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Vol. 26 = 551 (2022): 201-227
DOI: https://doi.org/10.21857/y6zolb6gzm

MATHEMATICAL ANALYSIS OF A MODEL FOR CHRONIC MYELOID LEUKEMIA

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Abstract. In this paper, a mathematical analysis of a model describing the evolution of chronic myeloid leukemic with effect of growth factors is considered. The corresponding dynamics are represented by a system of ordinary differential equations of dimension 5. This system described the interactions between hematopoietic stem cells (H.S.C), hematopoietic mature cells (M.C), cancer hematopoietic stem cells, cancer hematopoietic mature cells and the associated growth factor concentration. Our research is, henceforth, carried out on the existence and the uniqueness of the solution of this system. The next substantive concern will be a discussion on the local and global stability of the corresponding steady states. Three scenarios, however, corresponding to different actions of hematopoiesis on stem cells (differentiate cells or both cells) are considered.

1. Introduction

Chronic myeloid leukemia (CML) is a cancer of the bone marrow and blood. It accounts about 15 percent of newly diagnosed cases in leukemia in the world. Most of these are adults with an average of diagnosis in 64 years, but rare are those cases in children. CML grows very slowly over years in the sense that a patient may have it for long time before symptoms are noticed. Common signs of CML are anemia, splenomegaly, tiredness, weight loss, discomfort and goes through 3 phases: chronic phase, accelerated phase and blast phase. It affects a specific type of white blood cells which are known as the myelocytes. In fact, it is myelo-proliferative disorder originating from the myeloid hematopoietic stem cell. In turn, this results from the clonal expansion of pluripotent hematopoietic stem cells containing the active BCR-ABL fusion gene produced by a reciprocal translocation of the ABL gene to the BCR gene in chromosomes 22 and 9 (see [13, 17]). This new chromosome is named Philadelphia chromosome [4]. Through mitosis or division, thanks of

2020 *Mathematics Subject Classification.* 92B05, 34A34.
Key words and phrases. Myeloid chronic leukemia model, cancer modeling, existence of solutions, global stability analysis, Lyapunov stability.

growth factor, the multiplication of healthy cells is abundant and cancerous cells do not respect the cellular mechanisms in their proliferation. After being stimulated by a physiological signal, stem cells at rest start their renewing and differentiating. The balance between them is named Homeostasis. Thus CML has become one of the most extensively studied human malignancy. Even if many interesting studies on CML are given (see [10, 19, 22]), many information are unknown about the dynamic of how cancer cells are propagated. During the last decade, many several advances are mainly based, particulary, on advances in scientific solutions to capture the dynamics of CML, one of those promising dynamics approaches includes mathematical modeling by identifying interactions between all types of cells playing rule in propagation of leukemia and using estimate parameters based on experimental advances. CML mathematical models do not suggest an exact solution but provide useful results. Therefore, it is still a great need to continue studying and developing existing models in order to adapt biological discovers and recent clinical results and associate therapies [15, 25]. Those models are often represented by ordinary differential equations, partial differential equations or delay differential equations that represent different states of stem cells. For more details see for example [5–7, 11, 20, 23, 27, 31, 32].

The models given in [1, 2, 14, 26] describe particularly the dynamics of H.S.C population. Dingli and Michor [15] assumed that the H.S.C cancerous cells compete with normal H.S.C cells. In their model, the regeneration of H.S.C is governed by homeostasis, which controls the process of dividing according to the total number of H.S.C. They have developed model that involve H.S.C cells and M.C mature cells, where proliferation and death rates are introduced and interactions are also considered between x_0, x_1, y_0 and y_1.

The regeneration of (H.S.C) is generated by Homeostasis of x_0 represented by a function ϕ whereas that of y_0 is represented by function ψ (see [27]).

Ainseba and Benosman have developed a model given in [3] and proposed a structured model where the function ϕ depends on $\varepsilon_1(x_0+y_0)+\varepsilon_2(x_1+y_1)$ and such that the function ψ depends on $\varepsilon_1(x_0+\alpha y_0)+\varepsilon_2(x_1+\alpha y_1)$, where $\alpha \in]0,1[$ is a coefficient of competition [18] and $\varepsilon_1, \varepsilon_2 \in \{0,1\}$.

They have considered the following model:

$$
\left\{
\begin{array}{rcl}
\dfrac{dx_0}{dt} &=& n\Phi(\varepsilon_1(x_0+y_0)+\varepsilon_2(x_1+y_1))x_0 - d_0x_0 \\
\dfrac{dx_1}{dt} &=& rx_0 - (d-d_2)x_1 \\
\dfrac{dy_0}{dt} &=& m\Psi(\varepsilon_1(x_0+\alpha y_0)+\varepsilon_2(x_1+\alpha y_1))y_0 - g_0y_0 \\
\dfrac{dy_1}{dt} &=& qy_0 - (g-g_2)y_1
\end{array}
\right. \tag{1.1}
$$

where

$$\begin{aligned} \Phi(\varepsilon_1(x_0+y_0)+\varepsilon_2(x_1+y_1)) &= 1-\tfrac{\varepsilon_1(x_0+y_0)+\varepsilon_2(x_1+y_1)}{K} \\ \Psi(\varepsilon_1(x_0+\alpha y_0)+\varepsilon_2(x_1+\alpha y_1)) &= 1-\tfrac{\varepsilon_1(x_0+\alpha y_0)+\varepsilon_2(x_1+\alpha y_1)}{K} \end{aligned} \tag{1.2}$$

$x_0(t)$ is the number of normal hematopoietic stem cells (H.S.C) at time t,
$x_1(t)$ is the number of normal mature stem cells (M.C) at time t,
$y_0(t)$ is the number of cancer hematopoietic stem cells (H.S.C) at time t,
$y_1(t)$ is the number of cancer mature stem cells (M.C) at time t.

The parameters used in (1.1) - (1.2) are given in Table 1 given bellow and come from [9]. The value of K (the bone morrow receiving capacity) changes in each scenario as we shall see after.

Parameter	Explanation
n	Proliferation rate of normal (H.S.C) x_0
d_2	Proliferation rate of normal (M.C) x_1
r	Differentiate rate of normal (H.S.C) x_0
d_0	Death rate of normal (H.S.C) x_0
d	Death rate of normal (M.C) x_1
m	Proliferation rate of cancer (H.S.C) y_0
g_0	Death rate of cancer (H.S.C) y_0
q	Differentiate rate of cancer (H.S.C) y_0
g_2	Proliferation rate of cancer (H.S.C) y_0
g	Death rate of cancer (M.C) y_1
K	Bone morrow receiving capacity
α	$0<\alpha<1$
ε_1	$\varepsilon_1 \in \{0,1\}$
ε_2	$\varepsilon_2 \in \{0,1\}$

TABLE 1. Parameters used in (1.1) – (1.2)

In this paper, we propose an extension of this model taking into account the influence of the growth factor E on leukemia disease. This factor is studied particularly in [30] and plays an important rule in evolution of CML.

Our paper is organized as follows: In Section 2, the mathematical model of leukemia is proposed in details and three possible scenarios are set:

- scenario 1 corresponds to $\varepsilon_1 = 1$ and $\varepsilon_2 = 0$ where homeostasis acts only on stem cells x_0 and y_0.
- scenario 2 corresponds to $\varepsilon_1 = 0$ and $\varepsilon_2 = 1$ where homeostasis acts only on differentiate cells x_1 and y_1.
- scenario 3 corresponds to $\varepsilon_1 = 1$ and $\varepsilon_2 = 1$ where homeostasis acts on stem cells x_0 and y_0 and on differentiate cells x_1 and y_1.

In Section 3, the existence and uniqueness of a positive local solution of our model is proved for all scenarios, existence and uniqueness of a positive global solution is proved for scenario 1 and 3. The existence of steady states for the three scenarios is studied in Section 4 (trivial, blast, no pathologic and chronic states). In Section 5, local stability analysis for those steady states is developed followed in Section 6 by a global stability analysis. Biological interpretation of the obtained results is proposed and some perspectives are set in Section 7.

2. Mathematical Model

In this paper, we consider the following five-dimensional model which is an extension of the one proposed in [3, 9]:

$$\begin{cases} \dfrac{dx_0}{dt} &= n\Phi(\varepsilon_1(x_0+y_0)+\varepsilon_2(x_1+y_1))x_0 - d_0x_0 \\ \dfrac{dx_1}{dt} &= rx_0 - (d(E)-d_2)x_1 \\ \dfrac{dy_0}{dt} &= m\Psi(\varepsilon_1(x_0+\alpha y_0)+\varepsilon_2(x_1+\alpha y_1))y_0 - g_0y_0 \\ \dfrac{dy_1}{dt} &= qy_0 - g_1y_1 \\ \dfrac{dE}{dt} &= -K_0E(t) + \dfrac{a}{1+K_1x_0^{r_0}} \end{cases} \tag{2.1}$$

where safe (M.C) cells x_1 proliferate at a rate d_2 and are eliminated at a rate $d(E)$ such that $d(E) - d_2 > 0$.

In fact, the growth factor concentration E follows the evolution equation [32]

$$\frac{dE}{dt} = -K_0E(t) + f(x_0(t)).$$

The function f acts as negative feedback of the non proliferating (H.S.C) population on the production of growth factor.

We assume that f is positive and decreasing and according to [2]:

$$f(x_0(t)) = \frac{a}{1+K_1x_0^{r_0}}.$$

The associated growth factor concentration is given by

$$\frac{dE}{dt} = -K_0E(t) + \frac{a}{1+K_1x_0^{r_0}}. \tag{2.2}$$

The studied population is divided into two compartments: hematopoietic stem cells (H.S.C) and differentiated cells (M.C).

In model (2.3), the death rate of normal differentiated cells $d(E)$ undergoes a Hill function evolution and according to [2], $d(E)$ is given by

$$d(E) = 1 - \frac{K_1}{K_2 + E}. \tag{2.3}$$

In addition to the Table 1, the Table 2 lists the parameters used in our model. All those parameters are assumed to be positive.

Parameter	Explanation
$d(E)$	Death rate of norma(l M.C) x_1
K_0	Clearing rate of growth factors
K_1	Rate of maximum saturation of growth factors
K_2	Rate of half saturation of growth factors
r_0	Oscillation rate
a	Absorption rate of E by cells

TABLE 2. Parameters used in model (2.3)

Moreover, in all what follows, we assume that
$d_0 < n$, $g_0 < m$, $c = 1 - \dfrac{K_1}{K_2} - d_2$ is positive.

REMARK 2.1. As $d(E) - d_2 = 1 - \frac{K_1}{K_2+E} - d_2$, then $d(E) - d_2 \geq 1 - \frac{K_1}{K_2} - d_2$. So as $c = 1 - \frac{K_1}{K_2} - d_2$ is positive, then $d(E) - d_2$ is positive also.

3. Basic properties of model (2.3)

3.1. *Existence of a positively invariant attracting set.*

PROPOSITION 3.1. *The system (2.3) is positively invariant in the following cone:*

$$D = \{(x_0, x_1, y_0, y_1, E) \in \mathbb{R}^5; x_0 \geq 0, x_1 \geq 0, y_0 \geq 0, y_1 \geq 0, E \geq 0\}$$

PROOF. One has

$$\begin{aligned}
\text{at } (0, x_1, y_0, y_1, E) : \frac{dx_0}{dt} &= 0, \\
\text{at } (x_0, 0, y_0, y_1, E) : \frac{dx_1}{dt} &= r x_0 \geq 0, \\
\text{at } (x_0, x_1, 0, y_1, E) : \frac{dy_0}{dt} &= 0, \\
\text{at } (x_0, x_1, y_0, 0, E) : \frac{dy_1}{dt} &= q y_0 \geq 0, \\
\text{at } (x_0, x_1, y_0, y_1, 0) : \frac{dE}{dt} &= \frac{a}{1 + K_1 x_0^{r_0}} \geq 0.
\end{aligned}$$

Then the vector field is pointing in the direction of D and does not leave it, so according to [28], this system is positively invariant. ∎

3.2. *Existence and uniqueness of solution.* The Cauchy problem associated to the model (2.3) is given by

$$\left\{ \begin{array}{rcl} \dot{X} & = & F(X) \\ X(t_0) & = & X_0 \end{array} \right. \tag{3.1}$$

where $X = (x_0, x_1, y_0, y_1, E)^T$ is defined on the time interval $J = [0, T]$ for some $T > 0$ fixed, under fixed initial conditions $(x_0(0), x_1(0), y_0(0), y_1(0), E(0))$, $F : D \to \mathbb{R}^5_+$, $X \mapsto F(X)$, where $F(X)$ is defined by

$$F(X) := \begin{pmatrix} n\Phi(\varepsilon_1(x_0 + y_0) + \varepsilon_2(x_1 + y_1))x_0 - d_0 x_0 \\ rx_0 - (d(E) - d_2)x_1 \\ m\Psi(\varepsilon_1(x_0 + \alpha y_0) + \varepsilon_2(x_1 + \alpha y_1))y_0 - g_0 y_0 \\ qy_0 - g_1 y_1 \\ -K_0 E(t) + \frac{a}{1+K_1 x_0^{r_0}} \end{pmatrix}$$

Proposition 3.2. *A local solution of the Cauchy problem associated to (2.3) exists and is unique in D.*

Proof. Since the function F is of class C^1, then a local solution of the Cauchy problem associated to (2.3) exists and is unique in D. This is due to Picart-Lindeloff theorem [24]. ∎

Now, let us prove the global existence of the solution of the Cauchy problem associated to (2.3) for scenarios 1 and 3. In fact, it is sufficient to prove that the corresponding solution is bounded in a convenient set Γ of D. Here we shall consider

$$\Gamma = \Big\{ (x_0, x_1, y_0, y_1, E) : 0 < x_0 \leq m_1, 0 \leq x_1 \leq \frac{rm_1}{c}, \\ 0 < y_0 \leq m_2, 0 \leq y_1 \leq \frac{qm_2}{g_1}, 0 \leq E \leq \frac{a}{K_0} \Big\},$$

where $m_1 = \max\left(x_0(0), \frac{1}{K(1 - \frac{d_0}{n})}\right)$ and $m_2 = \max\left(y_0(0), \frac{1}{\frac{K}{\alpha}\left(1 - \frac{g_0}{m}\right)}\right)$.

Proposition 3.3. *The Cauchy problem associated to model (2.3) admits a global and unique solution defined on Γ for scenarios 1 and 3.*

Proof. The first and third equations of model (2.3) are given in scenario 1 by

$$\frac{dx_0}{dt} = n\left(1 - \frac{(x_0 + y_0)}{K}\right)x_0 - d_0 x_0 \tag{3.2}$$

$$\frac{dy_0}{dt} = m\left(1 - \frac{(x_0 + \alpha y_0)}{K}\right)y_0 - g_0 y_0 \tag{3.3}$$

and in scenario 3 by

$$\frac{dx_0}{dt} = n\left(1-\frac{(x_0+y_0)+(x_1+y_1)}{K}\right)x_0 - d_0x_0 \tag{3.4}$$

$$\frac{dy_0}{dt} = m\left(1-\frac{(x_0+\alpha y_0)+(x_1+\alpha y_1)}{K}\right)y_0 - g_0y_0 \tag{3.5}$$

For those two scenarios, one has those corresponding majorations

$$\begin{aligned}\frac{dx_0}{dt} &\leq n\left(1-\frac{x_0}{K}\right)x_0 - d_0x_0\\ \frac{dy_0}{dt} &\leq m\left(1-\frac{\alpha y_0}{K}\right)y_0 - g_0y_0\end{aligned}$$

The solution of (3.2) and (3.4) can be compared to the solution of the following Bernoulli equation with the same initial condition

$$\frac{dx_0}{dt} = n\left(1-\frac{x_0}{K}\right)x_0 - d_0x_0$$

which is

$$x_0(t) = \frac{1}{K(1-\frac{d_0}{n}) + l\exp(-(n-d_0)t)},$$

where $l = \dfrac{1}{x_0(0)} - K\left(1-\dfrac{d_0}{n}\right)$ and $x_0(0)$ is assumed to be different from 0.

According to the comparison Theorem [24], the solutions of (3.2) and (3.4) satisfy for all $t \geq 0$,

$$x_0(t) \leq \frac{1}{K\left(1-\frac{d_0}{n}\right) + l\exp(-(n-d_0)t)}.$$

Hence,

$$\limsup_{t\to+\infty} x_0(t) \leq m_1.$$

The solutions of (3.3) and (3.5) can be compared to the solution of the Bernoulli equation with the same initial condition

$$\frac{dy_0}{dt} = m\left(1-\frac{\alpha y_0}{K}\right)y_0 - g_0y_0,$$

which is

$$y_0(t) = \frac{1}{\frac{K}{\alpha}(1-\frac{g_0}{m}) + l'\exp(-(m-g_0)t)},$$

where $l' = \dfrac{1}{y_0(0)} - \dfrac{K}{\alpha}\left(1-\dfrac{g_0}{m}\right)$ and $y_0(0)$ is assumed to be different from 0.

According to the comparison Theorem, the solutions of (3.3) and (3.5) satisfy for all $t \geq 0$,

$$y_0(t) \leq \frac{1}{\frac{K}{\alpha}(1-\frac{g_0}{m}) + l'\exp(-(m-g_0)t)}.$$

Hence,

$$\limsup_{t\to+\infty} y_0(t) \leq m_2.$$

The second equation of (2.3) for scenarios 1 and 3 is given by

$$\begin{aligned} \frac{dx_1}{dt} &= rx_0 - \left(1 - \frac{K_1}{K_2+E} - d_2\right) x_1 \\ \frac{dx_1}{dt} &\leq rm_1 - \left(1 - \frac{K_1}{K_2} - d_2\right) x_1. \end{aligned} \tag{3.6}$$

In this case, the solution of (3.6) can be compared to the solution of the following differential equation with the same initial condition

$$\frac{dx_1}{dt} + \left(1 - \frac{K_1}{K_2} - d_2\right) x_1 = rm_1,$$

which is

$$x_1(t) = \frac{rm_1}{c} + \left(x_1(0) - \frac{rm_1}{c}\right) \exp(-ct).$$

According to the comparison theorem, the solution of (3.6) satisfies for all $t \geq 0$:

$$x_1(t) \leq \frac{rm_1}{c} + \left(x_1(0) - \frac{rm_1}{c}\right) \exp(-ct).$$

Hence,

$$\limsup_{t\to+\infty} x_1(t) \leq \frac{rm_1}{c}.$$

The forth equation of (2.3) for scenario 1 and 3 is given by

$$\begin{aligned} \frac{dy_1}{dt} &= qy_0 - g_1 y_1 \\ \frac{dy_1}{dt} &\leq qm_2 - g_1 y_1 \end{aligned} \tag{3.7}$$

In this case, the solution of (3.7) can be compared to that of the following differential equation with the same initial condition

$$\frac{dy_1}{dt} + g_1 y_1 = qm_2,$$

which is

$$y_1(t) = \frac{qm_2}{g_1} + \left(y_1(0) - \frac{qm_2}{g_1}\right) \exp(-g_1 t).$$

According to the comparison theorem, the solution of (3.7) satisfies for all $t \geq 0$

$$y_1(t) \leq \frac{qm_2}{g_1} + \left(y_1(0) - \frac{qm_2}{g_1}\right) \exp(-g_1 t).$$

Hence,

$$\limsup_{t\to+\infty} y_1(t) \leq \frac{qm_2}{g_1}.$$

The fifth equation of (2.3), for scenarios 1 and 3, is given by

$$\begin{aligned} \frac{dE}{dt} &= -K_0 E + \frac{a}{1+K_1 x_0^{r_0}} \\ \frac{dE}{dt} &\leq -K_0 E + a. \end{aligned} \tag{3.8}$$

In this case, the solution of (3.8) can be compared to the solution of the following differential equation with the same initial condition

$$\frac{dE}{dt} = -K_0 E + a,$$

which is

$$E(t) = \frac{a}{K_0} + (E(0) - \frac{a}{K_0}) \exp(-K_0 t).$$

According also to the comparison Theorem, the solution of (3.8) satisfies for all $t \geq 0$

$$E(t) \leq \frac{a}{K_0} + (E(0) - \frac{a}{K_0}) \exp(-K_0 t).$$

Hence,

$$\limsup_{t \to +\infty} E(t) \leq \frac{a}{K_0}.$$

Finally, for scenarios 1 and 3, any solution of (2.3) that starts in $\mathbb{R}^5_+$ is confined in Γ and since Γ is compact and positively invariant for model (2.3), according to [28], there exists an unique global solution of the Cauchy problem associated to (2.3) in Γ (for scenarios 1 and 3). □

4. Existence of steady states

The steady states of (2.3) are the following:

- The trivial steady state $S_0 = (0, 0, 0, 0, E_0)$ corresponds to the extinction of cell population, where $E_0 = \dfrac{a}{K_0} > 0$.
- The no pathologic steady state $S_{np} = (x_{0,np}, x_{1,np}, 0, 0, E_{np})$ corresponds to presence of normal cells without leukemic cells, where
  $E_{np} = \dfrac{a}{K_0\left(1 + K_1 x_{0,p}^{r_0}\right)}$, $x_{0,np} = K(1 - \dfrac{d_0}{n})$
  and $x_{1,np} = \dfrac{r}{d(E_{n,p}) - d_2} x_{0,np}$.
- The blast steady state $S_b = (0, 0, y_{0,b}, y_{1,b}, E_b)$ corresponds to presence of leukemic cells without normal cells, where
  $E_b = \dfrac{a}{K_0}$, $y_{0,b} = \dfrac{K}{\alpha}\left(1 - \dfrac{g_0}{m}\right)$ and $y_{1,b} = \dfrac{q}{g_1} y_{0,b}$.
- The chronic steady state $S_c = (x_{0,c}, x_{1,c}, y_{0,c}, y_{1,c}, E_c)$ corresponds to simultaneous presence of normal cells and leukemic cells, where

$$x_{0,c} = \frac{K}{1-\alpha}\left(1-\alpha+\frac{d_0\alpha}{n}-\frac{g_0}{m}\right),\ x_{1,c} = \frac{r}{d(E_c)-d_2}x_{0,c}$$
$$y_{0,c} = \frac{K}{1-\alpha}\left(-\frac{d_0}{n}+\frac{g_0}{m}\right),\ y_{1,c} = \frac{q}{g_1}y_{0,c},\ E_c = \frac{a}{K_0\left(1+K_1x_{0,c}^{r_0}\right)} > 0.$$

Now, put $T_1 := \dfrac{d_0 m}{g_0 n}$ and $T_2 := \dfrac{1}{\alpha}\left(\dfrac{1-\frac{g_0}{m}}{1-\frac{d_0}{n}}\right)$.

THEOREM 4.1. *For all the three scenarios:*

- *The trivial steady state S_0 always exists.*
- *If $n > d_0$ then the no pathologic steady state S_{np} exists.*
- *If $m > g_0$ then the blast steady state S_b exists.*
- *If $T_1 < 1 < T_2$ then chronic steady state S_c exists.*

PROOF. **Scenario 1:** $\varepsilon_1 = 1, \varepsilon_2 = 0$**:**
In this case, homeostasis functions are given by

$$\begin{cases} \Phi(x_0+y_0) &= 1-\dfrac{x_0+y_0}{K} \\ \Psi(x_0+y_0) &= 1-\dfrac{x_0+\alpha y_0}{K} \end{cases}$$

where $\alpha \in]0,1[$. Therefore,

- $E_0 = \dfrac{a}{K_0}$ then the trivial steady state S_0 always exists.
- $x_{0,np} = K(1-\dfrac{d_0}{n})$, $x_{1,np} = \dfrac{r}{d(E_{np})-d_2}x_{0,np}$, $E_{np} = \dfrac{a}{K_0\left(1+K_1x_{0,np}^{r_0}\right)}$
  Since $d(E_{np}) - d_2 > 0$ then $x_{0,np} > 0$ and $x_{1,np} > 0$ if $n > d_0$.
  Then the non pathologic steady state S_{np} exists if $n > d_0$.
- $y_{0,b} = \dfrac{K}{\alpha}\left(1-\dfrac{g_0}{m}\right)$, $y_{1,b} = \dfrac{q}{g_1}y_{0,b}$, $E_b = \dfrac{a}{K_0}$
  $y_{0,b} > 0$ and $y_{1,b} > 0$ if $m > g_0$.
  Then the blast steady state S_b exists if $m > g_0$.

- $x_{0,c} = \dfrac{K}{1-\alpha}\left(1-\alpha+\dfrac{d_0\alpha}{n}-\dfrac{g_0}{m}\right)$, $x_{1,c} = \dfrac{r}{d(E_c)-d_2}x_{0,c}$,
  $y_{0,c} = \dfrac{K}{1-\alpha}\left(-\dfrac{d_0}{n}+\dfrac{g_0}{m}\right)$, $y_{1,c} = \dfrac{q}{g_1}y_{0,c}$, $E_c = \dfrac{a}{K_0\left(1+K_1x_{0,c}^{r_0}\right)}$.
  Then the chronic steady state S_c exists if $T_1 < 1 < T_2$.

Scenario 2: $\varepsilon_1 = 0, \varepsilon_2 = 1$**:**
In this case, homeostasis functions are given by

$$\begin{cases} \Phi(x_1+y_1) &= 1-\frac{x_1+y_1}{K} \\ \Psi(x_1+y_1) &= 1-\frac{x_1+\alpha y_1}{K} \end{cases}$$

Therefore,

- $x_{0,t} = x_{1,t} = y_{0,t} = y_{1,t} = 0$ and $E_t = \frac{a}{K_0} > 0$.
  Then the trivial steady state S_0 always exists.
- $x_{0,np} = \frac{d(E_{np})-d_2}{r} x_{1,np}$, $x_{1,np} = K(1-\frac{d_0}{n})$, $y_{0,np} = y_{1,np} = 0$, $E_{np} > 0$.
  Then the no pathologic steady state S_{np} exists if $n > d_0$.
- $x_{0,b} = x_{1,b} = 0$, $y_{0,b} = \frac{g_1}{q} y_{1,b}$, $y_{1,b} = \frac{K}{\alpha}\left(1 - \frac{g_0}{m}\right)$, $E_b = \frac{a}{K_0} > 0$.
  Then the blast steady state S_b exists if $m > g_0$.

- $x_{1,c} = \frac{K}{1-\alpha}\left(1 - \alpha + \frac{d_0\alpha}{n} - \frac{g_0}{m}\right)$, $x_{0,c} = \frac{d(E_c)-d_2}{r} x_{1,c}$, $y_{1,c} = \frac{K}{1-\alpha}\left(-\frac{d_0}{n} + \frac{g_0}{m}\right)$, $y_{0,c} = \frac{g_1}{q} y_{1,c}$ and $E_c = \frac{a}{K_0(1+K_1 x_{0,c}^{r_0})}$.
  Then the chronic steady state S_c exists if $T_1 < 1 < T_2$.

Scenario 3: $\varepsilon_1 = 1, \varepsilon_2 = 1$**:**
In this case, homeostasis functions are given by

$$\begin{cases} \Phi(x_0 + y_0 + x_1 + y_1) &= 1 - \frac{x_0+y_0+x_1+y_1}{K}, \\ \Psi(x_0 + \alpha y_0 + x_1 + \alpha y_1) &= 1 - \frac{x_0+\alpha y_0+x_1+\alpha y_1}{K} \end{cases}$$

Therefore,

- $E_0 = \frac{a}{K_0} > 0$ then the trivial steady state S_0 always exists .
- $x_{0,np} = \frac{K(d(E_{np})-d_2)(1-\frac{d_0}{n})}{d(E_{np})-d_2+r}$, $x_{1,np} = \frac{r}{d(E_{np})-d_2} x_{0,np}$, $E_{np} > 0$.
  Then the no pathologic steady state S_{np} exists if $n > d_0$.
- $y_{0,b} = \frac{g_1 q}{\alpha(g_1+q)}(1 - \frac{g_0}{m})$, $y_{1,b} = \frac{Kq}{\alpha(g_1+q)}(1 - \frac{g_0}{m})$, $E_b = \frac{a}{K_0} > 0$.
  $y_{0,b} > 0$ and $y_{1,b} > 0$ if $m > g_0$.
  Then the blast steady state S_b exists if $m > g_0$.

- $x_{0,c} = \frac{K(1-\alpha-\frac{g_0}{m}+\alpha\frac{d_0}{n})}{(1-\alpha)(1+\frac{r}{d(E_c)-d_2})}$, $x_{1,c} = \frac{r}{d(E_c)-d_2} x_{0,c}$, $y_{0,c} = \frac{K(\frac{g_0}{m}-\frac{d_0}{n})}{(1-\alpha)(1+\frac{q}{g_1})}$, $y_{1,c} = \frac{q}{g_1} y_{0,c}$, $E_c > 0$.
  Then the chronic steady state S_c exists if $T_1 < 1 < T_2$.

□

5. Local stability analysis

The Jacobian matrix J of system (2.3) is given by

$$J(X) = \begin{pmatrix} n\frac{\partial\Phi}{\partial x_0}x_0 + n\Phi - d_0 & n\frac{\partial\Phi}{\partial x_1}x_0 & n\frac{\partial\Phi}{\partial y_0}x_0 & n\frac{\partial\Phi}{\partial y_1}x_0 & 0 \\ r & -d + d_2 & 0 & 0 & -\frac{\partial d}{\partial E}x_1 \\ m\frac{\partial\Psi}{\partial x_0}y_0 & m\frac{\partial\Psi}{\partial x_1}y_0 & m\frac{\partial\Psi}{\partial y_0}y_0 + m\Psi - g_0 & m\frac{\partial\Psi}{\partial y_1}y_0 & 0 \\ 0 & 0 & q & -g_1 & 0 \\ \frac{-aK_1 r_0 x_0^{r_0-1}}{(1+K_1 x_0^{r_0})^2} & 0 & 0 & 0 & -K_0 \end{pmatrix}$$

5.1. *Scenario 1.*

Proposition 5.1.

1. *The trivial steady state is LAS if $n < d_0$ and $m < g_0$.*

2. *The no pathologic steady state and the blast steady state are LAS if* $T_1 < 1 < T_2$.
3. *The blast steady state is the unique LAS state if* $T_2 > 1$ *and* $T_1 > 1$.
4. *The no pathologic steady state is the unique LAS state if* $T_1 < 1$ *and* $T_2 < 1$.
5. *The chronic steady state is unstable.*

PROOF. In this case, J is rewritten (and denoted J_1) for this scenario as

$$J_1(X) = \begin{pmatrix} n\Phi - d_0 - n\frac{x_0}{K} & 0 & -n\frac{x_0}{K} & 0 & 0 \\ r & -d + d_2 & 0 & 0 & -\frac{k_1}{(K_2+E)^2}x_1 \\ -m\frac{y_0}{K} & 0 & m\Psi - g_0 - \frac{m\alpha}{K}y_0 & -\frac{m\alpha}{K}y_0 & 0 \\ 0 & 0 & q & -g_1 & 0 \\ \frac{-aK_1r_0x_0^{r_0-1}}{(1+K_1x_0^{r_0})^2} & 0 & 0 & 0 & -K_0 \end{pmatrix}$$

Denote by

$$\begin{aligned} A_1 &= n\Phi - d_0 - n\frac{x_0}{K}, \\ B_1 &= -n\frac{x_0}{K}, \\ C_1 &= -d + d_2, \\ D_1 &= -\frac{k_1}{(K_2+E)^2}x_1, \\ F_1 &= m\Psi - g_0 - \frac{m\alpha}{K}y_0, \\ L_1 &= -m\frac{y_0}{K}, \\ G_1 &= \frac{-aK_1r_0x_0^{r_0-1}}{(1+K_1x_0^{r_0})^2}, \end{aligned}$$

so

$$J_1(X) = \begin{pmatrix} A_1 & 0 & B_1 & 0 & 0 \\ r & C_1 & 0 & 0 & D_1 \\ L_1 & 0 & F_1 & \alpha L_1 & 0 \\ 0 & 0 & q & -g_1 & 0 \\ G_1 & 0 & 0 & 0 & -K_0 \end{pmatrix}.$$

The corresponding eigenvalues of $J_1(X)$ are:
$\lambda_1 = -g_1 < 0$, $\lambda_2 = -d + d_2 < 0$, $\lambda_3 = -K_0 < 0$ and λ_4 and λ_5 satisfy $\lambda_4 + \lambda_5 = A_1 + F_1$, $\lambda_4\lambda_5 = A_1F_1 - B_1L_1$. Hence $J_1(X)$ has three negatives eigenvalues λ_1, λ_2 and λ_3 for all steady states.

- **At the trivial steady state.** One has
  $A_1 = n - d_0, C_1 = -d + d_2, F_1 = m - g_0, B_1 = D_1 = L_1 = G_1 = 0$,
  $\lambda_4 = A_1 = n - d_o$ and $\lambda_5 = F_1 = m - g_0$.
  Then the trivial steady state is LAS if $n < d_0$ and $m < g_0$.

- **At the no pathologic steady state.** One has
  $A_1 = B_1 = -\frac{nx_{0,s}}{K}, F_1 = m\left(1 - \frac{x_{0,s}}{K}\right), C_1 = -d + d_2, L_1 = 0,$
  $\lambda_4 = A_1 < 0$ and $\lambda_5 = F_1$,
  $\lambda_5 < 0 \quad \text{if} \quad F_1 < 0 \quad \text{i.e. if} \quad T_1 < 1.$
  Then, the no pathologic steady state is LAS if $T_1 < 1$.
- **At the blast steady state.** One has
  $A_1 = n\left(1 - \frac{y_{0,b}}{K}\right) - d_0, B_1 = D_1 = G_1 = 0, F_1 L_1 = -\frac{my_{0,b}}{K},$
  $\lambda_4 = A_1$ and $\lambda_5 = F_1 < 0$. Hence $\lambda_4 < 0 \quad \text{if} \quad T_2 > 1.$
  Then the blast steady state is LAS if $T_2 > 1$.
- **At the chronic steady state.** One has
  $A_1 = B_1 = -\frac{nx_{0,c}}{K}, C_1 = -d + d_2, F_1 = -\frac{my_{0,c}\alpha}{K}, L_1 = -\frac{my_{0,c}}{K}.$
  Then λ_4 and λ_5 satisfy
  $\lambda_4\lambda_5 = A_1F_1 - B_1L_1 = mn\frac{x_{0,c}y_{0,c}}{K}(\alpha - 1) < 0$ since $0 < \alpha < 1$.
  Then the chronic steady state is unstable.

□

5.2. *Scenario 2.*

PROPOSITION 5.2.

1. *The trivial steady state is LAS if* $n < d_0 \quad \text{and} \quad m < g_0$.
2. *The no pathologic steady state and the blast steady state are LAS if* $T_1 < 1 < T_2$.
3. *The blast steady state is the unique LAS state if* $T_2 > 1$ *and* $T_1 > 1$.
4. *The no pathologic steady state is the unique LAS state if* $T_1 < 1$ *and* $T_2 < 1$.
5. *The chronic steady state is unstable.*

PROOF. The Jacobian matrix is rewritten (and denoted J_2) for this scenario as

$$J_2(X) = \begin{pmatrix} n\Phi - d_0 & -\frac{nx_0}{K} & 0 & -\frac{nx_0}{K} & 0 \\ r & -d + d_2 & 0 & 0 & -\frac{K_1}{(K_2+E)^2}x_1 \\ 0 & -m\frac{y_0}{K} & m\Psi - g_0 & -\frac{m\alpha}{K}y_0 & 0 \\ 0 & 0 & q & -g_1 & 0 \\ \frac{-aK_1r_0x_0^{r_0-1}}{(1+K_1x_0^{r_0})^2} & 0 & 0 & 0 & -K_0 \end{pmatrix}$$

Denote by

$$\begin{aligned} A_2 &= n\Phi - d_0 \\ B_2 &= -n\frac{x_0}{K} \\ C_2 &= -d + d_2 \\ D_2 &= -\frac{K_1}{(K_2+E)^2}x_1 \\ F_2 &= m\Psi - g_0 \\ L_2 &= -m\frac{y_0}{K} \\ G_2 &= \frac{-aK_1r_0x_0^{r_0-1}}{(1+K_1x_0^{r_0})^2}, \end{aligned}$$

so

$$J_2(X) = \begin{pmatrix} A_2 & B_2 & 0 & B_2 & 0 \\ r & C_2 & 0 & 0 & D_2 \\ 0 & L_2 & F_2 & \alpha L_2 & 0 \\ 0 & 0 & q & -g_1 & 0 \\ G_2 & 0 & 0 & 0 & -K_0 \end{pmatrix}$$

- **At the trivial steady state.** One has
  $A_2 = n - d_0, B_2 = D_2 = G_2 = L_2 = 0, C_2 = -d + d_2, F_2 = m - g_0$.
  In this case, $J_2(X)$ has three negative eigenvalues: $\lambda_1 = -K_0$, $\lambda_2 = -g_1$, $\lambda_3 = C_2$ and the two others are given by $\lambda_4 = A_2$ and $\lambda_5 = F_2$.
  So the trivial steady state is LAS if $A_2 < 0$ and $F_2 < 0$ i.e.if $n < d_0$ and $m < g_0$.
- **At the no pathologic steady state.** One has
  $A_2 = L_2 = 0, B_2 = -n\frac{x_0}{K}, C_2 = -d + d_2, D_2 = -\frac{K_1}{(K_2+E)^2}x_1$,
  $F_2 = m\Psi - g_0, G_2 = \frac{-aK_1r_0x_0^{r_0-1}}{(1+K_1x_0^{r_0})^2}$.
  $J_2(X)$ has four negative eigenvalues as:
  $\lambda_1 = -K_0$, $\lambda_2 = -g_1$, $\lambda_3 + \lambda_4 = C_2 < 0$, $\lambda_3\lambda_4 = -rB_2 > 0$
  and $\lambda_5 = F_2$, $\lambda_5 < 0$ if $F_2 < 0$ i.e. $T_1 < 1$.
  Thus the no pathologic steady state is LAS if $T_1 < 1$.
- **At the blast steady state.** One has
  $A_2 = n\Phi - d_0, B_2 = F_2 = G_2 = D_2 = 0$,
  $C_2 = -d + d_2, L_2 = -m\frac{y_{0,b}}{K}$.
  J_2 has four negatives eigenvalues as:
  $\lambda_1 = -K_0$, $\lambda_2 = C_2 < 0$ and λ_3 and λ_4 satisfy $\lambda_3 + \lambda_4 = -g_1$ and $\lambda_3\lambda_4 = -q\alpha H_2 > 0$ and as $\lambda_5 = A_2$, so $\lambda_5 < 0$ if $T_2 > 1$.
  Then the blast steady point is LAS if $T_2 > 1$.
- **At chronic steady state.** One has
  $A_2 = F_2 = 0, C_2 = -d + d_2, B_2 = -\frac{ny_{0,c}}{K}$,
  $L_2 = -\frac{my_{0,c}}{K}D_2 = -\frac{K_1}{(K_2+E)^2}x_1$, $G_2 = \frac{-aK_1r_0x_0^{r_0-1}}{(1+K_1x_0^{r_0})^2}$.

The corresponding characteristic polynomial is given by
$P(\lambda) = a_5\lambda^5 + a_4\lambda^4 + a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0$
where

$$\begin{aligned}
a_5 &= 1,\\
a_4 &= K_0 - C_2 - g_1,\\
a_3 &= -K_0C_2 + -k_0g_1 - g_1C_2 - q\alpha L_2 - rB_2,\\
a_2 &= -G_2B_2D_2 - K_0C_2g_1 - K_0q\alpha L_2 + C_2q\alpha L_2 - K_0B_2r - g_1B_2r,\\
a_1 &= -G_2B_2D_2g_1 + K_0C_2q\alpha L_2 - K_0B_2G_1 + q\alpha L_2B_2r - B_2qrL_2,\\
a_0 &= G_2B_2D_2L_2q(\alpha - 1) - K_0qrB_2L_2 < 0.
\end{aligned}$$

The associated Hurwitz matrix is given by

$$M = \begin{pmatrix} a_5 & a_3 & a_1 & 0 & 0\\ a_4 & a_2 & a_0 & 0 & 0\\ b_3 & b_4 & 0 & 0 & 0\\ c_2 & c_1 & 0 & 0 & 0\\ d_1 & 0 & 0 & 0 & 0\\ e_0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

where

$$a_5 = 1, \qquad b_3 = -\frac{1}{a_4}(a_2a_5 - a_3a_4), \qquad b_4 = -\frac{1}{a_4}(a_0a_5 - a_1a_4),$$

$$c_2 = -\frac{1}{b_3}(a_4b_4 - a_2b_3), \qquad c_1 = a_0,$$

$$d_1 = -\frac{1}{c_2}(c_1b_3 - c_2b_4), \qquad e_0 = a_0 < 0 \quad \textit{since} \quad \alpha < 1.$$

So from Hurwitz criterion [21], as at least one element of the first column of M (here e_0) is negative then the chronic equilibrium state is unstable.

□

5.3. *Scenario 3.*

PROPOSITION 5.3.

1. *The trivial steady state is LAS if $n < d_0$ and $m < g_0$.*
2. *The no pathologic steady state is unstable.*
3. *The blast steady state is LAS if $T_2 > 1$.*
4. *The chronic steady state is unstable.*

PROOF. The Jacobian matrix is rewritten (and denoted J_3) for this scenario as

$$J_3(X) = \begin{pmatrix} -n\frac{x_0}{K} + n\Phi - d_0 & -n\frac{x_0}{K} & -n\frac{x_0}{K} & -n\frac{x_0}{K} & 0 \\ r & -d + d_2 & 0 & 0 & -\frac{K_1}{(K_2+E)^2}x_1 \\ -m\frac{y_0}{K} & -m\frac{y_0}{K} & m\Psi - g_0 - \frac{m\alpha}{K}y_0 & -\alpha m\frac{y_0}{K} & 0 \\ 0 & 0 & q & -g_1 & 0 \\ \frac{-aK_1r_0x_0^{r_0-1}}{(1+K_1x_0^{r_0})^2} & 0 & 0 & 0 & -K_0 \end{pmatrix}$$

Denote by

$$\begin{aligned} A_3 &= -n\frac{x_0}{K} + n\Phi - d_0, \\ B_3 &= -n\frac{x_0}{K}, \\ C_3 &= -d + d_2, \\ D_3 &= -\frac{K_1}{(K_2+E)^2}x_1, \\ F_3 &= m\Psi - g_0 - \frac{m\alpha}{K}y_0, \\ L_3 &= -m\frac{y_0}{K}, \\ G_3 &= \frac{-aK_1r_0x_0^{r_0-1}}{(1+K_1x_0^{r_0})^2}. \end{aligned}$$

Then

$$J_3(X) = \begin{pmatrix} A_3 & B_3 & B_3 & B_3 & 0 \\ r & C_3 & 0 & 0 & D_3 \\ L_3 & L_3 & F_3 & \alpha L_3 & 0 \\ 0 & 0 & q & -g_1 & 0 \\ G_3 & 0 & 0 & 0 & -K_0 \end{pmatrix}$$

- **At the trivial steady state.** One has
  $J_3(X)$ has three negatives eigenvalues:
  $\lambda_1 = -g_1$, $\lambda_2 = -K_0$, $\lambda_3 = -d + d_2$ and $\lambda_4 = n - d_0$, $\lambda_5 = m - g_0$ are negative if $n - d_0 < 0$ and $m - g_0 < 0$.
  So the trivial steady state is LAS if $n - d_0 < 0$ and $m - g_0 < 0$.
- **At the no pathologic steady state.**
  The corresponding characteristic polynomial is given by
  $P(\lambda) = (F_3 - \lambda)(-g_1 - \lambda)(Q(\lambda)$ where $Q(\lambda) = -(a_3'\lambda^3 + a_2'\lambda^2 + a_1'\lambda^1 + a_0')$

where

$$\begin{aligned} a_3' &= 1, \\ a_2' &= K_0 + d - d_2 + \frac{nx_{0,s}}{K} > 0, \\ a_1' &= K_0(d-d_2) + \frac{nx_{0,s}}{K}(K_0 + d - d_2 + r) > 0, \\ a_0' &= \frac{nx_{0,s}}{K}\left(K_0(d-d_2) + r - G_3\right) > 0. \end{aligned}$$

The associated Hurwitz matrix M' is given by

$$M' = \begin{pmatrix} a_3' & a_1' & 0 \\ a_2' & a_0' & 0 \\ b_1' & b_2' & 0 \\ c_0' & 0 & 0 \end{pmatrix}$$

where $a_3' > 0$, $b_2' = 0$, $c_0' = -a_0' < 0$ and $b_1' = -\frac{1}{a_2'}(a_0'a_3' - a_1'a_2')$.

Then from the Hurwitz criterion since one of the first column of M' is negative (here c_0'), the no pathologic steady state is unstable.

- **At the blast steady state.** One has
  $A_3 = n\Phi - d_0$, $B_3 = D_3 = G_3 = 0$, $C_3 = -d + d_2$,
  $L_3 = -m\frac{y_{0,b}}{K}$, $F_3 = \alpha L_3$.
  $J_3(X)$ has four negatives eigenvalues:
  $\lambda_1 = -K_0$, $\lambda_2 = -d + d_2$ and $\lambda_3 + \lambda_4 = -(\frac{\alpha m y_0}{K} + g_1) < 0$ and $\lambda_3\lambda_4 = \frac{\alpha m y_0 q}{K} > 0$, $\lambda_5 = n\Phi - d_0$, $\lambda_5 < 0$ if $T_2 > 1$.
  Then the blast steady state is L.A.S if $T_2 > 1$.
- **At the chronic steady state.** One has
  $A_3 = B_3 = -n\frac{x_{0,s}}{K}$, $C_3 = -d + d_2, D_3 = -\frac{K_1}{(K_2+E_s)^2}x_{1,s}$,
  $L_3 = -m\frac{y_{0,s}}{K}$, $F_3 = \alpha L_3$, $G_3 = \frac{-aK_1r_0x_{0,s}^{r_0-1}}{(1+K_1x_{0,s}^{r_0})^2}$.
  The corresponding characteristic polynomial is given by

$$P(\lambda) = a_5''\lambda^5 + a_4''\lambda^4 + a_3''\lambda^3 + a_2''\lambda^2 + a_1''\lambda + a_0''$$

where

$$\begin{aligned} a_5'' &= 1, \\ a_4'' &= -\alpha L_3 + A_3 + C_3 - K_0 - g_1, \\ a_3'' &= -q\alpha L_3 - A_3L_3 + (\alpha L_3 + K_0 + g_1)(A_3 + C_3) - \alpha L_3(K_0 + g_1) - A_3(C_3 - r) - K_0g_1, \\ a_2'' &= -G_3D_3A_3 - A_3L_3(q + g_1 + K_0 + r - C_3) + (q\alpha L_3 - K_0g_1)(A_3 + C_3) - q\alpha L_3K_0 \\ &- (\alpha L_3 + K_0 + g_1)(C_3 - r)A_3, \\ a_1'' &= -G_3D_3A_3(-g_1 + \alpha L_3 - L_3) - (q + g_1)(K_0 + r - C_3)A_3L_3 + L_3\alpha k_0(A_3 + C_3)(q - g_1) \\ &- A_3[(C_3 - r)q\alpha L_3 - L_3k_0 + (\alpha L_3 - 1)(K_0 + g_1)], \\ a_0'' &= [G_3D_3 + (r - C_3)k_0](q + g_1)A_3L_3(\alpha - 1). \end{aligned}$$

The associated Hurwitz matrix M'' is given by

$$M'' = \begin{pmatrix} a_5'' & a_3'' & a_1'' & 0 & 0 \\ a_4'' & a_2'' & a_0'' & 0 & 0 \\ b_3'' & b_4'' & 0 & 0 & 0 \\ c_2'' & c_1'' & 0 & 0 & 0 \\ d_1'' & 0 & 0 & 0 & 0 \\ e_0'' & 0 & 0 & 0 & 0 \end{pmatrix}$$

where

$$\begin{aligned} a_5'' &= 1, \\ b_3'' &= -\frac{1}{a_4''}(a_2''a_5'' - a_3''a_4''), \\ b_4'' &= -\frac{1}{a_4''}(a_0''a_5'' - a_1''a_4''), \\ c_2'' &= -\frac{1}{b_3''}(a_4''b_4'' - a_2''b_3''), \\ c_1'' &= a_0'', \\ d_1'' &= -\frac{1}{c_2''}(c_1''b_3'' - c_2''b_4''), \\ e_0'' &= a_0''. \end{aligned}$$

As that a_0'' is negative since $\alpha < 1$, $A_3 < 0$, $L_3 < 0$, $C_3 < 0$, $D_3 < 0$ and $G_3 < 0$. So at least one element of the first column of M'' is negative(here e_0'') then the chronic steady state is unstable(from Hurwitz criterion).

□

6. Global stability analysis

In this section, global stability analysis for steady states of model (2.3) is proposed for scenarios 1 and 3 .

6.1. *Study of global analysis of no pathologic and blast steady states for Scenario 1.* Recall that according to the theorem 4.1 given in section 4, the no pathologic steady state exists for $n > d_0$ and the blast steady state exists for $m > g_0$ .So, this is assumed in this section to deal with those two states.
To analyze the global stability of those steady states of system (2.3), we shall use the following theorem given in[28].

Theorem 6.1. *Consider the following uniformly bounded C^1 system of the form*

$$\left\{ \begin{array}{rcl} \dot{X}_1 &=& f(X_1) \\ \dot{X}_2 &=& g(X_1, X_2) \end{array} \right. \tag{6.1}$$

where $X_1 \in \mathbb{R}^{n_1}$ and $X_2 \in \mathbb{R}^{n_2}$ with a steady state (X_1^*, X_2^*) such that $f(X_1^*) = 0$ and $g(X_1^*, X_2^*) = 0$.

If X_1^* is globally asymptotically stable (GAS) for the subsystem $\dot{X}_1 = f(X_1)$
and (X_1^*, X_2^*) is GAS for the subsystem $\dot{X}_2 = g(X_1, X_2)$, then (X_1^*, X_2^*) is locally asymptotically stable(LAS) for the system (6.1). Moreover, if all the trajectories of (6.1) are forward bounded then (X_1^*, X_2^*) is also GAS for the system (6.1).

In order to apply this theorem, let us split our system (2.3) into two subsystems: the first one is a subsystem in (x_0, y_0) and the second one in (x_1, y_1, E)
So, first consider the following subsystem of (2.3) in (x_0, y_0) under initial conditions $x_0(0)$, $y_0(0)$

$$\left\{ \begin{array}{rcl} \frac{dx_0}{dt} & = & n(1 - \frac{x_0+y_0}{K})x_0 - d_0 x_0 = f_1(x_0, y_0) \\ \frac{dy_0}{dt} & = & m(1 - \frac{x_0+\alpha y_0}{K})y_0 - g_0 y_0 = f_2(x_0, y_0) \end{array} \right. \tag{6.2}$$

From Proposition 3.3, one has that the solution of (6.2) satisfies $x_0(t) \leq m_1$ and $y_0(t) \leq m_2$ for all $t \geq 0$.
According to this result, let us define the positively invariant compact set as

$$B = \{(x_0, y_0) \in \mathbb{R}_+^2 : 0 \leq x_0 \leq m_1, 0 \leq y_0 \leq m_2\}.$$

LEMMA 6.2. *The system (6.2) has no limit cycle in intB, where intB is the interior of B.*

PROOF. Let us consider the following Dulac functional Θ given by $\Theta(x_0, y_0) = \frac{1}{x_0 y_0}$

$$\vartheta(x_0, y_0) = \frac{\partial}{\partial x_0}(\Theta f_1) + \frac{\partial}{\partial y_0}(\Theta f_2) = -\frac{n x_0 + m\alpha y_0}{K x_0 y_0}.$$

Then $\vartheta(x_0, y_0) \leq 0$ for all (x_0, y_0) in int$B$. Applying Bendixon Dulac theorem [16], it comes that int$B$ doesn't contain any limit cycle. □

LEMMA 6.3. *The singular points $(x_{0,np}, y_{0,np})$ and $(x_{0,b}, y_{0,b})$ are GAS for the subsystem (6.2).*

PROOF. As the subsystem (6.2) has no limit cycle in the bounded set int$B \subset \mathbb{R}_+^2$, the GAS results are obtained from a direct application of the Poincaré-Bendixon theorem [8] to this subsystem. □

Now let us consider the second subsystem

$$\left\{ \begin{array}{rcl} \frac{dx_1}{dt} & = & r x_0 - (d - d_2)x_1 \\ \frac{dy_1}{dt} & = & q y_0 - g_1 y_1 \\ \frac{dE}{dt} & = & -K_0 E + \frac{a}{1 + K_1 x_0^{r_0}} \end{array} \right. \tag{6.3}$$

Using, the obtained results on L.A.S of no pathologic and blast steady states in section 5 for system (2.3), we underline that those results are available also for its subsystems (6.3).

PROPOSITION 6.4. *For any given initial conditions* $(x_0(0), y_0(0), x_1(0), y_1(0), E(0))$ *in* Γ,

a) the no pathologic steady state is GAS if $T_1 < 1 < T_2$,

b) the blast steady state is GAS if $T_1 > 1$ *and* $T_2 > 1$.

PROOF. As it is proved in the previous lemma, $(x_{0,np}, y_{0,np})$ and $(x_{0,b}, y_{0,b})$ are G.A.S for the subsystem (6.2). Moreover , one has that
If $T_1 < 1 < T_2$, then $(x_{0,np}, y_{0,np}, x_{1,np}, y_{1,np}, E_{np})$ is LAS for the subsystem (6.3).
If $T_1 > 1$ and $T_2 > 1$, then $(x_{0,b}, y_{0,b}, x_{1,b}, y_{1,b}, E_b)$ is LAS for the subsystem (6.3).

Moreover, one can directly see that by direct integration of subsystem (6.3) and majorations that $(x_{0,np}, y_{0,np}, x_{1,np}, y_{1,np}, E_{np})$ is G.A.S if $T_1 < 1 < T_2$ and $(x_{0,b}, y_{0,b}, x_{1,b}, y_{1,b}, E_b)$ is G.A.S if $T_1 > 1$ and $T_2 > 1$.

Hence according to Theorem 6.1, the non pathologic steady state is GAS if $T_1 < 1 < T_2$ and the blast steady state is GAS if $T_2 > 1$ and $T_2 > 1$ for model (2.3). ∎

6.2. *Study of global stability of the blast steady state for Scenario 3.* In this case, the model (2.3) is rewritten as

$$
(6.4)\qquad \begin{cases} \frac{dx_0}{dt} &= (n-d_0)x_0 - (\frac{n}{K})(x_0+y_0+x_1+y_1)x_0 \\ \frac{dx_1}{dt} &= rx_0 - (1-\frac{K_1}{K_2+E}-d_2)x_1 \\ \frac{dy_0}{dt} &= (m-g_0)y_0 - \frac{m}{K}(x_0+\alpha y_0+x_1+\alpha y_1)y_0 \\ \frac{dy_1}{dt} &= qy_0 - g_1 y1 \\ \frac{dE}{dt} &= -K_0E(t) + \frac{a}{1+K_1x_0^{r_0}} \end{cases}
$$

The components of the blast steady state are given by
$x_{0,b} = x_{1,b} = 0$, $y_{0,b} = \frac{g_1 q}{\alpha(g_1+q)}(1-\frac{g_0}{m})$, $y_{1,b} = \frac{Kq}{\alpha(g_1+q)}(1-\frac{g_0}{m})$, $E_b = \frac{a}{k_0}$.
Denote by $y_{0,b} + y_{1,b} = \frac{K}{\alpha}\left(1-\frac{g_0}{m}\right)$ and $g_1 = q\frac{y_{0,b}}{y_{1,b}}$.

Then the system (6.4) is rewritten as

(6.5)
$$
\begin{cases} \frac{dx_0}{dt} &= [n-d_0-\frac{n}{K}((y_{0,b}+y_{1,b})+(x_0+x_1)+(y_0-y_{0,b})+(y_1-y_{1,b})]x_0 \\ \frac{dx_1}{dt} &= rx_0-(d-d_2)x_1 \\ \frac{dy_0}{dt} &= -\frac{m}{K}[(x_0+x_1)+\alpha(y_0-y_{0,b})+\alpha(y_1-y_{1,b})]y_0 \\ \frac{dy_1}{dt} &= [y_1(y_0-y_{0,b})-y_0(y_1-y_{1,b})]\frac{q}{y_{1,b}} \\ \frac{dE}{dt} &= -K_0(E-E_b)-K_0E_b+\frac{a}{1+K_1x_0^{r_0}} \end{cases}
$$

To prove the global stability of blast steady state, let us construct an appropriate Lyapunov function and consider the following function V defined

by

$$V(x_0,x_1,y_0,y_1,E)=\alpha_1x_0+\frac{\alpha_2}{2}x_1^2+\alpha_3(y_0-y_{0,b}-y_{0,b}\ln\frac{y_0}{y_{0,b}}) \tag{6.6}$$
$$+\alpha_4(y_1-y_{1,b}-y_{1,b}\ln\frac{y_1}{y_{1,b}})+\alpha_5(E-E_b-E_b\ln\frac{E}{E_b})$$

where $\alpha_i, i=1,...,5$ are positive constants (that we will choose later).

Knowing that

$$\forall t>0 \quad \forall t_0>0: \quad (t-t_0)-t_0\ln\frac{t}{t_0}>0,$$

thus for all

$$(x_0,x_1,y_0,y_1,E)\in\Gamma: \quad V(x_0,x_1,y_0,y_1,E)>0$$

and also

$$V(x_0,x_1,y_0,y_1,E)=0\Leftrightarrow(x_0,x_1,y_0,y_1,E)=(x_{0,b},x_{1,b},y_{0,b},y_{1,b},E_b).$$

Moreover,

$$\frac{dV(x_0,x_1,y_0,y_1,E)}{dt}=\alpha_1\frac{dx_0}{dt}+\alpha_2x_1\frac{dx_1}{dt}+\alpha_3(\frac{y_0-y_{0,b}}{y_0})\frac{dy_0}{dt}$$
$$+\alpha_4(\frac{y_1-y_{1,b}}{y_1})\frac{dy_1}{dt}+\alpha_5(\frac{E-E_b}{E})\frac{dE}{dt}$$

and so after replacing, one has

$$\begin{aligned}\frac{dV(x_0,x_1,y_0,y_1,E)}{dt} &< -\frac{\alpha_1n}{K}x_0^2-\frac{\alpha_1n}{K}x_0x_1\\ &- \frac{\alpha_1n}{K}(y_0-y_{0,b})x_0-\frac{\alpha_1n}{K}(y_1-y_{1,b})x_0\\ &+ \alpha_2rx_0x_1-\alpha_2(d-d_2)x_0^2-\frac{\alpha_3m}{K}(y_0-y_{0,b})x_0\\ &- \frac{\alpha_3m}{K}(y_1-y_{1,b})x_1-\frac{m\alpha_3\alpha}{K}(y_0-y_{0,b})^2\\ &- \frac{m\alpha_3\alpha}{K}(y_0-y_{0,b})(y_1-y_{1,b})+\frac{\alpha_4q}{y_{1,b}}(y_0-y_{0,b})(y_1-y_{1,b})\\ &- \frac{\alpha_4q}{y_{1,b}y_1}y_0(y_1-y_{1,b})^2-K_0\alpha_5(E-E_b)^2\\ &- \frac{\alpha_5}{E}(a-\frac{a}{1+K_1x_0^{r_0}})(E-E_b).\end{aligned}$$

The coefficients α_i where $i=1,2,3,4,5$ will be chosen such that $\alpha_2r=\frac{\alpha_1n}{K}$ and $\frac{\alpha_4q}{y_{1,b}}=\frac{m\alpha\alpha_3}{K}$.

In this case,

$$\begin{aligned}\frac{dV(x_0,x_1,y_0,y_1,E)}{dt} &< -\frac{\alpha_1 n}{K}x_0^2-\alpha_2(d-d_2)x_0^2-\frac{m\alpha_3\alpha}{K}(y_0-y_{0,b})^2\\ &- \frac{\alpha_4 q}{y_{1,b}y_1}y_0(y_1-y_{1,b})^2-K_0\alpha_5(E-E_b)^2\\ &- (\frac{m\alpha_3+n\alpha_1}{K})x_0(y_0-y_{0,b})-\frac{\alpha_1 n}{K}(y_1-y_{1,b})x_0\\ &- \frac{\alpha_3 m}{K}(y_1-y_{1,b})x_1-\frac{\alpha_5 a}{Ex_0}(E-E_b)x_0\end{aligned}$$

and so

$$\begin{aligned}\frac{dV(x_0,x_1,y_0,y_1,E)}{dt} &< -\frac{\alpha_1 n}{K}x_0^2-\alpha_2(d-d_2)x_0^2-\frac{m\alpha_3\alpha}{K}(y_0-y_{0,b})^2\\ &- \frac{\alpha_4 q}{y_{1,b}y_1}y_0(y_1-y_{1,b})^2-K_0\alpha_5(E-E_b)^2\\ &+ (\frac{m\alpha_3+n\alpha_1}{K})x_0|y_0-y_{0,b}|+\frac{\alpha_1 n}{K}|y_1-y_{1,b}|x_0\\ &+ \frac{\alpha_3 m}{K}|y_1-y_{1,b}|x_1+\frac{\alpha_5 a}{Ex_0}|E-E_b|x_0\end{aligned}$$

Denote by $S=(x_0,x_1,|y_0-y_{0,b}|,|y_1-y_{1,b}|,|E-E_b|)^T$ and consider the following matrix:

$$\Pi=\begin{pmatrix} -n\alpha_1 & 0 & \frac{n\alpha_1+m\alpha_3}{K} & \frac{n\alpha_1}{2K} & \frac{a\alpha_5}{2KEx_0}\\ 0 & -\alpha_2(d-d_2) & 0 & \frac{m\alpha_3}{K} & 0\\ \frac{n\alpha_1+m\alpha_3}{K} & 0 & -\frac{m\alpha\alpha_3}{K} & 0 & 0\\ \frac{n\alpha_1}{2K} & \frac{m\alpha_3}{2K} & 0 & -\frac{\alpha_4 q y_0}{y_1 y_{1,b}} & 0\\ \frac{a\alpha_5}{2KEx_0} & 0 & 0 & 0 & -K_0\alpha_5\end{pmatrix}$$

Then

$$\frac{dV(x_0,x_1,y_0,y_1,E)}{dt}<S^T\Pi S.$$

So finally, let us choose $\alpha_1=\alpha_3=\alpha_5=2$, $n\alpha_1=m\alpha_3$, $\alpha_2=\frac{2n}{rK}$ and $\alpha_4=\frac{2m\alpha y_{1,b}}{K}$. Thus the matrix Π becomes

$$\Pi=\begin{pmatrix} -2n & 0 & \frac{2n}{K} & \frac{n}{K} & \frac{a}{Ex_0}\\ 0 & -\frac{2n}{rK}(d-d_2) & 0 & \frac{m}{K} & 0\\ \frac{2n}{K} & 0 & -\frac{2m\alpha}{K} & 0 & 0\\ \frac{n}{K} & \frac{m}{K} & 0 & -\frac{2m\alpha}{Ky_1} & 0\\ \frac{a}{Ex_0} & 0 & 0 & 0 & -2K_0\end{pmatrix}$$

and can be rewritten as $\Pi = (RW + W^T R)$, where

$$R = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & \frac{n}{rK} & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & \frac{m\alpha y_{1,b}}{qK} & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

and

$$W = \begin{pmatrix} -n & 0 & 2\frac{n}{\alpha} & \frac{y_1}{\alpha y_0} & \frac{a}{Ex_0} \\ 0 & -(d-d_2) & 0 & \frac{mr}{n} & 0 \\ 0 & 0 & -\frac{m\alpha}{k} & 0 & 0 \\ 0 & 0 & 0 & -\frac{qy_0}{y_{1,b}} & 0 \\ 0 & 0 & 0 & 0 & -K_0 \end{pmatrix}.$$

One obtains

$$-\Pi = R(-W) + (-W^T)R.$$

Since R is a diagonal matrix and $(-W)$ has all its eigenvalues negatives, thus $(-\Pi)$ is positive definite matrix and then Π is a negative definite matrix, this implies that

$$\frac{dV(x_0, x_1, y_0, y_1, E)}{dt} < 0.$$

Then, according to [29], the function V is a Lyapunov function for the system (6.4) and the blast steady state is G.A.S for scenario 3.

7. Interpretation results and some perspectives

The main results of this study are resumed in this two tables:

Steady states	Existence conditions	Stability conditions
trivial steady state	always exists	$n < d_0$ and $m < g_0$
no pathologic steady state	$n > d_0$	$T_2 > 1$
blast steady state	$m > g_0$	$T_1 < 1$
chronic steady state	$T_1 < 1 < T_2$	unstable

Table 3. Local and global stability in scenario 1 and local stability in scenario 2

In this study, we have shown that for any positive initial conditions the system (2.3) admits a unique global positive solution for scenarios 1 and 3. The trivial steady state is LAS if n and m (the proliferation rates) are lower than the mortality rates d_0 and g_0 respectively, however these conditions are clinically impracticable then the trivial balance is unstable. Furthermore, the chronic steady state being a saddle point, the coexistence of normal and

Steady states	Existence conditions	Stability conditions
trivial steady state	always exists	$n < d_0$ and $m < g_0$
no pathologic steady state	$n > d_0$	unstable
blast steady state	$m > g_0$	$T_1 < 1$
chronic steady state	$T_1 < 1 < T_2$	unstable

TABLE 4. Local and global stability in scenario 3

cancer cells does not maintain for long time and this is realist with biological observations.

The blast steady state in the third scenario is also a saddle point. Otherwise the local and global stability of the blast and no pathologic steady states is linked to coefficients T_1 and T_2:
If $T_1 > 1$ and $T_2 > 1$, the no pathologic steady state is the only stable state in this case there is no leukemia where all types of cells are in no pathological steady state therefore there is no cancer cells or their proliferation is practically zero.

If $T_1 < 1 < T_2$, the blast and no pathologic steady states are both LAS. In this case the state converges towards no pathologic steady where the number of healthy cells is higher than that corresponding to cancer cells. There may even be a conversion of cancerous cells into healthy ones or else the dynamics of our model converge towards blast steady state and cancer cells are in majority (if not all cells are diseased).

If $T_1 > 1$ and $T_2 < 1$, all steady states are unstable, it is corresponds to the final phase of leukemia.

Note that the overall stability of the steady states has been demonstrated in scenario 1 and scenario 3. The study of global stability in the scenario 2 is not possible by considering mathematical classic tools. We let it in a future work using simulations.

Biological interpretation of the results must be also developed. In parallel and in the case where the blast and no pathological steady states are LAS at the same time, a control could possibly be introduced on the growth factors so that the system converges towards the no pathological steady state, this will be also investigated in a future work.

REFERENCES

[1] M. Adimy, F. Crauste and S. Ruan, *A mathematical study of the hematopoiesis process with applications to chronic myelogenous leukemia*, SIAM J. Appl. Math. **65** (2005), 1328–1352.

[2] M. Adimy, F. Crauste, S. Bernard, J. Clairambault, S. Genieys and L. Pujo-Menjouet, *Modélisation de la dynamique de l'hématopoiese normale et pathologique*, Hematologie Revue **(14)(5)** (2008), 339–350.

[3] B. Ainsebaa and C. Benosman, *Global dynamics of hematopoietic stem cells and differentiated cells in a chronic myeloid leukemia model*, J. Math. Biol. **62(6)** (2011), 975–997.
[4] M. S. Almenshaw, I. A. Ibrahim, N. A. Khalifa and G. Z. Al-Mursy, *Angiogenic activity in chronic myeloid leukemia*, Journal of Leukemia **6(1)** (2018), 1–5.
[5] B. Appolo, Modélisation mathématique de la leucémie myéloïde chronique. Modélisation et simulation, Université de Lyon, 2017, (NNT : 2017LYSE1105).
[6] M. Askmyr, H. Agerstam, H. Lilljebjörn and al., *Modeling chronic myeloid leukemia in immunodeficient mice reveals an inflammatory state with expansion of aberrant mast cells and accumulation of Pre B cells*, Blood Cancer J. **124(21)** (2014), e269.
[7] J. Belair, M. C. Makey and J. M. Mahaffy, *Hematopoietic model with moving boundary condition and state dependant delay: Applications in erythropoiesis*, J. Theo. Biol. **190(2)** (1998), 135–146.
[8] I. Bendixson, *Sur les courbes définies pour des équations différentielles*, Acta Math. **24(1)** (1901), 1–88.
[9] C. Benosman, *Controle de la Dynamique de la Leucemie Myeloide Chronique par Imatinib*, Mathematiques [math], Univesité de Bordeaux 1, 2010.
[10] M. Bonifacio, F. Stagno, L. Scaffidi, M. Kramera and F. Di Raimondo, *Management of Chronic Myeloid Leukemia in Advanced Phase*, Frontiers in Oncology **9** (2019), Article 1132.
[11] M. Bouizem, B. Ainseba and A. Lakmeche, *Mathematical analysis of an age structured leukemia model*, Comm. Appl. Nonlinear Anal. **25(2)** (2018), 1–20.
[12] S. N. Cathir, P. Guttorp and J. L. Abkowitz, *The kinetics of clonal dominance in myeloproliferative disorders blood*, Blood **106(8)** (2005), 2688–2692.
[13] G. D. Clapp, T. Lepoutre, R. Echeikh and E. Bernards, *Implication of the autologous immune system in BCR-ABL transcript variations in chronic myelogenous leukemia patients treated with Imatinib*, Cancer Res. **75(19)** (2015), 4053–4062.
[14] C. Colijn and M. C. Mackey, *A mathematical model of hematopoiesis. II. Cyclical neutropenia*, J. Theoret. Biol. **237(2)** (2005), 133–146.
[15] D. Dingli and F. Michor, *Succesfull therapy must eradicate cancer stem cells*, Stem Cells **24(12)** (2006), 2603–2610.
[16] H. Dulac, *Sur les cycles limites*, Bull. Soc. Math. France **51** (1923), 45–188.
[17] R. Duval, L.-C. Bui, C. Mathieu and al., *Benzoquinone, a leukemogenic metabolite of benzene, catalytically inhibits the protein tyrosine phosphatase PTPN2 and alters STAT signaling*, J. Biol. Chem. **294(33)** (2019), 12483–12494.
[18] L. Han and A. Pugliese, *Epidemics in two competing species*, Nonlinear Anal. Real World Appl. **10** (2009), 723–744.
[19] R. Hehlmann, Chronic Myeloid Leukemia, Springer, 2018.
[20] M. Helal, A. Lakmeche and F. Souna, *Chronic myeloid leukemia model with periodic pulsed teatment*, ARIMA Rev. Afr. Rech. Inform. Math. Appl. 30 (2019), 123–144.
[21] R. A. Horn and C. R. Johnson, Matrix analysis, Cambridge University Press, 1985.
[22] M. Houshmand, G. Simonetti, P. Circosta and al., *Chronic myeloid leukemia stem cells*, Leukemia **33(7)** (2019), 1543–1556.
[23] E. Jabbour and H. Kantarjian, *Chronic Myeloid Leukemia: 2020 update on diagnosis, therapy and monitoring*, American Journal of Hematology **95(6)** (2020), 691–709.
[24] H. K. Khalil, Nonlinear Systems, Third edition, Prentice Hall, 2002.
[25] N. L. Komarova and D. Wodarz, *Effect of cellular quiescence on the success of targeted CML therapy*, PLoS One **2(10)** (2007), e990.
[26] M. C. Mackey, *Mathematical models of hematopoietic cell replication and control*, in: The Art of Mathematical Modelling: Case Studies in Ecology, Physiology and Biofluids, Prentice Hall, 1997, pp. 149–178.

[27] F. Michor, T. P. Hughes, Y. Iwasa, S. Branford, N. P. Shah, C. L. Sawyers and M. A. Nowack, *Dynamics of chronic myeloïd leukemia*, Nature **435** (2005), 1267–1270.
[28] J. Murray, Mathematical Biology: I. An Introduction, Third edition, Springer Science Busines Media, New York, 2011.
[29] P. C. Parks, *A. M. Lyapunov's stability theory – 100 years on*, IMA J. Math. Control Inform. **9(4)** (1992), 275–303.
[30] J. N. Poston and P. S. Becker, *Controversies regarding use of myeloid growth factors in leukemia*, J Natl Compr Canc Netw **15(12)** (2017), 1551–1557.
[31] I. Roeder, M. Herberg and M. Horn, *An "age"-structured model of hematopoietic stem cells organization with application to chronic myeloid leukemia*, Bull. Math. Biol. **71(3)** (2009), 602–626.
[32] N. Takahashi, *Chronic myeloid leukemia: State of the art management*, Rinsho Ketsueki **59(6)** (2018), 747–754.

Matematicka analiza modela kronične mijeloične leukemije

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Sažetak. U ovom članku razmatra se matematička analiza modela koji opisuje evoluciju kronične mijeloične leukemije s učinkom faktora rasta. Odgovarajuća dinamika predstavljena je sustavom običnih diferencijalnih jednadžbi dimenzije 5. Ovaj sustav opisuje interakcije između hematopoetskih matičnih stanica (H.S.C), hematopoetskih zrelih stanica (M.C), hematopoetskih matičnih stanica raka, zrelih hematopoetskih stanica raka i povezane koncentracije faktora rasta. Naše istraživanje se bavi postojanjem i jedinstvenošću rješenja ovog sustava. Sljedeća suštinska tema bit će rasprava o lokalnoj i globalnoj stabilnosti odgovarajućih stabilnih stanja. Razmatraju se tri scenarija koja odgovaraju različitim djelovanjima hematopoeze na matične stanice (diferencirane stanice ili obje stanice).

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Received: 17.9.2020.
Revised: 14.1.2021.; 9.2.2021.
Accepted: 16.3.2021.