A DYNAMIC MODEL OF CHRONIC MYELOID LEUKEMIA WITH DELAY

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Abstract: In this work, we investigate a time-delayed model describing the dynamics of the hematopoietic stem cell population with treatment. First we establish the existence of the steady states, trivial solution describing the extinction of the population and he nontrivial solution describing the persistence of the disease. Next, we analyze the asymptotic behavior of the model, and study the local asymptotic stability of steady states according to the delays values.

Keywords: Cell model, delay differential equation, leukemia, stability, steady states, existence of solutions.

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1. Introduction

The mathematical modeling of pathologic hematopoiesis is very large (see [2], [5], [6], [7], [9] [10], [14], [17]). In some works, stem cells models are studied using ordinary differential equations (ODEs), see for instance [8], [15] and [16]. Nevertheless, as the hematopoietic system is difficult, ODEs models in some cases do not suffice to describe kinds of dynamics observed in real life. The delay differential equations (DDEs) models constitute an interesting approach to model this disease (see [1]).

We are intersted by the following mathematical model with delay

$$\begin{cases} \dot{Q} &= -\gamma_Q Q - \eta_1 k_0 Q - \eta_2 k_0 Q - (1-\eta_1-\eta_2)\beta(Q)Q + \\ & \quad +2(1-\eta_1-\eta_2)\mathrm{e}^{-\gamma_Q \tau}\beta(Q_\tau)Q_\tau + \eta_1 k_0 \mathrm{e}^{-\gamma_Q \tau} Q_\tau - \tilde{r}_q(P)Q^{q+1}, \\ \dot{D} &= -\kappa D + K, \\ \dot{P} &= -vP + \kappa D, \end{cases} \tag{1}$$

where Q is the density of stem-cells population and D (resp. P) is the amount of drug in the absorption compartment (resp. in the plasmatic compartment). The parameters are described as follow:

η_1 is the percentage value of asymmetric division with daughter cell undistinguishable to the mother cell.

The stem cell population has a percentage η_2 which is symmetric differentiate and go to the line of mature cells.

The term $(1-\eta_1-\eta_2)$ has the property of self-renew, that means that the all cells resulting from mitosis coincide with the cell accessing in the cell cycle (see [18]).

In their paper, the authors assumed that all types of division has the same duration τ of cell cycle, where $Q_\tau(t) = Q(t-\tau)$ with the following definitions

The rate of self-renewal :$\beta(Q) = \beta_0 \frac{\theta^n}{\theta^n + Q^n},\ n > 1,$

The instant mortality rate: γ_Q,

The rate of differentiation and of asymmetric division: k_0,

The constant dose of administrated drug (imatinib):K.

The function modeling treatment effect is

$$\tilde{r}_q(P) = r(P)\frac{x_0 - R_0}{x_0^{q+1}} > 0$$

with $r(P) = \frac{P^m}{P^m + P_0^m}$,

where P_0 the half-maximum activity concentration,

m is a Hill coefficient,

x_0 is the number of infected cells,

R_0 is the number of cells resistent to treatment,

p is the probability of mutation, $q = -p \in (-1,0]$,

κ is the first order absorption rate,

v is the total plasma clearance of drug divided by the volume of distribution of the drug.

The model above describes the dynamics of leukemia stem cells under the treatment. It is studied in [4], [12], [18] and [19]. Inspired from the model above, we will present a new mathematical model describing the dynamics of leukemic stem cells with two delays τ_1 and τ_2 where τ_1 is the duration of the cell cycle for symmetric division (self-renew) and τ_2 is the duration of the cell cycle for asymmetric division. This leads to the following delayed differential equations (DDE) system

$$\begin{cases} \dot{x} & = & -\gamma_Q x - \eta_1 k_0 x - \eta_2 k_0 x - (1-\eta_1-\eta_2)\beta_0 \frac{x}{1+x^n} + \\ & & +2\mathrm{e}^{-\gamma_Q \tau_1}(1-\eta_1-\eta_2)\beta_0 \frac{x_{\tau_1}}{1+(x_{\tau_1})^n} + k_0\eta_1 \mathrm{e}^{-\gamma_Q \tau_2} x_{\tau_2} - r(P)x, \\ \dot{D} & = & -\kappa D + K, \\ \dot{P} & = & -vP + \kappa D. \end{cases} \tag{2}$$

Our paper is organized as follows. In Section 2 we establish the existence of steady states of system (2). A local asymptotic stability is establish in section 3. In the last section, we give some concluding remarks.

2. Existence of steady states

Let $\gamma := \gamma_Q + k_0\eta_1 + k_0\eta_2$. Then $\gamma + r_0(P) - k_0\eta_1 > 0$.

A solution $(x^*, D^*, P^*) \in \mathbb{R}_+^3$ is a steady state of (2) if and only if

$$\frac{dx^*}{dt} = \frac{dD^*}{dt} = \frac{dP^*}{dt} = 0.$$

The point $X_0 = (0, \frac{K}{\kappa}, \frac{K}{v})$ is called trivial steady state of (2), it exists for all $\tau_1, \tau_2 \geq 0$.

Let $(x^*, \frac{K}{\kappa}, \frac{K}{v})$ be a non-trivial steady state of (2) with $x^* \neq 0$.

Then x^* satisfies

$$\frac{\beta_0^*(2\mathrm{e}^{-\gamma_Q \tau_1} - 1)}{1 + x^{*n}} = r(P^*) + \gamma - k_0\eta_1 \mathrm{e}^{-\gamma_Q \tau_2} \tag{3}$$

where $\beta_0^* = (1-\eta_1-\eta_2)\beta_0$.

Remark 2.1 *Since $\gamma - k_0\eta_1 e^{-\gamma_Q \tau_2} > 0$, then a necessary condition of existence of solution of (3) is $2e^{-\gamma_Q \tau_1} > 1$, that is $\tau_1 < \tau_1^* := \frac{1}{\gamma_Q} ln2$.*

Let $k := k_0\eta_2 + r_0(P^*)$.

The system (2) has a nontrivial steady state $X_1 = \left(x^*, \frac{K}{\kappa}, \frac{K}{v}\right)$ where

$$(x^*)^n = \frac{\beta_0^*(2\mathrm{e}^{-\gamma_Q \tau_1} - 1) + k_0\eta_1 \mathrm{e}^{-\gamma_Q \tau_2} - \gamma_Q - k_0\eta_1 - k)}{\gamma_Q + k + k_0\eta_1 - k_0\eta_1 \mathrm{e}^{-\gamma_Q \tau_2}} \tag{4}$$

which exists for $\tau_1 < f_1(\tau_2) := \frac{1}{\gamma_Q} \ln\left(\frac{2\beta_0^*}{\beta_0^* + \gamma_Q + k + k_0\eta_1 - k_0\eta_1 \mathrm{e}^{-\gamma_Q \tau_2}}\right)$.

Since

$$f_1,(\tau_2) = \left(\frac{-k_0\eta_1 \mathrm{e}^{-\gamma_Q\tau_2}}{\beta_0^*+\gamma_Q+k+k_0\eta_1-k_0\eta_1\mathrm{e}^{-\gamma_Q\tau_2}}\right) < 0,$$

then we have the following cases

1. If $\lim_{\tau_2\to+\infty} f_1(\tau_2) \geq 0$ (*i.e.* $\beta_0^* \geq \gamma_Q + k + k_0\eta_1$), then X_1 exists for all $\tau_1 \in [0, f_1(\tau_2))$ and $\tau_2 \geq 0$.

2. If $\lim_{\tau_2\to+\infty} f_1(\tau_2) < 0$ and $f_1(0) > 0$ (*i.e.* $\gamma_Q + k < \beta_0^* < \gamma_Q + k + k_0\eta_1$), then X_1 exists for all $\tau_1 \in [0, f_1(\tau_2))$ and $\tau_2 \in [0, g_1(\beta_0^*)[$, where

$$g_1(\beta_0^*) := \frac{1}{\gamma_Q}\ln\left(\frac{k_0\eta_1}{\gamma_Q+k+k_0\eta_1-\beta_0^*}\right). \quad (5)$$

3. If $f_1(0) \leq 0$ (*i.e.* $\beta_0^* \leq \gamma_Q + k$), then X_1 doesn't exist for all $\tau_1, \tau_2 \geq 0$.

Let the following hypothesis

$H_1: \beta_0^* \leq \gamma_Q + k \ \ for \ \ \tau_1, \tau_2 \geq 0,$

$H_2: \gamma_Q + k < \beta_0^* < \gamma_Q + k + k_0\eta_1 \ for \ \tau_1 \in [0, f_1(\tau_2))$ and $\tau_2 \in [0, g_1(\beta_0^*))$,

$H_3: \beta_0^* \geq \gamma_Q + k + k_0\eta_1 \ for \ \ \tau_1 \in [0, f_1(\tau_2))$ and $\tau_2 \geq 0$,

$\overline{H}_2: \gamma_Q + k < \beta_0^* < \gamma_Q + k + k_0\eta_1 \ for \ either \ \tau_1 \notin [0, f_1(\tau_2)]$ or $\tau_2 \notin [0, g_1(\beta_0^*)]$ and

$\overline{H}_3: \beta_0^* \geq \gamma_Q + k + k_0\eta_1 \ for \ \ \tau_1 \notin [0, f_1(\tau_2)], \tau_2 \geq 0.$

The following theorem summarizes the existence of the steady states.

Theorem 2.2

1. The system (2) has always the trivial steady state $X_0 = (0, \frac{K}{\kappa}, \frac{K}{v})$.

2. Moreover, if either H_2 or H_3 is satisfied, then the system (2) has a nontrivial steady state $X_1 = (x^\star, \frac{K}{\kappa}, \frac{K}{v})$.

Furthermore $X_1 \to X_0$ when $\tau_1 \to f_1(\tau_2)$.

3 Stability of steady states

In this section, we focus on the local asymptotic stability of the steady states.

3.1 Stability of the trivial steady state X_0

Let $h(x) := \frac{x}{1+x^n}$, then $h'(0) = 1$.

The linearization of (2) at the point $(0, D^*, P^*)$ is given by

$$\begin{cases} \dot{x} &= -\gamma x - \beta_0^* x - r(P^*)x + 2\beta_0^* \mathrm{e}^{-\gamma_Q\tau_1} x_{\tau_1} + k_0\eta_1 e^{-\gamma_Q\tau_2} x_{\tau_2}, \\ \dot{y} &= -\kappa y, \\ \dot{z} &= -vz + \kappa y. \end{cases}$$

Then, the characteristic equation is given by

$$\Delta^0(\lambda, \tau) = det(\lambda I - M - e^{-\lambda\tau_1}N_1 - e^{-\lambda\tau_2}N_2) = 0 \quad (6)$$

with

$$M = \begin{pmatrix} -\gamma - \beta_0^* - r_0(P^*) & 0 & 0 \\ 0 & -\kappa & 0 \\ 0 & \kappa & -v \end{pmatrix},$$

$$N_1 = \begin{pmatrix} 2\beta_0^* \mathrm{e}^{-\gamma_Q \tau_1} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

and

$$N_2 = \begin{pmatrix} k_0 \eta_1 e^{-\gamma_Q \tau_2} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

Thus, (6) becomes

$$(\lambda + \kappa)(\lambda + \upsilon)[\lambda + \gamma_Q + \beta_0^* + k + k_0\eta_1 - 2\beta_0^* \mathrm{e}^{-\gamma_Q\tau_1}\mathrm{e}^{-\lambda\tau_1} - k_0\eta_1 \mathrm{e}^{-\gamma_Q\tau_2}\mathrm{e}^{-\lambda\tau_2}] = 0. \quad (7)$$

Since $\kappa > 0$ and $\upsilon > 0$, the stability depends on the third term in the left side of (7).

Put $A := \gamma_Q + k_0\eta_1 + k + \beta_0^*$, $B(\tau_1) := 2\beta_0^* \mathrm{e}^{-\gamma_Q\tau_1}$ and $C(\tau_2) := k_0\eta_1 \mathrm{e}^{-\gamma_Q\tau_2}$.

We obtain

$$\lambda + A - B(\tau_1)\mathrm{e}^{-\lambda\tau_1} - C(\tau_2)\mathrm{e}^{-\lambda\tau_2} = 0. \quad (8)$$

Our aim is to examine the solutions of the equation

$$M(\lambda) := \lambda + A - B(\tau_1)e^{-\lambda\tau_1} - C(\tau_2)\mathrm{e}^{-\lambda\tau_2} = 0, \quad \text{for} \quad \lambda \in \mathbb{C}. \quad (9)$$

Consider the mapping M as a function of real λ, which is an increasing function with $\lim_{\lambda\to+\infty} M(\lambda) = +\infty$ and $\lim_{\lambda\to-\infty} M(\lambda) = -\infty$. We deduce the existence of a unique real solution λ_0 of (9).

Therefore, we have $\lambda_0 = -A + B(\tau_1)e^{-\lambda_0\tau_1} + C(\tau_2)e^{-\lambda_0\tau_2}$.

Let λ be a solution of (4) such that $\lambda = \mu + i\omega \neq \lambda_0$ and $\omega \neq 0$. We have

$$\mu - \lambda_0 = B(\tau_1)[\mathrm{e}^{-\mu\tau_1}\cos(\omega\tau_1) - \mathrm{e}^{-\lambda_0\tau_1}] + C(\tau_2)[\mathrm{e}^{-\mu\tau_2}\cos(\omega\tau_2) - \mathrm{e}^{-\lambda_0\tau_2}] \leq \quad (10)$$

$$B(\tau_1)[\mathrm{e}^{-\mu\tau_1} - \mathrm{e}^{-\lambda_0\tau_1}] + C(\tau_2)[\mathrm{e}^{-\mu\tau_2} - \mathrm{e}^{-\lambda_0\tau_2}] \leq 0 \quad (11)$$

Then $\mu \leq \lambda_0$.

If $\mu = \lambda_0$, then (10) implies that $\cos(\omega\tau_1) = \cos(\omega\tau_2) = 1$.

It follows that $\sin(\omega\tau_1) = \sin(\omega\tau_2) = 0$.

The imaginary part of (9) yields

$$\omega + B(\tau_1)e^{-\mu\tau_1}\sin(\omega\tau_1) + C(\tau_2)\mathrm{e}^{-\mu\tau_2}\sin(\omega\tau_2) = 0. \quad (12)$$

We obtain $\omega = 0$, which is impossible. Thus, $\mu < \lambda_0$.

Hence, all possible solutions $\lambda \neq \lambda_0$ of (4) satisfy $\mathrm{Re}(\lambda) < \lambda_0$.

Since $M(0) = A - B(\tau_1) - C(\tau_2)$, then $\lambda_0 < 0$ for $A - B(\tau_1) - C(\tau_2) > 0$.

In this case all solutions of (9) have negative real parts. In this case, X_0 is locally asymptotically stable.

For $A - B(\tau_1) - C(\tau_2) < 0$, we have $\lambda_0 > 0$, in this case X_0 is unstable.

We deduce the following result.

Theorem 3.1 *The trivial steady state X_0 of (2) is locally asymptotically stable if one of the following hypothesis is satisfied H_1, $\overline{H}_2$ or $\overline{H}_3$.*

Remark 3.2 *The trivial steady state X_0 of (2) is unstable if either H_2 or H_3 is satisfied.*

3.2 Stability of the nontrivial steady state X_1

Assume that either H_2 or H_3 is satisfied.

Let $\beta_1 := h'(x_1^*) = \frac{1-(n-1)x_1^{*n}}{(1+x_1^{*n})^2}$. The linearization at the point (x^*, D^*, P^*) is given by

$$\begin{cases} \dot{x} & = -[\gamma + \beta_0^*\beta_1 + r_0(P^*)]x + 2\beta_0^*\beta_1 e^{-\gamma_Q\tau_1}x_{\tau_1} + k_0\eta_1 e^{-\gamma_Q\tau_2}x_{\tau_2}. -r_{0'}(P^*)x^*z, \\ \dot{y} & = -\kappa y, \\ \dot{z} & = -vz + \kappa y. \end{cases}$$

So, the characteristic equation is given by

$$\Delta_1^0(\lambda, \tau) := det(\lambda I - M_1 - e^{-\lambda\tau_1}N_3 - e^{-\lambda\tau_2}N_4) = 0 \tag{13}$$

with

$$M_1 = \begin{pmatrix} -\gamma - \beta_0^*\beta_1 - r_0(P^*) & 0 & -r_{0'}(P^*)x^* \\ 0 & -\kappa & 0 \\ 0 & \kappa & -v \end{pmatrix},$$

$$N_3 = \begin{pmatrix} 2\beta_0^*\beta_1 e^{-\gamma_Q\tau_1} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

and

$$N_4 = \begin{pmatrix} k_0\eta_1 e^{-\gamma_Q\tau_2} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

Then, (13) becomes

$$(\lambda + \kappa)(\lambda + v)[\lambda + \gamma + \beta_0^*\beta_1 + r_0(P^*) - 2\beta_0^*\beta_1 e^{-\gamma_Q\tau_1}e^{-\lambda\tau_1} - k_0\eta_1 e^{-\gamma_Q\tau_2}e^{-\lambda\tau_2}] = 0.$$

Since $\lambda_1 = -\kappa < 0$ and $\lambda_2 = -v < 0$, then the stability of X_1 depends on the following equation

$$\lambda + A_1(\tau_1, \tau_2) - B_1(\tau_1, \tau_2)e^{-\lambda\tau_1} - C(\tau_2)e^{-\lambda\tau_2} = 0 \tag{14}$$

where $A_1(\tau_1, \tau_2) := \gamma + \beta_0^*\beta_1 + r(P^*)$ and $B_1(\tau_1, \tau_2) := 2\beta_0^*\beta_1 e^{-\gamma_Q\tau_1}$.

Let $\lambda = u + iw$ be a solution of (14) then

$$u + iw + A_1(\tau_1, \tau_2) - B_1(\tau_1, \tau_2)e^{-(u+iw)\tau_1} - C(\tau_2)e^{-(u+iw)\tau_2} = 0.$$

Put

$$R(u) := u + A_1(\tau_1, \tau_2) - B_1(\tau_1, \tau_2)e^{-u\tau_1}cosw\tau_1 - C(\tau_2)e^{-u\tau_2}cosw\tau_2.$$

Proposition 3.3 *If $A_1(\tau_1, \tau_2) - |B_1(\tau_1, \tau_2)| - C(\tau_2) \geq 0$, then $\forall u > 0$, $\lambda = u + iw$ is not a solution of (14) which implies that X_1 is locally asymptotically stable.*

Proof. Since we have,

$$R(u) \geq u + A_1(\tau_1, \tau_2) - |B_1(\tau_1, \tau_2)|e^{-u\tau_1} - C(\tau_2)e^{-u\tau_2} =: R_1(u). \tag{15}$$

Then,

$R_{1'}(u) = 1 + \tau_1|B_1(\tau_1, \tau_2)|e^{-u\tau_1} + \tau_2 C(\tau_2)e^{-u\tau_2} > 0$ and $R_1(0) = A_1(\tau_1, \tau_2) - |B_1(\tau_1, \tau_2)| - C(\tau_2)$.

If $R_1(0) \geq 0$, then $\forall u > 0$, $R(u) \geq R_1(u) > 0$. We deduce that $\forall u > 0$, the eigenvalue $\lambda = u + iw$ is not a solution of (14). That is X_1 is locally asymptotically stable.

Next, we look for the sign of $R_1(0)$. We have

$$R_1(0) = \gamma + \beta_0^*\beta_1 + r(P^*) - 2\beta_0^*|\beta_1|e^{-\gamma_Q\tau_1} - k_0\eta_1 e^{-\gamma_Q\tau_2}$$
$$= \gamma + \beta_0^*\frac{1+(1-n)x^{*n}}{(1+x^{*n})^2} + r(P^*) - 2\beta_0^*\frac{|1+(1-n)x^{*n}|}{(1+x^{*n})^2}e^{-\gamma_Q\tau_1} - k_0\eta_1 e^{-\gamma_Q\tau_2}.$$

We have the following two cases.

- If $0 < x^{*n} \leq \frac{1}{n-1}$ then,

$$R_1(0) = \gamma + r_0(P^*) - k_0\eta_1 e^{-\gamma_Q\tau_2} + \beta_0^*(1 - 2e^{-\gamma_Q\tau_1})\frac{1+(1-n)x^{*n}}{(1+x^{*n})^2},$$

by using (3), we have

$$R_1(0) = \frac{anx^{*n}}{1+x^{*n}} > 0$$

where $a = \gamma_Q + k + k_0\eta_1 - k_0\eta_1 e^{-\gamma_Q\tau_2} > 0$.

- If $x^{*n} > \frac{1}{n-1}$, then

$$R_1(0) = \frac{H(x^{*n})}{(1+x^{*n})^2}$$

where

$$H(x^{*n}) = a(2-n)x^{*2n} + [a(4-n) + 2\beta_0^*(1-n)]x^{*n} + 2a + 2\beta_0^*$$

is a polynomial of second order in x^{*n}, with discriminant

$$\Delta = 4(n-1)^2\beta_0^{*2} + 4na(n-3)\beta_0^* + a^2n^2 > 0$$

for all $n \geq 3$. Hence, $R_1(0) \geq 0$ if and only if $\frac{1}{n-1} < x^{*n} \leq x_1^{*n}$, where

$$x_1^{*n} = \frac{a(n-4) + 2\beta_0^*(n-1) - \sqrt{\Delta}}{2a(2-n)}.$$

We deduce the following result.

Proposition 3.4 *If* $n \geq 3$ *and* $x^{*n} \leq x_1^{*n}$, *then* $R_1(0) > 0$.

Proposition 3.5

1. From (4), the inequality $x^{*n} > 0$ is equivalent to $\beta_0^* > a$.
2. The inequality $x^* < x_1^*$ is equivalent to $\tau_1 > f_2(\tau_2)$, where

$$f_2(\tau_2) := \frac{1}{\gamma_Q}\ln[\frac{4\beta_0^*(n-2)}{\sqrt{\Delta} + an - 2\beta_0^*}].$$

3. $\forall\tau_2 \geq 0$ we have $f_2(\tau_2) < f_1(\tau_2)$.
4. If $\gamma_Q + k < \beta_0^* \leq \frac{3n(\gamma_Q+k)}{3n-4}$, then $\forall\tau_2 > 0$ we have $f_2(\tau_2) < 0$.
5. If $\beta_0^* \geq \frac{3n(\gamma_Q+k+k_0\eta_1)}{3n-4}$, then $\forall\tau_2 > 0$ we have $f_2(\tau_2) > 0$.
6. If $\frac{3n(\gamma_Q+k)}{3n-4} < \beta_0^* < \frac{3n(\gamma_Q+k+k_0\eta_1)}{3n-4}$, then $\forall\tau_2 > g_2(\beta_0^*)$ (resp. $\forall\tau_2 \leq g_2(\beta_0^*)$) we have $f_2(\tau_2) < 0$ (resp. $f_2(\tau_2) \geq 0$), where

$$g_2(\beta_0^*) := \frac{1}{\gamma_Q}\ln\left(\frac{3nk_0\eta_1}{3n(\gamma_Q+k+k_0\eta_1) - (3n-4)\beta_0^*}\right).$$

7. If $k_0\eta_1 > \frac{4}{3n-4}(\gamma_Q + k)$ and $\frac{3n(\gamma_Q+k)}{3n-4} < \beta_0^* < (\gamma_Q + k + k_0\eta_1)$, then $g_2(\beta_0^*) < g_1(\beta_0^*)$.

In conclusion we have the following theorems.

Theorem 3.6 *Let* $k_0\eta_1 < \frac{4}{3n-4}(\gamma_Q + k)$. *Then we have the following results.*

(i). If $(\gamma_Q + k) < \beta_0^* < (\gamma_Q + k + k_0\eta_1)$, then X_1 is locally asymptotically stable for $\tau_2 \in [0, g_1(\beta_0^*))$ and $\tau_1 \in [0, f_1(\tau_2))$.

(ii). If $\gamma_Q + k + k_0\eta_1 \leq \beta_0^* \leq \frac{3n(\gamma_Q+k)}{3n-4}$, then X_1 is locally asymptotically stable for $\tau_2 \geq 0$ and $\tau_1 \in [0, f_1(\tau_2))$.

(iii). If $\frac{3n(\gamma_Q+k)}{3n-4} < \beta_0^* \leq \frac{3n(\gamma_Q+k+k_0\eta_1)}{3n-4}$, then X_1 is locally asymptotically stable for either $\tau_2 \geq g_2(\beta_0^*)$ with $\tau_1 \in [0, f_1(\tau_2))$, or $\tau_2 < g_2(\beta_0^*)$ with $\tau_1 \in (f_2(\tau_2), f_1(\tau_2))$.

(iv). If $\beta_0^* > \frac{3n(\gamma_Q+k+k_0\eta_1)}{3n-4}$, then X_1 is locally asymptotically stable for $\tau_2 \geq 0$ and $\tau_1 \in (f_2(\tau_2), f_1(\tau_2))$.

Theorem 3.7 *Let* $k_0\eta_1 > \frac{4}{3n-4}(\gamma_Q + k)$. *Then we have the following results.*

(i). If $(\gamma_Q + k) < \beta_0^* < \frac{3n(\gamma_Q+k)}{3n-4}$, then X_1 is locally asymptotically stable for $\tau_2 \in [0, g_1(\beta_0^*))$ and $\tau_1 \in [0, f_1(\tau_2))$.

(ii). If $\frac{3n(\gamma_Q+k)}{3n-4} \leq \beta_0^* \leq (\gamma_Q + k + k_0\eta_1)$, then X_1 is locally asymptotically stable for either $\tau_2 \in [0, g_2(\beta_0^*))$ with $\tau_1 \in (f_2(\tau_2), f_1(\tau_2))$, or $\tau_2 \in [g_2(\beta_0^*), g_1(\beta_0^*))$ with $\tau_1 \in [0, f_1(\tau_2))$.

(iii). If $(\gamma_Q + k + k_0\eta_1) < \beta_0^* \leq \frac{3n(\gamma_Q+k+k_0\eta_1)}{3n-4}$, then X_1 is locally asymptotically stable for either $\tau_2 \geq g_2(\beta_0^*)$ and $\tau_1 \in [0, f_1(\tau_2))$ or $\tau_2 < g_2(\beta_0^*)$ and $\tau_1 \in ((\tau_2), f_1(\tau_2))$.

(iv). If $\beta_0^* > \frac{3n(\gamma_Q+k+k_0\eta_1)}{3n-4}$, then X_1 is locally asymptotically stable for $\tau_2 \geq 0$ and $\tau_1 \in (f_2(\tau_2), f_1(\tau_2))$.

Theorem 3.8 *Let* $k_0\eta_1 = \frac{4}{3n-4}(\gamma_Q + k)$. *Then we have the following results.*

(i). If $(\gamma_Q + k) < \beta_0^* \leq \frac{3n}{3n-4}(\gamma_Q + k)$, then X_1 is locally asymptotically stable for $\tau_2 \in [0, g_1(\beta_0^*))$ and $\tau_1 \in [0, f_1(\tau_2))$.

(ii). If $\frac{3n}{3n-4}(\gamma_Q + k) < \beta_0^* \leq \left(\frac{3n}{3n-4}\right)^2 (\gamma_Q + k)$, then X_1 is locally asymptotically stable for either $\tau_2 \geq g_2(\beta_0^*)$ with $\tau_1 \in [0, f_1(\tau_2))$, or $\tau_2 < g_2(\beta_0^*)$ with $\tau_1 \in (f_2(\tau_2), f_1(\tau_2))$.

(iii). If $\beta_0^* > \left(\frac{3n}{3n-4}\right)^2 (\gamma_Q + k)$, then X_1 is locally asymptotically stable for $\tau_2 \geq 0$ and $\tau_1 \in (f_2(\tau_2), f_1(\tau_2))$.

Proof. From the previous results, one can easily show the results of theorems 3.6-3.8.

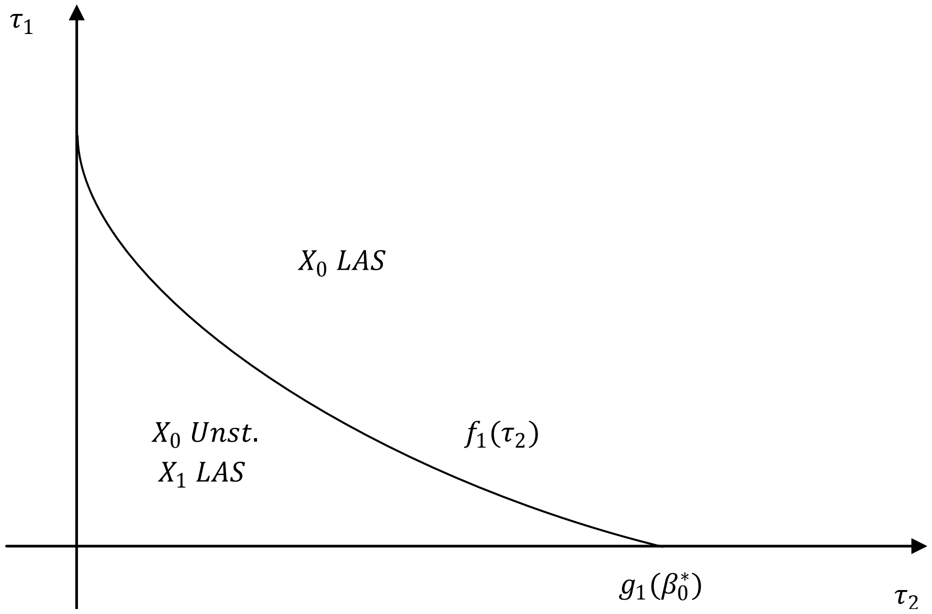

Figure 1: Existence and stability of the steady states X_0 and X_1 for the following cases.

1. $k_0\eta_1 < \frac{4}{3n-4}(\gamma_Q + k)$ and $(\gamma_Q + k) < \beta_0^* < (\gamma_Q + k + k_0\eta_1)$ (see (i), theorem 3.6).
2. $k_0\eta_1 > \frac{4}{3n-4}(\gamma_Q + k)$ and $(\gamma_Q + k) < \beta_0^* < \frac{3n(\gamma_Q+k)}{3n-4}$ (see (i), theorem 3.7).
3. $k_0\eta_1 = \frac{4}{3n-4}(\gamma_Q + k)$ and $\beta_0^* > \left(\frac{3n}{3n-4}\right)^2 (\gamma_Q + k)$ (see (i), theorem 3.8).

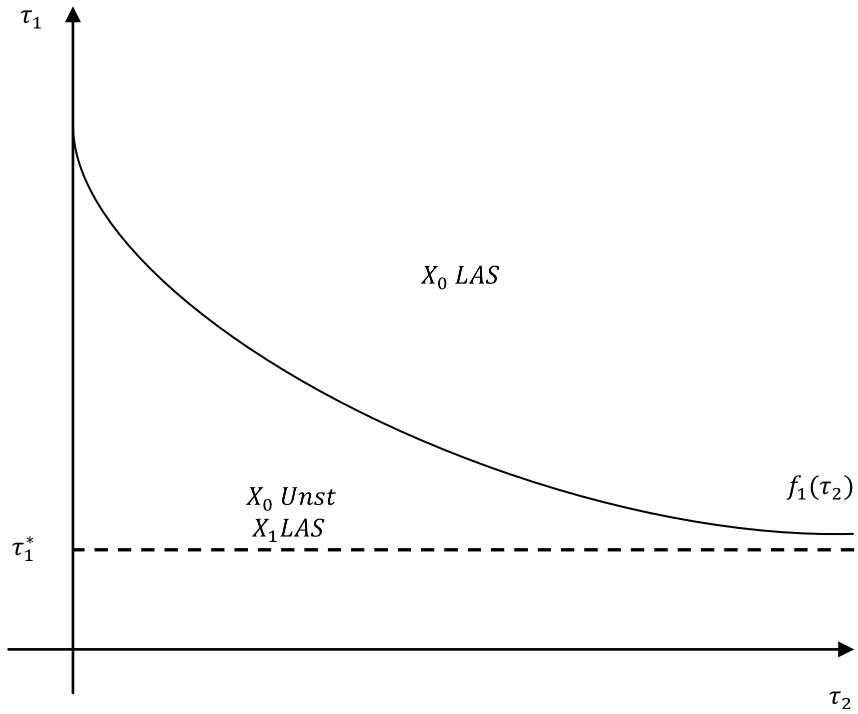

Figure 2: Existence and stability of the steady states X_0 and X_1 for the following case.

1. $k_0\eta_1 < \frac{4}{3n-4}(\gamma_Q + k)$ and $\gamma_Q + k + k_0\eta_1 \leq \beta_0^* \leq \frac{3n(\gamma_Q+k)}{3n-4}$ (see (ii), theorem 3.6) where $\tau_1^* = \lim_{\tau_2 \to +\infty} f_1(\tau_2)$.

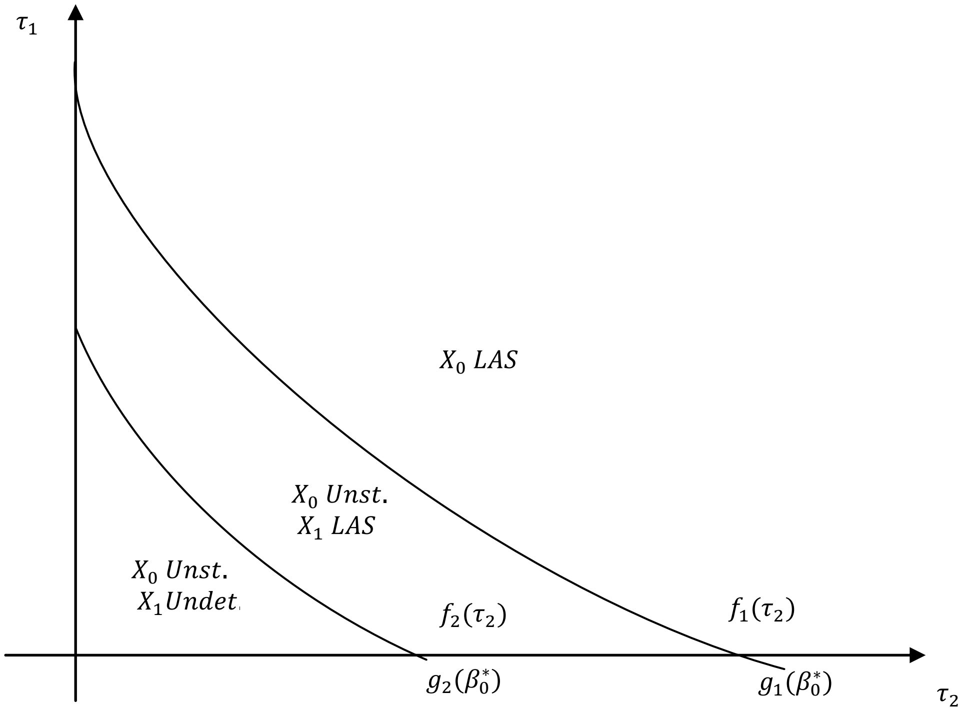

Figure 3: Existence and stability of the steady states X_0 and X_1 for the following case.

1. $k_0\eta_1 > \frac{4}{3n-4}(\gamma_Q + k)$ and $\frac{3n(\gamma_Q+k)}{3n-4} \leq \beta_0^* \leq (\gamma_Q + k + k_0\eta_1)$(see (ii), theorem 3.7).

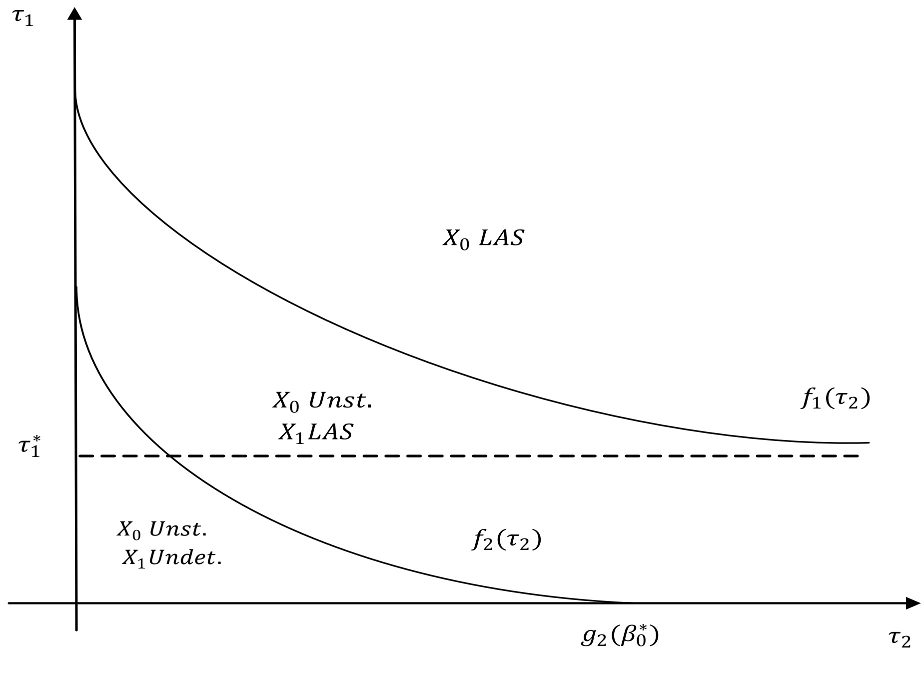

Figure 4: Existence and stability of the steady states X_0 and X_1 for the following cases.

1. $k_0\eta_1 < \frac{4}{3n-4}(\gamma_Q + k)$ and $\frac{3n(\gamma_Q+k)}{3n-4} < \beta_0^* \leq \frac{3n(\gamma_Q+k+k_0\eta_1)}{3n-4}$ (see (iii), theorem 3.6).
2. $k_0\eta_1 > \frac{4}{3n-4}(\gamma_Q + k)$ and $(\gamma_Q + k + k_0\eta_1) < \beta_0^* \leq \frac{3n(\gamma_Q+k+k_0\eta_1)}{3n-4}$ (see (iii), theorem 3.7).
3. $k_0\eta_1 = \frac{4}{3n-4}(\gamma_Q + k)$ and $\frac{3n}{3n-4}(\gamma_Q + k) < \beta_0^* < \left(\frac{3n}{3n-4}\right)^2 (\gamma_Q + k)$(see (ii), theorem 3.8) where $\tau_1^* = \lim_{\tau_2 \to +\infty} f_1(\tau_2)$.

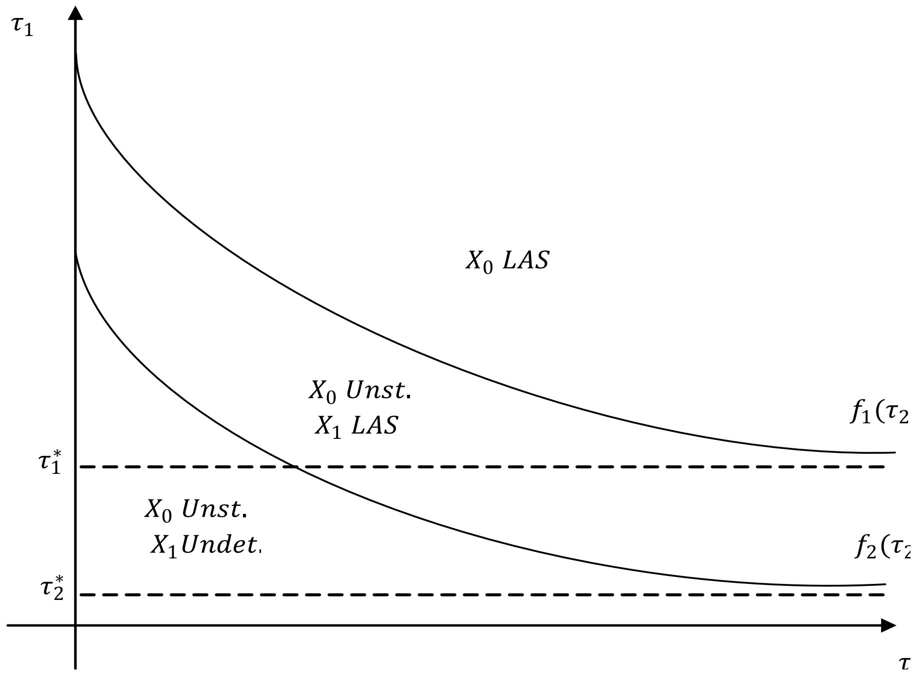

Figure 5: Existence and stability of the steady states X_0 and X_1 for the following cases.

1. $k_0\eta_1 < \frac{4}{3n-4}(\gamma_Q + k)$ and $\beta_0^* > \frac{3n(\gamma_Q+k+k_0\eta_1)}{3n-4}$ (see (iv), theorem 3.6).
2. $k_0\eta_1 > \frac{4}{3n-4}(\gamma_Q + k)$ and $\beta_0^* > \frac{3n(\gamma_Q+k+k_0\eta_1)}{3n-4}$ (see (iv), theorem 3.7).
3. $k_0\eta_1 = \frac{4}{3n-4}(\gamma_Q + k)$ and $\beta_0^* > \left(\frac{3n}{3n-4}\right)^2(\gamma_Q + k)$(see (iii), theorem 3.8) where $\tau_1^* = \lim_{\tau_2\to+\infty} f_1(\tau_2)$ and $\tau_2^* = \lim_{\tau_2\to+\infty} f_2(\tau_2)$.

4 Conclusion

In this work, we have established a new mathematical model for Leukemia which is inspired from the works in [4] and [18]. The existence and stability of steady states were established according to the parameter τ_1, τ_2 and β_0^*. We have showed that the trivial steady state X_0 exists for all $\tau_1 > 0$ and $\tau_2 > 0$ and is locally asymptotically stable when the nontrivial steady state X_1 doesn't exists. Moreover, when the trivial steady state X_0 is unstable we have showed the existence of a nontrivial steady state X_1 which is stable for some sufficient conditions.

For the future work, we plan to study the possible bifurcation of periodic solutions at some specific values of the delays parameter τ_1, τ_2 and also some numerical simulations to illustrate our theoretical results.

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