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Hybrid mathematical model of Leukemic diseases with resistance

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Abstract

The main objective of this paper is to examine an hybrid mathematical model that addresses leukemia diseases with resistance. Initially, we construct the foundational model comprising three equations, with one accounting for age structure and the others representing ordinary differential equations. Subsequently, we delve into understanding the behavior of our solutions by investigating the existence and stability of steady states. To validate our findings, we conduct some numerical simulations.

Key words: Chronic myeloid leukemia, Resistance model, Partial differential equation, Ordinary differential equation, Steady states, Local stability, Numerical simulations.

1 Introduction

To understand the dynamics of Chronic Myeloid Leukemia (CML) many studies have been conducted. In [14], the authors consider an hybrid mathematical model of CML as follow

$$\begin{cases} \dfrac{\partial u_1(t,a)}{\partial t} + \dfrac{\partial u_1(t,a)}{\partial a} = -\mu_1(a)u_1(t,a), & (t,a) \in (0,T) \times (0,A), \\ \dfrac{du_2}{dt} = \left[m\psi(U_1(t) + \alpha u_2(t)) - g_0\right] u_2(t), & t \in [0,T], \\ u_1(t,0) = \displaystyle\int_0^A \tilde{\varphi}_1 \left(a, k_1 \left[\int_0^A u_1(t,a)\,\mathrm{d}a + u_2(t)\right]\right) u_1(t,a)\,\mathrm{d}a, & t \in [0,T], \\ u_1(0,a) = \phi_1(a), & a \in [0,A], \\ u_2(0) = \phi_2, & \end{cases} \tag{1}$$

where

$u_1(t,a)$: size of normal stem cells at time $t \in (0,T)$ and age $a \in (0,A)$.

$u_2(t)$: size of leukemia stem cells at time $t \in (0,T)$.

$U_1(t) = \displaystyle\int_0^A u_1(t,a)\,\mathrm{d}a$, denote the total size of normal stem cells.

$\phi_1(a)$: initial condition of normal stem cells.

ϕ_2: initial condition of leukemia stem cells.

$\mu_1(a)$: death rate of normal stem cells.

g_0: death rate of leukemia stem cells.

m: division rate of leukemia stem cells.

Depending on Hill functional, the homeostasis of normal and leukemic stem cells are achieved by the following equations (see [6], [11] and [1])

$$\tilde{\varphi}_1\left(a, k_1\left[\int_0^A u_1(t,a)\,\mathrm{d}a + u_2(t)\right]\right) = \frac{\theta^n \varphi_1(a)}{\theta^n + \left(k_1\left[\int_0^A u_1(t,a)\,\mathrm{d}a + u_2(t)\right]\right)^n},$$

and

$$\psi(U_1(t) + \alpha u_2(t)) = \frac{1}{1 + c\,(U_1(t) + \alpha u_2(t))^n},$$

where

$\varphi_1(a)$: division rate for normal stem cells.

k_1: coefficient of interaction.

α: competition parameter between normal and leukemic stem cells with values in $]0,1[$([2], [3], [8] and [9]).

θ: crowding effect ([11] and [12]).

c: dimensionless parameter.

In [5], the authors establish the following age structured model of leukemic diseases with resistance,

$$\begin{cases}
\dfrac{\partial u_1(t,a)}{\partial t} + \dfrac{\partial u_1(t,a)}{\partial a} = -\mu_1(a)u_1(t,a), & (t,a) \in (0,T)\times(0,A),\\[2ex]
\dfrac{\partial u_2(t,a)}{\partial t} + \dfrac{\partial u_2(t,a)}{\partial a} = -\mu_2(a)u_2(t,a), & (t,a) \in (0,T)\times(0,A),\\[2ex]
\dfrac{\partial u_3(t,a)}{\partial t} + \dfrac{\partial u_3(t,a)}{\partial a} = -\mu_3(a)u_3(t,a), & (t,a) \in (0,T)\times(0,A),\\[2ex]
u_1(t,0) = \displaystyle\int_0^A \tilde{\varphi}_1\left(a, k_1 \int_0^A [u_1(t,a) + u_2(t,a)]\,\mathrm{d}a\right) u_1(t,a)\,\mathrm{d}a, & t \in [0,T],\\
u_2(t,0) = \displaystyle\int_0^A \tilde{\varphi}_2\left(a, k_2 \int_0^A [u_1(t,a) + \alpha u_2(t,a)]\,\mathrm{d}a\right) u_2(t,a)\,\mathrm{d}a, & t \in [0,T],\\
u_3(t,0) = \displaystyle\int_0^A \tilde{\varphi}_2\left(a, k_3 \int_0^A [u_1(t,a) + \alpha u_3(t,a)]\,\mathrm{d}a\right) u_2(t,a)\,\mathrm{d}a, & t \in [0,T],\\
u_1(0,a) = \phi_1(a), & a \in [0,A],\\
u_2(0,a) = \phi_2(a), & a \in [0,A],\\
u_3(0,a) = \phi_3(a), & a \in [0,A],
\end{cases} \tag{2}$$

Inspired by the models (1) and (2), we are interested in the study of an hybrid mathematical model of chronic myeloid leukemia diseases with resistance using the following system

$$\begin{cases} \dfrac{\partial u_1(t,a)}{\partial t} + \dfrac{\partial u_1(t,a)}{\partial a} = -\mu_1(a) u_1(t,a), & (t,a) \in (0,T) \times (0,A), \\ \\ \dfrac{du_2}{dt} = \left[m_0 \psi_0 (U_1(t) + \alpha u_2(t) + \alpha u_3(t)) - g_0 \right] u_2(t), & t \in [0,T], \\ \\ \dfrac{du_3}{dt} = \left[m_1 \psi_1 (U_1(t) + \alpha u_2(t) + \delta u_3(t) - g_1 \right] u_3(t), & t \in [0,T], \\ \\ u_1(t,0) = \displaystyle\int_0^A \tilde{\varphi}_1 \left(a, k_1 \left[\int_0^A u_1(t,a)\,\mathrm{d}a + u_2(t) + u_3(t) \right] \right) u_1(t,a)\,\mathrm{d}a, & t \in [0,T], \\ u_1(0,a) = \phi_1(a), & a \in [0,A], \\ u_2(0) = \phi_2, \\ u_3(0) = \phi_3, \end{cases} \tag{3}$$

where

$u_1(t,a)$: size of normal stem cells at time $t \in (0,T)$ and age $a \in (0,A)$.

$u_2(t)$: size of leukemia stem cells at time $t \in (0,T)$.

$u_3(t)$: size of resistance stem cells at time $t \in (0,T)$.

$U_1(t) = \displaystyle\int_0^A u_1(t,a)\,\mathrm{d}a$: total size of normal stem cells.

$\phi_1(a)$: initial condition of normal stem cells.

ϕ_2: initial condition of leukemia stem cells.

ϕ_3: initial condition of resistance stem cells.

$\mu_1(a)$: death rate of normal stem cells.

g_0: death rate of leukemia stem cells.

g_1: death rate of resistance stem cells.

m_0: rate division of leukemia stem cells.

m_1: rate division of resistance stem cells.

Depending on Hill functional, the homeostasis of normal and leukemic stem cells are achieved by the following equations (see [6], [11] and [1])

$$\tilde{\varphi}_1 \left(a, k_1 \left[\int_0^A u_1(t,a)\,\mathrm{d}a + u_2(t) + u_3(t) \right] \right) = \frac{\theta^n \varphi_1(a)}{\theta^n + \left(k_1 \left[\int_0^A u_1(t,a)\,\mathrm{d}a + u_2(t) + u_3(t) \right] \right)^n},$$

$$\psi_0(U_1(t) + \alpha u_2(t) + \alpha u_3(t)) = \frac{1}{1 + c_0 \left(U_1(t) + \alpha u_2(t) + \alpha u_3(t) \right)^n},$$

and

$$\psi_1(U_1(t) + \alpha u_2(t) + \delta u_3(t)) = \frac{1}{1 + c_1\left(U_1(t) + \alpha u_2(t) + \delta u_3(t)\right)^n},$$

where

$\varphi_1(a)$: division rate for normal stem cells.

k_1: coefficient of interaction.

α, δ: competition parameters between normal, leukemic and resistance stem cells with values in $]0,1[$ ([2], [3], [8] and [9]).

θ: crowding effect ([11] and [12]).

c_0, c_1: dimensionless parameters.

In ([2], [10], [13], [7] and [4]), the authors have already proved the existence of a global solution by specifying the conditions of the parameters in (3).

The structure of the paper is outlined as follows: Firstly, we analyze the model (3) by examining its steady states. Secondly, we investigate the stability of these steady states. Finally, we present simulations and draw conclusions based on our findings.

2 Existence of steady states

In this section, we analyse the existence of the steady states of (3), which will be given by $E_j = u(a) = (u_1(a), u_2^*, u_3^*)$, for $j = 0, ..., 7$.

From the second equation of (3), we have

$$\left[\frac{m_0}{1 + c_0\left(\displaystyle\int_0^A u_1(a)\,\mathrm{d}a + \alpha u_2^* + \alpha u_3^*\right)^n} - g_0\right] u_2^* = 0. \tag{4}$$

Then, we obtain either

$$u_2^* = 0 \text{ or } u_2^* = \frac{1}{\alpha}\left(\sqrt[n]{\frac{m_0 - g_0}{c_0\ g_0}} - U_1^* - \alpha u_3^*\right),$$

where $U_1^* = \displaystyle\int_0^A u_1(a)\,\mathrm{d}a$ and $0 \le U_1^* < \sqrt[n]{\dfrac{m_0 - g_0}{c_0\ g_0}} - \alpha u_3^*$.

On the other hand, the third equation of (3) gives,

$$\left[\frac{m_1}{1 + c_1\left(\displaystyle\int_0^A u_1(a)\,\mathrm{d}a + \alpha u_2^* + \delta u_3^*\right)^n} - g_1\right] u_3^* = 0. \tag{5}$$

Then, either

$$u_3^* = 0 \text{ or } u_3^* = \frac{1}{\delta}\left(\sqrt[n]{\frac{m_1 - g_1}{c_1 \ g_1}} - U_1^* - \alpha u_2^*\right),$$

where $0 \leq U_1^* < \sqrt[n]{\dfrac{m_1 - g_1}{c_1 g_1}} - \alpha u_2^*$.

Finally, from the first equation of (3), we have

$$\frac{du_1}{da} = -\mu_1(a)u_1(a), \tag{6}$$

Then,

$$u_1(a) = u_1(0)\pi_1(a),$$

where

$$u_1(0) = \int_0^A \left(\frac{\theta^n \varphi_1(a) u_1(a)}{\theta^n + \left(k_1 \left[\int_0^A u_1(a)\,\mathrm{d}a + u_2^* + u_3^*\right]\right)^n} \right) \mathrm{d}a \tag{7}$$

and $\pi_1(a) = e^{-\int_0^a \mu_1(s)ds}$ is the survival probability. Let

$$b_0 = \sqrt[n]{\frac{m_0 - g_0}{c_0 \ g_0}}, \quad b_1 = \sqrt[n]{\frac{m_1 - g_1}{c_1 \ g_1}} \quad \text{and} \quad L_1 = \int_0^A \pi_1(a)\,\mathrm{d}a.$$

We have the following cases.

1. If $u_1(0) = 0$ and $u_2^* = u_3^* = 0$, then the trivial steady state $E_0(0, 0, 0)$ exists always.
2. If $u_1(0) = 0$ and $u_2^* = 0$, then the blast steady state $E_1(0, 0, \dfrac{b_1}{\delta})$ exists when $m_1 > g_1$.
3. If $u_1(0) = 0$ and $u_3^* = 0$, then the blast steady state $E_2(0, \dfrac{b_0}{\alpha}, 0)$ exists when $m_0 > g_0$.
4. If $u_1(0) = 0$, $u_2^* \neq 0$ and $u_3^* \neq 0$, then the blast steady state $E_3\left(0, \dfrac{\delta b_0 - \alpha b_1}{\alpha(\delta - \alpha)}, \dfrac{b_1 - b_0}{\delta - \alpha}\right)$ exists when $m_1 > g_1$ and $\left(\dfrac{c_0}{\delta^n} \min\left(\alpha^n, \delta^n\right) b_1^n + 1\right) g_0 < m_0 < \left(\dfrac{c_0}{\delta^n} \max\left(\alpha^n, \delta^n\right) b_1^n + 1\right) g_0$
5. If $u_2^* = 0$, $u_1(0) \neq 0$ and $u_3^* \neq 0$, then from (7) we have

$$1 = \int_0^A \left(\frac{\theta^n \varphi_1(a) \pi_1(a)}{\theta^n + \left(k_1 \left[u_1(0)L_1 + \frac{b_1}{\delta} - \frac{u_1(0)L_1}{\delta}\right]\right)^n} \right) \mathrm{d}a. \tag{8}$$

Let $R_1 = \displaystyle\int_0^A \varphi_1(a)\pi_1(a)\,\mathrm{d}a$ is the net reproduction rate. Equation (8) is equivalent to

$$u_1(0) = \frac{\delta\theta_1 \sqrt[n]{R_1 - 1} - b_1}{L_1(\delta - 1)}, \tag{9}$$

where $\theta_1 = \dfrac{\theta}{k_1}$.

Therefore, the chronic steady state $E_4\left(\dfrac{\delta\theta_1\sqrt[n]{R_1-1}-b_1}{L_1(\delta-1)}\pi_1(a), 0, \dfrac{b_1-\theta_1\sqrt[n]{R_1-1}}{\delta-1}\right)$ exists when $m_1 > g_1$ and $\left(\dfrac{b_1}{\theta_1}\right)^n + 1 < R_1 < \left(\dfrac{b_1}{\delta\theta_1}\right)^n + 1$.

6. If $u_3^* = 0$, $u_1(0) \neq 0$ and $u_2^* \neq 0$, then equation (7) gives

$$1 = \int_0^A \left(\frac{\theta^n \varphi_1(a)\pi_1(a)}{\theta^n + \left(k_1\left[u_1(0)L_1 + \dfrac{1}{\alpha}(b_0 - u_1(0)L_1)\right]\right)^n}\right) \mathrm{d}a. \tag{10}$$

Equation (10) is equivalent to $u_1(0) = \dfrac{\alpha\theta_1\sqrt[n]{R_1-1}-b_0}{L_1(\alpha-1)}$.

Therefore, the chronic steady state $E_5\left(\dfrac{\alpha\theta_1\sqrt[n]{R_1-1}-b_0}{L_1(\alpha-1)}\pi_1(a), \dfrac{b_0-\theta_1\sqrt[n]{R_1-1}}{\alpha-1}, 0\right)$ exists when $m_0 > g_0$ and $\left(\dfrac{b_0}{\theta_1}\right)^n + 1 < R_1 < \left(\dfrac{b_0}{\alpha\theta_1}\right)^n + 1$.

7. If $u_2^* = 0$, $u_3^* = 0$ and $u_1(0) \neq 0$, then equation (7) gives

$$1 = \int_0^A \left(\frac{\theta^n \varphi_1(a)\pi_1(a)}{\theta^n + (k_1 u_1(0) L_1)^n}\right) \mathrm{d}a. \tag{11}$$

Then,

$$u_1(0) = \frac{\theta_1\sqrt[n]{R_1-1}}{L_1}. \tag{12}$$

That is, the nonpathological steady state $E_6 = (\dfrac{\theta_1\sqrt[n]{R_1-1}}{L_1}\pi_1(a), 0, 0)$ exists when $R_1 > 1$.

8. If $u_1(0) \neq 0$, $u_2^* \neq 0$ and $u_3^* \neq 0$, then we have

$$u_2^* + u_3^* = \frac{1}{\alpha}\left(b_0 - u_1(0)L_1\right), \tag{13}$$

and

$$\alpha u_2^* + \delta u_3^* = b_1 - u_1(0)L_1, \tag{14}$$

where

$$u_1(0) = \frac{\alpha\theta_1\sqrt[n]{R_1-1}-b_0}{L_1(\alpha-1)}. \tag{15}$$

Then, equations (13) and (14) gives

$$u_3^* = \frac{b_1-b_0}{\delta-\alpha}, \tag{16}$$

and

$$u_2^* = \frac{(\delta-\alpha)\theta_1\sqrt[n]{R_1-1} + (1-\delta)b_0 - (1-\alpha)b_1}{(1-\alpha)(\delta-\alpha)}. \tag{17}$$

Therefore, the chronic steady state $E_7 = \left(\frac{\alpha\theta_1 \sqrt[n]{R_1 - 1} - b_0}{L_1(\alpha - 1)} \pi_1(a), u_2^*, \frac{b_1 - b_0}{\delta - \alpha} \right)$ exists when $m_1 > g_1$, $\left(\frac{c_0}{\delta^n} \min(\alpha^n, \delta^n) b_1^n + 1 \right) g_0 < m_0 < \left(\frac{c_0}{\delta^n} \max(\alpha^n, \delta^n) b_1^n + 1 \right) g_0$ and $\left(\frac{(1-\alpha)b_1 - (1-\delta)b_0}{(\delta - \alpha)\theta_1} \right)^n + 1 < R_1 < \left(\frac{b_0}{\alpha\theta_1} \right)^n + 1$.

In conclusion, we have the following theorem.

Theorem 2.1. *The system (3) admits the following steady states.*

1. *The trivial steady state E_0 exists always.*
2. *If $m_1 > g_1$, then the blast steady state E_1 exists.*
3. *If $m_0 > g_0$, then the blast steady state E_2 exists.*
4. *If $m_1 > g_1$ and $\left(\frac{c_0}{\delta^n} \min(\alpha^n, \delta^n) b_1^n + 1 \right) g_0 < m_0 < \left(\frac{c_0}{\delta^n} \max(\alpha^n, \delta^n) b_1^n + 1 \right) g_0$, then the blast steady state E_3 exists.*
5. *If $m_1 > g_1$ and $\left(\frac{b_1}{\theta_1} \right)^n + 1 < R_1 < \left(\frac{b_1}{\delta\theta_1} \right)^n + 1$, then the chronic steady state E_4 exists.*
6. *If $m_0 > g_0$ and $\left(\frac{b_0}{\theta_1} \right)^n + 1 < R_1 < \left(\frac{b_0}{\alpha\theta_1} \right)^n + 1$, then the chronic steady state E_5 exists.*
7. *If $R_1 > 1$, then the nonpathological steady state E_6 exists.*
8. *If $m_1 > g_1$, $\left(\frac{c_0}{\delta^n} \min(\alpha^n, \delta^n) b_1^n + 1 \right) g_0 < m_0 < \left(\frac{c_0}{\delta^n} \max(\alpha^n, \delta^n) b_1^n + 1 \right) g_0$ and $\left(\frac{(1-\alpha)b_1 - (1-\delta)b_0}{(\delta - \alpha)\theta_1} \right)^n + 1 < R_1 < \left(\frac{b_0}{\alpha\theta_1} \right)^n + 1$, then the chronic steady state E_7 exists.*

3 Local stability of steady states

In this section, we study the local stability of steady states which is based on the linearization (see [5], [10], [13]) of the system (3). Let

$$\begin{cases} x_1(t,a) = u_1(t,a) - u_1(a), \\ x_2(t) = u_2(t) - u_2^*, \\ x_3(t) = u_3(t) - u_3^*, \end{cases} \tag{18}$$

where $(u_1(a), u_2^*, u_3^*)$ is one of the steady states of (3).

We derive the first equation of (18), so we obtain the following equation

$$\frac{\partial x_1}{\partial t}(t,a) + \frac{\partial x_1}{\partial a}(t,a) = -\mu_1(a)x_1(t,a), \tag{19}$$

with the boundary condition

$$x_1(t,0) = u_1(t,0) - u_1(0). \tag{20}$$

From (3), we have

$$\begin{aligned} u_1(t,0) &= \int_0^A \tilde{\varphi}_1\left(a, k_1\left[\int_0^A u_1(t,a)\mathrm{d}a + u_2(t) + u_3(t)\right]\right) u_1(t,a)\mathrm{d}a \\ &= \int_0^A \tilde{\varphi}_1\left(a, k_1\left[X_1(t) + U_1^* + x_2(t) + u_2^* + x_3(t) + u_3^*\right]\right)\left(x_1(t,a) + u_1(a)\right)\mathrm{d}a \\ &= \int_0^A \tilde{\varphi}_1\left(a, X(t) + \tilde{U}\right)\left(x_1(t,a) + u_1(a)\right)\mathrm{d}a, \end{aligned}$$

where $X(t) = k_1\left(X_1(t) + x_2(t) + x_3(t)\right)$, $\tilde{U} = k_1\left(U_1^* + u_2^* + u_3^*\right)$ and $X_1(t) = \displaystyle\int_0^A x_1(t,a)\,\mathrm{d}a$.
Moreover,

$$\begin{aligned} \tilde{\varphi_1}(a, X(t) + \tilde{U})(x_1(t,a) + u_1(a)) &= \left[\tilde{\varphi_1}(a,\tilde{U}) + \frac{\partial\tilde{\varphi_1}}{\partial\tilde{U}}X(t) + o(X(t))\right](x_1(t,a) + u_1(a)) \\ &= \tilde{\varphi_1}(a,\tilde{U})x_1(t,a) + \tilde{\varphi_1}(a,\tilde{U})u_1(a) + \frac{\partial\tilde{\varphi_1}}{\partial\tilde{U}}X(t)x_1(t,a) \\ &\quad + \frac{\partial\tilde{\varphi_1}}{\partial\tilde{U}}X(t)u_1(a) + o(X(t)). \end{aligned}$$

On the other hand, we have

$$u_1(0) = \int_0^A \tilde{\varphi_1}(a,\tilde{U})u_1(a)\,\mathrm{d}a.$$

Then, the linearized equation of (20) at $(0,0,0)$ is

$$x_1(t,0) = \int_0^A \tilde{\varphi_1}(a,\tilde{U})x_1(t,a)\,\mathrm{d}a + X(t)\int_0^A \frac{\partial\tilde{\varphi_1}}{\partial\tilde{U}}u_1(a)\,\mathrm{d}a \tag{21}$$

Now, we derive the second equation of (18)

$$\begin{aligned} \frac{dx_2}{dt} &= \left[\frac{m_0}{1 + c_0(X_1(t) + U_1^* + \alpha x_2(t) + \alpha u_2^* + \alpha x_3(t) + \alpha u_3^*)^n} - g_0\right](x_2(t) + u_2^*) \\ &= \frac{m_0 x_2(t)}{1 + c_0(X_1(t) + U_1^* + \alpha x_2(t) + \alpha u_2^* + \alpha x_3(t) + \alpha u_3^*)^n} - g_0 x_2(t) \\ &\quad + \frac{m_0 u_2^*}{1 + c_0(X_1(t) + U_1^* + \alpha x_2(t) + \alpha u_2^* + \alpha x_3(t) + \alpha u_3^*)^n} - g_0 u_2^*. \end{aligned}$$

Let $\dfrac{dx_2}{dt} = f(X_1(t), x_2(t), x_3(t))$.
By a Taylor development of the function $f_1(X_1(t), x_2(t), x_3(t)$ at (0,0,0) we have

$$\begin{aligned} \frac{dx_2}{dt} &= -\frac{n m_0 u_2^* c_0(U_1^* + \alpha u_2^* + \alpha u_3^*)^{n-1}}{[1 + c_0(U_1^* + \alpha u_2^* + \alpha u_3^*)^n]^2}(X_1(t) + \alpha x_3(t)) \\ &\quad + \left[\frac{m_0}{(1 + c_0(U_1^* + \alpha u_2^* + \alpha u_3^*)^n)} - \frac{n m_0 u_2^* \alpha c_0(U_1^* + \alpha u_2^* + \alpha u_3^*)^{n-1}}{(1 + c_0(U_1^* + \alpha u_2^* + \alpha u_3^*)^n)^2} - g_0\right]x_2(t) \\ &= A_1(X_1(t) + \alpha x_3(t)) + A_2 x_2(t), \end{aligned}$$

where

$A_1 = \dfrac{-nm_0u_2^*c_0(U_1^*+\alpha u_2^*+\alpha u_3^*)^{n-1}}{[1+c_0(U_1^*+\alpha u_2^*+\alpha u_3^*)^n]^2}$ and

$A_2 = \dfrac{m_0}{(1+c_0(U_1^*+\alpha u_2^*+\alpha u_3^*)^n)} - \dfrac{nm_0u_2^*\alpha c_0(U_1^*+\alpha u_2^*+\alpha u_3^*)^{n-1}}{(1+c_0(U_1^*+\alpha u_2^*+\alpha u_3^*)^n)^2} - g_0.$

Now, we derive the third equation of (18) we obtain

$$\begin{aligned}\frac{dx_3}{dt} &= \left[\frac{m_1}{1+c_1(X_1(t)+U_1^*+\alpha x_2(t)+\alpha u_2^*+\delta x_3(t)+\delta u_3^*)^n} - g_1\right](x_3(t)+u_3^*)\\ &= \frac{m_1x_3(t)}{1+c_1(X_1(t)+U_1^*+\alpha x_2(t)+\alpha u_2^*+\delta x_3(t)+\delta u_3^*)^n} - g_1x_3(t)\\ &\quad+\frac{m_1u_3^*}{1+c_1(X_1(t)+U_1^*+\alpha x_2(t)+\alpha u_2^*+\delta x_3(t)+\delta u_3^*)^n} - g_1u_3^*.\end{aligned}$$

Let $\dfrac{dx_3}{dt} = f_2(X_1(t), x_2(t), x_3(t))$.

By a Taylor development of the function $f_2(X_1(t), x_2(t), x_3(t)$ at point $(0,0,0)$ we obtain

$$\begin{aligned}\frac{dx_3}{dt} &= -\frac{nm_1u_3^*c_1(U_1^*+\alpha u_2^*+\delta u_3^*)^{n-1}}{[1+c_1(U_1^*+\alpha u_2^*+\delta u_3^*)^n]^2}(X_1(t)+\alpha x_2(t))\\ &\quad+\left[\frac{m_1}{(1+c_1(U_1^*+\alpha u_2^*+\delta u_3^*)^n)} - \frac{nm_1u_3^*\delta c_1(U_1^*+\alpha u_2^*+\delta u_3^*)^{n-1}}{(1+c_1(U_1^*+\alpha u_2^*+\delta u_3^*)^n)^2} - g_1\right]x_3(t)\\ &= A_3(X_1(t)+\alpha x_2(t)) + A_4x_3(t),\end{aligned}$$

where

$A_3 = \dfrac{-nm_1u_3^*c_1(U_1^*+\alpha u_2^*+\delta u_3^*)^{n-1}}{[1+c_1(U_1^*+\alpha u_2^*+\delta u_3^*)^n]^2}$ and

$A_4 = \dfrac{m_1}{(1+c_1(U_1^*+\alpha u_2^*+\delta u_3^*)^n)} - \dfrac{nm_1u_3^*\delta c_1(U_1^*+\alpha u_2^*+\delta u_3^*)^{n-1}}{(1+c_1(U_1^*+\alpha u_2^*+\delta u_3^*)^n)^2} - g_1.$

Then the linearized system of (3) at $u(a)$ is

$$\begin{cases}\dfrac{\partial x_1}{\partial t}(t,a)+\dfrac{\partial x_1}{\partial a}(t,a) = -\mu_1(a)x_1(t,a), & (t,a)\in(0,T)\times(0,A),\\ X(t) = k_1\left(X_1(t)+x_2(t)+x_3(t)\right), & t\in[0,T],\\ x_1(t,0) = \displaystyle\int_0^A \tilde{\varphi}_1(a,\tilde{U})x_1(t,a)\,\mathrm{d}a + X(t)\int_0^A \frac{\partial\tilde{\varphi}_1}{\partial\tilde{U}}u_1(a)\,\mathrm{d}a, & t\in[0,T],\\ \dfrac{dx_2}{dt} = A_1X_1(t)+A_2x_2(t)+\alpha A_2x_3(t), & t\in[0,T],\\ \dfrac{dx_3}{dt} = A_3X_1(t)+\alpha A_3x_2(t)+A_4x_3(t), & t\in[0,T].\end{cases} \tag{22}$$

We are looking for solutions in the form $x_1(t,a) = f_1(a)e^{\lambda t}$, $x_2(t) = f_2e^{\lambda t}$ and $x_3(t) = f_3e^{\lambda t}$, where $f_1(a) > 0$, $f_2 > 0$, $f_3 > 0$ and $\lambda\in\mathbb{C}$.

From (22), we obtain

$$\begin{cases} \dfrac{df_1}{da}+(\lambda+\mu_1(a))\,f_1(a)=0,\\ f_1(a)=f_1(0)e^{-\int_0^a(\lambda+\mu_1(s))\,\mathrm{d}s},\\ F_1=\displaystyle\int_0^A f_1(a)\,\mathrm{d}a,\\ f_1(0)=\displaystyle\int_0^A\tilde{\varphi}_1(a,\tilde{U})f_1(a)\,\mathrm{d}a+k_1\left[F_1+f_2+f_3\right]\int_0^A\frac{\partial\tilde{\varphi}_1}{\partial\tilde{U}}(a,\tilde{U})u_1(a)\,\mathrm{d}a,\\ (\lambda-A_2)f_2-A_1F_1-A_3f_3=0,\\ (\lambda-A_6)f_3-A_4F_1-A_5f_2=0. \end{cases} \tag{23}$$

From the fourth equation of (23) we have

$$\begin{aligned} f_1(0) &= \int_0^A\tilde{\varphi}_1(a,\tilde{U})f_1(a)\mathrm{d}a+k_1\left[\int_0^A f_1(a)\mathrm{d}a+f_2+f_3\right]\int_0^A\frac{\partial\tilde{\varphi}_1}{\partial\tilde{U}}(a,\tilde{U})u_1(a)\mathrm{d}a\\ &= \int_0^A\tilde{\varphi}_1(a,\tilde{U})f_1(0)e^{-\int_0^a(\lambda+\mu_1(s))\mathrm{d}s}\mathrm{d}a\\ &\quad +k_1\left[\int_0^A f_1(0)e^{-\int_0^a(\lambda+\mu_1(s))\mathrm{d}s}\mathrm{d}a+f_2+f_3\right]\int_0^A\frac{\partial\tilde{\varphi}_1}{\partial\tilde{U}}(a,\tilde{U})u_1(a)\mathrm{d}a\\ &= f_1(0)\int_0^A\tilde{\varphi}_1(a,\tilde{U})e^{-\int_0^a(\lambda+\mu_1(s))\mathrm{d}s}\mathrm{d}a\\ &\quad +\left[k_1f_1(0)\int_0^A e^{-\int_0^a(\lambda+\mu_1(s))\mathrm{d}s}\mathrm{d}a+k_1f_2+k_1f_3\right]\int_0^A\frac{\partial\tilde{\varphi}_1}{\partial\tilde{U}}(a,\tilde{U})u_1(a)\mathrm{d}a. \end{aligned}$$

Let $H_1=\int_0^A\frac{\partial\tilde{\varphi}_1}{\partial\tilde{U}}(a,\tilde{U})u_1(a)\,\mathrm{d}a$ and $K_1(a)=\tilde{\varphi}_1(a,\tilde{U})\pi_1(a)$, then we obtain

$$f_1(0)=f_1(0)\int_0^A K_1(a)e^{-\lambda a}\,\mathrm{d}a+k_1f_1(0)H_1\int_0^A e^{-\lambda a}\pi_1(a)\,\mathrm{d}a+k_1f_2H_1+k_1f_3H_1. \tag{24}$$

The integral in the equation (24) can be extended by zero to infinity, this leads that

$$\hat{K}_1(\lambda)=\int_0^\infty K_1(a)e^{-\lambda a}\mathrm{d}a,\ \text{and}\ \hat{\pi}_1(\lambda)=\int_0^\infty e^{-\lambda a}\pi_1(a)\mathrm{d}a,$$

denote respectively the Laplace transform of $K_1(a)$ and $\pi_1(a)$.

Then equation (24) is equivalent to

$$f_1(0)[1-(\hat{K}_1(\lambda)+k_1H_1\hat{\pi}_1(\lambda))]-k_1H_1f_2-k_1H_1f_3=0. \tag{25}$$

From (25), and the two last equation of (23), we obtain the following system

$$\begin{cases} f_1(0)[1-(\hat{K}_1(\lambda)+k_1H_1\hat{\pi}_1(\lambda))]-k_1H_1f_2-k_1H_1f_3=0, \\ (\lambda-A_2)f_2-A_1f_1(0)\hat{\pi}_1(\lambda)-\alpha A_1f_3=0, \\ (\lambda-A_4)f_3-A_3f_1(0)\hat{\pi}_1(\lambda)-\alpha A_3f_2=0. \end{cases} \tag{26}$$

System (26) is written in the following matrix

$$A(\lambda)\begin{pmatrix} f_1(0) \\ f_2 \\ f_3 \end{pmatrix}=\begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix},$$

where

$$A(\lambda)=\begin{pmatrix} 1-(\hat{K}_1(\lambda)+k_1H_1\hat{\pi}_1(\lambda)) & -k_1H_1 & -k_1H_1 \\ -A_1\hat{\pi}_1(\lambda) & \lambda-A_2 & -\alpha A_1 \\ -A_3\hat{\pi}_1(\lambda) & -\alpha A_3 & \lambda-A_4 \end{pmatrix}$$

The characteristic equation corresponds to the steady states $(u_1(a),u_2^*,u_3^*)$ is given by

$$\begin{aligned} det(A(\lambda)) &= \left[1-\left(\hat{K}_1(\lambda)+k_1H_1\hat{\pi}_1(\lambda)\right)\right]\left[(\lambda-A_2)(\lambda-A_4)-\alpha^2A_1A_3\right] \\ &\quad +k_1H_1\left[-A_1\hat{\pi}_1(\lambda)(\lambda-A_4)-\alpha A_1A_3\hat{\pi}_1(\lambda)-\alpha A_1A_3\hat{\pi}_1(\lambda)-A_3\hat{\pi}_1(\lambda)(\lambda-A_2)\right]=0. \end{aligned}$$

Now, we can establish the stability of each steady states.

3.1 Stability of the trivial steady state E_0

For $E_0=(0,0,0)$ we have $H_1=0$, $A_2=m_0-g_0$, $A_1=0$ and $A_4=m_1-g_1$.

Then the characteristic equation becomes
$\left(1-\hat{K}_1(\lambda)\right)(\lambda-(m_0-g_0))(\lambda-(m_1-g_1))=0$, which implies that $1=\hat{K}_1(\lambda)$ or $\lambda_i=m_i-g_i$ for $i=1,2$.

To complete our study, we need the following proposition.

Proposition 3.1. *Let* $K_1(a)\geq 0$.

1. *If* $\int_0^\infty K_1(a)\,\mathrm{d}a>1$, *then the equation* $1-\hat{K}_1(\lambda)=0$ *has a real positive solution* λ.
2. *If* $\int_0^\infty K_1(a)\,\mathrm{d}a<1$, *then the equation* $1-\hat{K}_1(\lambda)=0$ *has no complex solution* λ *with* $Re(\lambda)>0$.

Since

$$\hat{K}_1(0)=R_1=\int_0^\infty K_1(a)\,\mathrm{d}a,$$

we deduce the following proposition.

Proposition 3.2.

1. *If* $R_1 > 1$, *then the equation* $1 - \hat{K}_1(\lambda) = 0$ *has a real positive solution* λ.
2. *If* $R_1 < 1$, *then the equation* $1 - \hat{K}_1(\lambda) = 0$ *has no complex solution* λ *with* $Re(\lambda) > 0$.

From proposition 3.2, we have the following results.

Theorem 3.3.

1. *If* $m_0 < g_0$, $m_1 < g_1$ *and* $R_1 < 1$, *then the trivial steady state* E_0 *is locally asymptotically stable.*
2. *If either* $m_0 > g_0$, $m_1 > g_1$ *or* $R_1 > 1$, *then the trivial steady state* E_0 *is unstable.*

3.2 Stability of the blast steady state E_1

For $E_1 = (0, 0, \frac{b_1}{\delta})$ we have $H_1 = 0$, $A_1 = 0$, $A_2 = \dfrac{\delta^n(m_0 - g_0) - \alpha^n c_0 g_0 b_1^n}{\delta^n + \alpha^n c_0 b_1^n}$ and $A_4 = \dfrac{-n g_1(m_1 - g_1)}{m_1} < 0$.

Then, the characteristic equation becomes

$$\left(1 - \hat{K}_1(\lambda)\right)(\lambda - A_2)(\lambda - A_4) = 0.$$

We obtain $1 = \hat{K}_1(\lambda)$, $\lambda = A_2$ or $\lambda = A_4 < 0$. In this case, we have

$$\hat{K}_1(0) = \frac{R_1}{\dfrac{k_1^n b_1^n}{\delta^n \theta^n} + 1}.$$

We have the following results.

Proposition 3.4.

1. *If* $m_1 > g_1$ *and* $R_1 > \dfrac{k_1^n b_1^n}{\delta^n \theta^n} + 1$, *then the equation* $1 - \hat{K}_1(\lambda) = 0$ *has a real positive solution* λ.
2. *If* $m_1 > g_1$ *and* $R_1 < \dfrac{k_1^n b_1^n}{\delta^n \theta^n} + 1$, *then the equation* $1 - \hat{K}_1(\lambda) = 0$ *has no complex solution* λ *with* $Re(\lambda) > 0$.

From proposition 3.4, we deduce the following theorem.

Theorem 3.5.

1. *If* $m > g_1$, $m_0 < g_0\left[\dfrac{c_0 \alpha^n b_1^n}{\delta^n} + 1\right]$ *and* $R_1 < \dfrac{k_1^n b_1^n}{\delta^n \theta^n} + 1$, *then the blast steady state* E_1 *is locally asymptotically stable.*
2. *If* $m > g_1$ *and either* $m_0 > g_0\left[\dfrac{c_0 \alpha^n b_1^n}{\delta^n} + 1\right]$ *or* $R_1 > \dfrac{k_1^n b_1^n}{\delta^n \theta^n} + 1$, *then the blast steady state* E_1 *is unstable.*

3.3 Stability of the blast steady state E_2

For $E_2 = (0, \dfrac{b_0}{\alpha}, 0)$ we have $H_1 = 0$, $A_3 = 0$, $A_2 = \dfrac{-ng_0(m_0 - g_0)}{m_0} < 0$ and $A_4 = \dfrac{(m_1 - g_1) - c_1 g_1 b_0^n}{1 + c_1 b_0^n}$.
Then, the characteristic equation becomes

$$\left(1 - \hat{K}_1(\lambda)\right)(\lambda - A_2)(\lambda - A_4) = 0.$$

Therefore, we have $1 = \hat{K}_1(\lambda)$, $\lambda = A_2 < 0$ or $\lambda = A_4$.

In this case, we obtain

$$\hat{K}_1(0) = \frac{R_1}{\dfrac{k_1^n b_0^n}{\alpha^n \theta^n} + 1}.$$

We have the following results.

Proposition 3.6.

1. *If $m_0 > g_0$ and $R_1 > \dfrac{k_1^n b_0^n}{\alpha^n \theta^n} + 1$, then the equation $1 - \hat{K}_1(\lambda) = 0$ has a real positive solution λ.*
2. *If $m_0 > g_0$ and $R_1 < \dfrac{k_1^n b_0^n}{\alpha^n \theta^n} + 1$, then the equation $1 - \hat{K}_1(\lambda) = 0$ has no complex solution λ with $Re(\lambda) > 0$.*

From proposition 3.6, we deduce the following theorem.

Theorem 3.7.

1. *If $m_0 > g_0$, $m_1 < g_1(c_1 b_0^n + 1)$ and $R_1 < \dfrac{k_1^n b_0^n}{\alpha^n \theta^n} + 1$, then the blast steady state E_2 is locally asymptotically stable.*
2. *If $m_0 > g_0$ and either $m_1 > g_1(c_1 b_0^n + 1)$ or $R_1 > \dfrac{k_1^n b_0^n}{\alpha^n \theta^n} + 1$, then the blast steady state E_2 is unstable.*

3.4 Stability of the blast steady state E_3

For $E_3 = (0, \dfrac{\delta b_0 - \alpha b_1}{\alpha(\delta - \alpha)}, \dfrac{b_1 - b_0}{\delta - \alpha})$ we have $H_1 = 0$, $A_2 = \dfrac{-nc_0 g_0^2 b_0^{n-1}(\delta b_0 - \alpha b_1)}{(\delta - \alpha)}$, $A_4 = \dfrac{-n\delta c_1 g_1^2 b_1^{n-1}(b_1 - b_0)}{m_1(\delta - \alpha)}$, $\alpha A_1 = A_2$ and $A_3 = \dfrac{-nc_1 g_1^2 b_1^{n-1}(b_1 - b_0)}{m_1(\delta - \alpha)}$.
Then, the characteristic equation becomes

$$\left(1 - \hat{K}_1(\lambda)\right)\left[(\lambda - A_2)(\lambda - A_4) - \alpha^2 A_1 A_3\right] = 0.$$

Therefore, we obtain either $1 = \hat{K}_1(\lambda)$ or $(\lambda - A_2)(\lambda - A_4) - \alpha^2 A_1 A_3 = 0$. In this case, we obtain

$$\hat{K}_1(0) = \frac{R_1}{\dfrac{k_1^n b_0^n}{\theta^n \alpha^n} + 1}.$$

We have the following results.

Proposition 3.8.

1. *If* $m_1 > g_1$, $\left(\frac{c_0}{\delta^n}\min(\alpha^n,\delta^n)\, b_1^n + 1\right) g_0 < m_0 < \left(\frac{c_0}{\delta^n}\max(\alpha^n,\delta^n)\, b_1^n + 1\right) g_0$ *and* $R_1 > \frac{k_1^n b_0^n}{\theta^n \alpha^n} + 1$, *then the equation* $1 - \hat{K}_1(\lambda) = 0$ *has a real positive solution* λ.
2. *If* $m_1 > g_1$, $\left(\frac{c_0}{\delta^n}\min(\alpha^n,\delta^n)\, b_1^n + 1\right) g_0 < m_0 < \left(\frac{c_0}{\delta^n}\max(\alpha^n,\delta^n)\, b_1^n + 1\right) g_0$ *and* $R_1 < \frac{k_1^n b_0^n}{\theta^n \alpha^n} + 1$, *then the equation* $1 - \hat{K}_1(\lambda) = 0$ *has no complex solution* λ *with* $Re(\lambda) > 0$.

On the other hand, we have

$$\lambda^2 - (A_4 + A_2)\lambda + A_2(A_4 - \alpha A_3) = 0. \tag{27}$$

1. If $m_1 > g_1$ and $(c_0 b_1^n + 1)\, g_0 < m_0 < \left(\frac{\alpha^n}{\delta^n} c_0 b_1^n + 1\right) g_0$, then we have $A_2 > 0$, $A_4 > 0$ and $A_4 - \alpha A_3 = \frac{-n c_1 b_1^{n-1} g_1^2 (b_1 - b_0)(\delta + \alpha)}{m_1(\delta - \alpha)} < 0$, and equation (27) has one positive eigenvalue $\lambda > 0$.
2. If $m_1 > g_1$ and $\left(\frac{\alpha^n}{\delta^n} c_0 b_1^n + 1\right) g_0 < m_0 < (c_0 b_1^n + 1)\, g_0$, then we have we have $A_2 < 0$, $A_4 < 0$, $A_4 - \alpha A_3 = \frac{-n c_1 b_1^{n-1} g_1^2 (b_1 - b_0)(\delta + \alpha)}{m_1(\delta - \alpha)} < 0$, and equation (27) has two eigenvalue with real part negative.

From proposition 3.10, we deduce the following theorem.

Theorem 3.9. *Let* $m_1 > g_1$.

1. *If* $m_1 > g_1$ *and* $\left(\frac{\alpha^n}{\delta^n} c_0 b_1^n + 1\right) g_0 < m_0 < (c_0 b_1^n + 1)\, g_0$ *and* $R_1 < \frac{k_1^n b_0^n}{\theta^n \alpha^n} + 1$, *then the blast steady state* E_3 *is locally asymptotically stable.*
2. *If* $m_1 > g_1$ *and* $(c_0 b_1^n + 1)\, g_0 < m_0 < \left(\frac{\alpha^n}{\delta^n} c_0 b_1^n + 1\right) g_0$ *and* $R_1 < \frac{k_1^n b_0^n}{\theta^n \alpha^n} + 1$, *then the blast steady state* E_3 *is unstable.*
3. *If* $m_1 > g_1$ *and* $\left(\frac{\alpha^n}{\delta^n} c_0 b_1^n + 1\right) g_0 < m_0 < (c_0 b_1^n + 1)\, g_0$ *and* $R_1 > \frac{k_1^n b_0^n}{\theta^n \alpha^n} + 1$, *then the blast steady state* E_3 *is unstable.*
4. *If* $m_1 > g_1$ *and* $(c_0 b_1^n + 1)\, g_0 < m_0 < \left(\frac{\alpha^n}{\delta^n} c_0 b_1^n + 1\right) g_0$ *and* $R_1 > \frac{k_1^n b_0^n}{\theta^n \alpha^n} + 1$, *then the blast steady state* E_3 *is unstable.*

3.5 Stability of the chronic steady state E_4

For $E_4 = \left(\frac{\delta\theta_1 \sqrt[n]{R_1 - 1} - b_1}{L_1(\delta - 1)}\pi_1(a), 0, \frac{b_1 - \theta_1 \sqrt[n]{R_1 - 1}}{\delta - 1}\right)$ we have, $A_1 = 0$,

$$H_1 = -\frac{n(R_1 - 1)\left(\delta\theta_1 \sqrt[n]{R_1 - 1} - b_1\right)}{k_1\theta_1 L_1(\delta - 1) R_1 \sqrt[n]{R_1 - 1}}, \quad A_2 = g_0 \left[\frac{b_0^n - \left(\frac{(\delta - \alpha)\theta_1 \sqrt[n]{R_1 - 1} - (1 - \alpha) b_1}{(\delta - 1)}\right)^n}{\frac{1}{c_0} + \left(\frac{(\delta - \alpha)\theta_1 \sqrt[n]{R_1 - 1} - (1 - \alpha) b_1}{(\delta - 1)}\right)^n}\right], \quad A_3 = \frac{-n c_1 g_1^2 b_1^{n-1}}{m_1} \left(\frac{b_1 - \theta_1}{\delta}\right.$$

and $A_4 = \delta A_3$

Then, the characteristic equation becomes

$$[(1 - S_1(\lambda))(\lambda - A_4) - A_3 k_1 H_1 \hat{\pi}_1(\lambda)](\lambda - A_2) = 0,$$

where

$$S_1(\lambda) = \hat{K}_1(\lambda) + k_1 H_1 \hat{\pi}_1(\lambda).$$

Then, we obtain either $T_0(\lambda) := (1 - S_1(\lambda))(\lambda - A_4) - A_3 k_1 H_1 \hat{\pi}_1(\lambda) = 0$ or $\lambda = A_2$. We have the following proposition.

Proposition 3.10. *For all $m_1 > g_1$ and $\left(\frac{b_1}{\theta_1}\right)^n + 1 < R_1 < \left(\frac{b_1}{\delta\theta_1}\right)^n + 1$, the equation $T_0(\lambda) = 0$ has a unique solution $\lambda_1 > 0$.*

Proof. Since $\lim_{\lambda\to\infty} T_0(\lambda) = +\infty$ and

$$\begin{aligned} T_0(0) &= -A_4\left(1 - \int_0^A K_1(a)\mathrm{d}a - k_1 H_1 \int_0^A \pi_1(a)\mathrm{d}a\right) - \int_0^A A_3 k_1 H_1 \pi_1(a)\mathrm{d}a \\ &= -A_3(1-\delta)k_1 H_1 L_1 < 0. \end{aligned}$$

Then, there exists $\lambda_1 > 0$ such that $T_0(\lambda_1) = 0$. □

From proposition 3.10, we deduce the following theorem.

Theorem 3.11. *If $m_1 > g_1$ and $\left(\frac{b_1}{\theta_1}\right)^n + 1 < R_1 < \left(\frac{b_1}{\delta\theta_1}\right)^n + 1$, then the chronic steady state E_4 is unstable.*

3.6 Stability of the chronic steady state E_5

For $E_5 = \left(\frac{\alpha\theta_1\sqrt[n]{R_1-1} - b_0}{L_1(\alpha-1)}\pi_1(a), \frac{b_0 - \theta_1\sqrt[n]{R_1-1}}{\alpha-1}, 0\right)$ we have, $A_1 = \frac{-ng_0^2 u_2^* c_0 b_0^{n-1}}{m_0}$, $A_2 = -\alpha A_1$, $A_3 = 0$, $A_4 = g_1\left[\frac{b_1^n - b_0^n}{\frac{1}{c_1} + b_0^n}\right]$ and $H_1 = -\frac{n(R_1-1)}{k_1\theta_1\sqrt[n]{R_1-1}R_1}u_1(0)$.

Then, the characteristic equation becomes

$$[(1 - S_1(\lambda))(\lambda - A_2) - A_1 k_1 H_1 \hat{\pi}_1(\lambda)](\lambda - A_4) = 0,$$

where

$$S_1(\lambda) = \hat{K}_1(\lambda) + k_1 H_1 \hat{\pi}_1(\lambda).$$

Then, we obtain either $T_1(\lambda) := (1 - S_1(\lambda))(\lambda - A_2) - A_1 k_1 H_1 \hat{\pi}_1(\lambda) = 0$ or $\lambda = A_4$. We have the following proposition.

Proposition 3.12. *For all $m_0 > g_0$ and $\left(\frac{b_0}{\theta_1}\right)^n + 1 < R_1 < \left(\frac{b_0}{\alpha\theta_1}\right)^n + 1$, the equation $T_1(\lambda) = 0$ has a unique solution $\lambda_1 > 0$.*

Proof. Since $\lim_{\lambda\to\infty} T_1(\lambda) = +\infty$ and

$$\begin{aligned} T_1(0) &= -A_2\left(1 - \int_0^A K_1(a)\mathrm{d}a - k_1H_1\int_0^A \pi_1(a)\mathrm{d}a\right) - \int_0^A A_1k_1H_1\pi_1(a)\mathrm{d}a \\ &= -(1-\alpha)A_1k_1H_1L_1 < 0. \end{aligned}$$

Then, there exists $\lambda_1 > 0$ such that $T_1(\lambda_1) = 0$. □

From proposition 3.12, we deduce the following theorem.

Theorem 3.13. *If $m_1 > g_1$ and $\left(\frac{b_1}{\theta_1}\right)^n + 1 < R_1 < \left(\frac{b_1}{\delta\theta_1}\right)^n + 1$, then the chronic steady state E_5 is unstable.*

3.7 Stability of the nonpathological steady state E_6

For $E_6 = \left(\frac{\theta_1\sqrt[n]{R_1-1}}{L_1}\pi_1(a), 0, 0\right)$, we have $A_3 = A_1 = 0$, $H_1 = \frac{-n(R_1-1)}{k_1L_1R_1}$, $K_1(a) = \frac{\varphi(a)\pi_1(a)}{R_1}$, $A_2 = \frac{(m_0-g_0) - g_0c_0\theta_1^n(R_1-1)}{1+c_0\theta_1^n(R_1-1)}$ and $A_4 = \frac{(m_1-g_1) - g_1c_1\theta_1^n(R_1-1)}{1+c_1\theta_1^n(R_1-1)}$.
The characteristic equation becomes

$$(1 - S_1(\lambda))(\lambda - A_2)(\lambda - A_4) = 0,$$

where

$$S_1(\lambda) = \hat{K}_1(\lambda) + k_1H_1\hat{\pi}_1(\lambda).$$

Then, we obtain $1 - S_1(\lambda) = 0$, $\lambda = A_2$ or $\lambda = A_4$.

Lemma 1. *Let $\eta_1 = \min_{a\in[0,A]} \varphi_1(a)$ and $\eta_2 = \max_{a\in[0,A]} \varphi_1(a)$.*

1. *If $1 < R_1 < \frac{\eta_1}{n}L_1 + 1$, then $0 < S_1(\lambda) < 1$.*
2. *If $R_1 > \frac{\eta_2}{n}L_1 + 1$, then $S_1(\lambda) < 0$.*

Proof 1. *We have*

$$\begin{aligned} S_1(\lambda) &= \int_0^A e^{-\lambda a}\left(K_1(a) + k_1H_1\pi_1(a)\right)\mathrm{d}a \\ &= \int_0^A e^{-\lambda a}\frac{\pi_1(a)}{L_1R_1}\left[\varphi_1(a)L_1 - n(R_1-1)\right]\mathrm{d}a. \end{aligned}$$

On the one hand, $S_1(\lambda) > 0$ *(resp.* $S_1(\lambda) < 0$*) for all* $\lambda > 0$ *if*

$$\varphi_1(a)L_1 - n(R_1 - 1) > 0 \,(resp.\ \varphi_1(a)L_1 - n(R_1 - 1) < 0),$$

For all $a \in (0, A)$*.*
The last inequality implies that $1 < R_1 < \frac{\eta_1}{n}L_1 + 1$ *(resp.* $R_1 > \frac{\eta_2}{n}L_1 + 1$*).*
On the other hand, for $1 < R_1 < \frac{\eta_1}{n}L_1 + 1$ *(resp.* $R_1 > \frac{\eta_2}{n}L_1 + 1$*) the function* $S_1(\lambda)$ *is decreasing (resp. increasing) since*

$$\frac{d}{d\lambda}S_1(\lambda) = -\int_0^A ae^{-\lambda a}\left(K_1(a) + k_1 H_1 \pi_1(a)\right) \mathrm{d}a.$$

Moreover, $\lim\limits_{\lambda \to \infty} S_1(\lambda) = 0$ *and*

$$S_1(0) = \int_0^A K_1(a)\mathrm{d}a + k_1 H_1 \int_0^A \pi_1(a)\mathrm{d}a = 1 - \frac{n(R_1 - 1)}{R_1} < 1.$$

Since $1 < R_1 < \frac{\eta_1}{n}L_1 + 1$ *(resp.* $R_1 > \frac{\eta_2}{n}L_1 + 1$*), then* $S_1(0) > S_1(\lambda) > 0$ *(resp.* $S_1(0) < S_1(\lambda) < 0$*).*

We have the following proposition.

Proposition 3.14. *If either* $1 < R_1 < \frac{\eta_1}{n}L_1 + 1$ *or* $R_1 > \frac{\eta_2}{n}L_1 + 1$*, then the equation* $S_1(\lambda) = 1$ *has no complex solution* λ *with* $Re(\lambda) > 0$*.*

From proposition 3.14, we deduce the following theorem.

Theorem 3.15.

1. *If either* $\max\left(1, \frac{b_0^n}{\theta_1^n}, \frac{b_1^n}{\theta_1^n}\right) < R_1 < \frac{\eta_1}{n}L_1 + 1$ *or* $R_1 > \max\left(\frac{\eta_2}{n}L_1 + 1, \frac{b_0^n}{\theta_1^n}, \frac{b_1^n}{\theta_1^n}\right)$*, then the pathological steady state* E_6 *is stable.*
2. *If either* $1 < R_1 < \min\left(\frac{\eta_1}{n}L_1 + 1, \frac{b_0^n}{\theta_1^n}, \frac{b_1^n}{\theta_1^n}\right)$ *or* $\frac{\eta_2}{n}L_1 + 1 < R_1 < \min\left(\frac{b_0^n}{\theta_1^n}, \frac{b_1^n}{\theta_1^n}\right)$*, then the pathological steady state* E_6 *is unstable.*

3.8 Stability of the chronic steady state E_7

For $E_7 = \left(\frac{\alpha\theta_1 \sqrt[n]{R_1 - 1} - b_0}{L_1(\alpha - 1)}\pi_1(a), u_2^*, \frac{b_1 - b_0}{\delta - \alpha}\right)$ we have, $A_1 = \frac{-ng_0^2 c_0 u_2^* b_0^{n-1}}{m_0}$, $A_2 = -\alpha A_1$, $A_3 = \frac{-ng_1^2 c_1 u_3^* b_1^{n-1}}{m_1}$, $A_4 = -\delta A_3$ and $H_1 = -\frac{n\theta^n (R_1 - 1)}{k_1 \frac{1}{\alpha}(b_0 - (1 - \alpha)u_1(0)L_1)\theta^n R_1} u_1(0)$
Then, the characteristic equation becomes

$$T_3(\lambda) := T_1(\lambda)\left(\lambda - \delta A_3\right) + T_2(\lambda) = 0$$

where

$$T_1(\lambda) := \left(1 - S_1(\lambda)\right)\left(\lambda - A_2\right) - A_1 k_1 H_1 \hat{\pi}_1(\lambda),$$

$$T_2(\lambda) := -A_3\left[\alpha^2 A_1\left(1 - S_1(\lambda)\right) + k_1 H_1 \hat{\pi}_1(\lambda)\left(\lambda + \alpha A_1\right)\right],$$

and

$$S_1(\lambda) = \hat{K}_1(\lambda) + k_1 H_1 \hat{\pi}_1(\lambda).$$

We have the following proposition.

Proposition 3.16. *For all* $\delta < \alpha$, $m_1 > g_1$, $\left(c_0 b_1^n + 1\right) g_0 < m_0 < \left(\frac{c_0\alpha^n}{\delta^n} b_1^n + 1\right) g_0$ *and* $\left(\frac{(1-\alpha)b_1 - (1-\delta)b_0}{(\delta-\alpha)\theta_1}\right)^n + 1 < R_1 < \left(\frac{b_0}{\alpha\theta_1}\right)^n + 1$, *the equation* $T_3(\lambda) = 0$ *has a unique solution* $\lambda_1 > 0$.

Proof. Since $\lim\limits_{\lambda\to\infty} T_3(\lambda) = +\infty$ and

$$\begin{aligned}
T_3(0) &= \delta A_1 A_3\left[\alpha\left(1 - \int_0^A K_1(a)\mathrm{d}a - k_1 H_1 \int_0^A \pi_1(a)\mathrm{d}a\right) + k_1 H_1 \int_0^A \pi_1(a)\mathrm{d}a\right] \\
&\quad -\alpha A_1 A_3\left[\alpha\left(1 - \int_0^A K_1(a)\mathrm{d}a - k_1 H_1 \int_0^A \pi_1(a)\mathrm{d}a\right) + k_1 H_1 \int_0^A \pi_1(a)\mathrm{d}a\right] \\
&= (\delta-\alpha) A_1 A_3 (1-\alpha) k_1 H_1 L_1 < 0
\end{aligned}$$

when $\delta < \alpha$. That is, there exists $\lambda_1 > 0$ such that $T_3(\lambda_1) = 0$. □

From proposition 3.16, we deduce the following theorem.

Theorem 3.17.
If $\delta < \alpha$, $m_1 > g_1$, $\left(c_0 b_1^n + 1\right) g_0 < m_0 < \left(\frac{c_0\alpha^n}{\delta^n} b_1^n + 1\right) g_0$ *and* $\left(\frac{(1-\alpha)b_1 - (1-\delta)b_0}{(\delta-\alpha)\theta_1}\right)^n + 1 < R_1 < \left(\frac{b_0}{\alpha\theta_1}\right)^n + 1$, *then the chronic steady state* E_5 *is unstable.*

4 Different zones of existence and stability of steady states

Next we draw different zones of existence and stability of steady states according to the values of m_0, m_1 and R.

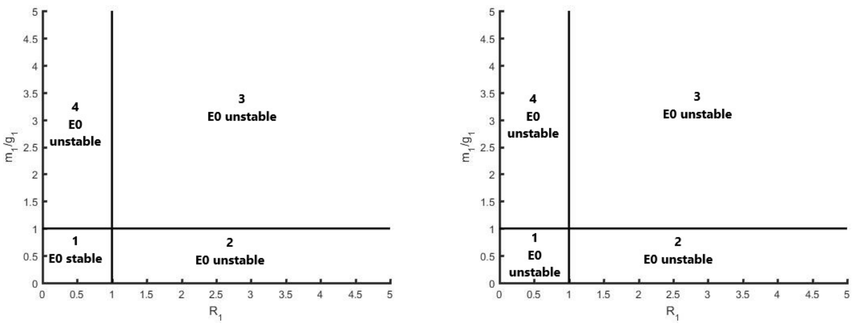

Figure 1: Different zones of existence and stability of the steady states E_0, (case $m_0 < g_0$ in left and $m_0 > g_0$ in right, see theorem 3.1).

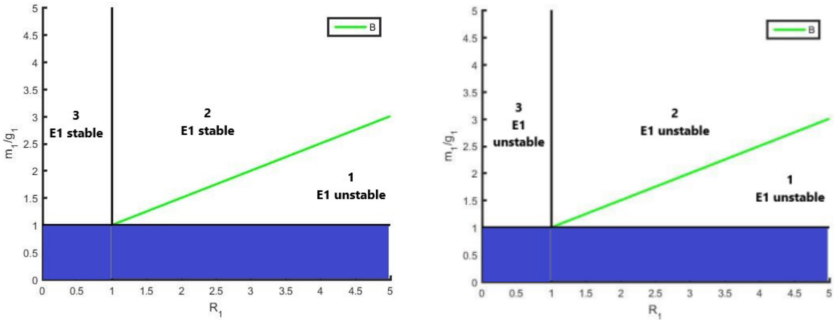

Figure 2: Different zones of existence and stability of the steady states E_1 (case $m_0 < g_0 A$ in left and $m_0 > g_0 A$ in right, with: $A = \frac{\alpha^n c_0}{\delta^n c_1}(\frac{m_1}{g_1} - 1) + 1$ and $B = \frac{\theta^n \delta^n c_1}{k_1^n}(R_1 - 1) + 1$, see theorem 3.2)

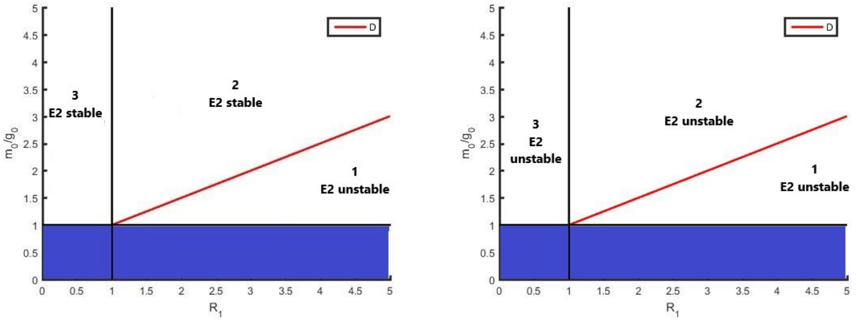

Figure 3: Different zones of existence and stability of E_2, (case $m_1 < \frac{c_1 g_1}{c_0}(\frac{m_0}{g_0} - 1) + g_1$ in left and $m_1 > \frac{c_1 g_1}{c_0}(\frac{m_0}{g_0} - 1) + g_1$ in right, with $D = \frac{\theta^n \alpha^n c_0}{k_1^n}(R_1 - 1) + 1$, see theorem 3.3)

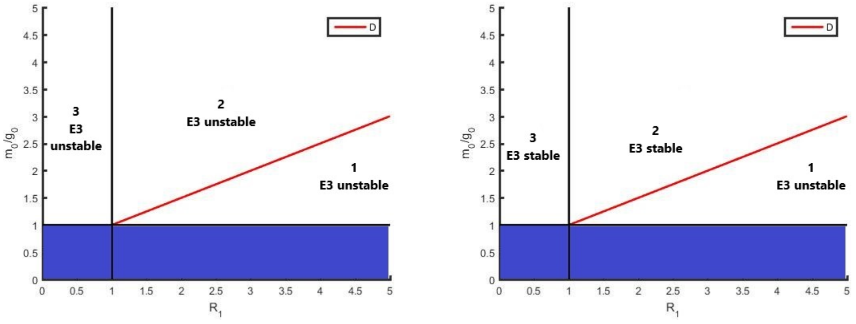

Figure 4: Different zones of existence and stability of E_3, (case $\alpha > \delta$ and $m_1 < g_1 \frac{c_1}{c_0}(\frac{m_0}{g_0} - 1) + g_1 < g_1 \frac{\alpha^n}{\delta^n}(\frac{m_1}{g_1} - 1) + g_1$ in left, and $\alpha < \delta$ and $m_1 > g_1 \frac{c_1}{c_0}(\frac{m_0}{g_0} - 1) + g_1 > g_1 \frac{\alpha^n}{\delta^n}(\frac{m_1}{g_1} - 1) + g_1$ in right, with $D = \frac{\theta^n \alpha^n c_0}{k_1^n}(R_1 - 1) + 1$, see theorem 3.4)

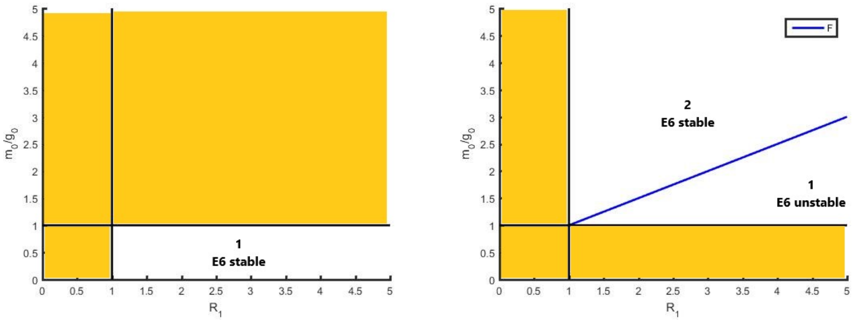

Figure 5: Different zones of existence and stability of E_6, (case $m_1 < g_1$ in left and $m_1 > g_1$ in right, see theorem 3.6)

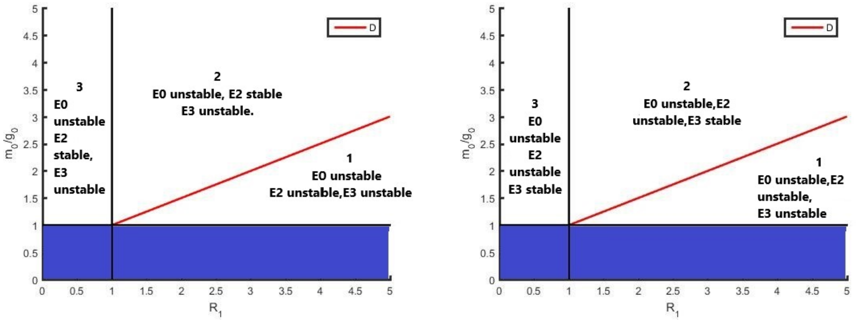

Figure 6: Different zones of existence and stability of steady state, case $\frac{\alpha}{\delta} > 1$ and $\frac{m_1}{g_1} < \frac{c_1}{c_0}(\frac{m_0}{g_0} - 1) + 1 < \frac{\alpha^n}{\delta^n}(\frac{m_1}{g_1} - 1) + 1$ in left and $\frac{\alpha}{\delta} < 1$ and $\frac{\alpha^n}{\delta^n}(\frac{m_1}{g_1} - 1) + 1 < \frac{c_1}{c_0}(\frac{m_0}{g_0} - 1) + 1 < \frac{m_1}{g_1})$ in right, with $D = \frac{c_0\theta^n\alpha^n}{k_1^n}(R_1 - 1) + 1$.

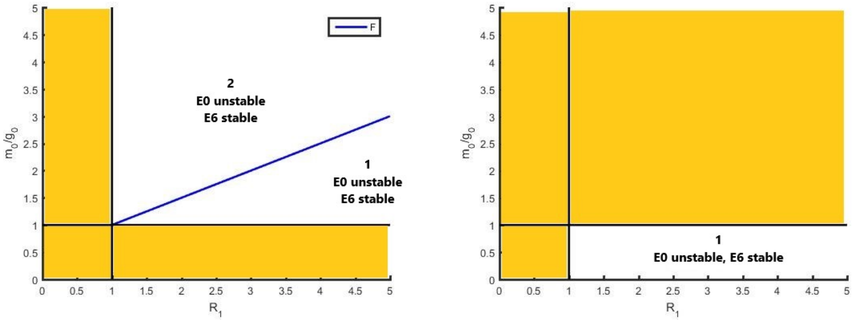

Figure 7: Different zones of existence and stability of steady state, case $\frac{m_1}{g_1} > 1$ in left, with $F = \frac{c_0\theta^n}{k_1^n}(R_1 - 1) + 1$, and case $\frac{m_1}{g_1} < 1$.

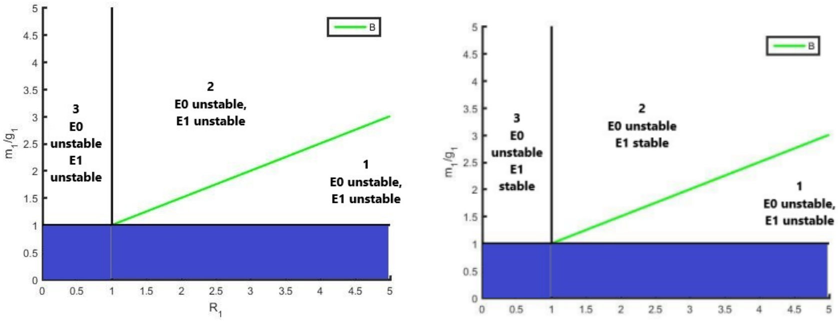

Figure 8: Different zones of existence and stability of the steady states, case $\frac{m_0}{g_0} > A$ and case $\frac{m_0}{g_0} < A$ with $A = \frac{\alpha^n c_0}{\delta^n c_1}(\frac{m_1}{g_1} - 1) + 1$ and $B = \frac{\theta^n \delta^n c_1}{k_1^n}(R_1 - 1) + 1$

5 Numerical Simulations

In this section, we give some numerical simulations to illustrate our theoretical results.

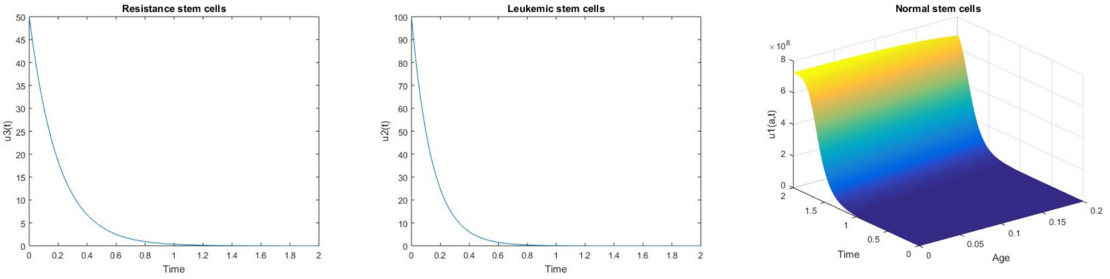

Figure 9: Different zones of existence and stability of the steady states (zone1 figure 11), for parameters: $\mu_1 = 0.005$, $m_0 = 8$, $m_1 = 6$, $k_1 = 1$, $n = 2$, $\theta = 1.62 \times 10^8$, $\varphi_1(a) = 10 \times exp(-a)$, $\alpha = 0.9$, $\delta = 0.004$, $g_0 = 7$, $g_1 = 5$, $c_0 = 0.009$, $c_1 = 0.4$.

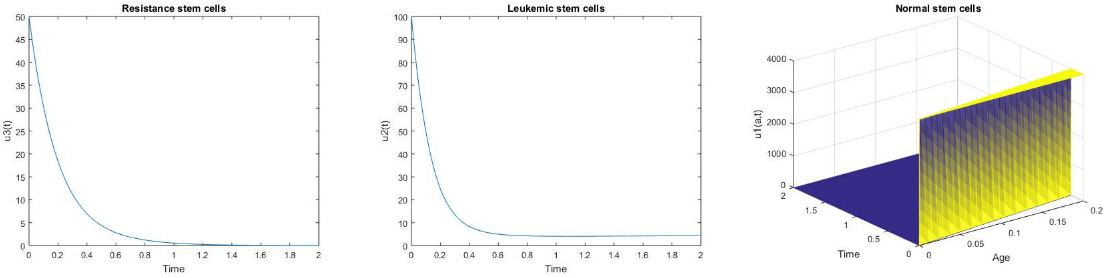

Figure 10: Different zones of existence and stability of the steady states (zone2 figure 11), for parameters: $\mu_1 = 0.005$, $m_0 = 8$, $m_1 = 6$, $k_1 = 4.44 \times 10^8$, $n = 2$, $\theta = 1.62 \times 10^8$, $\varphi_1(a) = 10 \times exp(-a)$, $\alpha = 0.9$, $\delta = 0.004$, $g_0 = 7$, $g_1 = 5$, $c_0 = 0.009$, $c_1 = 0.4$.

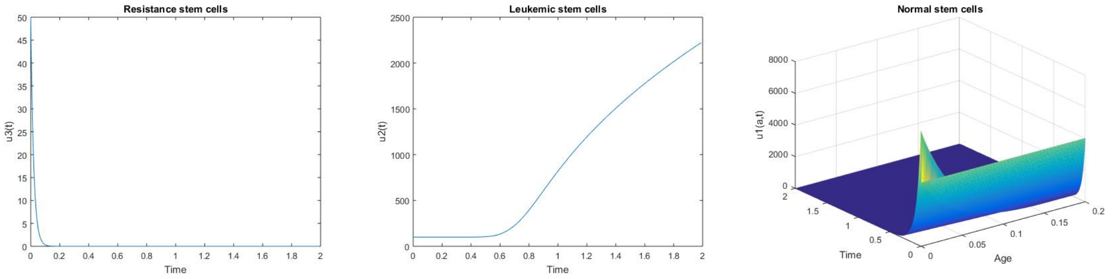

Figure 11: Different zones of existence and stability of the steady states (zone3 figure 11), for parameters: $\mu_1 = 20$, $m_0 = 8$, $m_1 = 80$, $k_1 = 1$, $n = 2$, $\theta = 1.62 \times 10^8$, $\varphi_1(a) = 10 \times exp(-a)$, $\alpha = 0.9$, $\delta = 0.000004$, $g_0 = 0.0007$, $g_1 = 50$, $c_0 = 0.9$, $c_1 = 0.9$.

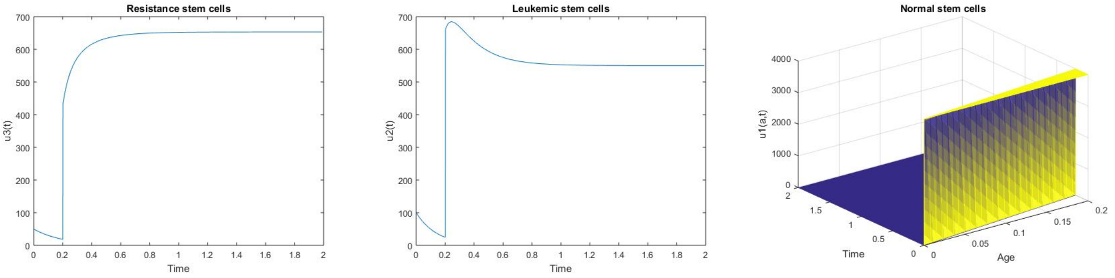

Figure 12: Different zones of existence and stability of the steady states (zone3 figure 12), for parameters: $\mu_1 = 0.005$, $m_0 = 80000$, $m_1 = 60000$, $k_1 = 4.44 \times 10^8$, $n = 3$, $\theta = 1.62 \times 10^8$, $\varphi_1(a) = 0.10 \times exp(-a)$, $\alpha = 0.009$, $\delta = 0.04$, $g_0 = 7$, $g_1 = 5$, $c_0 = 9$, $c_1 = 0.4$.

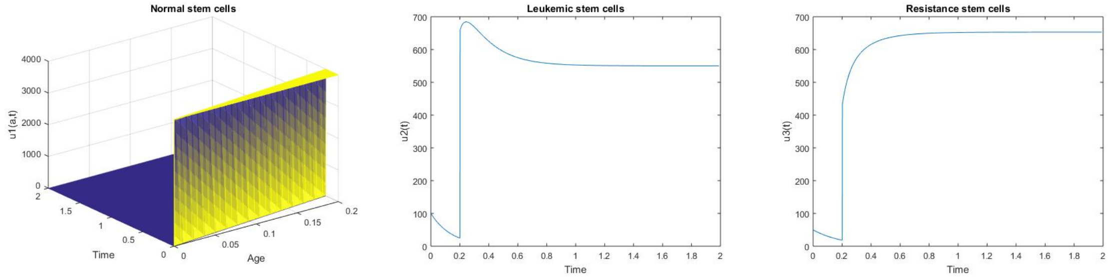

Figure 13: Different zones of existence and stability of the steady states (zone2 figure 12), for parameters: $\mu_1 = 0.005$, $m_0 = 80000$, $m_1 = 60000$, $k_1 = 4.44 \times 10^8$, $n = 3$, $\theta = 1.62 \times 10^8$, $\varphi_1(a) = 10 \times exp(-a)$, $\alpha = 0.009$, $\delta = 0.04$, $g_0 = 7$, $g_1 = 5$, $c_0 = 9$, $c_1 = 0.4$.

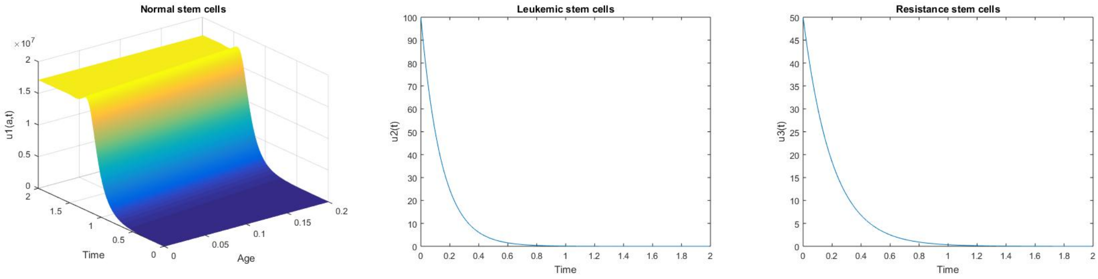

Figure 14: Different zones of existence and stability of the steady states (zone1 figure 12), for parameters: $\mu_1 = 0.005$, $m_0 = 80000$, $m_1 = 60000$, $k_1 = 44$, $n = 3$, $\theta = 1.62 \times 10^8$, $\varphi_1(a) = 10 \times exp(-a)$, $\alpha = 0.009$, $\delta = 0.04$, $g_0 = 7$, $g_1 = 5$, $c_0 = 9$, $c_1 = 0.4$.

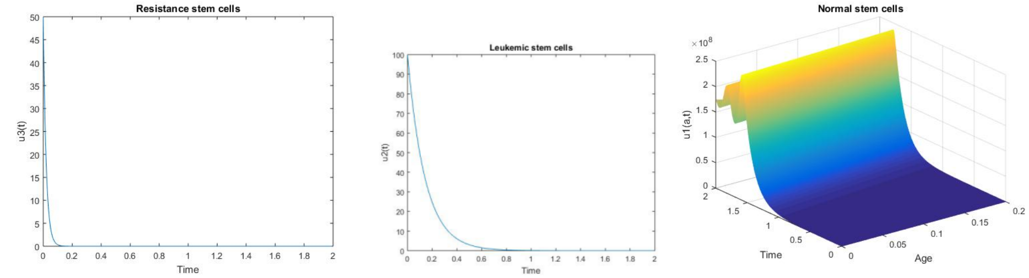

Figure 15: Different zones of existence and stability of the steady states (zone1 figure 14), for parameters: $\mu_1 = 0.2$, $m_0 = 0.8$, $m_1 = 0.60$, $k_1 = 4.4$, $n = 10$, $\theta = 1.62 \times 10^8$, $\varphi_1(a) = 10 \times exp(-a)$, $\alpha = 0.9$, $\delta = 0.004$, $g_0 = 7$, $g_1 = 50$, $c_0 = 9$, $c_1 = 0.4$.

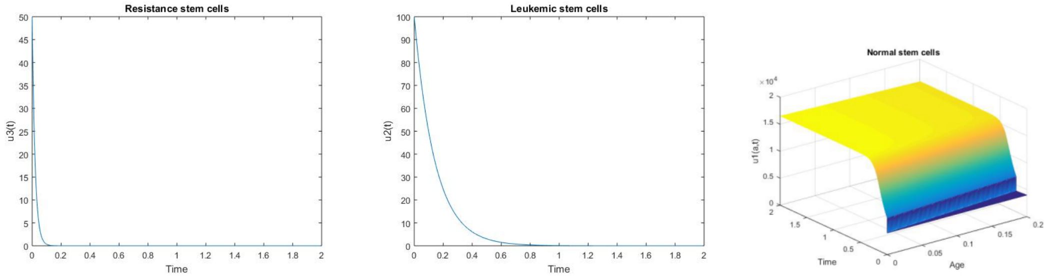

Figure 16: Different zones of existence and stability of the steady states (zone1 figure 13), for parameters: $\mu_1 = 0.2$, $m_0 = 80$, $m_1 = 60$, $k_1 = 44000$, $n = 2$, $\theta = 1.62\times 10^8$, $\varphi_1(a) = 10\times exp(-a)$, $\alpha = 0.9$, $\delta = 0.004$, $g_0 = 7$, $g_1 = 50$, $c_0 = 9$, $c_1 = 0.4$.

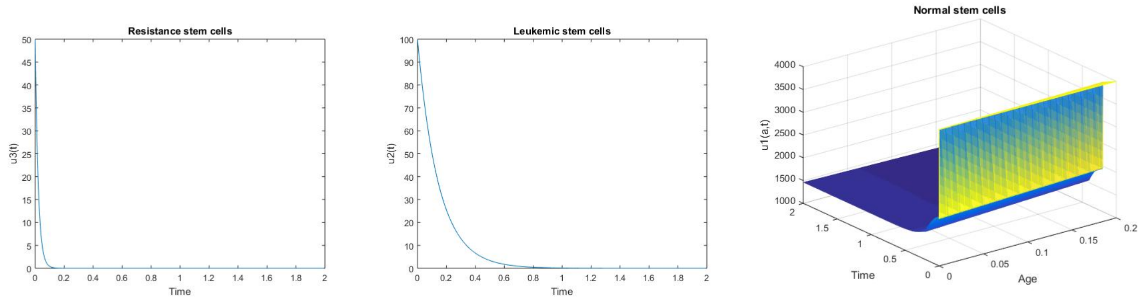

Figure 17: Different zones of existence and stability of the steady states (zone2 figure 13), for parameters: $\mu_1 = 0.2$, $m_0 = 80$, $m_1 = 60$, $k_1 = 440000$, $n = 1$, $\theta = 1.62 \times 10^8$, $\varphi_1(a) = 10 \times exp(-a)$, $\alpha = 0.009$, $\delta = 0.4$, $g_0 = 7$, $g_1 = 50$, $c_0 = 0.0009$, $c_1 = 0.00004$.

6 Conclusion

In this work, we have established an hybrid mathematical model of chronic myeloid leukemia diseases with resistance inspired by the works in ([6], [2], [5]). Our mathematical study was based on the research of the steady states and the demonstration of the stability that give us an idea about the behavior of our solutions.

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