantities of megakaryocytes $M(t)$ and $P(t)$ downregulate the total amount of TPO $T(t)$ which in turn upregulates the speed of maturation of MkPs.*

We introduce a new variable, and note $W(t) = \alpha_M M(t) + \alpha_P P(t)$ for all $t \geq$, which represents the total amount of c-Mpl receptors in the system. We prove the following basic properties.

PROPOSITION 3.1. *Assume that initial conditions $M(s), P(s)$ are such that $W(s) \geq T_{prod}/\alpha_T$ for $s \in [0, t_1]$, $2A\alpha_P \geq \alpha_M$, and $\alpha_M \kappa > T_{prod}/\alpha_T \max(\delta, \gamma)$. Then solutions of system* (3.1) *are nonnegative and eventually bounded, and $W(t)$ stays above T_{prod}/α_T for all $t \geq t_1$.*

Proof. We divide the proof into three steps.

1. Eventual boundedness of the solutions: if t is such that $\gamma P(t) + 2A\delta M(t) \geq 2A\kappa$, then

$$\frac{dP}{dt} + 2A\frac{dM}{dt} = -\gamma P(t) - 2A\delta M(t) + 2A\kappa \leq 0.$$

   This implies that if $P(t_1)$ and $M(t_1)$ are finite, $P(t)$ and $M(t)$ remain finite for all $t \geq t_1$, i.e., the system is bounded (as both variables are nonnegative).
2. Positivity of the solutions: assume that there exists a $\bar{t} \geq t_1$ such that $P(\bar{t}) = 0$ and $M(\bar{t}) > 0$. Therefore

$$\frac{d}{dt}P(\bar{t}) = 2A\kappa \frac{\mathcal{V}(\alpha_M M(\bar{t}))}{\mathcal{V}(\alpha_M M(\bar{t} - \tau(\bar{t})) + \alpha_P P(\bar{t} - \tau(\bar{t})))} e^{-\delta\tau(\bar{t})},$$

   which is always positive. This implies that P is always positive.
   In order to prove the positivity of M, we recall that it is defined as $M(t) = \int_0^1 m(t,x)\,\mathrm{d}x$. On the other hand, we know that for all $t > t_1$ and all $x \in [0,1]$, there exists a $\sigma(t,x) \in \mathbb{R}_+^*$ such that $\int_{t-\sigma(t,x)}^{t} \tilde{V}(y)\,\mathrm{d}y = x$, and the method of characteristics implies $m(t,x) = m(t - \sigma(t,x), 0)e^{-\delta\sigma(t,x)}$. Finally, for all $t > t_1$, $m(t,0) = \kappa/\mathcal{V}(\alpha_P P(t) + \alpha_M M(t))$ is positive, implying the positivity of $m(t,x)$ for all $t > t_1$, $x \in [0,1]$, which in turns implies the positivity of $M(t)$ for all $t > t_1$.
3. $W(t)$ stays above $T_{\mathrm{prod}}/\alpha_T$ for all $t \geq t_1$: we write

$$\frac{dW}{dt}(t) = \alpha_P(\delta - \gamma)P(t) - \delta W(t) + \kappa\left[\alpha_M + (2A\alpha_P - \alpha_M)\frac{\mathcal{V}(W(t))e^{-\delta\tau(t)}}{\mathcal{V}(W(t - \tau(t)))}\right].$$

We first notice that given $M(t) > 0$, $W(t) > \alpha_P P(t)$ such that

$$\alpha_P(\delta - \gamma)P(t) - \delta W(t) \geq -\max(\delta, \gamma)W(t).$$

Therefore if $W(t) = T_{\text{prod}}/\alpha_T$, we use $2A\alpha_P > \alpha_M$, $\kappa\alpha_M > \frac{T_{\text{prod}}}{\alpha_T}\max(\delta, \gamma)$ and the positivity of $\mathcal{V}$ to obtain $\frac{dW}{dt}(t) > 0$. Because $\frac{dW}{dt}(t) > 0$ when $W(t) = T_{\text{prod}}/\alpha_T$, then there exists $\underline{W} > T_{\text{prod}}/\alpha_T$ such that $W(t) = \underline{W}$ implies $\frac{dW}{dt}(t) \geq 0$: $W(t) > T_{\text{prod}}/\alpha_T$ for all $t > 0$. ∎

Provided that initial conditions satisfy the conditions given in Proposition 3.1, system (3.1) is a closed system of differential equations with a delay defined by threshold. But in order to study the stability of our system, in the next section we transform it into a system of functional differential equations using a change of variable. We also use this formulation to obtain a result on existence and uniqueness of the solutions.

4. A change of variable transforms the threshold-defined delay differential equation model into a system of functional differential equations. Following Smith's method [51], we introduce a new time variable θ. It is linked to the original time scale by the function $\bar{t}$, which for every solution $(M(t), P(t)), t \geq 0$ associates to every $\theta > 0$ the value $\bar{t}(\theta)$ such that

$$\int_0^{\bar{t}(\theta)} \mathcal{V}(\alpha_M M(s) + \alpha_P P(s))\,\mathrm{d}s = \theta. \tag{4.1}$$

This function represents the "physiological" time scale along which the maturation of progenitors is a linear process.

We see that by definition of the function τ, if θ is such that $\bar{t}(\theta) > t_1$, then

$$\begin{aligned}\int_0^{\bar{t}(\theta-1)} \mathcal{V}(\alpha_M M(s) + \alpha_P P(s))ds &= \theta - 1 \\ &= \int_0^{\bar{t}(\theta)} \mathcal{V}(\alpha_M M(s) + \alpha_P P(s))ds - \int_{\bar{t}(\theta)-\tau(\bar{t}(\theta))}^{\bar{t}(\theta)} \mathcal{V}(\alpha_M M(s) + \alpha_P P(s))ds, \\ &= \int_0^{\bar{t}(\theta)-\tau(\bar{t}(\theta))} \mathcal{V}(\alpha_M M(s) + \alpha_P P(s))ds.\end{aligned}$$

Because $\mathcal{V}$ is a positive function, the integral is always positive, which implies that $\bar{t}(\theta - 1) = \bar{t}(\theta) - \tau(\bar{t}(\theta))$. Next we notice that (4.1) implies, for $\theta \geq 1$,

$$1 = \frac{d\theta}{d\theta} = \frac{d}{d\theta}\int_0^{\bar{t}(\theta)} \mathcal{V}(\alpha_M M(s) + \alpha_P P(s))ds = \frac{d\bar{t}(\theta)}{d\theta}\mathcal{V}(\alpha_M M(\bar{t}(\theta)) + \alpha_P P(\bar{t}(\theta))).$$

For all $\theta > 1$, we now define $\mathcal{M}(\theta) := M(\bar{t}(\theta))$, $\mathcal{P}(\theta) := P(\bar{t}(\theta))$, $\mathcal{W}(\theta) := W(\bar{t}(\theta))$. We then deduce from above

$$\tau(\bar{t}(\theta)) = \bar{t}(\theta) - (\bar{t}(\theta) - \tau(\bar{t}(\theta))) = \bar{t}(\theta) - \bar{t}(\theta - 1) = \int_{-1}^{0} \frac{1}{\mathcal{V}(\mathcal{W}_\theta(r))}\,\mathrm{d}r,$$

where $\mathcal{W}_\theta(.)$ is defined on $[-1, 0]$ by $\mathcal{W}_\theta(r) = \mathcal{W}(\theta + r)$.

We define $\tau_0 : C^0 \to \mathbb{R}$ as $\tau_0 : \phi \mapsto \int_{-1}^{0} 1/\mathcal{V}(\phi(r))\,\mathrm{d}r$ and we use (3.1) to obtain, for $\theta \geq 1$,

$$\frac{d\mathcal{P}}{d\theta}(\theta) = \frac{dP}{dt}(\bar{t}(\theta))\frac{d\bar{t}(\theta)}{d\theta} = \left(-\gamma\mathcal{P}(\theta) + 2A\frac{\kappa e^{-\delta\tau_0(\mathcal{W}_\theta)}\mathcal{V}(\mathcal{W}(\theta))}{\mathcal{V}(\mathcal{W}(\theta - 1))}\right)\mathcal{V}(\mathcal{W}(\theta))^{-1}.$$

Reproducing the calculation for $\mathcal{M}$, (3.1) becomes, for $\theta \geq 1$,

$$\begin{cases} \dfrac{d\mathcal{M}}{d\theta} = -\delta \dfrac{\mathcal{M}(\theta)}{\mathcal{V}(\mathcal{W}(\theta))} + \kappa \left[\dfrac{1}{\mathcal{V}(\mathcal{W}(\theta))} - \dfrac{e^{-\delta\tau_0(\mathcal{W}_\theta)}}{\mathcal{V}(\mathcal{W}(\theta-1))} \right], \\ \dfrac{d\mathcal{P}}{d\theta} = \dfrac{-\gamma\mathcal{P}(\theta)}{\mathcal{V}(\mathcal{W}(\theta))} + \dfrac{2A\kappa e^{-\delta\tau_0(\mathcal{W}_\theta)}}{\mathcal{V}(\mathcal{W}(\theta-1))}. \end{cases} \tag{4.2}$$

We notice that for $\theta \geq 1$,

$$\frac{d\mathcal{W}}{d\theta} = \frac{\alpha_P(\delta-\gamma)\mathcal{P}(\theta) - \delta\mathcal{W}(\theta)}{\mathcal{V}(\mathcal{W}(\theta))} + \kappa \left[\frac{\alpha_M}{\mathcal{V}(\mathcal{W}(\theta))} + (2A\alpha_P - \alpha_M) \frac{e^{-\delta\tau_0(\mathcal{W}_\theta)}}{\mathcal{V}(\mathcal{W}(\theta-1))} \right],$$

allowing us to write (4.2) of the form

$$\begin{cases} \dfrac{d\mathcal{W}}{d\theta} = \dfrac{\alpha_P(\delta-\gamma)\mathcal{P}(\theta) - \delta\mathcal{W}(\theta)}{\mathcal{V}(\mathcal{W}(\theta))} + \kappa \left[\dfrac{\alpha_M}{\mathcal{V}(\mathcal{W}(\theta))} + \dfrac{(2A\alpha_P - \alpha_M)e^{-\delta\tau_0(\mathcal{W}_\theta)}}{\mathcal{V}(\mathcal{W}(\theta-1))} \right], \\ \dfrac{d\mathcal{P}}{d\theta} = \dfrac{-\gamma\mathcal{P}(\theta)}{\mathcal{V}(\mathcal{W}(\theta))} + \dfrac{2A\kappa e^{-\delta\tau_0(\mathcal{W}_\theta)}}{\mathcal{V}(\mathcal{W}(\theta-1))}. \end{cases} \tag{4.3}$$

Now defining for all $w \in \mathbb{R}$, $f(w) := 1/\mathcal{V}(w) = \dfrac{w}{\alpha T_{\text{prod}}/\alpha_T + \beta w}$, (4.3) becomes, for $\theta \geq 1$,

$$\begin{cases} \dfrac{d\mathcal{W}}{d\theta}(\theta) = (\alpha_P(\delta-\gamma)\mathcal{P}(\theta) - \delta\mathcal{W}(\theta)) f(\mathcal{W}(\theta)) \\ \qquad\qquad + \kappa\big[\alpha_M f(\mathcal{W}(\theta)) + (2A\alpha_P - \alpha_M) e^{-\delta\tau_0(\mathcal{W}_\theta)} f(\mathcal{W}(\theta-1))\big], \\ \dfrac{d\mathcal{P}}{d\theta}(\theta) = -\gamma\mathcal{P}(\theta) f(\mathcal{W}(\theta)) + 2A\kappa e^{-\delta\tau_0(\mathcal{W}_\theta)} f(\mathcal{W}(\theta-1)), \end{cases} \tag{4.4}$$

where τ_0 is defined as $\tau_0(\phi) = \int_{-1}^{0} f(\phi(r))\,\mathrm{d}r$. We use this formulation to obtain existence and uniqueness of the solutions.

PROPOSITION 4.1. *We assume that $\alpha_M \leq 2A\alpha_P$. For every positive initial data $\mathcal{M}(s), \mathcal{P}(s)$ for $\theta \in [0,1]$ such that $\mathcal{W}(\theta) \geq T_{prod}/\alpha_T$ for $\theta \in [0,1]$, there exists a unique solution of (4.4) on $\theta \geq 1$ which is nonnegative and bounded.*

Proof. Boundedness and positivity are deduced from the previous section. To show that the solution exists and is unique, we introduce $\mathbf{x}(\theta) = (\mathcal{W}(\theta), \mathcal{P}(\theta))$ such that system (4.3) writes $\dot{\mathbf{x}}(t) = \mathcal{G}(\mathbf{x}_t) = \mathbf{g}(\mathbf{x}_t(0)) + \mathbf{h}(\mathbf{x}_t)$ where $\mathbf{x}_t(.)$ is defined on $[-1,0]$ by $\mathbf{x}_t(r) = \mathbf{x}(t+r)$ and functions $\mathbf{g} = (g_1, g_2) \in C^1(\mathbb{R}^2)$, $\mathbf{h} = (h_1, h_2) : C^1(\mathbb{R}^2) \to \mathbb{R}_+^2$ are defined as

$$\begin{cases} \mathbf{g}(\mathbf{x}) = f(x_1) \begin{pmatrix} \alpha_P(\delta-\gamma)x_2 - \delta x_1 + \alpha_M\kappa \\ -\gamma x_2 \end{pmatrix}, \\ \mathbf{h}(\boldsymbol{\phi}) = \kappa e^{-\delta \int_{-1}^{0} f(\phi_1(r))\,\mathrm{d}r} f(\phi_1(-1)) \begin{pmatrix} 2A\alpha_P - \alpha_M \\ 2A \end{pmatrix}. \end{cases}$$

We give the outline of the proof that $\mathcal{G}$ is Lipschitz continuous, which according to Diekmann et al. [20, section VII.6] implies that for every continuous initial condition $\boldsymbol{\psi}(\theta), \theta \in [0,1]$, a unique solution exists.

We show that $\mathcal{G}$ is Lipschitz continuous by defining, for all neighborhood $N \in C^1(\mathbb{R}^2)$ of $\boldsymbol{\psi}$, a constant L_N such that for all $\boldsymbol{\chi} \in N$,

(4.5)
$$\begin{aligned} &| g_1(\boldsymbol{\psi}(0)) - g_1(\boldsymbol{\chi}(0)) | + | g_2(\boldsymbol{\psi}(0)) - g_2(\boldsymbol{\chi}(0)) | \\ &\qquad + | h_1(\boldsymbol{\psi}) - h_1(\boldsymbol{\chi}) | + | h_2(\boldsymbol{\psi}) - h_2(\boldsymbol{\chi}) | \\ &\qquad \leq L_N \max\{ \sup_{t\in[-1,0]} | \psi_1(t) - \chi_1(t) |, \sup_{t\in[-1,0]} | \psi_2(t) - \chi_2(t)\}, \end{aligned}$$

where $\psi_i^0 = \psi_i(0), \Delta_i = \chi_i(0) - \psi_i^0, i = 1, 2$. We define

$$\begin{aligned} L_N = F_1^0 \big|\alpha_P(\delta - \gamma) - \delta\big| + F_1^{'0} \big|(\alpha_P(\delta - \gamma)M_2^0 + \alpha_M \delta M_2^0 + \alpha_M \kappa\big| + |M_2^0 F_1^{'0} + F_1^0| \\ + |2A(1 + \alpha_P) - \alpha_M|\kappa|E_N F_1^1 + S_1 F_1^{'1}|, \end{aligned}$$

where $F_1 = \max_{\boldsymbol{\phi}\in N}(\max_{t\in[-1,0]} |f(\phi_1(t))|)$, $F_1' = \max_{\boldsymbol{\phi}\in N}(\max_{t\in[-1,0]} |f'(\phi_1(t))|)$, $M_2^0 = \max_{\boldsymbol{\phi}\in N} |\phi_2(0)|$, $S_i = \sup_{t\in[-1,0]} |\psi_i(t) - \chi_i(t)|, i = 1, 2$, and E_N is a strictly positive value such that for all $\boldsymbol{\phi}, \boldsymbol{\chi} \in N$,

$$| e^{-\delta \int_{-1}^0 f(\chi_1(r))\,\mathrm{d}r} - e^{-\delta \int_{-1}^0 f(\phi_1(r))\,\mathrm{d}r} | < E_N,$$

which exists as the image of a bounded domain by f is bounded and the exponential function is locally Lipschitz continuous. Simple calculations then show that L_N satisfies (4.5): we prove existence and uniqueness of solutions. ∎

Finally, we introduce the function $\overline{\theta}_{(.,.)} : C_1^2(\mathbb{R}_+) \to C_0([0, +\infty])$, defined as $\overline{\theta}_{(.,.)} : (\mathcal{M}(\theta), \mathcal{P}(\theta))_{\theta\geq 0} \mapsto \overline{\theta}_{(\mathcal{M}(.),\mathcal{P}(.))}$, where $\overline{\theta}_{(\mathcal{M}(.),\mathcal{P}(.))}$ is a function which associates $t \in [0, +\infty]$ to a value $\overline{\theta}_{(\mathcal{M}(.),\mathcal{P}(.))}(t)$ such that

$$\int_0^{\overline{\theta}_{(\mathcal{M}(.),\mathcal{P}(.))}(t)} \frac{1}{\mathcal{V}(\alpha_M \mathcal{M}(s) + \alpha_P \mathcal{P}(s))}\,\mathrm{d}s = t.$$

Therefore, if $(\mathcal{M}(\theta), \mathcal{P}(\theta))_{\theta\geq 0}$ is a solution of system (4.2) for $\theta \geq 1$, then $(\mathcal{M}(\overline{\theta}(t)), \mathcal{P}(\overline{\theta}(t))_{t\geq 0}$ is solution of (3.1) for $t \geq \overline{\theta}_{(\mathcal{M}(.),\mathcal{P}(.))}(1)$.

With this new formulation of our model, we study the stability of our system using a more general formulation of (4.4). In order to study the onset of oscillations, we focus our work more particularly on possible changes in stability due to Hopf bifurcations.

5. Stability analysis for the delay-differential system. Consider a generalized formulation of our system,

$$\begin{cases} \dfrac{d\mathcal{W}}{d\theta}(\theta) = (\alpha_P(\delta - \gamma)\mathcal{P}(\theta) - \delta\mathcal{W}(\theta))f(\mathcal{W}(\theta)) \\ \qquad\qquad + \kappa\big[\alpha_M f(\mathcal{W}(\theta)) + (2A\alpha_P - \alpha_M)e^{-\delta\tau_0(\mathcal{W}_\theta)} f(\mathcal{W}(\theta - 1))\big], \\ \dfrac{d\mathcal{P}}{d\theta}(\theta) = -\gamma\mathcal{P}(\theta)f(\mathcal{W}(\theta)) + 2A\kappa e^{-\delta\tau_0(\mathcal{W}_\theta)} f(\mathcal{W}(\theta - 1)), \end{cases} \tag{5.1}$$

where f is a continuous function on $\mathbb{R}_+$ such that $f(0) = 0$ and f is strictly increasing on $\mathbb{R}_+$ (unlike in (4.4) where f is specifically defined as $1/\mathcal{V}$).

We assume that

$$2A\alpha_P \geq \alpha_M, \tag{5.2a}$$

$$\alpha_M \kappa / \max(\delta, \gamma) > x_0 \tag{5.2b}$$

for some value $x_0 > 0$. Therefore, according to Proposition 3.1, $\mathcal{W}(\theta) > x_0$ for $\theta \in [0,1]$ implies $\mathcal{W}(\theta) > x_0$ for $\theta \geq 0$.

We start by identifying the steady states.

5.1. Equilibrium. We consider an equilibrium $(\mathcal{W}_0, \mathcal{P}_0)$ of (5.1) such that

$$\begin{cases} 0 = [\alpha_P(\delta-\gamma)\mathcal{P}_0 - \delta\mathcal{W}_0]f(\mathcal{W}_0) + \kappa\big[\alpha_M f(\mathcal{W}_0) + (2A\alpha_P - \alpha_M)e^{-\delta f(\mathcal{W}_0)}f(\mathcal{W}_0)\big], \\ 0 = -\gamma\mathcal{P}_0 f(\mathcal{W}_0) + 2A\kappa e^{-\delta f(\mathcal{W}_0)}f(\mathcal{W}_0). \end{cases}$$

For every $\mathcal{P}_0 > 0$, the point $(0, \mathcal{P}_0)$ is a steady state. But as mentioned above, assumptions (5.2a) and (5.2b) imply that this steady state can be ignored if we assume that $\mathcal{W}(\theta) > x_0$ for $\theta \in [0,1]$.

We introduce the function u defined for all $X \in I_{x_0} :=]x_0, +\infty)$ by

$$u(X) := X - \kappa\left[\alpha_M/\delta + \left(\frac{2A\alpha_P}{\gamma} - \frac{\alpha_M}{\delta}\right)e^{-\delta f(X)}\right].$$

We have the following result.

THEOREM 5.1. *If condition* (5.2b) *holds, then the system* (5.1) *has a steady state* $(\mathcal{W}_0, \mathcal{P}_0)$ *such that* $\mathcal{W}_0 > x_0$ *defined as a solution of*

$$\begin{cases} \mathcal{W}_0 &= \kappa\big[\alpha_M/\delta + (\frac{2A\alpha_P}{\gamma} - \frac{\alpha_M}{\delta})e^{-\delta f(\mathcal{W}_0)}\big], \\ \mathcal{P}_0 &= 2A\kappa e^{-\delta f(\mathcal{W}_0)}/\gamma. \end{cases} \tag{5.3}$$

Furthermore, if (5.2b) *is verified and* $2A\alpha_p\delta - \gamma\alpha_M \geq 0$*, then this steady state is the only one such that* $\mathcal{W}_0 > x_0$*.*

Indeed, if $(\mathcal{W}_0, \mathcal{P}_0)$ with $\mathcal{W}_0 > x_0$ is an equilibrium, then $\mathcal{W}_0$ is a root of u. The condition (5.2b) implies that 0 is contained in the image of I_{x_0} by u, and $2A\alpha_p\delta - \gamma\alpha_M \geq 0$ implies that u is strictly increasing on I_{x_0} (as f is an increasing function on I_{x_0}). Therefore the theorem is proved.

From this point on we assume that $2A\alpha_p\delta - \gamma\alpha_M \geq 0$.

5.2. Linearization about $(\mathcal{W}_0, \mathcal{P}_0)$**.** Before linearizing about the equilibrium, we rewrite (5.1) as

$$\begin{pmatrix} \dot{\mathcal{W}}(\theta) \\ \dot{P}(\theta) \end{pmatrix} = H\left(\begin{pmatrix} \mathcal{W}(\theta) \\ \mathcal{P}(\theta) \end{pmatrix}, \begin{pmatrix} \mathcal{W}(\theta-1) \\ \mathcal{P}(\theta-1) \end{pmatrix}, \begin{pmatrix} \mathcal{W}_\theta \\ \mathcal{P}_\theta \end{pmatrix}\right),$$

where for $\mathbf{X}, \mathbf{Y} \in \mathbb{R}^2$ and $\boldsymbol{\phi} \in C^0([-1,0])$, H denotes

$$H(\mathbf{X}, \mathbf{Y}, \boldsymbol{\phi}) = \begin{pmatrix} (\alpha_P(\delta-\gamma)X_2 - \delta X_1 + \kappa\alpha_M)f(X_1) + \kappa(2A\alpha_P - \alpha_M)e^{-\delta\int_{-1}^0 f(\phi_1(r))\,\mathrm{d}r}f(Y_1) \\ -\gamma X_2 f(X_1) + 2A\kappa e^{-\delta\int_{-1}^0 f(\phi_1(r))\,\mathrm{d}r}f(Y_1) \end{pmatrix}.$$

Using (5.3), we compute $\overline{J_0}$, the Jacobian of H with respect to $\mathbf{X}$ applied at the point $(\mathcal{P}_0, \mathcal{W}_0)$:

$$\overline{J_0} = -\begin{pmatrix} (2A\alpha_P - \alpha_M)\kappa e^{-\delta f(\mathcal{W}_0)}f'(\mathcal{W}_0) + \delta f(\mathcal{W}_0) & -\alpha_P(\delta-\gamma)f(\mathcal{W}_0) \\ 2A\kappa e^{-\delta f(\mathcal{W}_0)}f'(\mathcal{W}_0) & \gamma f(\mathcal{W}_0) \end{pmatrix}.$$

We also compute $\overline{J_1}$ and $\overline{J_2}$, the Jacobian of H with respect to $\mathbf{Y}$ and $\boldsymbol{\phi}$, respectively, both applied at the point $(\mathcal{P}_0, \mathcal{W}_0)$:

$$\overline{J_1} = \begin{pmatrix} 2A\alpha_P - \alpha_M & 0 \\ 2A & 0 \end{pmatrix} \kappa f'(\mathcal{W}_0) e^{-\delta f(\mathcal{W}_0)}, \quad \text{and} \quad \overline{J_2} = -\delta f(\mathcal{W}_0)\overline{J_1}.$$

We set $p(\theta) = \mathcal{P}(\theta) - \mathcal{P}_0$ and $w(\theta) = \mathcal{W}(\theta) - \mathcal{W}_0$. Then (4.3) linearized about $(\mathcal{W}_0, \mathcal{P}_0)$ is

$$\begin{pmatrix} \dot{w}(\theta) \\ \dot{p}(\theta) \end{pmatrix} = \overline{J_0} \begin{pmatrix} w(\theta) \\ p(\theta) \end{pmatrix} + \overline{J_1} \begin{pmatrix} w(\theta-1) \\ p(\theta-1) \end{pmatrix} + \overline{J_2} \begin{pmatrix} \int_{-1}^{0} w(\theta+r)\,\mathrm{d}r \\ \int_{-1}^{0} p(\theta+r)\,\mathrm{d}r \end{pmatrix}.$$

5.3. Characteristic equation. We equate $p(\theta)$ and $w(\theta)$ to $e^{\lambda\theta}$, obtaining the following expression:

(5.4)
$$\begin{aligned} \Delta(\lambda) = \lambda I &+ \begin{pmatrix} \delta f(\mathcal{W}_0) & -\alpha_P(\delta-\gamma) f(\mathcal{W}_0) \\ 0 & \gamma f(\mathcal{W}_0) \end{pmatrix} \\ &+ \begin{pmatrix} 2A\alpha_P - \alpha_M & 0 \\ 2A & 0 \end{pmatrix} \kappa e^{-\delta f(\mathcal{W}_0)} f'(\mathcal{W}_0)(1 - e^{-\lambda} + \delta f(\mathcal{W}_0) \int_{-1}^{0} e^{\lambda r}\,\mathrm{d}r). \end{aligned}$$

This gives the characteristic equation $\det(\Delta(\lambda)) = 0$. We verify easily that the assumption $2A\delta\alpha_P \geq \gamma\alpha_M$ implies $\det(\Delta(0)) > 0$, hence $\lambda \neq 0$. This means that the integral in (5.4) is computed so that

$$\delta f(\mathcal{W}_0) \int_{-1}^{0} e^{\lambda r}\,\mathrm{d}r = \frac{\delta f(\mathcal{W}_0)}{\lambda}(1 - e^{-\lambda}).$$

Therefore, if we multiply both sides of the equation $\det(\Delta(\lambda)) = 0$ by λ, we get $\det(\hat{\Delta}(\lambda)) = 0$, a new equation which has the same roots plus $\lambda = 0$ with

$$\begin{aligned} \hat{\Delta}(\lambda) = &\begin{pmatrix} \lambda^2 + \lambda\delta f(\mathcal{W}_0) & -\lambda\alpha_P(\delta-\gamma) f(\mathcal{W}_0) \\ 0 & \lambda^2 + \lambda\gamma f(\mathcal{W}_0) \end{pmatrix} \\ &+ \begin{pmatrix} 2A\alpha_P - \alpha_M & 0 \\ 2A & 0 \end{pmatrix} \kappa e^{-\delta f(\mathcal{W}_0)} f'(\mathcal{W}_0)(\lambda + \delta f(\mathcal{W}_0))(1 - e^{-\lambda}). \end{aligned}$$

Now, we compute $\det(\hat{\Delta}(\lambda))$:

$$\begin{aligned} \det(\hat{\Delta}(\lambda)) = &\lambda^4 + \lambda^3(\gamma+\delta) f(\mathcal{W}_0) + \lambda^2\gamma\delta f(\mathcal{W}_0)^2 + \kappa e^{-\delta f(\mathcal{W}_0)} f'(\mathcal{W}_0)(\lambda + \delta f(\mathcal{W}_0)) \\ &(1 - e^{-\lambda})\big[\lambda^2(2A\alpha_P - \alpha_M) + \lambda f(\mathcal{W}_0)(2A\alpha_P\delta - \gamma\alpha_M)\big]. \end{aligned}$$

For $\lambda \neq 0$, $\det(\hat{\Delta}(\lambda)) = 0$ is equivalent to

$$\lambda^3 + a\lambda^2 + b\lambda + c + (d\lambda^2 + g\lambda - c)e^{-\lambda} = 0, \tag{5.5}$$

where

$$\begin{aligned} &a = a_1 + a_2, \quad b = b_1 + c_1 + \delta f(\mathcal{W}_0) a_2, \quad c = \delta f(\mathcal{W}_0) c_1, \\ &d = -a_2, \quad g = -(c_1 + \delta f(\mathcal{W}_0) a_2), \end{aligned}$$

with

$$\begin{aligned} &a_1 = (\gamma+\delta) f(\mathcal{W}_0) > 0, \quad a_2 = K(2A\alpha_P - \alpha_M) > 0, \\ &b_1 = \gamma\delta f(\mathcal{W}_0)^2 > 0, \quad c_1 = K f(\mathcal{W}_0)(2A\alpha_P\delta - \gamma\alpha_M) > 0, \end{aligned}$$

and $K = \kappa e^{-\delta f(\mathcal{W}_0)} f'(\mathcal{W}_0)$.

5.4. A framework for stability analysis. Equation (5.5) is a third-order transcendental equation. In Beretta and Kuang [6], these authors proposed a geometric method to assess whether or not a change in the delay τ affects the stability of a given system. That is, for a characteristic equation of the form

$$D(\lambda,\tau) := P(\lambda,\tau) + Q(\lambda,\tau)e^{-\lambda\tau} = 0, \tag{5.6}$$

where P, Q are polynomials in λ with τ-dependent complex coefficients. This relies on detecting the appearance of purely imaginary eigenvalues, which corresponds to a Hopf bifurcation leading to a change in stability.

However, in our case, the delay is fixed at $\tau = 1$ by construction. Therefore, to study Hopf bifurcations, we need to adapt Beretta and Kuang's framework: we study the changes in eigenvalues of transcendental equations with respect to a variable $\nu \in \mathbb{R}_+$ which is not the delay. In such a case the characteristic equation is written

$$D(\lambda,\nu) := P(\nu,\lambda) + Q(\nu,\lambda)e^{-\lambda} = 0, \tag{5.7}$$

where P, Q are polynomials in λ with ν-dependent complex coefficients, which we divide between real and imaginary part as

$$P(\lambda,\nu) = P_R(\lambda,\nu) + iP_I(\lambda,\nu), \quad Q(\lambda,\nu) = Q_R(\lambda,\nu) + iQ_I(\lambda,\nu). \tag{5.8}$$

Now, we define $\omega(\nu)$ as the solution of

$$F(\omega,\nu) := |P(i\omega,\nu)|^2 - |Q(i\omega,\nu)|^2 = 0, \tag{5.9}$$

and $I \subseteq \mathbb{R}_{+0}$ the subset such that there exists a solution $\omega(\nu)$ if and only if $\nu \in I$.

For every such ν, we define two functions

$$\begin{cases} \psi(\nu) &= -P_R(i\omega(\nu),\nu)Q_I(i\omega(\nu),\nu) &+ &P_I(i\omega(\nu),\nu)Q_R(i\omega(\nu),\nu), \\ \phi(\nu) &= P_R(i\omega(\nu),\nu)Q_R(i\omega(\nu),\nu) &+ &P_I(i\omega(\nu),\nu)Q_I(i\omega,\nu) \end{cases}$$

and then a third

$$\zeta(\nu) = \begin{cases} \arctan(-\psi(\nu)/\phi(\nu)) & \text{if} \quad \psi(\nu) > 0, \phi(\nu) < 0, \\ \pi/2 & \text{if} \quad \psi(\nu) = Q_R^2 + Q_I^2, \phi(\nu) = 0, \\ \pi/2 + \arctan(-\psi(\nu)/\phi(\nu)) & \text{if} \quad \phi(\nu) > 0, \\ 3\pi/2 & \text{if} \quad \psi(\nu) = -(Q_R^2 + Q_I^2), \phi(\nu) = 0, \\ 2\pi + \arctan(-\psi(\nu)/\phi(\nu)) & \text{if} \quad \psi(\nu) < 0, \phi(\nu) < 0. \end{cases} \tag{5.10}$$

Finally, for all $n \in \mathbb{N}$ we introduce a function $S_n(\nu)$ defined for $\nu \in I$ by

$$S_n(\nu) := \omega(\nu) - (\zeta(\nu) + 2n\pi). \tag{5.11}$$

Given these notations, we state the following result.

LEMMA 5.2. *Assume that $\omega(\nu)$ is a positive real root of (5.9) defined for $\nu \in I$, and at some $\nu^* \in I$,*

$$S_n(\nu^*) = 0 \quad \text{for some } n \in \mathbb{N}.$$

Then a pair of simple conjugate pure imaginary roots $\lambda_+(\nu^*) = i\omega(\nu^*)$, $\lambda_-(\nu^*) = -i\omega(\nu^*)$ of (5.7) exists at $\nu = \nu^*$ which crosses the imaginary axis from left to right if $\sigma(\nu^*) > 0$ and crosses the imaginary axis from right to left if $\sigma(\nu^*) < 0$, where

$$\sigma(\nu^*) = \operatorname{sign}\left\{ \frac{\mathrm{d}\operatorname{Re}\lambda}{\mathrm{d}\nu}\Big|_{\lambda=i\omega(\nu^*)} \right\} = \operatorname{sign}\left\{F'_\omega(\omega(\nu^*),\nu^*)\right\} \operatorname{sign}\left\{ \frac{\mathrm{d}S_n(\nu)}{\mathrm{d}\nu}\Big|_{\nu=\nu^*} \right\}. \tag{5.12}$$

Proof. First, we notice that if $\lambda = i\omega$, then (5.7) is equivalent to

$$\begin{cases} \sin(\omega) = \dfrac{-P_R(i\omega,\nu)Q_I(i\omega,\nu) + P_I(i\omega,\nu)Q_R(i\omega,\nu)}{|Q(i\omega,\nu)|^2}, \\ \cos(\omega) = \dfrac{-P_R(i\omega,\nu)Q_R(i\omega,\nu) + P_I(i\omega,\nu)Q_I(i\omega,\nu)}{|Q(i\omega,\nu)|^2}. \end{cases}$$

Let $i\omega(\nu)$ be a root of (5.7): the above system implies that $F(\omega(\nu),\nu) = 0$. Moreover, as in [6], we easily prove that it also implies that if $\zeta(\nu)$ is given by (5.10), then $\zeta(\nu) \in [0, 2\pi]$ and

$$\begin{cases} \sin(\zeta(\nu)) = \dfrac{-P_R(i\omega(\nu),\nu)Q_I(i\omega(\nu),\nu) + P_I(i\omega(\nu),\nu)Q_R(i\omega(\nu),\nu)}{|Q(i\omega(\nu),\nu)|^2}, \\ \cos(\zeta(\nu)) = \dfrac{-P_R(i\omega(\nu),\nu)Q_R(i\omega(\nu),\nu) + P_I(i\omega(\nu),\nu)Q_I(i\omega(\nu),\nu)}{|Q(i\omega(\nu),\nu)|^2}. \end{cases}$$

This implies that $\lambda_+(\nu^*) = i\omega(\nu^*)$, $\lambda_-(\nu^*) = -i\omega(\nu^*)$ are a pair of pure imaginary roots of (5.7) if and only if $F(\omega(\nu^*),\nu^*) = 0$ and there exists $n \in \mathbb{N}$ such that $\omega(\nu^*) - (\theta(\nu^*) + 2n\pi) = 0$.

The proof of the geometric criterion (5.12) is similar to that of Lemma 2.1 of Beretta and Kuang [6]. Differentiating both sides of (5.7) by ν gives

$$\frac{\mathrm{d}\lambda}{\mathrm{d}\nu} = -\frac{P'_\nu(\lambda,\nu) + Q'_\nu(\lambda,\nu)e^{-\lambda}}{P'_\lambda(\lambda,\nu) + (Q'_\lambda(\lambda,\nu) - Q(\lambda,\nu))e^{-\lambda}}.$$

The same (5.7) also gives $e^\lambda = -\frac{Q(\nu,\lambda)}{P(\nu,\lambda)}$ such that

$$\left(\frac{\mathrm{d}\lambda}{\mathrm{d}\nu}\right)^{-1} = \left(-\frac{P'_\lambda(\lambda,\nu)}{P(\nu,\lambda)} + \frac{Q'_\lambda(\lambda,\nu)}{Q(\nu,\lambda)} - 1\right) \Big/ \left(\frac{P'_\nu(\lambda,\nu)}{P(\nu,\lambda)} - \frac{Q'_\nu(\lambda,\nu)}{Q(\nu,\lambda)}\right).$$

Assume that $\lambda = i\omega(\nu)$, where $\omega(\nu)$ is a solution of (5.9); then

$$\left(\frac{\mathrm{d}\lambda}{\mathrm{d}\nu}\right)^{-1} = \frac{-P'_\lambda(\lambda,\nu)\overline{P(\lambda,\nu)} + Q'_\lambda(\lambda,\nu)\overline{Q(\lambda,\nu)} - |P(i\omega,\nu)|^2}{P'_\nu(\lambda,\nu)\overline{P(\lambda,\nu)} - Q'_\nu(\lambda,\nu)\overline{Q(\lambda,\nu)}} \tag{5.13}$$

Now we remark that $iP'_\lambda(i\omega,\nu) = P'_\omega(i\omega,\nu)$ and $iQ'_\lambda(i\omega,\nu) = Q'_\omega(i\omega,\nu)$; hence,

$$\begin{aligned} &-P'_\lambda(i\omega,\nu)\overline{P(i\omega,\nu)} + Q'_\lambda(i\omega,\nu)\overline{Q(i\omega,\nu)} \\ &= i[(P'_{R_\omega}P_R + P'_{I_\omega}P_I) - (Q'_{R_\omega}Q_R + Q'_{I_\omega}QI)] \\ &\quad - [(P'_{I_\omega}P_R - P_IP'_{R_\omega}) - (Q'_{I_\omega}Q_R - Q_IQ'_{R_\omega})]. \end{aligned} \tag{5.14}$$

We notice that differentiating (5.9) with respect to ν gives

$$F'_\omega(\omega,\nu)\omega' + F'_\nu(\omega,\nu) = 0, \quad \nu \in I, \tag{5.15}$$

where

$$\begin{cases} F'_\omega &= 2[(P'_{R_\omega}P_R + P'_{I_\omega}P_I) - (Q'_{R_\omega}Q_R + Q'_{I_\omega}Q_I)], \\ F'_\nu &= 2[(P'_{R_\nu}P_R + P'_{I_\nu}P_I) - (Q'_{R_\nu}Q_R + Q'_{I_\nu}Q_I)]. \end{cases}$$

Therefore, (5.14) becomes

$$-P'_\lambda(i\omega,\nu)\overline{P(i\omega,\nu)}+Q'_\lambda(i\omega,\nu)\overline{Q(i\omega,\nu)}$$
$$=i\frac{F'_\omega(\omega,\nu)}{2}-[(P_{I_\omega}P_R-P_IP_{R_\omega})-(Q_{I_\omega}Q_R-Q_IQ_{R_\omega})].$$

Similarly, we have

$$P'_\nu(\lambda,\nu)\overline{P(i\omega,\nu)}-Q'_\nu(\lambda,\nu)\overline{Q(i\omega,\nu)}$$
$$=\frac{F'_\nu(\omega,\nu)}{2}+i[(P'_{I_\omega}P_R-P_IP'_{R_\omega})-(Q'_{I_\omega}Q_R-Q_IQ'_{R_\omega})].$$

Using these two equalities and (5.15), (5.13) becomes

$$\left(\frac{\mathrm{d}\lambda}{\mathrm{d}\nu}\right)^{-1}=\frac{-2(U+|P(i\omega,\nu)|^2)+iF'_\omega(\omega,\nu)}{-\omega'F'_\omega(\omega,\nu)+2iV}$$
$$=\Big(2(U+|P(i\omega,\nu)|^2)\omega'F'_\omega(\omega,\nu)+2VF'_\omega(\omega,\nu)$$
$$+i(4(U+|P(i\omega,\nu)|^2)V-\omega'F'_\omega(\omega,\nu)^2)\Big)/\Big((\omega')^2F'_\omega(\omega,\nu)^2+4V^2\Big),$$

where

$$U:=(P_{I_\omega}P_R-P_IP_{R_\omega})-(Q_{I_\omega}Q_R-Q_IQ_{R_\omega}),$$
$$V:=(P'_{I_\omega}P_R-P_IP'_{R_\omega})-(Q'_{I_\omega}Q_R-Q_IQ'_{R_\omega}).$$

This implies that

$$\mathrm{Re}\left(\left(\frac{\mathrm{d}\lambda}{\mathrm{d}\nu}\right)^{-1}\right)=\big((U+|P(i\omega,\nu)|^2)\omega'+V\big)\frac{2F'_\omega(\omega,\nu)}{(\omega')^2F'_\omega(\omega,\nu)^2+4V^2}.$$

Therefore, we have

$$\mathrm{sign}\left\{\frac{\mathrm{d}\,\mathrm{Re}\,\lambda}{\mathrm{d}\nu}\Big|_{\lambda=i\omega}\right\}=\mathrm{sign}\Big\{F'_\omega(\omega,\nu)\Big\}\,\mathrm{sign}\Big\{V+(U+|P(i\omega,\nu)|^2)\omega'\Big\}.$$

Finally we use $S_n(\nu)\equiv\omega(\nu)-(\zeta(\nu)+2n\pi)$ to get

$$S'_n(\nu)=\omega'(\nu)-\theta'(\nu).$$

Since $\theta'(\nu)=-\frac{U\omega'+V}{|P(i\omega,\nu)|^2}$, we conclude that

$$\mathrm{sign}\left\{\frac{\mathrm{d}\,\mathrm{Re}\,\lambda}{\mathrm{d}\nu}\Big|_{\lambda=i\omega}\right\}=\mathrm{sign}\Big\{F'_\omega(\omega,\nu)\Big\}\,\mathrm{sign}\Big\{S'_n(\nu)\Big\}.$$

∎

This lemma provides a tool to analyze any characteristic equation of the form (5.7). Because our model of platelet production induces (5.5) which is of degree three, we now apply this lemma to a transcendental equation of degree three.

5.5. Application to a system with a third-degree transcendental equation. Using the framework presented above on system (5.1), we obtain the following result.

PROPOSITION 5.3. *Let ν be a parameter of system* (5.1) *among $A,\delta,\gamma,\ \alpha_P,\alpha_M$ as defined in section* 2. *Let $\rho(\nu):=2A\alpha_P\delta-\gamma\alpha_M$.*

1. *Let $\nu=\nu_0$ the solution of $\rho(\nu)=0$. Then*

$$(\mathcal{W}_0,\mathcal{P}_0)=\Big(\kappa\alpha_M/\delta,2A\kappa e^{-\delta f(\kappa\alpha_M/\delta)}/\gamma\Big)$$

is a locally asymptotically stable equilibrium of (5.1).

2. *Suppose that ν takes a value ν^* such that $\rho(\nu^*) > 0$. Then if (5.9) has a positive solution, it is unique and given by*

$$\omega = \sqrt{4\kappa e^{-\delta f(\mathcal{W}_0)} f'(\mathcal{W}_0) A\alpha_P(\delta-\gamma) f(\mathcal{W}_0) - \gamma^2 f(\mathcal{W}_0)^2},$$

where ν^* replaces the appropriate parameter.
In addition, suppose that for such a value ν^* of ν, $\rho'(\nu^*) > 0$ (resp., $\rho'(\nu^*) < 0$). We consider two possible cases.

(a) *If for all $\overline{\nu} \in [0, \nu^*]$ (resp., $\overline{\nu} \in [\nu^*, +\infty]$) and all $n \in \mathbb{N}$ we have $S_n(\overline{\nu}) \neq 0$ (where S_n is given by (5.11)), then the equilibrium of the system for $\nu = \nu^*$ is locally asymptotically stable.*

(b) *Suppose there exists a sequence of pairs $(n_i, \nu_i)_{i=0,\dots,I}$ with $\nu_i < \nu^*$ (resp., $\nu_i > \nu^*$) such that $S_{n_i}(\nu_i) = 0$. We index the pairs such that the sequence $(\nu_i)_{i=0,\dots,I}$ is increasing (resp., decreasing). Then, when $\nu = \nu_0$ a Hopf bifurcation occurs at $(\mathcal{W}_0, \mathcal{P}_0)$ and periodic solutions appear.*
Moreover, $(\mathcal{W}_0, \mathcal{P}_0)$ for $\nu = \nu^*$ is a locally asymptotically stable equilibrium if and only if

$$\sum_{i=0}^{I} \operatorname{sign}\left\{ S'_{n_i}(\nu_i) \right\} = 0.$$

Otherwise, $(\mathcal{W}_0, \mathcal{P}_0)$ is an unstable equilibrium.

We remark that ν_0 exists if and only if $\max_\nu(S_0(\nu)) > 0$ and $\max_\nu(S_0(\nu)) - \min_\nu(S_0(\nu)) > 2\pi$.

Proof. We present the proof in several steps.

1. We start by noticing that if $2A\alpha_P\delta - \gamma\alpha_M = 0$ and $2A\alpha_P - \alpha_M = 0$, then $\delta = \gamma$ such that (5.5) becomes

$$0 = \lambda^2 + 2\lambda\delta f(\mathcal{W}_0) + \delta^2 f(\mathcal{W}_0)^2 = (\lambda + \delta f(\mathcal{W}_0))^2.$$

There is a negative double root $\lambda = -\delta f(\mathcal{W}_0) < 0$, implying that the equilibrium is locally asymptotically stable.
In the case where $2A\alpha_P\delta - \gamma\alpha_M = 0$ and $2A\alpha_P - \alpha_M > 0$, (5.5) for $\lambda \neq 0$ is equivalent to

$$\lambda^2 + a\lambda + b + d\lambda e^{-\lambda} + g e^{-\lambda} = 0 \tag{5.16}$$

with

$$a = (\gamma+\delta) f(\mathcal{W}_0) + K(2A\alpha_P - \alpha_M), \quad d = -K(2A\alpha_P - \alpha_M),$$
$$b = \gamma\delta f(\mathcal{W}_0)^2 + \delta f(\mathcal{W}_0) K(2A\alpha_P - \alpha_M), \quad g = -\delta f(\mathcal{W}_0) K(2A\alpha_P - \alpha_M).$$

From Beretta and Kuang [6], we know that if $\lambda = i\omega$ is a solution of this characteristic equation, then we have

$$\cos(\omega) = -\frac{(b-\omega^2)g + \omega^2 ad}{\omega^2 d^2 + g^2} = 1 + \frac{\gamma f(\mathcal{W}_0)}{K(2A\alpha_P - \alpha_M)} > 1.$$

Therefore, it is impossible for (5.16) to have purely imaginary roots. Combined with the fact that all eigenvalues have a negative real part for $2A\alpha_P - \alpha_M = 0$, this implies that $(\mathcal{W}_0, \mathcal{P}_0)$ is always a locally asymptotically stable equilibrium of (5.1) for $2A\alpha_P\delta - \gamma\alpha_M = 0$ and $2A\alpha_P - \alpha_M > 0$.

2. In the case of (5.1), the characteristic equation is written in the form of (5.7), where

$$D(\nu,\lambda) = \lambda^3 + a(\nu)\lambda^2 + b(\nu)\lambda + c(\nu) + (d(\nu)\lambda^2 + g(\nu)\lambda - c(\nu))e^{-\lambda} \tag{5.17}$$

such that the decomposition of D given by (5.7) and (5.8) gives

$$\begin{cases} P_R(i\omega,\nu) = c - a\omega^2, & Q_R(i\omega,\nu) = -d\omega^2 - c, \\ P_I(i\omega,\nu) = \omega^3 - b\omega, & Q_I(i\omega,\nu) = g\omega. \end{cases}$$

This implies that $F(\omega,\nu) = \omega^2(\omega^4 + p\omega^2 + q)$, and since we excluded 0 as a solution, (5.9) is equivalent to

$$\omega^4 + p\omega^2 + q = 0 \tag{5.18}$$

with $p = a^2 - 2b - d^2$ and $q = -2ac + b^2 - 2cd - g^2$. We apply this to our case with

$$\begin{aligned} &a = a_1 + a_2, \quad b = b_1 + c_1 + \delta f(\mathcal{W}_0)a_2, \quad c = \delta f(\mathcal{W}_0)c_1, \\ &d = -a_2, \quad g = -(c_1 + \delta f(\mathcal{W}_0)a_2), \end{aligned}$$

with

$$\begin{aligned} &a_1 = (\gamma+\delta)f(\mathcal{W}_0), \quad a_2 = K(2A\alpha_P - \alpha_M), \\ &b_1 = \gamma\delta f(\mathcal{W}_0)^2, \quad c_1 = Kf(\mathcal{W}_0)(2A\alpha_P\delta - \gamma\alpha_M), \end{aligned}$$

and $K = \kappa e^{-\delta f(\mathcal{W}_0)} f'(\mathcal{W}_0)$. We easily show that

$$q = \delta^2 f(\mathcal{W}_0)^3\Big[4KA\alpha_P(\gamma-\delta) + \gamma^2 f(\mathcal{W}_0)\Big], \qquad p = \frac{q + \delta^4 f(\mathcal{W}_0)^4}{\delta^2 f(\mathcal{W}_0)^2}.$$

Because $p > q$, $q > 0$ implies $p > 0$ such that (5.18) has one nonzero positive root if and only if $q < 0$. In such a case, this root is given by

$$\omega(\nu) = \sqrt{\frac{-p + \sqrt{p^2 - 4q}}{2}} = \sqrt{4KA\alpha_P(\delta-\gamma)f(\mathcal{W}_0) - \gamma^2 f(\mathcal{W}_0)^2}.$$

Finally, as $\omega(\nu)$ is the largest of the roots of $F(\omega,\nu)$ and $\lim_{\omega\to\infty} F(\omega,\nu) = +\infty$, the derivative of F at $\omega(\nu)$ is always positive. Therefore, the geometrical criterion (5.12) is now given by

$$\delta(\nu^*) = \left\{ \frac{\mathrm{d}S_n(\nu)}{\mathrm{d}\nu}\Big|_{\nu=\nu^*} \right\}.$$

According to Lemma 5.2, as ν shifts away from ν_0 the number of pairs of conjugate roots with a positive real part is given by $\sum_{i<\bar{i}} \mathrm{sign}\{S'_{n_i}(\nu_i)\}$. Noticing that $(\mathcal{W}_0, \mathcal{P}_0)$ is a locally asymptotically stable equilibrium of (5.1) if and only if all roots of (5.7) have negative real part, we complete the proof. ∎

In the next section, we use this criterion to assess the impact of an increase of MkP death rate on the stability of our system.

6. Application of the framework for stability analysis on the megakaryopoiesis model.

6.1. Choice of parameters. Except for the expansion rate A, our choice of parameters is a combination of what is found in the literature and what is deducible from fitting our model to single values available in the literature (like P^* the average platelet count). Below, we give details for parameters requiring calculation or fitting. Other parameters are given in Table 6.1.

TABLE 6.1
Parameters obtained independently from our model.

Name	Interpretation	Unit	Value	Source
κ	Progenitor input rate	cells/kg*day^{-1}	3.7×10^3	[7, 16]
δ	Progenitor death rate	days^{-1}	0.069	[37]
α_M	TPO receptors per progenitor	receptor/MkP	1.04×10^3	[32, 35, 42]
γ	Platelet death rate	days^{-1}	0.27	[29]
α_P	TPO receptors per platelet	receptor/Pl.	56	[35]
P_0	Average platelet count	Pl./kg	20.28×10^9	[25]
P_-	Pl. count without TPO	–	10%	[17]
n	TPO clearance Hill coefficient	–	2	[19]
K_T	TPO half-max clearance	pg/ml	5.7×10^3	[24, 35]
T_0	Mean TPO concentration	pg/ml	80.1	[43]

- By fitting a G_0 model for HSC differentiation and renewal to mouse data, Mackey [37] managed to infer the rate of differentiation and the rate of random death of HSCs. We use the inferred value for HSC death rate as the death rate of MkPs: $\delta = 0.069$ days^{-1}.
  Furthermore, the product of the inferred value for HSC differentiation rate 0.010 days^{-1} and the value for HSC density 1.1×10^6 cells/kg obtained from mice data by Bernard, Belair, and Mackey [7] gives us the differentiation rate to the megakaryocytic line,
  $$\kappa = 1.1 \times 10^6 \times 0.010/3 = 3.7 \times 10^3 \text{ cells/kg*days}^{-1},$$
  where we assume that HSCs differentiate equally to all three hematopoietic cell lines.
- Using the mean platelet volume of 6.6 fL (6.6×10^{-15}L) obtained by Paulus [42] and considering a platelet as a perfect sphere, we compute the area of the surface of a platelet as $a_P = 17 \times 10^{-12}\text{m}^2 = 17$ pm^2. The area of MkP surface is computed using a diameter of 10 μm [32], and considering them also as a perfect spheres we get
  $$a_M = 4\pi 5^2 = 314 \text{ pm}^2.$$
  The amount of c-Mpl receptor per platelet is evaluated in [35] to be on average $\alpha_P = 56$. Considering that the amount of c-Mpl on the surface of a megakaryocytic cell is proportional to the area of its surface, we get
  $$\alpha_M = \alpha_P \frac{a_M}{a_P} = 1.04 \times 10^3.$$
- If we fit the differential equation $P'(t) = -\gamma P(t)$ using linear regression to the platelet disappearance curve available in [29], we obtain a death rate for platelet of $\gamma = 0.27$ day^{-1}.
- Using the average platelet count per liter of blood P_0 from [43] and assuming 5L of blood for a person of 70kg we get
  $$P_0 = 284 \times 10^9 \times 5/70 = 20.28 \times 10^9 \text{ platelets/kg}.$$
- According to Li, Xia, and Kuter [35], platelet binding sites for TPO have an average binding dissociation affinity $K_T = 163\text{pM} = 163 \times 10^{-12}\text{mol/L}$. We convert this value to pg/mL, using the molecular mass of TPO 35 kg/mol [24]:
  $$K_T = 5.7 \times 10^{-9} \text{ kg/L} = 5.7 \times 10^3 \text{ pg/ml}.$$

- When the c-Mpl receptors are deactivated, the platelet count drops to $P_- = P_0/10$ [17] and $f(\mathcal{W}_0)$ takes the value $1/\beta$. Therefore, (5.3) implies
$$\beta = \delta/\Big(\log(2A\kappa) - \log(\gamma P_-)\Big).$$
- Knowing the normal value of platelet count P_0 and (5.3), we obtain the value of $f(\mathcal{W}_0)$ at steady state as $f(\mathcal{W}_0) = \big(\log(2A\kappa) - \log(\gamma P_0)\big)/\delta$. We use this value to first compute $\mathcal{W}_0$ from (5.3), and then α from (2.5):
$$\alpha = \Big(1/f(\mathcal{W}_0) - \beta\Big)\frac{(K_T^n + T_0^n)}{T_0^n}.$$
The value of $\mathcal{W}_0$ is also used to compute T_{prod}/α_T from the quasi-steady state approximation (2.7):
$$\frac{T_{\text{prod}}}{\alpha_T} = \frac{\mathcal{W}_0 T_0^n}{K_T^n + T_0^n}.$$

Recall from the introduction that CT can be explained through two different pathogenesis: platelet-specific antibodies and antibodies targeting megakaryocytes and progenitors. Therefore, Table 6.1 and Proposition 5.3 tell us that our model cannot reproduce platelet-specific antibody-induced CT. Indeed, γ, the platelet death rate, is larger than that of progenitors, δ, while Proposition 5.3 says that $\gamma < \delta$ is a necessary condition for oscillations to appear. Therefore, oscillations cannot be obtained through increasing the platelet destruction rate, i.e., γ. In contrast, Proposition 5.3 is compatible with the pathogenesis of amegakaryocytic CT, which corresponds to an increase of δ.

6.2. An increase in progenitor death rate δ leads to oscillations, then a return to stability. With the parameters chosen as above, changes of stability occur only when $A \geq 7.5 \times 10^7$. As announced in section 4, the amplitude of A needs to account both for the fragmentation of platelets from megakaryocytes and for the successive divisions of progenitors not represented in our model. Figure 6.1 represents the result of stability analysis when setting $A = 2^{16} \times 2000$, that is, accounting for a total of 17 divisions before platelet shedding with 2000 platelets per shed by each megakaryocyte [28]. The results are presented using the time variable t corresponding to system (3.1): solutions are computed from system (5.1), then transformed as explained at the end of section 4.

We see that $(0, 0.6)$ and $(0, 4.02)$ are the only two pairs $(n, \delta) \in \mathbb{N} \times \mathbb{R}_+$ such that $S_n(\delta) = 0$. Using Proposition 5.3, we deduce the stability of our system from the above graph as follows:

- From $\underline{\delta} = \gamma\alpha_M/(2A\alpha_P)$, i.e., such that $\rho(\underline{\delta}) = 0$, to $\delta = \delta_0 = 0.67$, there is no pair $(n_i, \delta_i) \in \mathbb{N} \times [\underline{\delta}, \delta_0]$ such that $S_{n_i}(\delta_i) = 0$. Therefore the equilibrium is locally asymptotically stable.
- As δ_0 is the smallest value of δ such that for some $n \in \mathbb{N}$ (here $n = 0$) we have $S_n(\delta) = 0$, a Hopf bifurcation occurs at $\delta = \delta_0$.
- $(0, \delta_0)$ and $(0, \delta_1)$, where $\delta_1 = 4.02$, are the only pairs of $\mathbb{N} \times \mathbb{R}_+$ such that $S_{n_i}(\delta_i) = 0$. Plus, $S_0'(\delta_0) > 0$ and $S_0'(\delta_1) < 0$. Therefore, first, for $\delta \in [\delta_0, \delta_1]$ the equilibrium gets unstable and solutions are oscillating as shown on Figure 6.2. Second, for $\delta > \delta_1$ we have $\sum_i \operatorname{sign} S_{n_i}'(\delta_i) = 0$ such that the equilibrium is locally asymptotically stable.

Overall our system generates oscillations upon an increase in the death rate of megakaryocytes, reproducing qualitatively the pathogenesis of amegakaryocytic CT [26].

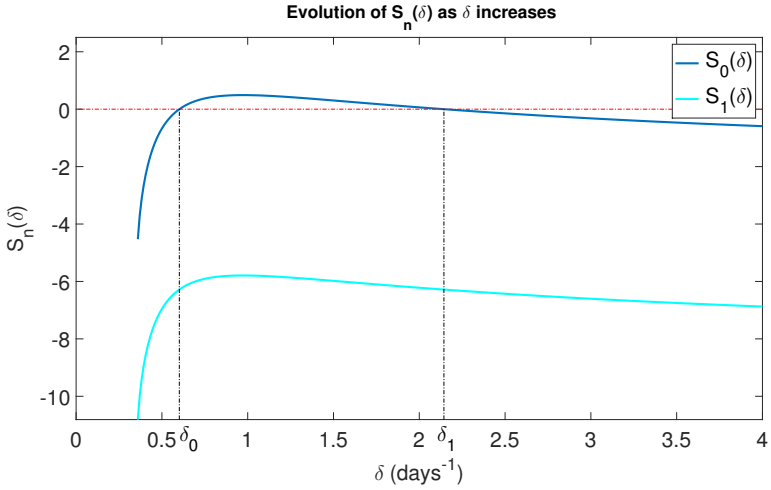

FIG. 6.1. *The scores $S_0(\delta)$ (dark blue line) and $S_1(\delta)$ (light blue line) are plotted against δ. $S_0(\delta)$ intersects with 0 (dashed red line) twice, as indicated by the black dotted lines, for $\delta_0 = 0.6$ (first vertical line) and for $\delta_1 = 2.14$ (second vertical line).*

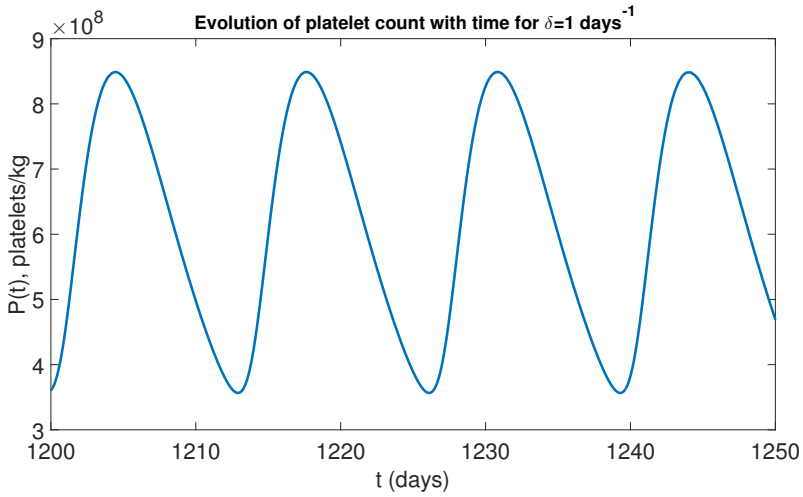

FIG. 6.2. *Long-term behavior of platelet count: when the death rate of progenitors is set to $\delta = 1$ days^{-1}, we have $\delta \in [\delta_0, \delta_1]$ such that the quantity of platelets oscillates, as predicted by Proposition* 5.3.

7. Discussion. Previous attempts to build a model of megakaryopoiesis were based on the assumption that the enhancement by TPO of endomitosis, with enhancement of progenitor division, is the key to understanding dynamics in platelet count. This assumption led to the successful reproduction of periodic dynamics as observed in CT, but stability analysis could not give a clear interpretation of how CT is explained through the parameters [2, 34]. Therefore we have decided to explore a new hypothesis based on recent biological results [40, 41], that is, that the main action of TPO is to enhance progenitors division. We considered a population of progenitors structured in maturity with TPO increasing maturation speed, a population of platelet

structured in age, and the concentration of TPO, with the hypothesis of quasi-steady-state for TPO concentration with respect to the quantity of platelets and progenitors. This led to a system of two delay differential equations with a state-dependent delay. We started with a preliminary analysis of this model, showing well-posedness of the system, as well as eventual boundedness and positivity of the solutions. These results required to assume that $2A\alpha_P \geq \alpha_M$, that is, that the amount of c-Mpl receptors that appear when a megakaryocyte sheds its platelets is bigger than the amount of c-Mpl receptors of this megakaryocyte (in accordance with all available biological data; see Table 6.1). It also required $\alpha_M \kappa > T_{\text{prod}}/\alpha_T \max(\delta, \gamma)$, that is, to ensure that the rate of production of c-Mpl receptors is big enough for the quasi-steady-state equilibrium to be possible at all times. Next, we used the change of variable proposed by Smith [51] to transform the state-dependent delay into a fixed delay. It allowed to prove that given the conditions exposed earlier for positivity and well-posedness, the solution to our system exists and is unique. This new formulation was then used to perform a stability analysis of our system. Upon linearization, we established that the stability of the unique nontrivial equilibrium is assessed using a transcendental polynomial of degree three. We decided to adapt the framework proposed by Beretta and Kuang [6] to analyze the effect of parameters other than the delay on the stability of equilibriums. It resulted in a new geometrical criterion for the appearance of eigenvalues with positive real parts. This framework was then used on the characteristic equation of the system describing megakaryopoiesis, leading to a result linking changes in parameters of the system to the occurrence of Hopf bifurcations, that is, the onset of periodic solutions. Finally, parameters of the model were obtained and computed from existing literature such that the ability of our model to reproduce qualitatively the pathogenesis of amegakaryocytic CT could be evaluated. Parameters were used to compute the evolution of the geometrical criterion mentioned earlier as the megakaryocyte death rate δ increases. This revealed that increasing the death rate of progenitors lead to the onset of oscillations in platelet count, in agreement with observations of amegakaryocytic CT cases [26].

Because Lemma 5.2 is given for the general form (5.7), it could be used for any model with a threshold-defined delay differential equation transformed into a equation with fixed delay using [51]. Although the threshold used to define the delay might be different from 1 (for example, in [16]), the function of maturation or aging speed $V(.)$ is a tool rather than the exact description of a quantitative process: rescaling it to bring the threshold to 1 has little consequence. Moreover, we expect that Lemma 5.2 can be adapted to a version of (5.7) with $e^{-\tau\lambda}$ instead of $e^{-\lambda}$. However, it is unlikely that Lemma 5.2 could be adapted for systems with more than one delay like that of Langlois et al. [34]. Unlike Lemma 5.2, Proposition 5.3 relies on the fact that our model yields a characteristic equation of the form (5.17). We did not have to modify our initial model in order to obtain this particular form; therefore, we expect it to appear in other problems than platelet production. However, up to now previous works relied on characteristics equations too complicated to obtain an explicit expression for $\omega(\nu)$ as we did, and when stability was studied analytically, authors of [11, 30, 39] chose to fix the maturation speed to $\overline{V}(t) := 1$. Proposition 5.3 could therefore be adapted to other systems (among which other hematopoietic cells lines), providing a compromise between mathematical analysis and accuracy with respect to biology.

Regarding biology, our goal was to assess whether underlying anomalies observed in CT patients could indeed be the changes leading to oscillations. We provided an example in which oscillations appear when the death rate of progenitors δ is

increased 10-fold, which is consistent with the pathogenesis of amegakaryocytic CT. The conceptual way in which oscillations appear, however, is not compatible with cases characterized by antiplatelet antibodies, as explained at the beginning of section 6. Langlois et al. [34] were successful in generating oscillations in a model of megakaryopoiesis after an alteration of the platelet destruction mechanism, namely, an increase in the maximal removal rate of platelets by macrophages. Therefore we plan on adding a macrophage-mediated clearance of platelets to our model in order to reproduce qualitatively both amegakaryocytic and autoimmune CT.

Additionally, we could not reproduce the quantitative features of CT: as our example shows, we did not manage to produce a simulation of platelet count matching the amplitude observed in CT patients (fluctuations of a span above 7×10^9 platelets/kg [26]). Currently, the amplitude is only accessible through numerical simulations of solutions, such that an exhaustive exploration of the effect of parameters on amplitude is a heavy computational task: we could try to see if an explicit expression of the amplitude as a function of parameters can be obtained via a simplification of the model, as can be seen, for example, in [44]. On the other hand, we might obtain simulations closer to clinical data if we increase the complexity of our modeling of the expansion of progenitors. Indeed, our choice of a TPO-dependent speed of cell division (rather than overall volume expansion as in [34]) together with the necessity of an $A >> 3000$ implies that a progenitor divides multiple times as it goes from one end of the compartment M (see Figure 2.1) to the other. Taking this feature into account in the computation of the concentration on c-Mpl receptors (instead of $\alpha_M M(t)+\alpha_P P(t)$ currently) could be enough to reproduce the clinical features of CT. An example of a model for megakaryopoiesis with multiple compartments, although with a fixed division time τ, is found in [8].

The system formed with (2.3), (2.4), and (2.8) is such that the tools developed in [51] can be used to obtain a system of differential equations with a fixed delay on which the tools developed in [6] can be used. However, subsequent versions of the model might not be suitable for such a transformation, and it might be necessary to perform the stability analysis on the state-dependant delay formulation following works like [3, 31] or even on the age- and maturity-structured PDE formulation using results on Hopf bifurcation such as [13, 36]. This is the object of our future work.

Problem (5.7) has been addressed in its general form by Pontryagin: using functions $F(\omega)$ and $G(\omega)$ defined as, respectively, the real and imaginary part of $D(i\omega, \nu)$, he proved a theorem giving sufficient conditions for all eigenvalues to have a negative real part [5, section 13.6]. This theorem was applied by Cahlon and Schmidt [12] to a transcendental characteristic equation of third degree of a more general form than (5.17). However, we did not use these results for our problem: on one hand the necessary condition for stability [12, theorem 3.1] cannot be applied to our problem as (5.17) is studied for $\lambda \neq 0$, and on the other hand computations necessary for the "general algorithmic stability test" renders this test unfit for finding changes in stability. Nevertheless, many results for simpler characteristic equations relying on this same theorem from Pontryagin are found in [5, 12]. Other results for characteristic equations of second degree are found in [4, 51]: these results cannot be extended to our problem because our characteristic equation involves W_0, a term given by an implicit function of parameters of interest. Some authors encountered the same problem in two papers on erythropoiesis [11, 39], and each time a geometrical method specific to the model was developed to find Hopf bifurcations. Finally, other authors also relied on exclusively numerical methods to handle more complicated forms of (5.7). In [34], Langlois et al. used a method from Mahaffy [38] to compute the eigenvalues

of a characteristic equation of degree four with three distinct delays. Computations show that as four parameters vary linearly from values associated with normal platelet count (i.e., a stable solution) to values associated with CT patients (i.e., an oscillating solution), the eigenvalues cross the imaginary axis from left to right. In comparison, our work allows us to study the specific effect of each parameter on stability.

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