



HAL
open science

Analysis of Blood Cell Production under Growth Factors Switching

Walid Djema, Hitay Ozbay, C. Bonnet, E Fridman, Frédéric Mazenc, J Clairambault

► **To cite this version:**

Walid Djema, Hitay Ozbay, C. Bonnet, E Fridman, Frédéric Mazenc, et al.. Analysis of Blood Cell Production under Growth Factors Switching. IFAC 2017 - 20th World Congress of the International Federation of Automatic Control, Jul 2017, Toulouse, France. pp.13312-13317, 10.1016/j.ifacol.2017.08.1331 . hal-01677914

HAL Id: hal-01677914

<https://inria.hal.science/hal-01677914>

Submitted on 8 Jan 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Analysis of Blood Cell Production under Growth Factors Switching [★]

W. Djema ^{*} H. Özbay ^{**} C. Bonnet ^{*} E. Fridman ^{***}
F. Mazenc ^{*} J. Clairambault ^{****}

^{*} Inria, Université Paris-Saclay, CentraleSupélec - Laboratory of Signal & Systems (L2S), Paris, France.

^{**} Department of Electrical and Electronics Engineering, Bilkent University, Ankara, Turkey.

^{***} School of Electrical Engineering, Tel-Aviv University, Israel.

^{****} Inria, Sorbonne Université, UPMC, Laboratoire Jacques-Louis Lions, Paris, France.

Abstract: Hematopoiesis is a highly complicated biological phenomenon. Improving its mathematical modeling and analysis are essential steps towards consolidating the common knowledge about mechanisms behind blood cells production. On the other hand, trying to deepen the mathematical modeling of this process has a cost and may be highly demanding in terms of mathematical analysis. In this paper, we propose to describe hematopoiesis under growth factor-dependent parameters as a switching system. Thus, we consider that different biological functions involved in hematopoiesis, including aging velocities, are controlled through multiple growth factors. Then we attempt a new approach in the framework of time-delay switching systems, in order to interpret the behavior of the system around its possible positive steady states. We start here with the study of a specific case in which switching is assumed to result from drug infusions. In a broader context, we expect that interpreting cell dynamics using switching systems leads to a good compromise between complexity of realistic models and their mathematical analysis.

Keywords: Modeling, Switching, Distributed delay, Population dynamics.

1. INTRODUCTION

Huge number of works devoted to the study of blood cells creation and renewing mechanisms reflects the strong interest from mathematicians on these biological mechanisms. The long list of works includes: Burns & Tannok (1970), Mackey (1978), Bélair *et al.* (1995), Mahaffy *et al.* (1998), Adimy & Crauste (2007), Adimy *et al.* (2008), Marciniak *et al.* (2009), Özbay *et al.* (2012), Billy *et al.* (2012), Avila *et al.* (2012), Fridman *et al.* (2016), Djema *et al.* (2017), and Adimy *et al.* (2016), to name a few. The challenging problem is to steadily extend both modeling and analysis aspects to constantly improve our understanding of the complex hematopoietic system. An interesting trend in the modeling of hematopoiesis highlights the role played by growth factors (hormone-like molecules) in the regulation of the various biological functionalities involved in the mechanism of blood cell formation. Ideally, growth factors manage to maintain almost quasi-constant level of production and replenishment of blood cells in a healthy situation. For instance, they stimulate the production of cells to replace the diminution of their number by natural death, after an hemorrhage, or due to blood donation. In other situations, the body needs to react in

an effective manner to deal with changes in body health (e.g. the *eosinophil* normal count moves from one state to another one when facing some allergic diseases and infections). We quote the following works that deal with hematopoietic systems involving growth factor-dependent parameters: Bélair *et al.* (1995), Mahaffy *et al.* (1998), Adimy *et al.* (2006), Adimy & Crauste (2007), Adimy & Crauste (2009), and, Adimy *et al.* (2016). It is worth mentioning that despite of their paramount importance, growth factors are evoked in only few works among a large list of papers dedicated to the whole subject. The reason behind that is quite simple: including growth-factor dynamics notably complicates the resulting models, as well as their analysis. Not surprisingly, the dependence of the biological functions on growth-factors is usually neglected.

Furthermore, we can also mention that some mathematical models with distributed delay terms are usually used to describe hematopoiesis. It should however be pointed out that the latter representation gives cells the ability to divide with a high degree of freedom during their cell-cycle. This is one of the features that we do not find in the models with growth-factor dependent parameters in the literature (in this case, cells are usually assumed to divide only at one fixed moment, for the sake of simplicity).

Owing a great deal to the previously mentioned works, we discuss in the present paper a generalized model of hematopoiesis that includes multiple growth-factor effects.

[★] This work is supported by ALMA-project on the «Analysis of Acute Myeloid Leukemia», Paris-Saclay (France), also in part by the PHC Bosphore 2016 France-Turkey under project numbers 35634QM (France) and EEEAG-115E820 TÜBİTAK).

We complement early works in the following way:

○ We consider a model with several discrete maturity stages, where all the biological parameters, and aging velocities, are affected by different growth-factors. In addition, we consider that cells may divide at any moment during their cell-cycle.

○ Regarding mathematical analysis, we focus on the stability properties of positive steady states, which were less studied in the literature despite the fact that they are the most important ones. For that, we interpret hematopoiesis mechanisms from a different perspective: we consider the hematopoietic system as a possibly switching one, in the sense that growth-factors concentrations exert a form of event-triggered control on different biological features involved in the model. The latter approach is expected to be particularly useful for introducing therapeutic control (where drug concentrations act as growth-factors).

2. MODELING GROWTH FACTORS DYNAMICS

In Bélair *et al.* (1995) (and in almost all the subsequent works), the dynamics of growth factors are governed by an evolution equation of the form:

$$\dot{\epsilon}_j(t) = -\alpha_j \epsilon_j(t) + f_j(M(t)), \quad (1)$$

where ϵ_j is the concentration of a growth factor j , $\alpha_j > 0$, $M(t)$ is the total density of mature cells, f_j are some positive decreasing functions, and $\lim_{\ell \rightarrow +\infty} f_j(\ell) = 0$. In fact, a more general expression that may also cover the option of therapeutic action can be represented by

$$\dot{\epsilon}_j(t) = \mathbf{g}_j(t, \epsilon_j, M(t)), \quad (2)$$

where \mathbf{g}_j is a function that depends also on time. In this case, a time-triggered switching can be modeled, for instance, by infusing periodic doses of drugs.

In this paper, we consider five different growth factors (i.e. $j \in \{1, \dots, 5\}$), each one is acting on a particular biological function. More precisely, we study the case where growth factors are stimulating proliferation, differentiation (of resting and proliferating cells) and aging velocities; while they are blocking apoptosis rates (that

is the death rate of proliferating cells). It is agreed that the secretion of growth factors is very fast in comparison to population cell response (i.e. regulating hormones and cells proliferation have different time-scales). This assertion is actually behind the cell dynamics models with static biological parameters. More importantly, the previously mentioned time-scale difference allowed the study of models where parameters depend on growth-factors that are in a quasi-steady state (see Marciniak *et al.* (2009)). For instance, since the half-life for erythropoietins (which are the EPO hormones that regulate erythropoiesis) is very short compared to hematopoietic cells proliferation, a quasi-steady state approximation to growth-factors dynamics described by (1) was considered in Bélair *et al.* (1995). Moreover, through our modeling via systems with possibly switching parameters, we will be able to represent unhealthy situations where brutal changes may occur in (1). Indeed, new biological evidences point out for instance that unhealthy hematopoiesis may appear suddenly due to epigenetic mutations, which can be represented as an abnormal jump in one or multiple parameter values (e.g. the survival of unhealthy cells as a result of an abrupt change in apoptosis rates, or dysfunctional maturation and the blockade in the differentiation mechanisms). In other situations, the growth-factor concentration can be modified through drug infusion, which induces a change in ϵ_j (and thereby in the model parameters). The latter situation suggests that growth-factor concentrations are not fully determined by the feedback from mature cells M , as implied by (1). Therefore, as a first step, we introduce a general model where growth factors concentrations are governed by (2), without wondering about time-scale in growth-factor evolution. Subsequently, we will introduce a new interpretation in the resulting mathematical model, where we will also consider that growth-factor concentrations approach very quickly their steady states. However, differently from works where constant biological parameters are assumed for all the time, we allow growth-factors concentrations to move from one quasi-steady state to another one. This behavior is well-approximated by step-like functions and it is representative of actions initiated

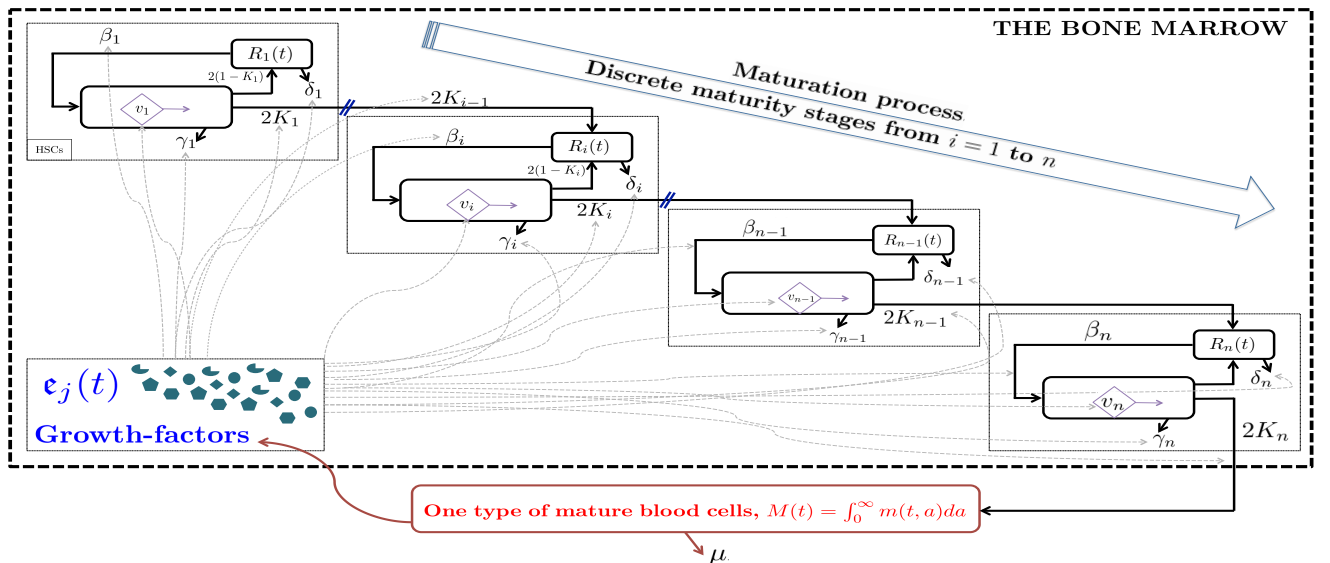


Fig. 1. Schematic representation of the studied model. In our interpretation, growth-factor concentration can be seen as drugs targeting the biological parameters involved in hematopoiesis.

by the body itself to meet its requirement, or it can emerge from sudden therapeutic measures (drug infusions or bone marrow transplantation), when facing some blood disorders. Thus, by relying on this key feature, we infer how the behavior of the different biological functionalities will be, as discussed in the sequel.

In Figure 1, we have n different (discrete) maturity stages as introduced in Adimy *et al.* (2008). The first compartment represents the hematopoietic stem cells (HSCs, Figure 1) living in the bone marrow. For all $i \in I_n = \{1, \dots, n\}$, $R_i(t)$ is the total density of resting cells of the i -th immature generation, while $M(t)$, as mentioned previously, is the total density of one type of mature cells (e.g. white blood cells) in the bloodstream. Resting cells may die or differentiate to other lineages (red blood cells or platelets) at a rate $0 < \delta_i < 1$. They can also re-enter into the proliferating stage according to a particular function that we classically denote β_i , for all $i \in I_n$. During their cell-cycle, cells may die with an apoptosis rate γ_i , or they can complete their mitosis (i.e. each mother cell divides into two daughter cells). We assume that mitosis occurs before a maximal finite age τ_i . At each division, a proportion $0 < K_i < 1$ of new daughter cells will differentiate (i.e. join the next *more mature* stage $i + 1$, in the cascade of immature stages, as illustrated in Figure 1). The remaining portion, $0 < 1 - K_i < 1$, will join the same maturity level as the one of mother cells: this is known as self-renewing process, which is necessary to maintain the pool of cells. After n immature stages, cells are ready to leave the bone marrow and join the blood circulation. In this paper, we consider in addition an aging velocity v_i in the proliferating phases, as illustrated in Figure 1. Next, and this is the key point, we consider that the growth-factors concentrations (\mathbf{e}_j , $j \in \{1, \dots, 5\}$) are acting on the biological functionalities as follows:

- * $\delta_i(\cdot)$ depends on \mathbf{e}_1 . Increasing \mathbf{e}_1 yields to increase δ_i , across all maturity levels. We also consider that $\lim_{\mathbf{e}_1 \rightarrow \infty} \delta_i(\mathbf{e}_1) = \bar{\delta}_i < 1$, for all $i \in I_n$.

- * $\beta_i(\cdot, \cdot)$ is a function that depends on \mathbf{e}_2 and on the total density of resting cells, R_i for all $i \in I_n$. We consider that for each fixed \mathbf{e}_2 , the mapping $\beta_i(\mathbf{e}_2, R_i)$ is *continuously* decreasing with respect to R_i , and $\lim_{R_i \rightarrow \infty} \beta_i(\cdot, R_i) = 0$ (see Mackey (1978)). On the other hand, for a fixed R_i , the mapping $\beta_i(\mathbf{e}_2, R_i)$ is increasing when \mathbf{e}_2 increases, and where $\beta_i(0, R_i) = 0$, and $\lim_{\mathbf{e}_2 \rightarrow \infty} \beta_i(\mathbf{e}_2, R_i) = \bar{\beta}_i > 0$.

- * The apoptosis rate, $\gamma_i(\cdot)$, depends on the concentration \mathbf{e}_3 . Since, by convention, a growth factor stimulates the production of cells, we consider that the mapping $\gamma_i(\mathbf{e}_3)$ is decreasing with respect to \mathbf{e}_3 .

- * Differentiation, $K_i(\cdot)$, increases with respect to \mathbf{e}_4 and $\lim_{\mathbf{e}_4 \rightarrow \infty} K_i(\mathbf{e}_4) = K_{i \max} < 1$.

- * Similarly, the aging-velocities v_i , which are affected by the concentration \mathbf{e}_5 , for all $i \in I_n$, are increasing from a normal velocity-values (normalized to 1), until reaching a maximum velocity $v_{i \max} > 1$.

Remark 1. On one hand, we assumed that the evolution of growth-factor concentrations with respect to time is approximated by step-like functions. On the other hand, we discussed how the model parameters (K_i , γ_i , ...) may vary with respect to growth-factor concentrations (i.e. with respect to the set of discrete values \mathbf{e}_j resulting from the step-functions). It follows that changes in growth-

factor concentrations with respect to time exert a kind of triggered-event control on model parameters. Thus, by knowing the evolution of growth-factor concentrations (e.g. predefined therapeutic protocols) we can determine how the affected biological parameters evolve with respect to time (an illustration is provided in Figures (a),(b) in Table 2, with only two changing parameters γ_i and v_i).

3. MODEL EQUATIONS

We consider that growth factors concentrations are governed by (2) and we focus now on cell dynamics. The model described in Figure 1 is governed by an age-structured McKendrick model with a set of boundary conditions and suitable initial conditions (details about the PDE version of the model are omitted here). By following Bélair *et al.* (1995) (see also Foley & Mackey (2009), and the references therein), who themselves were inspired by techniques of Metz & Diekmann (1986) and Smith (1993), we can transform the age-structured system into a time-delay system using the method of characteristics. The obtained result is given in Table 1, however, its exploitation in that form is not a trivial task. Indeed, the implicitly defined variable T_a , and the state variables that appear in the distributed delay terms (R_i and the growth-factor concentrations \mathbf{e}_2 , \mathbf{e}_3 and \mathbf{e}_5) are not easy to manipulate in order to investigate the existence of positive steady states and their stability properties. Now, we use the switching behavior of the growth factors on the model parameters in order to provide a new representation of the model given in Table 1.

□ First, we start by assuming that the fourth equation in Table 1 has a unique piecewise continuous solution for all $j \in \{1, \dots, 5\}$. Whatever the behavior of the states $\mathbf{e}_j(t)$, for all $t \geq 0$, (whether driven by a body requirement or resulting from drug infusions), the effect on biological functions (δ_i , β_i , γ_i , K_i and v_i) is similar. We recall from Sections 1, 2 that knowing the solutions \mathbf{e}_j allows us to determine the variation of the biological parameters with respect to time. An illustration is provided in Figures (a-b)-Table 2, in which we give a qualitative example with two parameters, v_i and γ_i (the remaining biological parameters can be represented in a similar way). For all $t \geq 0$, we define the time duration \mathfrak{h} that corresponds to the smallest time-interval during which all the biological parameters (not only those represented in the corresponding Figure) are invariant with respect to the possible change in their respective growth-factor concentrations. Therefore, we can distinguish between two interesting situations:

① The case $\mathfrak{h} < \tau_i$: In this situation, studying the resulting model without extra assumptions is not an easy task. The difficulty comes from the distributed delay terms that may cover, in the general case, a large period of time, involving several switches (Figure(a)-Table 2).

② The case $\mathfrak{h} \gg \tau_i$: This is a more suitable situation for the analysis (see Figure(b)-Table 2). Indeed, since the biological parameters do not vary during a sufficiently large period of time, we can rewrite the system in Table 1 in a more convenient form, especially in the region (\mathfrak{D}_3) which is illustrated in Figure (b)-Table 2. That region coincides with the time interval $[t_{s1} + \tau_i, t_{s2}]$, where t_{s1} and t_{s2} are two consecutive switching time-instants. The particularity of (\mathfrak{D}_3) is that the model in Table 1 can be rewritten as a system without switching dynamics, even

$$\begin{cases} \dot{R}_1(t) = -[\delta_1(\mathbf{e}_1(t)) + \beta_1(\mathbf{e}_2(t), R_1(t))] R_1(t) + 2(1 - K_1(\mathbf{e}_4(t))) \mathfrak{S}_1(R_{1t}, \mathbf{e}_{2t}, \mathbf{e}_{3t}, \mathbf{e}_{5t}), & \text{and, for all } i \geq 2, \\ \dot{R}_i(t) = -[\delta_i(\mathbf{e}_1(t)) + \beta_i(\mathbf{e}_2(t), R_i(t))] R_i(t) + 2(1 - K_i(\mathbf{e}_4(t))) \mathfrak{S}_i(R_{it}, \mathbf{e}_{2t}, \mathbf{e}_{3t}, \mathbf{e}_{5t}) \\ \quad + 2K_{i-1}(\mathbf{e}_4(t)) \mathfrak{S}_{i-1}(R_{i-1t}, \mathbf{e}_{2t}, \mathbf{e}_{3t}, \mathbf{e}_{5t}), \\ \dot{M}(t) = -\mu M(t) + 2K_n(\mathbf{e}_4(t)) \mathfrak{S}_n(R_{nt}, \mathbf{e}_{2t}, \mathbf{e}_{3t}, \mathbf{e}_{5t}), \\ \dot{\mathbf{e}}_j(t) = -\mathbf{g}_j(t, \mathbf{e}_j(t), M(t)), \quad \text{for all } j \in \{1, \dots, 5\}, \end{cases}$$

where the distributed delay terms are defined for all $i \in \{1, \dots, n\}$ by:

$$\mathfrak{S}_i = \int_0^{\tau_i} h_i(a) e^{-\int_0^{\tau_i} h_i(w) dw} - \gamma_i(\mathbf{e}_3(t - T_a + \ell)) \beta_i(\mathbf{e}_2(t - T_a), R_i(t - T_a)) R_i(t - T_a) da,$$

with the abuse of notation: $\mathfrak{S}_i := \mathfrak{S}_i(R_{it}, \mathbf{e}_{2t}, \mathbf{e}_{3t}, \mathbf{e}_{5t})$, and where, T_a is implicitly defined by:

$$a = \int_{t-T_a}^t v_i(\mathbf{e}_5(\ell)) d\ell, \quad \text{for all } a \in [0, \tau_i].$$

Table 1. The resulting nonlinear system with distributed delays obtained after reducing the PDEs system describing the model in Figure 1, associated with its boundary conditions.

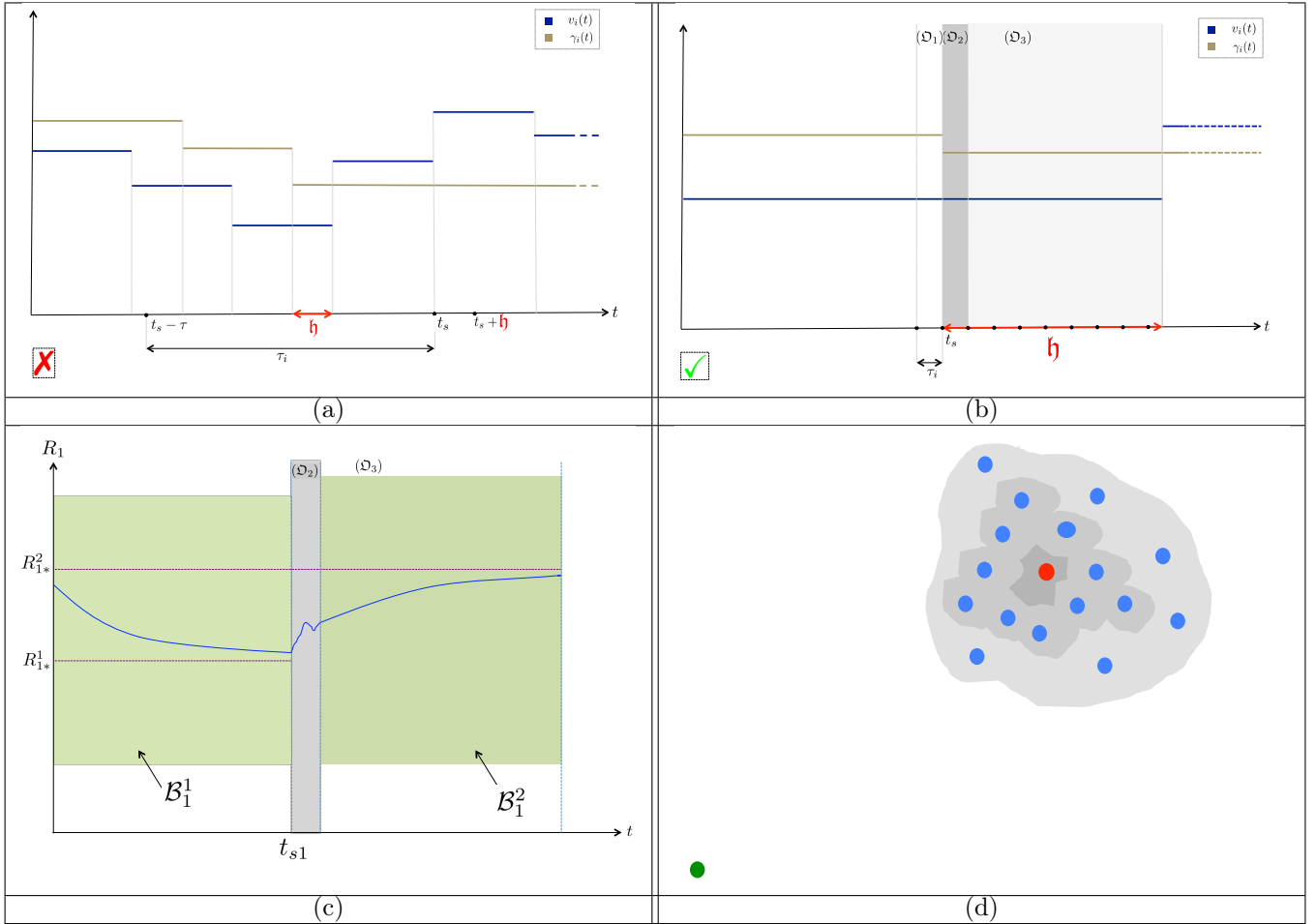


Table 2. **(a)** The case ①, where $h < \tau_i$. **(b)** The case ②, where $h \gg \tau_i$. **(c)** Illustration of the trajectory $R_1(t)$. The values R_{1*}^1 and R_{1*}^2 represent, respectively, the positive steady states of the subsystems $\sigma = 1$ and $\sigma = 2$. The green regions \mathcal{B}_1^1 and \mathcal{B}_1^2 are the plausible regions of attraction of, respectively, R_{1*}^1 and R_{1*}^2 . **(d)** Equilibrium points (of interest) of the studied model: the green point represents the origin of the studied model. Blue points (and the red one) represent the different positive equilibria, for different subsystems. The red point represents the favourable steady state that the hematopoiesis process achieves after a series of switching (e.g. by following a therapeutic strategy).

inside its distributed delay terms (the corresponding model equations are in Table 3). If a switching (in at least one of the model parameters) occurs at a time instant $t_{s1} > 0$, then -by definition- the next switching instant will not occur before $t_{s1} + \mathfrak{h}$. We use the following notation: the parameter $\sigma \in \mathbb{N}$ identifies which sub-system is activated at any time instant $t \geq 0$ (e.g. when at least one parameter changes at $t_{s1} > 0$, then the system in Table 3 switches from a sub-system $\sigma = 1$, to a sub-system $\sigma = 2$). In the region (\mathfrak{D}_3) , the system is exclusively defined by specifying σ . However, it is not the case in the region (\mathfrak{D}_2) since the distributed delay terms appeal the history of the system in the region (\mathfrak{D}_1) , which complicates its analysis. Without loss of generality, we select in Table 3 the non-switching dynamical subsystem defined by $\sigma = 1$ to be activated during the (\mathfrak{D}_2) - (\mathfrak{D}_3) - time-period, between two consecutive switching time-instants t_{s1} and t_{s2} .

□ At this juncture, from the previous discussion, we assume in our model that $\mathfrak{h} \gg \tau_i$ (case ②). In the sequel, stability properties of our model are discussed. An interesting observation is that, by focusing on the behavior of the fixed subsystem on (\mathfrak{D}_3) , the portion on (\mathfrak{D}_2) appears as nothing more than the initial condition associated to the studied sub-system.

4. STABILITY PROPERTIES OF THE FAVOURABLE STEADY STATE

We focus on the new representation of the model as in Table 3, where $\sigma = 1$, on the time interval $t \in [t_{s1}, t_{s1} + \mathfrak{h}] \subseteq [t_{s1}, t_{s2}]$. In order to determine the asymptotic behavior of this system, we start by assuming that no switch will occur (i.e. $t_{s2} \rightarrow \infty$). Then, one may investigate the existence of a strictly positive steady state, $E^{\sigma=1} = (R_{1*}^1, \dots, R_{n*}^1, M_*^1)$, of the studied system. We notice also that the origin of the system described in Tables 2-3 is always an equilibrium point. However we are focusing on strictly positive equilibria since they are biologically more relevant. We refer to Adimy *et al.* (2008) for a complete discussion on the existence of equilibrium points for a similar model (for $v_i = 1$ and a fixed σ). Of course, by changing σ , the equilibrium point $E^\sigma = (R_{1*}^\sigma, \dots, R_{n*}^\sigma, M_*^\sigma)$ will change. Whether through medication or by an action of the body, we expect that the dynamics \mathbf{e}_j (Eq.(2)) converge to a favourable state \mathbf{e}_j^f , which is desired by the body or by the therapy. The corresponding equilibrium point (i.e. E_j^σ for a fixed desired σ_j), is assumed to be the

red point in Figure(d)-Table 2. Now, let us come-back to the subsystem ($\sigma = 1$) in Table 3. We assume that its positive equilibrium, $E^{\sigma=1}$, exists. By classical arguments, one can study the local stability properties of $E^{\sigma=1}$. We refer to Özbay *et al.* (2012), for the stability analysis of a similar system, based on Input-Output approaches and to Djema *et al.* (2017), for similar results derived using a Lyapunov approach. For a particular form of the functions β_i , a subset of the region of attraction of the positive equilibrium is provided in Djema *et al.* (2017). This region is expressed as a sub-level of a Lyapunov-Krasovskii functional (LKF) (see Hahn (1967) and Kolmanovskii & Myshkis (1999)). Recall that the estimate of the region of attraction quantifies the set of all initial conditions such that the states of the system converge to the positive equilibrium point. In the case of the present paper, we assume that switching occurs between a finite family of sub-systems. This situation is represented in Figure(c)-Table 2, where a possible trajectory $R_1(t)$ is illustrated. For $\sigma = 2$, the positive equilibrium point is denoted R_{1*}^2 . The region \mathcal{B}_1^2 is a representation of the region of attraction of R_{1*}^2 , that we can estimate as in Djema *et al.* (2017). A first observation is that if the portion of the trajectory R_{1t} , for $t \in (\mathfrak{D}_2)$, satisfies the LKF-sublevel condition defining the region of attraction of R_{1*}^2 , then the trajectory $R_1(t)$ converges exponentially to its positive equilibrium point. Extra-assumptions on the model ensure that this conditions are always satisfied (using the fact the trajectories of the studied system are bounded), and for sufficiently close successive equilibrium points R_{i*}^σ (i.e. moderate jumps in the parameters values). Moreover, in Özbay *et al.* (2012), a conjuncture was stated from numerical simulations: systems of the studied class (for each fixed σ) seem to have a region of attraction which is much bigger than the one rigorously provided by the LKF-approach. In summary, we suggest that when the switching model admits a positive solution, the behavior of the trajectories during the (\mathfrak{D}_2) periods does not impact the (\mathfrak{D}_3) phases, and the system converges to the positive equilibrium E_*^σ if the local exponential stability conditions (see Özbay *et al.* (2012), Djema *et al.* (2017)) are satisfied for each sub-system $\sigma \in \mathbb{N}$.

5. A NUMERICAL EXAMPLE

We give a simple example where a switching system has three sub-systems. Each one is composed of three generations of immature cells and one generation of mature cells.

for all $t \in [t_{s1} + \tau_i, t_{s2}] \cup [t_{s2} + \tau_i, t_{s2}] \cup \dots$

$$\begin{cases} \dot{R}_1(t) = -[\delta_1^\sigma + \beta_1^\sigma(R_1(t))] R_1(t) + 2(1 - K_1^\sigma) \mathfrak{S}_1^\sigma(R_{1t}), & \text{and, for all } i \geq 2, \\ \dot{R}_i(t) = -[\delta_i^\sigma + \beta_i^\sigma(R_i(t))] R_i(t) + 2(1 - K_i^\sigma) \mathfrak{S}_i^\sigma(R_{it}) + 2K_{i-1}^\sigma \mathfrak{S}_{i-1}^\sigma(R_{i-1t}), \\ \dot{M}(t) = -\mu M(t) + 2K_n^\sigma \mathfrak{S}_n^\sigma(R_{nt}), \\ \dot{\mathbf{e}}_j(t) = 0, \quad \text{for all } j \in \{1, \dots, 5\}, \end{cases}$$

where, $\sigma \in \mathbb{N}$ is implicitly controlled by the dynamics of \mathbf{e}_j . For instance, if we consider that, $\forall t \in [t_{s1} + \tau_i, t_{s1} + \mathfrak{h}] \subseteq [t_{s1} + \tau_i, t_{s2}]$, we have $\sigma = 1$, then, the distributed delay terms are rewritten as

$$\mathfrak{S}_i^1(R_{it}) = \int_0^{\tau_i} h_i(a) e^{-\int_0^a \frac{1}{v_i} h_i(v_i \ell) d\ell} e^{-\frac{a\gamma_i^1}{v_i}} \beta_i^1 \left(R_i \left(t - \frac{a}{v_i} \right) \right) R_i \left(t - \frac{a}{v_i} \right) da.$$

Table 3. The new representation of the studied system when $\mathfrak{h} \gg \tau_i$ (case ②), on the time-intervals $t \in [t_{s\ell} + \tau_i, t_{s(\ell+1)}]$, $\ell \in \mathbb{N}$.

- ❶ For $\sigma = 1$: \triangleright For $i = 1$: $K_1 = 0.05$, $\tau_1 = 1.109$, $\gamma_1 = 0.28$, $v_1 = 1$, $\delta_1 = 0.14$, and, $\beta_1(R_1) = \frac{0.5}{1+R_1^2}$.
- \triangleright For $i = 2$: $K_2 = 0.05$, $\tau_2 = 1.2$, $\gamma_2 = 0.28$, $v_2 = 1$, $\delta_2 = 0.26$, and, $\beta_2(R_2) = \frac{1}{1+R_2^2}$.
- \triangleright For $i = 3$: $K_3 = 0.08$, $\tau_3 = 1.36$, $\gamma_3 = 0.4$, $v_3 = 1$, $\delta_3 = 0.35$, and, $\beta_3(R_3) = \frac{3}{1+R_3^2}$.
- \triangleright For M : $\mu = 0.042$. The positive steady state is: $E^1 = (0.73867, 0.89927, 1.21625, 3.86030)$.
- ❷ For $\sigma = 2$: We consider that $\beta_1(R_1) = \frac{0.55}{1+R_1^2}$, $\beta_2(R_2) = \frac{1.13}{1+R_2^2}$, and, $\beta_3(R_3) = \frac{3.15}{1+R_3^2}$. All the other parameters are the same as for $\sigma = 1$. The positive steady state is: $E^2 = (0.83677, 0.96778, 1.26532, 4.01943)$.
- ❸ For $\sigma = 3$: We consider that the functions β_1 , β_2 , and β_3 , and the parameters δ_1 , δ_2 and δ_3 are similar to those in $\sigma = 2$. On the other hand, we consider that in this case we have: $\gamma_1 = 0.18$, $K_1 = 0.06$, $\gamma_2 = 0.18$, $K_2 = 0.045$, $\gamma_3 = 0.3$, and, $K_3 = 0.055$. The positive steady state is: $E^3 = (1.10952, 1.14432, 1.72306, 2.70245)$.

Switching from the subsystem $\sigma = 1$, to $\sigma = 2$ occurs at $t = 90$, then switching from $\sigma = 2$ to $\sigma = 3$ occurs at $t = 160$. The trajectories are illustrated in Figure 2.

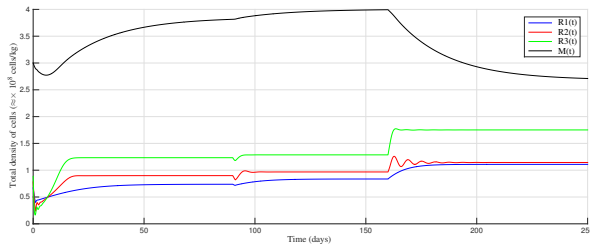


Fig. 2. Trajectories of the switching system in the example.

6. CONCLUDING REMARKS

This work is a step-forward in refining the analysis of healthy and unhealthy hematopoiesis. Here we introduced the basics of a new representation of hematopoietic processes as a switching system, through event-triggered parameters. However, many issues remain to be addressed. In this paper we emphasize on a particular case in which it is assumed that the behavior of the growth factors is *known*. This situation is representative of a well-defined therapeutic protocol in which drugs are administrated. Thus, after laying the foundation of this switching model, future work will focus on the role of mature cells (in Eq (2)) in the control exerted on growth-factors, in order to find out switching rules that achieve healthy hematopoiesis.

REFERENCES

M. Adimy, Y. Bourfia, M. L. Hbib, C. Marquet, *Age-Structured Model of Hematopoiesis Dynamics with Growth Factor-Dependent Coefficients*, Electronic Journal of Differential Equations, No. 140, pp. 1-20, (2016).

M. Adimy, F. Crauste, A. Abdllaoui, *Discrete Maturity-Structured Model of Cells Differentiation with Applications to Acute Myelogenous Leukemia*, J. Biological Systems, No. 3, pp. 395-424, (2008).

M. Adimy, F. Crauste, S. Ruan, *Modelling Hematopoiesis Mediated by Growth-factors with Applications to Peri-*

odic Hematological Diseases, Bull. Math. Biol. 68, No. 8, pp. 2321-2351, (2006).

M. Adimy, F. Crauste, *Modelling and Asymptotic Stability of a Growth-factor Dependent Stem Cell Dynamics Model with Distributed Delay*, Discrete Contin. Dyn. Syst. Ser. B 8, No. 1, pp. 19-38, (2007).

M. Adimy, F. Crauste, *Mathematical Model of Hematopoiesis Dynamics with Growth Factor-dependent Apoptosis and Proliferation regulations*, Math. Comput. Modelling 49, No. 11-12, pp. 2128-2137, (2009).

J. L. Avila, et al., *A new model of cell dynamics in acute myeloid leukemia involving distributed delays*, IFAC TDS, pp. 55-60, (2012).

J. Bélair, M.C. Mackey, J. M. Mahaffy, *Age-structured and Two-delay Models for Erythropoiesis*, Math. Biosci. 128, No. 1-2, pp. 317-346, (1995).

F. Billy, J. Clairambault, F. Delaunay, C. Feillet, N. Robert, *Age-structured cell population model to study the influence of growth factors on cell cycle dynamics*, Math. Biosci. and Eng., Vol. 10, No. 1, pp. 1-17, (2013).

F.J. Burns, I.F. Tannock, *On the existence of a G₀-phase in the cell cycle*, Cell Tissue Kinet, 19, pp. 321-34, (1970).

W. Djema, F. Mazenc, C. Bonnet, *Stability analysis and robustness results for a nonlinear system with distributed delays describing hematopoiesis*, Systems & Control Letters, Vol. 102, pp. 93-101, (2017).

C. Foley, M.C. Mackey, *Dynamic hematological disease: a review*, J. Math. biology, 58.1-2: pp. 285-322, (2009).

C. Foley, S. Bernard, M.C. Mackey, *Cost-effective G-CSF therapy strategies for cyclical neutropenia: Mathematical modelling based hypotheses*, Journal of theoretical biology, 238.4, pp. 754-763, (2006).

E. Fridman, C. Bonnet, F. Mazenc, W. Djema, *Stability of the cell dynamics in Acute Myeloid Leukemia*, Systems and Control Letters 88, pp. 91-100, (2016).

W. Hahn, *Stability of Motion*, Springer, New York, (1967).

V. Kolmanovskii, A. Myshkis, *Introduction to the Theory and Applications of Functional Differential Equations*, Kluwer Academic Publishers, Dordrecht, 1999.

M. C. Mackey, *Unified Hypothesis of the Origin of Aplastic Anemia and Periodic Hematopoiesis*, Blood, 51, pp. 941-956, (1978).

J. M. Mahaffy, J. Bélair, M.C. Mackey, *Hematopoietic Model with Moving Boundary Condition and State-delay: Applications in Erythropoiesis*, Journal of Theoretical Biology, 190. No. 2, pp. 135-146, (1998).

A. Marciniak-Czochra, et al., *Modeling of asymmetric cell division in hematopoietic stem cells-regulation of self-renewal is essential for efficient repopulation*, Stem cells and development 18.3, pp. 377-386, (2009).

J. A. J. Metz, O. Diekmann, *The Dynamics of Physiologically Structured Populations*, Lect. Notes Biomath. 68, Springer-Verlag, Berlin, (1986). Blood, 51, pp. 941-956, (1978).

H. Özbay, C. Bonnet, H. Benjelloun, J. Clairambault, *Stability analysis of cell dynamics in leukemia*. Math. Model Nat. Phenom., Vol. 7, No. 1, pp. 203-234, (2012).

H. L. Smith, *Reduction of Structural Population Models to Threshold-type Delay Equations and Functional Differential Equations: a Case Study*. Math. Biosci. 113:1-23, (1993).