A mathematical model for leukaemia cell dynamics during treatment

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1 Introduction

In this work, a mathematical model for the dynamics of leukemic cells during treatment is introduced. The process of the evolution of leukemic pluripotent short-term cells and of multipotent progenitor cells (all these are assembled under the name of stem-like cells) will be modeled by a delay differential equation. Treatment is included in the model through two state variables: D, the amount of drug in the absorbtion compartment and P, the amount of drug in the plasmatic compartment,(see [1],[2] et [4]). Let Q denote the density of stem-cells population. A percentage η_1 of these ones are supposed to undergo asymmetric division with one daughter cell identical to the mother cell and the other one committed to differentiation. A percentage η_2 of the stem-like population differentiate symmetrically and go to the line of mature cells. The rest of them, a percentage $(1 - \eta_1 - \eta_2)$, is supposed to self-renew: both cells that result from mitosis are identical to the cell that entered the cell cycle. The same duration τ of the cell cycle is supposed for all types of division. The equations that describe the evolution are:

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

where $Q_\tau(t) = Q(t-\tau)$, $\beta(Q) = \beta_0 \dfrac{\theta^n}{\theta^n + Q^n}$, $n > 1$, is the rate of self-renewal, γ_Q is the instant mortality rate, k_0 is the rate of differentiation and of asymmetric division that usually depends on different exogen factors but is taken to be constant in this model. The function modeling treatment effect (including resistance) is

$$r(P) = \frac{P^m}{P^m + P_0^m}\frac{x_0 - R_0}{x_0} > 0$$

where P_0 is the half maximum activity concentration, m is a Hil coefficient(see [1]), x_0 is the number of infected cells, R_0 is the number of cells resistant to treatment, κ is the first order absorption rate, v is the total plasma clearance of drug divided by the volume of distribution of the drug and K is the dose of drug administrated in a unit of time that is taken to be constant.

2 Existence and Uniqueness of solutions

Consider the system ($\star$) with initial conditions,

$$Q(t) = \varphi(t) \quad t \in [-\tau, 0], \qquad D(0) = D_0 \quad \text{and} \quad P(0) = P_0.$$

If the system $(\star)$ admits, for all non-negative initial conditions, a unique solution, then this solution remains non-negative for $t \geq 0$. In fact for a solution $(Q(t), D(t), P(t))$ of the system $(\star)$ we have that D and P positive for any positive initial condition.
Suppose that $t_0 > 0$ is the first time such that $Q(t_0) = 0$, then $Q(t) > 0$ for $t < t_0$ and $Q(t_0) \leq 0$. From $(\star)$ we have

$$\dot{Q}(t_0) = 2(1-\eta_1-\eta_2)\mathrm{e}^{-\gamma_Q\tau}\beta(Q(t-\tau))Q(t-\tau) + \eta_1 k_0 \mathrm{e}^{-\gamma_Q\tau}Q(t-\tau) > 0,$$

which is impossible. Then , $Q(t) > 0$ for all $t > 0$.

Proposition 2.1. *For all initial conditions* $(\varphi, D_0, P_0) \in C([-\tau, 0], \mathbb{R}_+) \times \mathbb{R}_+^2$ *the system* $(\star)$ *has a unique positive solution in* $[0, +\infty[$.

Proof. From [3], for any continuous initial condition, the system $(\star)$ admits a maximal continuous solution $(Q(t), D(t), P(t))$, well defined for $t \in [0, T)$ and this solution is bounded.
In fact, D and P are bounded. It remains to prove that Q is bounded.
For $t \in [0, T[$,

$$\begin{aligned}
Q(t) =& \mathrm{e}^{-\gamma t}Q(0) - (1-\eta_1-\eta_2)\int_0^t \mathrm{e}^{-\gamma(t-s)}\beta(Q(s))Q(s)\,ds \\
&+ 2(1-\eta_1-\eta_2)\mathrm{e}^{-\gamma_Q\tau}\int_0^t \mathrm{e}^{-\gamma(t-s)}\beta(Q(s-\tau))Q(s-\tau)\,ds \\
&+ \eta_1\, k_0\, \mathrm{e}^{-\gamma_Q\tau}\int_0^t \mathrm{e}^{-\gamma(t-s)}Q(s-\tau)ds - \int_0^t \mathrm{e}^{-\gamma(t-s)}\tilde{r}(P)Q\,ds \\
\leq& \mathrm{e}^{-\gamma t}Q(0) + 2(1-\eta_1-\eta_2)\mathrm{e}^{-\gamma_Q\tau}\int_0^t \mathrm{e}^{-\gamma(t-s)}\beta(Q(s-\tau))Q(s-\tau)\,ds \\
&+ \eta_1\, k_0\, \mathrm{e}^{-\gamma_Q\tau}\int_0^t \mathrm{e}^{-\gamma(t-s)}Q(s-\tau)\,ds.
\end{aligned}$$

Then,

$$\begin{aligned}
Q(t) \leq& Q(0) + 2(1-\eta_1-\eta_2)\mathrm{e}^{(-\gamma_Q+\gamma)\tau}\beta(0)\int_{-\tau}^{t-\tau} \mathrm{e}^{\gamma\theta}Q(z)dz + \eta_1 k_0 \mathrm{e}^{-(\gamma_Q+\gamma)\tau}\int_{-\tau}^{t-\tau} \mathrm{e}^{\gamma\theta}Q(z)dz \\
\leq& Q(0) + \int_{-\tau}^t U\mathrm{e}^{\gamma\theta}Q(z)dz.
\end{aligned}$$

Where $U = [2(1-\eta_1-\eta_2)\mathrm{e}^{(-\gamma_Q+\gamma)\tau}\beta(0) + \eta_1 k_0 \mathrm{e}^{-(\gamma_Q+\gamma)\tau}]$. By virtue of Gronwall's lemma, we deduce that $Q(t) \leq Q(0)\exp(\int_{-\tau}^t U\,\mathrm{e}^{\gamma\theta}d\theta)$. Therefore, we have
$Q(t) \leq Q(0)\exp\left[\dfrac{U(\mathrm{e}^{\gamma T} - \mathrm{e}^{-\gamma\tau})}{\gamma}\right]$. Thus, $(\star)$ has a unique solution in $\mathbb{R}_+$. $\square$

3 Existence of equilibrium point

Let $Q = \theta x$. The system $(\star)$ is written as follows,

$$\begin{cases}
\dot{x} = & -\gamma_Q x - \eta_1 k_0 x - \eta_2 k_0 x - (1-\eta_1-\eta_2)\beta_0 \dfrac{x}{1+x^n} + \\
& + \mathrm{e}^{-\gamma_Q\tau}[2(1-\eta_1-\eta_2)\beta_0 \dfrac{1}{1+x_\tau^n} + k_0\eta_1]x_\tau - r(P)x \\
\dot{D} = & -\kappa D + K \\
\dot{P} = & -vP + \kappa D
\end{cases} \tag{1}$$

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

A solution $(x^*, D^*, P^*) \in \mathbb{R}_+^3$ is an equilibrium point of (1) if $\dfrac{dx^*}{dt} = \dfrac{dD^*}{dt} = \dfrac{dP^*}{dt} = 0$. The equilibrium point $X_0 = \left(0, \dfrac{K}{\kappa}, \dfrac{K}{v}\right)$ is called the trivial equilibrium point of (1),it

exists for all $\tau \geq 0$.
Let $\left(x^*, \frac{K}{\kappa}, \frac{K}{v}\right)$ be a non-trivial equilibrium point of (1) i.e. $x^* \neq 0$. Then, x^* satisfies

$$\frac{\beta_0^*(2\mathrm{e}^{-\gamma_Q \tau} - 1)}{1 + x^{*n}} = r(P^*) + \gamma - k_0\eta_1 \mathrm{e}^{-\gamma_Q \tau} \text{ where } \beta_0^* = (1 - \eta_1 - \eta_2)\beta_0. \tag{2}$$

Remark 1. *Since* $r(P^*) > 0$ *and* $\gamma - k_0\eta_1\mathrm{e}^{-\gamma_Q\tau} > 0$, *then a necessary condition, for the existence of the solutions of* (2), *is* $2\mathrm{e}^{-\gamma_Q\tau} > 1$.

The system (1) has two equilibrium points X_0 and $X_1 = \left(x_1^*, \frac{K}{\kappa}, \frac{K}{v}\right)$ where

$$(x_1^*)^n = \frac{[2\beta_0^* + k_0\eta_1]\,\mathrm{e}^{-\gamma_Q\tau} - \beta_0^* - \gamma - r(P^*)}{\gamma + r(P^*) - k_0\eta_1\mathrm{e}^{-\gamma_Q\tau}} \tag{3}$$

which exists for any τ such that $\tau < \bar{\tau} := \frac{-1}{\gamma_Q} \ln\left(\frac{\beta_0^* + \gamma + r(P^*)}{2\beta_0^* + k_0\eta_1}\right)$.

Remark 2. $\bar{\tau} > 0$ *if and only if* $\beta_0^* > \gamma + r(P^*) - k_0\eta_1$.

We have the following result.

Theorem 3.1. *1. If* $\beta_0^* \leq \gamma + r(P^*) - k_0\eta_1$, *then* (1) *admits a unique equilibrium point, denoted by* X_0 *for all* $\tau \geq 0$.

2. If $\beta_0^* > \gamma + r(P^*) - k_0\eta_1$, *then* (1) *has two equilibrium points* X_0 *and* $X_1 = (x_1^*, \frac{K}{\kappa}, \frac{K}{v})$ *which exists for all* τ *in* $[0, \bar{\tau}[$.
In addition, $X_1 \to X_0$ *when* $\tau \to \bar{\tau}$.

4 Stability of the trivial equilibrium point X_0

Let $h(x) := \frac{x}{1 + x^n}$, then $h'(0) = 1$.
The linearized system of (1) with respect to $(0, D^*, P^*)$ is given by

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

The characteristic equation is given by

$$\mathrm{Det}(\lambda I - M - e^{-\lambda\tau}N) = 0, \tag{4}$$

where $M = \begin{pmatrix} -\gamma - \beta_0^* - r(P^*) & 0 & 0 \\ 0 & -\kappa & 0 \\ 0 & \kappa & -v \end{pmatrix}$, $N = \begin{pmatrix} e^{-\gamma_Q\tau}[2\beta_0^* + k_0\eta_1] & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$.
Thus, (4) becomes

$$(\lambda + \kappa)(\lambda + v)[\lambda + \gamma + \beta_0^* + r(P^*) - \mathrm{e}^{-\gamma_Q\tau}(2\beta_0^* + k_0\eta_1)\mathrm{e}^{-\lambda\tau}] = 0. \tag{5}$$

Let $\kappa > 0$ and $v > 0$, then the stability depends on the third term on the left-hand side (5).
Let $A_0 := \gamma + \beta_0^* + r(P^*)$ and $B_0(\tau) := \mathrm{e}^{-\gamma_Q\tau}(2\beta_0^* + k_0\eta_1)$. Then we obtain

$$\lambda + A_0 - B_0(\tau)\mathrm{e}^{-\lambda\tau} = 0. \tag{6}$$

The objective is to examine the solutions of the equation

$$f(\lambda) := \lambda + A(\tau) - B(\tau)e^{-\lambda\tau} = 0, \quad \text{for} \quad \lambda \in \mathbb{C}. \tag{7}$$

Proposition 4.1. *Let* $B(\tau) \geq 0$ *for* $\tau \geq 0$.

1. *If* $A(\tau) - B(\tau) > 0$, *then any solution* $\lambda \in \mathbb{C}$ *of* (7) *satisfies* $\mathrm{Re}(\lambda) < 0$.

2. If $A(\tau) - B(\tau) < 0$, then (7) admits a real solution $\lambda_0 > 0$.

Proof. Consider f as a function of reel λ, which is increasing from $-\infty$ to $+\infty$. From this, we can deduce the existence of a unique real solution λ_0 of (7). Then, we have $\lambda_0 = -A(\tau) + B(\tau)e^{-\lambda_0\tau}$. If λ is a solution of (7) such that $\lambda = \mu + i\omega \neq \lambda_0$ and $\omega \neq 0$, then

$$\mu - \lambda_0 = B(\tau)[\mathrm{e}^{-\mu\tau}\cos(\omega\tau) - \mathrm{e}^{-\lambda_0\tau}] \leq B(\tau)(\mathrm{e}^{-\mu\tau} - \mathrm{e}^{-\lambda_0\tau}). \tag{8}$$

Thus $\mu \leq \lambda_0$. If $\mu = \lambda_0$ then (8) implies that $\cos(\omega\tau) = 1$, for $\tau \geq 0$. It follows that $\sin(\omega\tau) = 0$. The imaginary part in (7) gives $\omega + B(\tau)e^{-\mu\tau}\sin(\omega\tau) = 0$. from which we obtain $\omega = 0$, which is impossible. Then, $\mu < \lambda_0$. Hence, any eventual solution $\lambda \neq \lambda_0$ of (7) satisfies $\mathrm{Re}(\lambda) < \lambda_0$. Since $f(0) = A(\tau) - B(\tau)$, then $\lambda_0 < 0$ for $A(\tau) - B(\tau) > 0$. In this case any solution of (7) has a negative real part. For $A(\tau) - B(\tau) < 0$, we have $\lambda_0 > 0$. □

We obtain the following result.

Theorem 4.1. *The trivial equilibrium point X_0 of (1) is locally asymptotically stable for $\tau > \bar{\tau}$ and unstable for $\tau < \bar{\tau}$.*

Proof. If $\tau > \bar{\tau}$ then $A(\tau) - B(\tau) = A_0 - B_0(\tau) > 0$, then from the Proposition 4.1, all solution $\lambda \in \mathbb{C}$ of (6) satisfies $\mathrm{Re}(\lambda) < 0$. In addition, X_0 is locally asymptotically stable for $\tau > \bar{\tau}$. And if $\tau < \bar{\tau}$ then $A_0 - B_0(\tau) < 0$. Hence (6) has a real solution $\lambda_0 > 0$. Therefore, X_0 is unstable for $\tau < \bar{\tau}$. □

5 Stability of non-trivial equilibrium point X_1

X_1 exists for $\tau \in [0, \bar{\tau}[$ if the inequality $\beta_0^* > \gamma + r(P^*) - k_0\eta_1$ is satisfied.
Let $\beta_1 := h'(x_1^*)$. The linearization around (x_1^*, D^*, P^*) is given by

$$\begin{cases} \dot{x} &= -[\gamma + \beta_0^*\beta_1 + r(P^*)]x + e^{-\gamma_Q\tau}[2\beta_0^*\beta_1 + k_0\eta_1].x_\tau - r'(P^*)x_1^*z, \\ \dot{y} &= -\kappa y, \\ \dot{z} &= -vz + \kappa y. \end{cases}$$

Therefore, the characteristic equation is given by

$$\Delta_1^0(\lambda, \tau) := \mathrm{Det}(\lambda I - M_1 - e^{-\lambda\tau}N_1) = 0 \tag{9}$$

with $M_1 = \begin{pmatrix} -\gamma - \beta_0^*\beta_1 - r(P^*) & 0 & -r'(P^*)x_1^* \\ 0 & -\kappa & 0 \\ 0 & \kappa & -v \end{pmatrix}$, $N_1 = \begin{pmatrix} e^{-\gamma_Q\tau}[2\beta_0^*\beta_1 + k_0\eta_1] & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$.
Then, (9) becomes

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

Then, the stability of X_1 depends on the following equation,

$$\lambda + A_1(\tau) - B_1(\tau)e^{-\lambda\tau} = 0, \tag{10}$$

where $\quad A_1(\tau) := \gamma + \beta_0^*\beta_1 + r(P^*) \quad$ and $\quad B_1(\tau) := e^{-\gamma_Q\tau}[2\beta_0^*\beta_1 + k_0\eta_1]$.

Proposition 5.1. *For τ in $[0, \bar{\tau}[$, we have $A_1(\tau) - B_1(\tau) > 0$.*

Proof.

$$\begin{aligned} A_1(\tau) - B_1(\tau) &= \gamma + r(P^*) + \beta_0^*\beta_1 - \mathrm{e}^{-\gamma_Q\tau}[2\beta_0^*\beta_1 + k_0\eta_1], \\ &= \gamma + r(P^*) - k_0\eta_1\mathrm{e}^{-\gamma_Q\tau} - \frac{\beta_0^*(2\mathrm{e}^{-\gamma_Q\tau} - 1)}{1 + x_1^{*n}} + \frac{nx_1^{*n}\beta_0^*(2\mathrm{e}^{-\gamma_Q\tau} - 1)}{(1 + x_1^{*n})^2}, \\ &= \frac{nx_1^{*n}\beta_0^*(2e^{-\gamma_Q\tau} - 1)}{(1 + x_1^{*n})^2} > 0. \end{aligned}$$

□

Remark 3. *From the Propositions 4.1 and 5.1, we deduce that the stability of X_1 is satisfied for $B_1(\tau) \geq 0$, for $0 \leqslant \tau < \bar{\tau}$.*

We suppose the following assumptions

(H_0)**:** $\beta_0^\star > \gamma + r(P^\star) - k_0\eta_1$,

(H_1)**:** $(\gamma + r(P^*)) > \dfrac{nk_0\eta_1}{n-1}$ and $\dfrac{2nk_0\eta_1}{(n-1)^2} < \beta_0^* < \dfrac{2n(\gamma + r(P^*) - k_0\eta_1)^2}{2(\gamma + r(P^*))(n-1) - (2n-1)k_0\eta_1}$.

Lemma 5.1. *If (H_0) or (H_1) are satisfied, then $B_1(\tau) \geq 0$ for all $\tau \in [0, \bar{\tau}[$.*

Proof. The signs of $B_1(\tau)$ and $2\beta_0^*\beta_1 + k_0\eta_1$ are the same.
We have $2\beta_0^*\beta_1 + k_0\eta_1 = 2\beta_0^* \dfrac{1 + (x_1^*)^n(1-n)}{(1 + (x_1^*)^n)^2} + k_0\eta_1$. Then,

$$2\beta_0^*\beta_1 + k_0\eta_1 = \frac{1}{(1 + (x_1^*)^n)^2}[k_0\eta_1(x_1^*)^{2n} + [2k_0\eta_1 + 2\beta_0^*(1-n)](x_1^*)^n + k_0\eta_1 + 2\beta_0^*]$$

.

The term $k_0\eta_1(x_1^*)^{2n} + [2k_0\eta_1 + 2\beta_0^*(1-n)](x_1^*)^n + k_0\eta_1 + 2\beta_0^*$ is a polynomial of the second degree in $(x_1^*)^n$, with discriminant $\Delta = \beta_0^*[\beta_0^*(n-1)^2 - 2nk_0\eta_1]$. From (H_0) we have $\Delta \leq 0$ therefore $B_1(\tau) \geq 0$ for all $\tau \in [0, \bar{\tau}[$. From (H_1) we have $\beta_0^* > \dfrac{2nk_0\eta_1}{(n-1)^2}$, then $\Delta > 0$. Therefore, the polynomial considered has roots s_1, s_2 such that
$s_1 = \dfrac{-k_0\eta_1 + \beta^*(n-1) + \sqrt{\Delta}}{k_0\eta_1}$, $\quad s_2 = \dfrac{-k_0\eta_1 + \beta^*(n-1) - \sqrt{\Delta}}{k_0\eta_1}$ and $s_1 > s_2$.
Since $\beta_0^* > \dfrac{2nk_0\eta_1}{(n-1)^2}$, we have $\beta_0^* > \dfrac{k_0\eta_1}{n-1}$. Then s_1 and s_2 are positive.
From (3) we must have $s_i = (x_1^*)^n = \dfrac{[2\beta_0^* + k_0\eta_1]e^{-\gamma_Q\tau} - \beta_0^* - \gamma - r(P^*)}{\gamma + r(P^*) - k_0\eta_1 e^{-\gamma_Q\tau}} =: g(\tau)$.
Since $g'(\tau) = \dfrac{-\gamma_Q\beta_0^* e^{-\gamma_Q\tau}\,[2(\gamma + r(P^*)) - k_0\eta_1]}{\left[r(P^*) + \gamma - k_0\eta_1 e^{-\gamma_Q\tau}\right]^2} < 0$, then g is a decreasing function on $]\frac{-1}{\gamma_Q}\ln(\frac{\gamma + r(P^*)}{k_0\eta_1}), +\infty[$. So there are τ_1 τ_2, such that $s_i = g(\tau_i)$, $i = 1, 2$, where
$\tau_1 = -\dfrac{1}{\gamma_Q}\ln\left[\dfrac{\beta_0^* k_0\eta_1 + (\gamma + r(P^*))\beta_0^*(n-1) + (\gamma + r(P^*))\sqrt{\Delta}}{k_0\eta_1\beta_0^*(n+1) + k_0\eta_1\sqrt{\Delta}}\right]$ and
$\tau_2 = -\dfrac{1}{\gamma_Q}\ln\left[\dfrac{\beta_0^* k_0\eta_1 + (\gamma + r(P^*))\beta_0^*(n-1) - (\gamma + r(P^*))\sqrt{\Delta}}{k_0\eta_1\beta_0^*(n+1) - k_0\eta_1\sqrt{\Delta}}\right]$.
Since $s_1 > s_2 > 0$, then $g(\tau_1) > g(\tau_2) > 0 = g(\bar{\tau})$ thus $\tau_1 < \tau_2 < \bar{\tau}$. Then, $B_1(\tau) < 0$ for $\tau \in]\tau_1, \tau_2[$ and $B_1(\tau) > 0$ for $\tau < \tau_1$ or $\tau \in]\tau_2, \bar{\tau}[$. From (H_1) we have $\tau_2 < 0$. Then $B_1(\tau) > 0$ for $\tau \in [0, \bar{\tau}[$. □

We deduce the following result.

Theorem 5.1. *If (H_0) or (H_1) is satisfied, then X_1 is locally asymptotically stable for $\tau \in [0, \bar{\tau}.[$*

Proof. From the lemma 5.1, the Propositions 5.1 and 4.1, all solution of (10) have a negative real part. Then, X_1 is locally asymptotically stable for $\tau \in [0, \bar{\tau}[$. □

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