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STABILITY ANALYSIS IN A MODEL FOR STEM-LIKE HEMATOPOIETIC CELLS DYNAMICS IN LEUKEMIA UNDER TREATMENT *

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Abstract

A one dimensional delay differential equation modeling leukemia under treatment is investigated to decide over the stability of equilibria and existence of Hopf bifurcations. All three types of stem cell division (asymmetric division, symmetric renewal and symmetric differentiation) are considered. The effect of drug resistance is considered through the Goldie-Coldman law.

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1 Introduction

The population of cells whose evolution is modeled in the paper consists of stem cells and progenitors that preserve the capacity of self-renewal. The model is adapted from the Mackey-Glass model where, besides differentiation and self-renewal, asymmetric division is included. Thus, a percentage η_1 of population is supposed to undergo asymmetric division: one daughter cell proceeds to differentiation and maturation while the other one re-enters

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the stem cell compartment. A percentage η_2 of the population differentiate symmetrically with both daughter cells going to a phase of maturation. The percentage $(1-\eta_1-\eta_2)$ of the population is supposed to self-renew: both cells that come out of mitosis are stem cells (see [26]).

The same duration τ of the cell cycle is supposed for all types of division.

Let Q denote the density of the stem-like cell population. The equation that describes its evolution is

$$\begin{aligned} \dot{Q} &= -\gamma_Q Q - \eta_2 k_0 Q - \eta_1 k_0 Q - (1-\eta_1-\eta_2)\beta(Q)Q + \\ &+ 2(1-\eta_1-\eta_2)e^{-\gamma_Q\tau}\beta(Q_\tau)Q_\tau + \eta_1 k_0 e^{-\gamma_Q\tau}Q_\tau \end{aligned} \tag{1.1}$$

where $Q_\tau(t) = Q(t-\tau)$,

$$\beta(Q) = \beta_0 \frac{\theta^n}{\theta^n + Q^n} \tag{1.2}$$

is the rate of self-renewal (see [20], [21]), γ_Q is the instant mortality rate and k_0 is the rate of differentiation and of asymmetric division. Actually, k_0 depends on different exogen factors: the number of mature cells in circulation, growth factors, etc (see [10], [2], [4], [5]) but in this model will be considered constant. When a scaling is done through $Q = \theta x$ equation (1.1) becomes

$$\begin{aligned} \dot{x} &= -\gamma_Q x - \eta_2 k_0 x - \eta_1 k_0 x - (1-\eta_1-\eta_2)\frac{\beta_0}{1+x^n}x + \\ &+ e^{-\gamma_Q\tau}\left[2(1-\eta_1-\eta_2)\frac{\beta_0}{1+x_\tau^n} + k_0\eta_1\right]x_\tau \end{aligned}$$

It is convenient to introduce

$$\gamma = \gamma_Q + \eta_1 k_0 + \eta_2 k_0 \tag{1.3}$$

so the equation to be studied becomes

$$\begin{aligned} \dot{x} &= -\gamma x - (1-\eta_1-\eta_2)\frac{\beta_0}{1+x^n}x + \\ &+ e^{-\gamma_Q\tau}\left[2(1-\eta_1-\eta_2)\frac{\beta_0}{1+x_\tau^n} + k_0\eta_1\right]x_\tau. \end{aligned} \tag{1.4}$$

One can easily see that if $x(\theta) > 0$ for all θ in $[-\tau, 0]$ then $x(t) > 0$ for all $t > 0$. Indeed, if $x(T) = 0$ for some $T > 0$ then

$$\dot{x}(T) = e^{-\gamma_Q\tau}\left[2(1-\eta_1-\eta_2)\frac{\beta_0}{1+x^n(T-\tau)} + k_0\eta_1\right]x(T-\tau) > 0$$

and this is a contradiction to the fact that x must decrease in order to become zero.

In what follows the stability of equilibria of (1.4) will be investigated, through the use of the linear approximation. The main references for the stability in the first approximation are [15] and [17]. It will be also proved that if the delay depasses a certain threshold, a Hopf bifurcation appears. The stability of the limit cycles will be studied by computing the first Lyapunov coefficient (see [18]). In section 4, the treatment with Imatinib will be incorporated in the model. Effects of drug resistance are taken into consideration through the Goldie-Coldman law ([16]). Numerical results and simulations in Section 5 illustrate the theory in previous sections. Some Concluding remarks will end the paper.

2 Stability of equilibria

An equilibrium point x^* of (1.4) verifies

$$\gamma x^* + (1-\eta_1-\eta_2)\frac{\beta_0}{1+x^{*n}}x^* = e^{-\gamma_Q\tau}\left[\frac{2(1-\eta_1-\eta_2)\beta_0}{1+x^{*n}} + k_0\eta_1\right]x^*.$$

The first equilibrium point is $x_1^* = 0$. It corresponds to the extinction of the cell population. Another equilibrium point is given by

$$x^{*n} = \frac{(1-\eta_1-\eta_2)\beta_0(2e^{-\gamma_Q\tau}-1)}{\gamma-\eta_1 k_0 e^{-\gamma_Q\tau}} - 1$$

so, if the later expressions is greater then zero, a second equilibrium point will be given by

$$x_2^* = \left[\frac{(1-\eta_1-\eta_2)\beta_0(2e^{-\gamma_Q\tau}-1)}{\gamma-\eta_1 k_0 e^{-\gamma_Q\tau}} - 1\right]^{1/n}. \tag{2.1}$$

For convenience, introduce

$$h(x) = \frac{x}{1+x^n}.$$

Since $h'(0) = 1$ the linearization of (1.4) around $x = 0$ is

$$\dot{x} = -\gamma x - (1-\eta_1-\eta_2)\beta_0 x + e^{-\gamma_Q\tau}[k_0\eta_1 + 2(1-\eta_1-\eta_2)\beta_0]x_\tau.$$

Denote, as in [15], [11],

$$a = -\gamma - \beta_0(1 - \eta_1 - \eta_2), \quad b = e^{-\gamma_Q \tau}[2(1 - \eta_1 - \eta_2)\beta_0 + k_0\eta_1].$$

Obviously $a < 0$ and $b > 0$ so, if $a + b > 0$ the zero solution is unstable and if $a + b < 0$ the zero solution is asymptotically stable. Remark that

$$a + b = (1 - \eta_1 - \eta_2)\beta_0(2e^{-\gamma_Q \tau} - 1) + e^{\gamma_Q \tau} k_0\eta_1 - \gamma.$$

If there exists the solution (2.1) then $a + b$ must have the same sign as $\gamma - e^{-\gamma_Q \tau}\eta_1 k_0$ so $a + b > 0$ if and only if $\gamma > e^{-\gamma_Q \tau}\eta_1 k_0$. Since $\dfrac{\eta_1 k_0}{\gamma} < 1$ it follows that $e^{\gamma_Q \tau} > \dfrac{\eta_1 k_0}{\gamma}$ for every $\tau \geq 0$ so $a+b > 0$ and the zero solution of the linear system is unstable. By [17] Ch.9, Corollary 2.3, the zero solution is unstable for (1.4) too. We have thus proved the following

Proposition 2.1. If equation (1.4) has a nonzero equilibrium point the zero solution is unstable.

Consider now that a second equilibrium point x_2^*, given by (2.1), exists. Denote

$$\beta_1 = h'(x_2^*). \tag{2.2}$$

The linearization of (1.4) around x_2^* is

$$\begin{aligned} \dot{x}(t) &= -[\gamma + (1 - \eta_1 - \eta_2)\beta_0\beta_1]x(t) + \\ &+ e^{-\gamma_Q \tau}[2(1 - \eta_1 - \eta_2)\beta_0\beta_1 + k_0\eta_1]x(t - \tau) \end{aligned} \tag{2.3}$$

Introduce

$$\begin{aligned} a(\tau) &= -\gamma - (1 - \eta_1 - \eta_2)\beta_0\beta_1 \\ b(\tau) &= e^{-\gamma_Q \tau}[2(1 - \eta_1 - \eta_2)\beta_0\beta_1 + k_0\eta_1] \end{aligned} \tag{2.4}$$

The characteristic equation of (2.3) is

$$\Delta(\lambda, \tau) := \lambda - a(\tau) - b(\tau)e^{-\lambda\tau} = 0 \tag{2.5}$$

The study of stability for (2.3) will follow the approach in [8], [12].

Define $P(z, \tau) = z - a(\tau)$ and $Q(z, \tau) = -b(\tau)$.

Then obviously $P(iy, \tau) \neq Q(iy, \tau)$, $\overline{P(-iy, \tau)} = P(iy, \tau)$, $\overline{Q(-iy, \tau)} = Q(iy, \tau)$.

Suppose that $a(\tau) + b(\tau) \neq 0$. Then $P(0, \tau) + Q(0, \tau) \neq 0$. Also $\lim_{|\lambda| \to \infty} \left| \frac{Q(\lambda, \tau)}{P(\lambda, \tau)} \right| = 0$, the equation

$$F(y, \tau) := |P(iy, \tau)|^2 - |Q(iy, \tau)|^2 = 0$$

has a finite number of roots and if $y(\tau)$ is such a root it is a C^1-function due to the implicit function theorem. The stability of the zero solution of (2.3) (thus of x_2^*) relies on the relation between $|a(\tau)|$ and $|b(\tau)|$. Namely, if $|a(\tau)| > |b(\tau)|$, $\forall \tau \in [0, T]$, $T > 0$, then $F(y, \tau) = 0$ has no real zeros so, if x_2^* is asymptotically stable for $\tau = 0$, it remains so for $\tau \in [0, T)$ (see [8], [12]).

Suppose now that $|a(0)| < |b(0)|$. Then $|a(\tau)| < |b(\tau)|$ for $\tau \in [0, T_1)$, $T_1 > 0$.

If $b(\tau) > 0$, since $-a(\tau) \leq |a(\tau)| < b(\tau)$ it follows that $a(\tau) + b(\tau) > 0$ and x_2^* is unstable (see [11], [15]).

Suppose $b(\tau) < 0$, $\forall \tau \in [0, T_1)$. The equation $F(y, \tau) = 0$ has a positive root ω.

Then $\Delta(i\omega, \tau) = 0$ if and only if

$$\begin{aligned} \sin \tau\omega &= -\frac{\omega}{b(\tau)} \\ \cos \tau\omega &= -\frac{a(\tau)}{b(\tau)}. \end{aligned} \tag{2.6}$$

Since $|a(\tau)| < |b(\tau)|$ the system (2.6) has the solution

$$\tau\omega(\tau) = \arccos\left(-\frac{a(\tau)}{b(\tau)}\right) \overset{def}{=} \alpha(\tau) \in (0, \pi).$$

Let τ_0 be a solution of (2.6) corresponding to $\omega_0 > 0$ (so $\lambda = i\omega_0$ is a root of (2.5) for $\tau = \tau_0$) such that $x_2^*(\tau)$ is locally asymptotically stable for $\tau \in [0, \tau_0)$.

Then the following theorem holds true

Theorem 2.2. *Suppose that $\beta_1 < 0$ and that $b(\tau) < 0$, $\forall \tau \in [0, T_1)$. Then there exists $\tau_0 > 0$ such that the equilibrium x_2^* is locally asymptotically stable for $\tau \in [0, \tau_0)$ and becomes unstable when $\tau = \tau_0$. The Hopf bifurcation theorem ensures that periodic solutions of equation (1.4) exist for $\tau = \tau_0$.*

Proof. By [12], Re $\lambda'(\tau_0) > 0$ so one can apply [17] Ch. 11, Theorem 1.1.

Remark. A more detailed analysis, on the lines in [27] may prove that other bifurcating points τ_j can exist. Namely if

$$S_j(\tau) = \tau - \frac{\lambda(\tau) + 2j\pi}{\omega(\tau)}$$

satisfies

$$S_j'(\tau_j) \neq 0 \tag{2.7}$$

for

$$S(\tau_j) = 0 \tag{2.8}$$

then a Hopf bifurcation appears for $\tau_j \in [0, T_1)$. See [27], Th. 2.7 and also [8].

The periodic solutions given by Hopf Theorem are limit cycles. Their stability will be investigated in the next paragraph.

3 Stability of the limit cycles

Denote by τ_0 the solution that verifies

$$\omega_0 \tau_0 = \alpha(\tau_0) = \arccos\left(-\frac{a(\tau)}{b(\tau)}\right) \tag{3.1}$$

If condition (2.7) is satisfied all the reasonings can be transfered to τ_c that is a solution of (2.8).

Define for $t \geq 0$, $y(t) = x(t) - x_2^*$ and define $\mu = \tau - \tau_0$. Then (1.4) translates into

$$\dot{y}(t) = G_\mu(y_t) \tag{3.2}$$

where $y_t(\theta) = y(t+\theta)$ and for $\varphi \in C_\mu := C([-\mu - \tau_0, 0], \mathbf{C})$, G_μ is defined by

$$\begin{aligned} G_\mu(\varphi) = -\gamma[\varphi(0) + x_2^*] - (1 - \eta_1 - \eta_2)\beta_0 \frac{\varphi(0) + x_2^*}{1 + [\varphi_0 + x_2^*]^n} + \\ + e^{-\gamma_Q(\tau_0+\mu)} \left[\frac{2(1-\eta_1-\eta_2)\beta_0}{1 + [\varphi(-\mu-\tau_0) + x_2^*]^n} + k_0\eta_1\right][\varphi(-\mu - \tau_0) + x_2^*]. \end{aligned} \tag{3.3}$$

The linearized equation, for $y = 0$, corresponding to (3.3) is

$$\dot{y}(t) = L_\mu y_t \tag{3.4}$$

where $L_\mu = (D_\varphi G_\mu)(0)$, the Frechét derivative of G_μ in $\varphi = 0$. Explicitly

$$L_\mu \varphi = a(\mu)\varphi(0) + b(\mu)\varphi(-\mu - \tau_0) \tag{3.5}$$

with $a(\mu)$ and $b(\mu)$ defined in (2.4) for $\tau = \mu + \tau_0$. If

$$F_\mu = G_\mu - L_\mu \tag{3.6}$$

then $F_\mu(0) = F'_\mu(0) = 0$ and (3.2) becomes

$$\dot{y}(t) = L_\mu y_t + F_\mu(y_t) \tag{3.7}$$

Following [18], [3],[25], introduce $X_0 : [-\mu - \tau_0, 0] \to \mathbf{R}$ through

$$X_0(\theta) = \begin{cases} 0 & -\mu - \tau_0 \le \theta < 0 \\ 1 & \theta = 0 \end{cases}$$

For $c \in \mathbf{R}$ define $(X_0 c)(\theta) = X_0(\theta)c$, $\theta \in [-\mu - \tau_0, 0]$ and then define the space

$$\langle X_0 \rangle = \{X_0 c | c \in \mathbf{C}\}$$

By [17], the linear equation (3.4) gives a C_0-semigroup with generator A_μ defined by

$$\mathcal{D}(A_\mu) = \{\varphi \in C^1([-\mu - \tau_0, 0], \mathbf{C}),\ \varphi'(0) = L_\mu \varphi\},\ A_\mu \varphi = \varphi',\ \varphi \in \mathcal{D}(A_\mu).$$

Define $\tilde{C}_\mu = C_\mu \oplus \langle X_0 \rangle$. The extension $\tilde{A}_\mu$ of A_μ to $\tilde{C}_\mu$ given by

$$\mathcal{D}(\tilde{A}_\mu) = C^1([-\mu - \tau_0, 0], \mathbf{C})$$

$$\tilde{A}_\mu(\varphi) = \varphi' + X_0(L_\mu \varphi - \varphi'(0)), \quad \varphi \in \mathcal{D}(\tilde{A}_\mu)$$

is a Hille-Yosida operator on $\tilde{C}_\mu$ (see [1]).

If y is a solution of (3.7) on $[0, T)$ with an initial condition $\varphi \in C_\mu$ then the function $u : [0, T] \to C_\mu$, $t \mapsto y_t$ verifies

$$\begin{aligned} &\frac{d}{dt} y_t = \tilde{A}_\mu y_t + X_0 F_\mu(y_t) \\ &u(0)(\theta) = y_0(\theta) = \varphi(\theta), \quad \theta \in [-\mu - \tau_0, 0] \end{aligned} \tag{3.8}$$

and conversely if $u : [0, T] \to C_\mu$ is such that

$$\frac{du}{dt} = \tilde{A}_\mu u(t) + X_0 F_\mu[u(t)]$$

$$u(0) = \varphi$$

then $u(t) = y_t$, $\forall t \in [0, T]$ with

$$y(t) = \begin{cases} u(t)(0), & t \in [0, T] \\ \varphi(t), & t \in [-\mu - \tau_0, 0]. \end{cases}$$

By [7] and [14] the Banach space Cauchy Problem for the ODE (3.8) is well posed for $\varphi \in \overline{\mathcal{D}(\tilde{A}_\mu)} = C_\mu$. Consider now the space $C^0_\mu = C([0, \mu + \tau_0], \mathbf{C})$ and define, according to [17], the bilinear form

$$\begin{aligned} \langle \psi, \varphi \rangle &= \overline{\psi(0)}\varphi(0) - \int_{-\mu-\tau_0}^{0} \left(\int_0^s \overline{\psi(\theta - s)}\varphi(\theta) d\theta \right) d\eta(s) = \\ &= \overline{\psi(0)}\varphi(0) + b(\mu) \int_{-\tau_0-\mu}^{0} \overline{\psi}(\theta + \mu + \tau_0)\varphi(\theta) d\theta. \end{aligned} \tag{3.9}$$

Here $d\eta(\cdot)$ corresponds to the distribution

$$a(\mu)\delta_0 + b(\mu)\delta_{-\mu-\tau_0}.$$

Define $\tilde{C}^0_\mu = C^0_\mu \oplus \langle X^0_0 \rangle$ where

$$X^0_0(\theta) = \begin{cases} 0, & 0 < \theta \le \mu + \tau_0 \\ 1, & \theta = 0, \end{cases} \qquad (X^0_0 c)(\theta) = X^0_0(\theta)c, \; c \in \mathbf{C}$$

and $\langle X^0_0 \rangle = \{X^0_0 c | c \in \mathbf{C}\}$

(3.9) extends to $\tilde{C}^0_\mu$ through

$$\langle \psi + X^0_0 a, \; \varphi + X^0_0 b \rangle = \langle \psi, \varphi \rangle + \overline{a}b, \quad a, b \in \mathbf{C}.$$

The adjoint operator $\tilde{A}^*_\mu$ defined with respect to this bilinear form verifies

$$\langle\psi,\tilde{A}_{\mu_0}\varphi\rangle=\overline{\psi(0)}L_\mu\varphi+$$
$$+b(\mu)\int_{-\tau_0-\mu}^{0}\overline{\psi}(s+\mu+\tau_0)\varphi'(s)ds=\overline{\psi(0)}[a(\mu)\varphi(0)+$$
$$+b(\mu)\varphi(-\tau_0-\mu)]+b(\mu)[\overline{\psi}(s+\mu+\tau_0)\varphi(s)|_{s=-\tau_0-\mu}^{0}-$$
$$-\int_{-\mu-\tau_0}^{0}\overline{\psi}'(s+\mu+\tau_0)\varphi(s)ds]=$$
$$=\overline{\psi(0)}[a(\mu)\varphi(0)+b(\mu)\varphi(-\tau_0-\mu)]+b(\mu)\overline{\psi}(\mu+\tau_0)\varphi(0)-$$
$$-b(\mu)\overline{\psi}(0)\varphi(-\mu-\tau_0)-b(\mu)\int_{-\mu-\tau_0}^{0}\overline{\psi}'(s+\mu+\tau_0)\varphi(s)ds=$$
$$=\varphi(0)[a(\mu)\overline{\psi(0)}+b(\mu)\overline{\psi}(\mu+\tau_0)]-$$
$$-b(\mu)\int_{-\mu-\tau_0}^{0}\overline{\psi}'(s+\mu+\tau_0)\varphi(s)ds=\langle\tilde{A}_\mu^*\psi,\varphi\rangle.$$

So $\mathcal{D}(\tilde{A}_\mu^*)=C^1([0,\mu+\tau_0],\mathbf{C})$ and

$$\tilde{A}_\mu^*\psi=-\psi'+X_0^0[a(\mu)\psi(0)+b(\mu)\psi(\mu+\tau_0)+\psi'(0)]$$

Take $q(s)=e^{i\omega_0 s}$. Then $(\tilde{A}_0 q)(s)=i\omega_0 q(s)$ for $s>0$,

$$(\tilde{A}_0 q)(0)=a(0)q(0)+b(0)q(-\tau_0)=i\omega_0$$

and this is equation (2.5) and is verified since $\tau_0\omega_0$ is a solution of (2.6). It follows that $q^*(s)=de^{i\omega_0 s}$ is an eigenvector of $\tilde{A}_0^*$ associated to the eigenvalue $(-i\omega_0)$. $d\in\mathbf{C}$ is choosed such that the norming condition $\langle q^*,q\rangle=1$ is satisfied. It is not difficult to see that this gives

$$\bar{d}=\frac{1}{1+\tau_0 b(0)e^{-i\omega_0\tau_0}} \tag{3.10}$$

and that for this d, $\langle q^*,\overline{q}\rangle=0$.

Let y be a solution of (3.7).

To compute the coordinates of the section $\mathcal{C}_0$ of the center manifold corresponding to $\mu=0$, define, following [18],[25] for $t\geq 0$

$$z(t)=\langle q^*,y_t\rangle=\overline{d}y(t)+b(\mu)\int_{-\tau_0}^{0}e^{-i\omega_0(s+\tau_0)}y(t+s)ds$$

z and $\overline{z}$ will be used as local coordinates in the directions q^* and $\overline{q}^*$.

Define next, for $t \geq 0$ and $s \in [-\tau_0, 0]$,

$$\begin{aligned} w(t,s) &= y_t(s) - z(t)q(s) - \overline{z}(t)\overline{q}(s) = \\ &= y_t(s) - 2\mathrm{Re}\,[z(t)q(s)] = W[z(t), \overline{z}(t), s] \end{aligned} \tag{3.11}$$

where

$$W(z,\overline{z},s) = w_{20}(s)\frac{z^2}{2} + w_{11}(s)z\overline{z} + w_{02}(s)\frac{\overline{z}^2}{2} + \ldots \overset{not}{=} w(s). \tag{3.12}$$

Since for real y, w is also real, one must have $w_{02} = \overline{w}_{20}$. Remark also that

$$\begin{aligned} \langle q^*, w\rangle &= \langle q^*, y_t\rangle - \langle q^*, zq\rangle - \langle q^*, \overline{zq}\rangle = \\ &= z(t) - z(t)\langle q^*, q\rangle - \overline{z}(t)\langle q^*, \overline{q}\rangle = 0 \end{aligned}$$

(recall $\langle q^*, q\rangle = 1$, $\langle q^*, \overline{q}\rangle = 0$). Since $\mathcal{C}_0$ is locally invariant under (3.8) (see [18], [9]), for $y_t \in \mathcal{C}_0$ one has

$$\begin{aligned} \dot{z}(t) &= \langle q^*, \dot{y}_t\rangle = \langle q^*, \tilde{A}_0 y_t + X_0 F_0(y_t)\rangle = \\ &= \langle \tilde{A}_0^* q^*, y_t\rangle + \langle q^*, X_0 F_0(y_t)\rangle = i\omega_0\langle q^*, y_t\rangle + \\ &+ \overline{d}F_0[W(z(t), \overline{z}(t), \cdot) + 2\mathrm{Re}\,[z(t)q(\cdot)]|_{s=0} = \\ &= i\omega_0 z(t) + g[z(t), \overline{z}(t)] \end{aligned} \tag{3.13}$$

where g is defined by

$$g(z,\overline{z}) = \overline{d}F_0[W(z,\overline{z},\cdot) + 2\mathrm{Re}\,[zq(\cdot)]|_{s=0}. \tag{3.14}$$

From (3.3), (3.5) and (3.6) it follows that

$$F_0(\varphi) = -(1-\eta_1-\eta_2)\beta_0\frac{h''(x_2^*)}{2}\varphi^2(0) + e^{-\gamma_Q\tau_0}2(1-\eta_1-\eta_2)\beta_0\frac{h''(x_2^*)}{2}\cdot\varphi^2(-\tau_0) +$$

$$+\frac{1}{6}[-(1-\eta_1-\eta_2)\beta_0 h'''(x_2^*)\varphi^3(0) + e^{-\gamma_Q\tau_0}2(1-\eta_1-\eta_2)\beta_0 h'''(x_2^*)\cdot\varphi^3(-\tau_0)] + \ldots$$

It is convenient to introduce the following notations:

$$\begin{aligned} &\beta_2 = h''(x_2^*), && \beta_3 = h'''(x_2^*) \\ &c_{12} = -(1-\eta_1-\eta_2)\frac{\beta_0\beta_2}{2}, && c_{22} = e^{-\gamma_Q\tau_0}2(1-\eta_1-\eta_2)\beta_0\beta_2 \\ &C_{13} = -\frac{1}{6}\beta_0\beta_3, && c_{23} = \frac{1}{3}e^{-\gamma_Q\tau_0}2(1-\eta_1-\eta_2)\beta_0\beta_3 \end{aligned} \tag{3.15}$$

With these notations F_0 becomes

$$F_0(\varphi) = c_{12}\varphi^2(0) + c_{22}\varphi^2_{\tau_0}(0) + c_{13}\varphi^3(0) + c_{23}\varphi^3_{\tau_0}(0) + \dots \tag{3.16}$$

(3.14) and (3.16) imply that

$$\begin{aligned} g(z,\overline{z}) &= \overline{d}\{c_{12}[w(0) + z + \overline{z}]^2 + c_{13}[w(0) + z + \overline{z}]^3 + \\ &+ O(|w(0) + z + \overline{z})^4| + c_{22}[w(-\tau_0) + ze^{-i\omega_0\tau_0} + \overline{z}e^{i\omega_0\tau_0}]^2 + \\ &+ c_{23}[w(-\tau_0) + ze^{-i\omega_0\tau_0} + \overline{z}e^{i\omega_0\tau_0}]^3 + \\ &+ O(|w(-\tau_0) + ze^{-i\omega_0\tau_0} + \overline{z}e^{i\omega_0\tau_0}|^4) := \\ &= \frac{g_{20}}{2}z^2 + g_{11}z\overline{z} + \frac{g_{02}}{2}\overline{z}^2 + \frac{1}{2}g_{21}z^2\overline{z} + \dots \end{aligned} \tag{3.17}$$

These coefficients of z^2, $z\overline{z}$, $\overline{z}^2$ and $z^2\overline{z}$ in (3.17) are essential for the computation of the first Lyapunov coefficient.

It follows directly from (3.17) that

$$\begin{aligned} \frac{1}{2}g_{20} &= \overline{d}(c_{12} + c_{22}e^{-i\omega_0\tau_0}) \\ g_{11} &= 2\overline{d}(c_{12} + c_{22}) \\ \frac{1}{2}g_{02} &= \overline{d}(c_{12} + c_{22}e^{i\omega_0\tau_0}) \\ \frac{1}{2}g_{21} &= \overline{d}[c_{12}(2w_{11}(0) + w_{20}(0))3c_{13} + c_{22}(2w_{11}(-\tau_0) \\ &\quad e^{-i\omega_0\tau_0} + w_{20}(-\tau_0)e^{i\omega_0\tau_0}) + 3c_{23}e^{-i\omega_0\tau_0}] \end{aligned}$$

so one needs to find the expressions of $w_{20}(0)$, $w_{20}(-\tau_0)$, $w_{11}(0)$ and $w_{11}(-\tau_0)$. Recall from (3.12) that $w(s) = w_{20}(s) + \frac{z^2}{2} + w_{11}(s)z\overline{z} + w_{02}(s)\frac{\overline{z}^2}{2} + \dots$ Taking the derivative with respect to t in (3.11) and taking into account (3.8) and (3.11) it follows that

$$\begin{aligned} \frac{d}{dt}w(t,\cdot) &= \frac{d}{dt}y_t - \frac{d}{dt}[z(t)q(\cdot) + \overline{z}(t)\overline{q}(\cdot)] = \\ &= \tilde{A}_0 y_t + X_0F_0(y_t) - 2\mathrm{Re}\,[\dot{z}(t)q(\cdot)] = \\ &= \tilde{A}_0[w(t,\cdot) + 2\mathrm{Re}\, z(t)q(\cdot)] + X_0F_0[w(t,\cdot) + \\ &+ 2\mathrm{Re}\,(z(t)q(\cdot))] - 2\mathrm{Re}\,[\dot{z}(t)q(\cdot)]. \end{aligned}$$

But $\tilde{A}_0(2\text{Re}\, z(t)q(\cdot)) = 2\text{Re}\,[i\omega_0 z(t)q(\cdot)]$ and from (3.13) it follows that

$$\text{Re}[\dot{z}(t)q(\cdot)] = \text{Re}\, i\omega_0 z(t)q(\cdot) + \text{Re}[g(z(t),\overline{z}(t))q(\cdot)].$$

Finally

$$\frac{d}{dt}w(t,\cdot) = \tilde{A}_0 w(t,\cdot) + H(z,\overline{z},\cdot) \tag{3.18}$$

where

$$H(z,\overline{z},s) = -2\text{Re}[g(z,\overline{z})q(s)] + X_0(s)F_0[W(z,\overline{z},s) + 2\text{Re}(zq(s))]. \tag{3.19}$$

Then, for $s \in [-\tau_0, 0)$

$$\begin{aligned} H(z,\overline{z},s) &= -2\text{Re}[g(z,\overline{z})q(s)] = \\ &= -\left(g_{20}\frac{z^2}{2} + g_{11}z\overline{z} + g_{02}\frac{\overline{z}^2}{2} + \ldots\right)q(s) - \\ &- \left(\overline{g}_{20}\frac{\overline{z}^2}{2} + \overline{g}_{11}z\overline{z} + \overline{g}_{02}\frac{z^2}{2} + \ldots\right)\overline{q}(s) = \\ &= H_{20}(s)\frac{z^2}{2} + H_{11}(s)z\overline{z} + H_{02}(s)\frac{\overline{z}^2}{2} + \ldots \end{aligned} \tag{3.20}$$

It follows that

$$\begin{aligned} H_{20}(s) &= -g_{20}q(s) - \overline{g}_{02}\overline{q(s)} \\ H_{11}(s) &= -g_{11}q(s) - \overline{g}_{11}\overline{q(s)} \\ H_{02}(s) &= \overline{H}_{20}(s) \end{aligned} \tag{3.21}$$

From (3.12), (3.13), (3.18) and (3.21) we infer that

$$\begin{aligned} &\tilde{A}_0 w(t,\cdot) + H[z(t),\overline{z}(t),\cdot] = w_{20}(\cdot)z(t)\dot{z}(t) + \\ &+ w_{11}(\cdot)[\dot{z}(t)\overline{z}(t) + z(t)\dot{\overline{z}}(t)] + w_{02}(\cdot)\overline{z}(t)\dot{\overline{z}}(t) + \ldots = \\ &= w_{20}(\cdot)z(t)[i\omega_0 z(t) + g(z(t),\overline{z}(t)] + \\ &+ w_{11}(\cdot)\overline{z}(t)[i\omega_0 z(t)] + g(z(t),\overline{z}(t))] + \\ &+ w_{11}(\cdot)z(t)[-i\omega_0\overline{z}(t) + \overline{g(z(t),\overline{z}(t))}] + \\ &+ w_{02}(\cdot)\overline{z}(t)[-i\omega_0\overline{z}(t) + \overline{g(z(t),\overline{z}(t))}]. \end{aligned} \tag{3.22}$$

Identification of the coefficients of z^2, $z\overline{z}$ and $\overline{z}^2$ in (3.22) yields

$$\begin{aligned}(\tilde{A}_0 - 2i\omega_0)w_{20}(s) &= -H_{20}(s)\\ \tilde{A}_0 w_{11}(s) &= -H_{11}(s)\\ (\tilde{A}_0 + 2i\omega_0)w_{02}(s) &= -H_{02}(s)\end{aligned} \tag{3.23}$$

so, for $s \in [-\tau_0, 0)$ one has

$$\dot{w}_{20}(s) = 2i\omega w_{20}(s) + g_{20}e^{i\omega_0 s} + \overline{g}_{02}e^{-i\omega_0 s}$$

whence

$$w_{20}(s) = -\frac{g_{20}}{i\omega_0}e^{i\omega_0 s} - \frac{\overline{g}_{02}}{3i\omega_0}e^{-i\omega_0 s} + C_1 e^{2i\omega_0 s}.$$

For $s = 0$ the definition of $\tilde{A}_0$ and (3.23) give

$$a(0)\left(-\frac{g_{20}}{i\omega_0} - \frac{\overline{g}_{02}}{3i\omega_0} + C_1\right) + 2g_{20} + \frac{2}{3}\overline{g}_{02} - 2i\omega_0 C_1 +$$

$$+b(0)\left(-\frac{g_{20}}{i\omega_0}e^{i\omega_0\tau_0} - \frac{\overline{g}_{02}}{3i\omega_0}e^{-i\omega_0\tau_0} + C_1 e^{2i\omega_0\tau_0}\right) = -H_{20}(0).$$

Setting $s = 0$ in (3.19) gives, by (3.13),

$$H(z, \overline{z}, 0) = -2\text{Re}\,[g(z, \overline{z})] + F_0[W(z, \overline{z}, s) + 2\text{Re}\,(zq(s))]|_{s=0} =$$

$$= -g(z, \overline{z}) - \overline{g(z, \overline{z})} + \frac{1}{\overline{d}}\, g(z, \overline{z})$$

so

$$\begin{aligned}H_{20}(0) &= -g_{20} - \overline{g}_{02} + \frac{1}{\overline{d}}\, g_{20}\\ H_{11}(0) &= -g_{11} - \overline{g}_{11} + \frac{1}{\overline{d}}\, g_{11}\end{aligned} \tag{3.24}$$

and it follows that

$$\begin{aligned}C_1 = \frac{1}{a(0) - 2i\omega_0 + b(0)e^{2i\omega_0\tau_0}} &\left[-g_{20} + \frac{1}{3}\,\overline{g}_{02} - \frac{1}{\overline{d}}\, g_{20} + \right.\\ \left. +a(0)\left(\frac{g_{20}}{i\omega_0} + \frac{\overline{g}_{02}}{3i\omega_0}\right) + b(0)\left(\frac{\overline{g}_{20}}{i\omega_0}e^{i\omega_0\tau_0} + \frac{\overline{g}_{02}}{3i\omega_0}e^{-i\omega_0\tau_0}\right)\right]&.\end{aligned} \tag{3.25}$$

In a similar way, for $s \in [-\tau_0, 0)$,

$$\dot{w}_{11} = g_{11}e^{i\omega_0 s} + \overline{g}_{11}e^{-i\omega_0 s}$$

whence

$$w_{11}(s) = \frac{g_{11}}{i\omega_0}(e^{i\omega_0 s} - 1) - \frac{\overline{g}_{11}}{i\omega_0}(e^{-i\omega_0 s} - 1) + C_2.$$

For $s = 0$ (3.23) gives

$$a(0)w_{11}(0) + b(0)w_{11}(-\tau_0) = -H_{11}(0)$$

that is

$$a(0)C_2 + b(0)\left[\frac{g_{11}}{i\omega_0}(e^{-i\omega_0\tau_0} - 1) - \frac{\overline{g}_{11}}{i\omega_0}(e^{i\omega_0\tau_0} - 1) + C_2\right] = -H_{11}(0)$$

so, by (3.24), C_2 is given by

$$\begin{aligned} C_2 &= \frac{1}{a(0)+b(0)}\{b(0)\left[-\frac{g_{11}}{i\omega_0}(e^{-i\omega_0\tau_0} - 1) + \frac{\overline{g}_{11}}{i\omega_0}(e^{i\omega_0\tau_0} - 1)\right] - \\ &- H_{11}(0)\} = \frac{1}{a(0)+b(0)}\left\{b(0)\left[-\frac{g_{11}}{i\omega_0}(e^{-i\omega_0\tau_0} - 1) + \right.\right. \\ &+ \left.\left.\frac{\overline{g}_{11}}{i\omega_0}(e^{i\omega_0\tau_0} - 1)\right] + g_{11} + \overline{g}_{11} - \frac{1}{\overline{d}}g_{11}\right\} \end{aligned} \tag{3.26}$$

Once C_1 and C_2 are calculated, one has the values $w_{20}(0)$, $w_{20}(-\tau_0)$, $w_{11}(0)$ and $w_{11}(-\tau_0)$ and from (3.17) the following formula is obtained for g_{21}

$$\begin{aligned} \frac{g_{21}}{2} = \overline{d}\,[c_{12}(2w_{11}(0) + w_{20}(0)) + 3c_{13} + c_{22}(2w_{11}(-\tau_0)e^{-i\omega_0\tau_0} + \\ + w_{20}(-\tau_0)e^{i\omega_0\tau_0}) + 3c_{23}e^{-i\omega_0\tau_0}] \end{aligned} \tag{3.27}$$

The Lyapunov coefficient is given by

$$l_1(0) = \text{Re } L_1(0)$$

with

$$L_1(0) = \frac{1}{2\omega_0}\left(g_{20}\, g_{11} - 2|g_{11}|^2 - \frac{1}{3}|g_{02}|^2\right) + \frac{1}{2}g_{21} \tag{3.28}$$

Introduce also

$$\begin{aligned} \mu_2 &= -\frac{l_1(0)}{\text{Re } \lambda'(\tau_0)} \\ T_2 &= -\frac{\text{Im } L_1(0) + \mu_2 \text{Im } \lambda'(\tau_0)}{\omega_0}. \end{aligned} \tag{3.29}$$

The following theorem summs up the informations on the limit cycle that can be obtained from the above calculations (see [18]).

Theorem 3.1. *If $l_1(0) < 0$ bifurcating periodic solutions exist for $\tau > \tau_0$, $\tau - \tau_0$ small, and are orbitally stable. The period of the cycle is approximatelly $\frac{2\pi}{\omega_0}$ and is increasing if $T_2 > 0$ and decreasing if $T_2 < 0$. With $\varepsilon = \left(\frac{\tau - \tau_0}{\mu_2}\right)^{1/2}$ the cycle is given by*

$$\begin{aligned} x(t) &= x_2^*(\tau_0) + 2\left(\frac{\tau - \tau_0}{\mu_2}\right)^{1/2} \mathrm{Re}\,(e^{i\omega_0 t}) + \\ &+ \frac{\tau - \tau_0}{\mu_2} \mathrm{Re}\,(C_1 e^{2i\omega_0 t} + C_2) + O(\varepsilon^3) \end{aligned}$$

for

$$0 \leq t \leq T \leq \frac{2\pi}{\omega_0}(1 + T_2\varepsilon^2 + \ldots)$$

4 The model for treatment of CML with Imatinib

Chronic Myelogenous Leukemia (CML), one of the most frequent types of leukemia is believed to arise from a precursor in the myeloid line in hematopoiesis. It is characterized by a reciprocal translocation between one chromosome 9 and one chromosome 22. As a result, a new chromosome, called Philadelphia chromosome, appears and with it a fusion gene that causes the production of an abnormal tyrosine kinase protein BCR-ABL1.

This protein is no longer controlled by the normal mechanisms and unregulated activates multiple pathways that are responsible for apoptosis regulation and cells' proliferation.

In the last ten years the standard treatment against CML is the use of Imatinib, a molecular targeted drug that selectively inhibits BCR-ABL1 action ([6]). The standard dose used in adults is 400 mg/day. Imatinib is well absorbed after oral administration with a bioavailability exceeding 90%. Pharmako-kinetics studies ([22], [23]) show that imatinib exhibits linear pharmakokinetics.

Imatinib shows a very good therapeutic efficiency induceing complete hematological remission in almost all pacients and cytogenetic remission in 75% - 80% of cases ([13]). Nevertheless an important problem is represented by the appearance of resistance to imatinib treatment ([24]). The generation of clone mutations in the ABL1 kinase domain is considered the main cause of resistance.

Let us suppose that every time a cell traverses the cell cycle there is a constant probability p that a mutation toward resistance appear in one of the two daughter cells. This p does not depend on time or on the amount of drug that is used in the therapy.

Then, following the Goldie-Coldman law ([16]) the population of resistant cells would be $Q\left(1 - k_1\frac{x_0 - k_0}{x_0^{-p+1}}Q^q\right)$ with $q = -p$. Thus, the number of cells susceptible to treatment is $k_1\frac{x_0 - R_0}{x_0^{-p+1}}Q^{p+1}$ where x_0 is the number of infected cells and R_0 is the number of resistant cells at the moment of diagnosis. It follows that the action of the treatment on the stem-like cell compartment is given by the function $k_1\frac{x_0 - R_0}{x_0^{-p+1}}Q^{q+1}$ with $k_1 = \frac{1}{6,543}$ ([19]).

Denote $\tilde{k} = k_1\frac{x_0 - R_0}{x_0^{-p+1}}$.

Then equation (1.1) is replaced by

$$\begin{aligned} \dot{Q} &= -\gamma_Q Q - (\eta_1 + \eta_2)k_0 Q - (1 - \eta_1 - \eta_2)\beta(Q)Q - \tilde{k}Q^{q+1} + \\ &+ 2e^{-\gamma_Q\tau}(1 - \eta_1 - \eta_2)\beta(Q_\tau)Q_\tau + \eta_1 k_0 e^{-\gamma_Q\tau}Q_\tau. \end{aligned}$$

When the scaling $Q = \theta x$ is performed one obtains

$$\begin{aligned} \dot{x} &= -\gamma_Q x - (\eta_1 + \eta_2)k_0 x - (1 - \eta_1 - \eta_2)\beta_0 h(x) - \tilde{k}\theta^q x^{q+1} + \\ &+ 2e^{-\gamma_Q\tau}[2(1 - \eta_1 - \eta_2)\beta_0 h(x_\tau) + k_0\eta_1 x_\tau. \end{aligned} \tag{4.1}$$

Define $k = \tilde{k}\theta^q = \frac{1}{6,543}\frac{x_0 - R_0}{x_0^{-p+1}}\theta^q$.

Since $q + 1 > 0$ the equation (4.1) will still have $x = 0$ as an equilibrium point but this time, since $q < 0$, one cannot use first approximation stability analysis.

Consider instead the candidate Lyapunov-Krasovskii functional (see [15])

$$V(x,t) = x^2(t) + 2\alpha\int_{t-\tau}^{t} x(s)^2 ds, \quad \alpha > 0.$$

Write equation (4.1) in the simplified form

$$\dot{x} = -c_1 x - c_2 h(x) + c_3 x(t-\tau) + c_4 h[x(t-\tau)] - kx^{q+1}.$$

Then the derivative of V along (4.1) is

$$\begin{aligned}
\dot{V} &= 2x(t)\dot{x}(t) + 2\alpha x(t)^2 - 2\alpha x(t-\tau)^2 = \\
&= 2x(t)\{-c_1 x(t) - c_2 h[x(t)] + c_3 x(t-\tau) + c_4 h[x(t-\tau)] - \\
&- kx(t)^{q+1}\} + 2\alpha x(t)^2 - 2\alpha x(t-\tau)^2 = \\
&= -2[(c_1-\alpha)x(t)^2 - c_3 x(t)x(t-\tau) + \alpha x(t-\tau)^2] - \\
&- 2x(t)\{c_2 h[x(t)] - c_4 h[x(t-\tau)\} - 2kx(t)^{q+2}.
\end{aligned}$$

One can conclude that if there exists a Lyapunov-Krasovskii functional related to the trivial equillibrium, that has a negative derivative along the system, for the model without treatment (thus the trivial solution is locally asymptotically stable) then the same holds when treatment is introduced.

The functional V can be generally used to study asymptotic stability for the trivial solution of (4.1).

The formula for the nontrivial equilibrium point becomes more involved

$$\gamma - e^{-\gamma_Q \tau}\eta_1 k_0 + kx^{*q} = \frac{1-\eta_1-\eta_2}{1+x^{*n}}\beta_0(2e^{\gamma_Q\tau}-1). \tag{4.2}$$

When (4.2) has a solution $x^* > 0$ the linearization of (4.1) around x^* is the following equation

$$\begin{aligned}
\dot{x}(t) &= -[\gamma + (1-\eta_1-\eta_2)\beta_0\beta_1 + (q+1)kx^{*q}]x(t) + \\
&+ e^{-\gamma_Q\tau}[2(1-\eta_1-\eta_2)\beta_0\beta_1 + k_1\eta_1]x(t-\tau).
\end{aligned} \tag{4.3}$$

The reasonings in §2 can be easily adapted with

$$a(\tau) = -\gamma - (1-\eta_1-\eta_2)\beta_0\beta_1 - (q+1)kx^{*q} \tag{4.4}$$

and the same $b(\tau)$.

When ω_0 and τ_0 verify

$$\omega_0\tau_0 = \arccos\left(-\frac{a(\tau_0)}{b(\tau_0)}\right)$$

one can study the stability of the limit cycles on the line in §3. This time

$$G_\mu(\varphi) = -\gamma[\varphi(0) + x^*] - (1 - \eta_1 - \eta_2)\beta_0 h[\varphi(0) + x^*] - k[\varphi(0) + x^*]^{q+1} +$$

$$+e^{-\gamma_Q(\mu+\tau_0)}[2(1 - \eta_1 - \eta_2)\beta_0 h[\varphi(-\mu - \tau_0) + x^*] + k_0\eta_1(\varphi(-\mu - \tau_0) + x^*)].$$

One has the same formula for $L_\mu\varphi$ but with $a(\tau)$ given by (4.4). Formulas (3.9) and (3.10) rest unchanged

$$F_0(\varphi) = -(1-\eta_1-\eta_2)\beta_0\frac{h''(x^*)}{2}\varphi(0)^2 + e^{-\gamma_Q\tau_0}(1-\eta_1-\eta_2)\beta_0 h''(x^*)\varphi(-\tau_0)^2 -$$

$$-\frac{1}{2}(q+1)qx^{*q-1}\varphi(0)^2 - \frac{1}{6}(1 - \eta_1 - \eta_2)\beta_0 h'''(x^*)\varphi(0)^3 -$$

$$-\frac{1}{6}(q+1)q(q-1)x^{*q-2}\varphi(0)^3 - \frac{1}{3}e^{-\gamma_Q\tau_0}(1 - \eta_1 - \eta_2)\beta_0 h'''(x^*)\varphi(-\tau_0)^3 + \ldots$$

so

$$\begin{aligned} c_{12} &= -(1 - \eta_1 - \eta_2)\frac{\beta_0\beta_2}{2} - \frac{1}{2}(q+1)qx^{*q-1} \\ c_{13} &= -\frac{1}{6}(1 - \eta_1 - \eta_2)\beta_0\beta_3 - \frac{1}{6}(q+1)q(q-1)x^{*q-2}. \end{aligned} \tag{4.5}$$

These new coefficients are then used in formulas (3.17), (3.20), (3.21), (3.23), (3.24), (3.25), (3.26) and (3.27) and provide new values for $l_1(0)$, μ_2 and T_2 by (3.28) and (3.29).

5 Numerical results and simulations

In what follows the previous formulae are used for the calculation of the relevant coefficients for the limit cycles. The tables that follow contain the values of the parameters of the system and the values calculated for the nontrivial equilibrium, for the values of τ where bifurcation occur and for the description of the limit cycles. Simulations in some particular cases illustrate these computations. The evolution is shown with and without treatment.

Table 1. Description of parameters used for numerical simulation

Interpretation	Name	Values	Units	References	Observations
The percent of SC population with asymmetric division (SC +M)	η_1	[0.1, 0.2, 0.4]		model	Structure of stem cell population
The percent of SC populations with symmetric differentiation of mature cells (M+M)	η_2	[0.1, 0.2, 0.4]		model	
Percent of SC populations with symetric self renewal cells (SC+SC)	$1-\eta_1-\eta_2$	[0.2, 0.4, 0.5,0.6,..]		model	
Maximal self renewal rate	β_0	1.77	day^-1	Mackey (1978,2004) Bernard (2004)	Stem cell compartment parameters
The parameter controlling the sensitivity of the self renewal rate to changes in the size of SC compartment	n	4			
The rate of instant mortality/apoptosis for short-term hematopietic stem cells	γ_Q	0.1	day^-1		
The value for which beta(Q)(negative feedback function for SC) attains half of its maximum value	θ	0.5*10^6	cells Kg^-1		
Stem cell proliferation time	τ	2.8	days		
Maximal rate of differentiation / asymmetric division for leukocytes	k0	[0.1, 0.5, 1.5]	day^-1	Mackey (1978,2001) Bernard (2003)	Maturation cells compartment (leukocytes line)
The constant dose of administrated drug (imatinib)	K	[200, 400, 800]	mg/day	Widmer 2006	Parameters for pharmacokinetic model
The first order absorbtion rate	λ0	0.61	day^-1		
The total plasma clearance of imatinib	CL	14.3	l/h		
The volume of distribution of imatinib	V	347	l		
CL/V	v	0.0412			
Initial number of LSC	x0	2.5*10^4	cells Kg^-1	(Tomasseti & Levi)	The effect of the treatment (imatinib) with possible appearance of resistance to imatinib for stem cells
Initial number of LSC resistant to imatinib	R0	R01=x01*1/25*p	cells Kg^-2		
The influence of treatment for leukemic stem cells	k0	1/(1+5.543)			
The probability of mutation of stem cell and develop resistance to treatment (imatinib)	p	1/1000			

Table 2. The results of calculation for a constant influence of imatinib treatment k=0.15

case	η_1	η_1	k0	k	x_+	τ_0	ω_0	$L_1(0)$	T_2	μ_2	Osc.period	β_1	a0	b0
1	0.1	0.1	0.5	0.15	1.4061	1.1701	1.0939	-7.1595	9.0201	-10.347	5.7439	-0.4451	0.3275	-1.142
2	0.1	0.2	0.5	0.15	1.2698	1.1524	1.1421	-5.8506	7.3084	-8.1921	5.5012	-0.5247	0.2973	-1.18
3	0.1	0.3	0.5	0.15	1.1251	1.3182	1.0533	-6.6392	7.8333	-10.018	5.9652	-0.5622	0.1942	-1.071
8	0.2	0.1	0.5	0.15	1.3347	1.3117	1.0103	-6.0285	7.9187	-9.7899	6.219	-0.4892	0.2533	-1.042
9	0.2	0.2	0.5	0.15	1.1845	1.3946	0.9918	-5.1823	6.4243	-8.5652	6.3353	-0.5567	0.1884	-1.01
14	0.3	0.1	0.5	0.15	1.2478	1.5468	0.8978	-4.8344	6.501	-9.3305	6.9984	-0.535	0.1653	-0.913
15	0.3	0.2	0.5	0.15	1.0518	2.1196	0.7247	-8.8989	10.596	-21.153	8.6706	-0.5402	0.0252	-0.725
20	0.4	0.1	0.5	0.15	1.1234	2.1135	0.7137	-5.1263	6.3404	-13.457	8.8035	-0.562	0.0446	-0.715
33	0.1	0.1	1	0.15	1.3265	1.1129	1.1923	-6.8769	8.7382	-9.6244	5.2699	-0.494	0.2966	-1.229
34	0.1	0.2	1	0.15	1.1398	1.1713	1.2047	-7.1207	8.3221	-9.8912	5.2157	-0.5625	0.1941	-1.22
40	0.2	0.1	1	0.15	1.2454	1.3605	1.0417	-5.619	7.4083	-9.5649	6.0318	-0.536	0.1613	-1.054
41	0.2	0.2	1	0.15	0.997	2.1863	0.7633	-17.018	21.389	-36.589	8.2317	-0.497	-0.0751	-0.767
46	0.3	0.1	1	0.15	1.1276	1.9444	0.8114	-5.8422	7.2778	-13.927	7.7432	-0.5623	-0.0057	-0.812
65	0.1	0.1	1.5	0.15	1.2582	1.0959	1.2554	-6.5628	8.2357	-9.1072	5.0049	-0.5303	0.248	-1.28
66	0.1	0.2	1.5	0.15	1.0138	1.5288	1.0384	-17.717	20.759	-28.194	6.0509	-0.5129	-0.0173	-1.039
72	0.2	0.1	1.5	0.15	1.1621	1.5153	1.0092	-6.0408	7.5169	-11.269	6.226	-0.5608	0.0419	-1.01

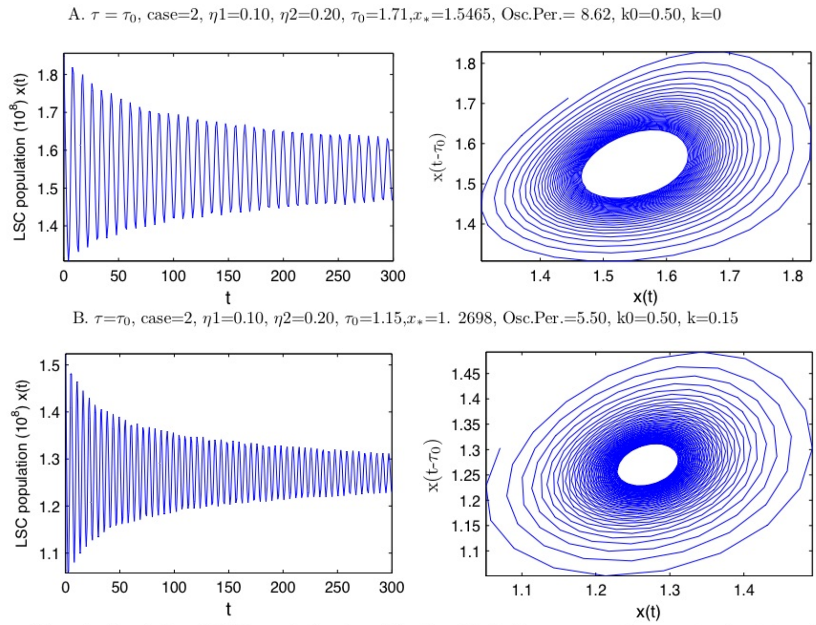

Figure 1. Simulation of LSC population (case 2 in the table 2) for $\tau=\tau_0$, starting near steady state pointx_*; CML conditions simulated by a percent of asymmetric division small ($\eta 1$=0.10) and a rate of differention small (k0=0.5); A represents simulations for the model without treatment, B represents simulations for the model with treatment.

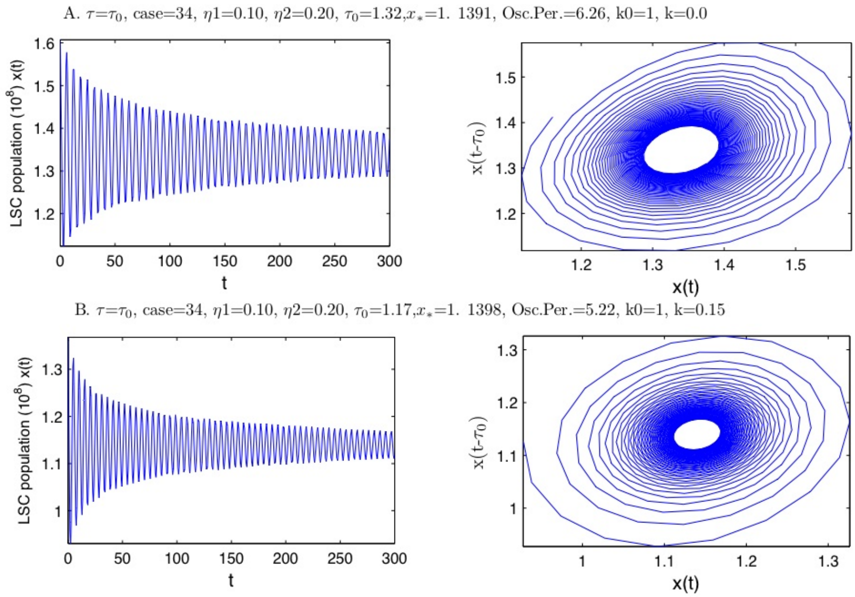

Figure 2. Simulation of LSC population (case 34 in the table 2) for τ=τ_0, starting near steady state pointx_*; CML conditions simulated by a percent of asymmetric division small (η1=0.10) and a rate of differention medium (k0=1.0); A represents simulations for the model without treatment, B represents simulations for the model with treatment.

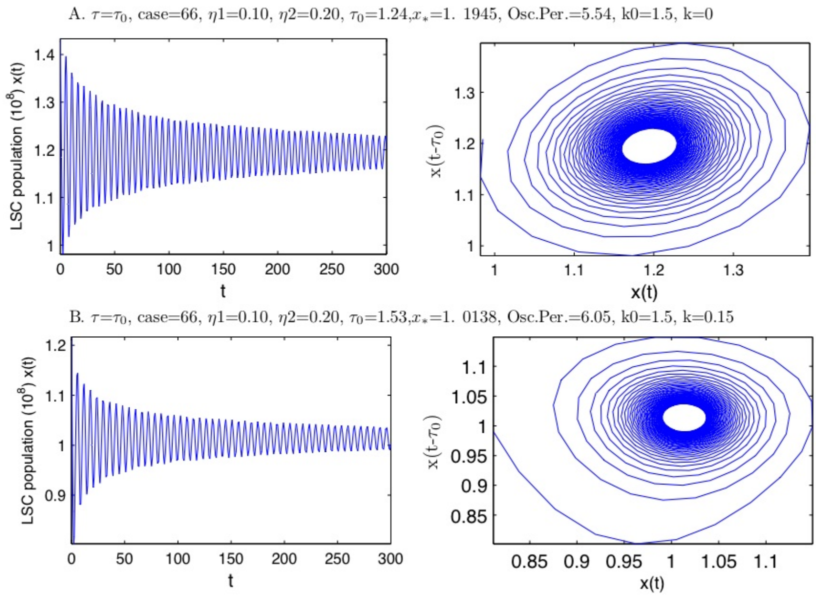

Figure 3. Simulation of LSC population (case 66 in the table 2) for τ=τ_0, starting near steady state pointx_*; CML conditions simulated by a percent of asymmetric division small (η1=0.10) and a rate of differention big (k0=1.5); A represents simulations for the model without treatment, B represents simulations for the model with treatment.

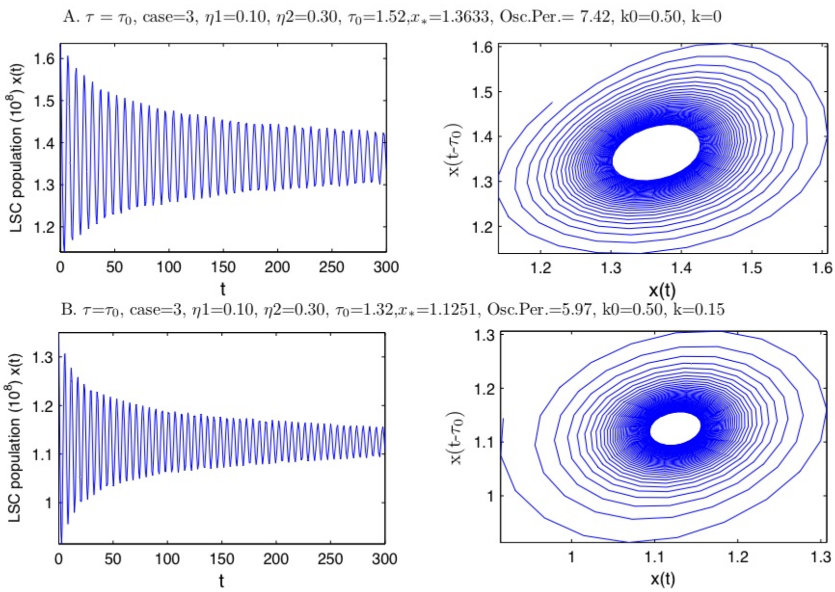

Figure 4. Simulation of LSC population (case 3 in the table 2) for τ=τ_0, starting near steady state pointx_*; CML conditions simulated by a percent of asymmetric division small (η1=0.10) and a rate of differention small (k0=0.1); A represents simulations for the model without treatment, B represents simulations for the model with treatment.

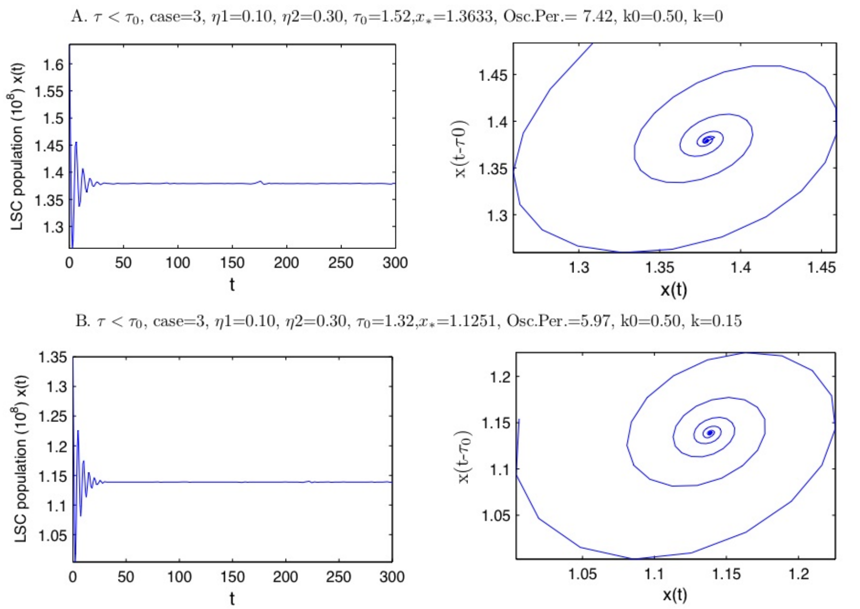

Figure 5. Simulation of LSC population (case 3 in the table 2) for $\tau < \tau_0$,, starting near steady state pointx_*; CML conditions simulated by a percent of asymmetric division small (η1=0.10) and a rate of differention small (k0=0.1); A represents simulations for the model without treatment, B represents simulations for the model with treatment.

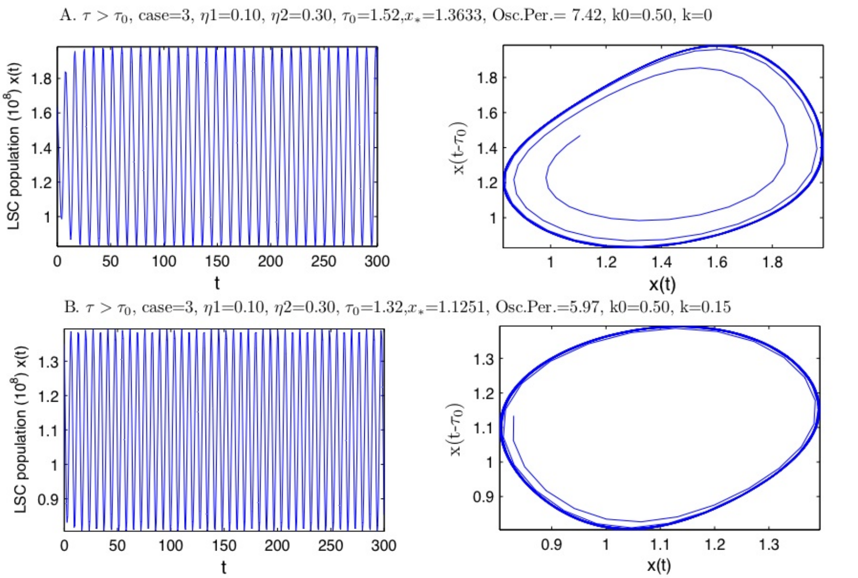

Figure 6. Simulation of LSC population (case 3 in the table 2) for $\tau > \tau_0$,, starting near steady state pointx_*; CML conditions simulated by a percent of asymmetric division small (η1=0.10) and a rate of differention small (k0=0.1); A represents simulations for the model without treatment, B represents simulations for the model with treatment.

6 Concluding remarks

One of the main issues of the approach in the paper was the consideration of asymmetric division in the dynamics of stem cell population. Phenomena as bifurcations, already known to appear as the delay is varied (see [3], [4], [5]), are now studied in this new approach. Corresponding formulae for the stability of the limit cycles are deduced on the lines in [18], [25]. One step further is the consideration of Imatinib treatment for CML, taking into consideration recent studies of pharmakokinesis as well as the already classical low Goldie-Coldman, that tries to capture the appearance of resistance to drug therapy in cancer.

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