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 $\eta_1$ 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 $\eta_2$ 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 $\tau$ 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

$$\frac{\dot{Q}}{Q} = -\gamma Q - \eta_2 k_0 Q - \eta_1 k_0 Q - (1 - \eta_1 - \eta_2) \beta(Q) + 2(1 - \eta_1 - \eta_2) e^{-\gamma Q \tau} \beta(Q) + \eta_1 k_0 e^{-\gamma Q \tau}$$

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

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

is the rate of self-renewal (see [20], [21]), $\gamma_Q$ 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

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

It is convenient to introduce

$$\gamma = \gamma_Q + \eta_1 k_0 + \eta_2 k_0$$

so the equation to be studied becomes

$$\dot{x} = -\gamma x - (1 - \eta_1 - \eta_2) \frac{\beta_0}{1 + x^n} x + e^{-\gamma Q \tau} \left[2(1 - \eta_1 - \eta_2) \frac{\beta_0}{1 + x^n} + k_0 \eta_1 \right] x_\tau. \quad (1.4)$$

One can easily see that if $x(\theta) > 0$ for all $\theta$ 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

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

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

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

(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

$$
\dot{x} = -\gamma x - (1 - \eta_1 - \eta_2) \beta_0 x + e^{-\gamma Q \tau} [k_0 \eta_1 + 2(1 - \eta_1 - \eta_2) \beta_0] x_{\tau}.
$$
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Denote, as in \[15\], \[11\],
\[
a = -\gamma - \beta_0(1 - \eta_1 - \eta_2), \quad b = e^{-\gamma \tau}[2(1 - \eta_1 - \eta_2)\beta_0 + k_0\eta_1].
\]

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

If there exists the solution (2.1) then $a + b$ must have the same sign as $\gamma - e^{-\gamma \tau}\eta_1k_0$ so $a + b > 0$ if and only if $\gamma > e^{-\gamma \tau}\eta_1k_0$. Since $\frac{\eta_1k_0}{\gamma} < 1$ it follows that $e^{\gamma \tau} > \frac{\eta_1k_0}{\gamma}$ 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
\[
\beta_1 = h'(x_2^*). \quad (2.2)
\]

The linearization of (1.4) around $x_2^*$ is
\[
\dot{x}(t) = -[\gamma + (1 - \eta_1 - \eta_2)\beta_0\beta_1]x(t) + e^{-\gamma \tau}[2(1 - \eta_1 - \eta_2)\beta_0\beta_1 + k_0\eta_1]x(t - \tau) \quad (2.3)
\]

Introduce
\[
a(\tau) = -\gamma - (1 - \eta_1 - \eta_2)\beta_0\beta_1
\]
\[
b(\tau) = e^{-\gamma \tau}[2(1 - \eta_1 - \eta_2)\beta_0\beta_1 + k_0\eta_1] \quad (2.4)
\]

The characteristic equation of (2.3) is
\[
\Delta(\lambda, \tau) := \lambda - a(\tau) - b(\tau)e^{-\lambda \tau} = 0 \quad (2.5)
\]

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 $P(iy, \tau) \neq Q(iy, \tau)$, $P(-iy, \tau) = P(iy, \tau)$, $Q(-iy, \tau) = Q(iy, \tau)$. 
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
\[
F(y, \tau) := |P(i\lambda, \tau)|^2 - |Q(i\lambda, \tau)|^2 = 0
\]
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 \( \omega \).

Then \( \Delta(i\omega, \tau) = 0 \) if and only if
\[
\sin \tau \omega = -\frac{\omega}{b(\tau)}, \quad \cos \tau \omega = -\frac{a(\tau)}{b(\tau)}. \tag{2.6}
\]

Since \( |a(\tau)| < |b(\tau)| \) the system (2.6) has the solution
\[
\tau \omega(\tau) = \arccos \left( -\frac{a(\tau)}{b(\tau)} \right) \overset{\text{def}}{=} \alpha(\tau) \in (0, \pi).
\]

Let \( \tau_0 \) 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], \( \text{Re} \lambda'(\tau_0) > 0 \) 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 \( \tau_j \) can exist. Namely if

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

satisfies

\[
S_j'(\tau_j) \neq 0 \quad (2.7)
\]

for

\[
S(\tau_j) = 0 \quad (2.8)
\]

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 \( \tau_0 \) the solution that verifies

\[
\omega_0\tau_0 = \alpha(\tau_0) = \arccos\left(-\frac{a(\tau)}{b(\tau)}\right) \quad (3.1)
\]

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

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

\[
\dot{y}(t) = G_\mu(y_t) \quad (3.2)
\]

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

\[
G_\mu(\varphi) = -\gamma[\varphi(0) + x^*_2] - (1 - \eta_1 - \eta_2)\beta_0 \frac{\varphi(0) + x^*_2}{1 + [\varphi(0) + x^*_2]^n} + e^{-\gamma_Q(\tau_0 + \mu)}\left[\frac{2(1 - \eta_1 - \eta_2)\beta_0}{1 + [\varphi(-\mu - \tau_0) + x^*_2]^n} + k_0\eta_1\right]\varphi(-\mu - \tau_0) + x^*_2]. \quad (3.3)
\]

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

\[
\dot{y}(t) = L_\mu y_t \quad (3.4)
\]
\[ L_\mu \varphi = a(\mu)\varphi(0) + b(\mu)\varphi(-\mu - \tau_0) \]  
(3.5)

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

\[ F_\mu = G_\mu - L_\mu \]
(3.6)

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

\[ \dot{y}(t) = L_\mu y_t + F_\mu(y_t) \]
(3.7)

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

\[ X_0(\theta) = \begin{cases} 
0 & -\mu - \tau_0 \leq \theta < 0 \\
1 & \theta = 0 
\end{cases} \]

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

\[ \langle X_0 \rangle = \{ X_0 c | c \in \mathbb{C} \} \]

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

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

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

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

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

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

\[ \frac{d}{dt} y_t = \tilde{A}_\mu y_t + X_0 F_\mu(y_t) \]
(3.8)

\[ u(0)(\theta) = y_0(\theta) = \varphi(\theta), \theta \in [-\mu - \tau_0, 0] \]

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

\[ \frac{du}{dt} = \tilde{A}_\mu u(t) + X_0 F_\mu[u(t)] \]
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\[ u(0) = \varphi \]

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 \( \varphi \in \overline{D(\overline{A}_\mu)} = C_\mu \). Consider now the space \( C^0_\mu = C([0, \mu + \tau_0], \mathbb{C}) \) and define, according to [17], the bilinear form

\[
\langle \psi, \varphi \rangle = \bar{\psi}(0)\varphi(0) - \int_{-\mu - \tau_0}^{0} \left( \int_{0}^{s} \bar{\psi}(\theta - s)\varphi(\theta)d\theta \right) d\eta(s) = \\
= \bar{\psi}(0)\varphi(0) + b(\mu) \int_{-\tau_0 - \mu}^{0} \bar{\psi}(\theta + \mu + \tau_0)\varphi(\theta)d\theta.
\]

(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

\[
X^0_0(\theta) = \begin{cases} 0, & 0 < \theta \leq \mu + \tau_0 \\ 1, & \theta = 0, \end{cases} \]

and \( \langle X^0_0 \rangle = \{ X^0_0 c| c \in \mathbb{C} \} \)

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

\[
\langle \psi + X^0_a, \varphi + X^0_b \rangle = \langle \psi, \varphi \rangle + \overline{a}b, \quad a, b \in \mathbb{C}.
\]

The adjoint operator \( \tilde{A}^*_\mu \) defined with respect to this bilinear form verifies
\[ \langle \psi, \tilde{A}_{\mu} \varphi \rangle = \overline{\psi(0)} L_{\mu} \varphi + \]
\[ + b(\mu) \int_{-\tau_0 - \mu}^{0} \overline{\psi(s + \mu + \tau_0)} \varphi'(s) ds = \overline{\psi(0)} [a(\mu) \varphi(0) + \]
\[ + b(\mu) \varphi(-\tau_0 - \mu)] + b(\mu) [\overline{\psi(s + \mu + \tau_0)} \varphi(s)]_{s = -\tau_0 - \mu}^{0} - \]
\[ - \int_{-\mu - \tau_0}^{0} \overline{\psi}'(s + \mu + \tau_0) \varphi(s) ds = \]
\[ = \overline{\psi(0)} [a(\mu) \varphi(0) + b(\mu) \varphi(-\tau_0 - \mu)] + b(\mu) \overline{\psi}(\mu + \tau_0) \varphi(0) - \]
\[ - b(\mu) \overline{\psi}(0) \varphi(-\mu - \tau_0) - b(\mu) \int_{-\mu - \tau_0}^{0} \overline{\psi}'(s + \mu + \tau_0) \varphi(s) ds = \]
\[ = \varphi(0) [a(\mu) \overline{\psi}(0) + b(\mu) \overline{\psi}(\mu + \tau_0)] - \]
\[ - b(\mu) \int_{-\mu - \tau_0}^{0} \overline{\psi}'(s + \mu + \tau_0) \varphi(s) ds = \langle \tilde{A}^*_\mu \psi, \varphi \rangle. \]

So \( D(\tilde{A}^*_\mu) = C^1([0, \mu + \tau_0], \mathbb{C}) \) 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 \( (-i\omega_0) \). \( d \in \mathbb{C} \) is choosed such that the norming condition \( \langle q^*, q \rangle = 1 \) is satisfied. It is not difficult to see that this gives

\[ \tilde{d} = \frac{1}{1 + \tau_0 b(0) e^{-i\omega_0 \tau_0}} \] (3.10)

and that for this \( d \), \( \langle q^*, q \rangle = 0 \).

Let \( y \) be a solution of (3.7).

To compute the coordinates of the section \( C_0 \) of the center manifold corresponding to \( \mu = 0 \), define, following [18],[25] for \( t \geq 0 \)

\[ z(t) = \langle q^*, y_t \rangle = \overline{\tilde{d} y(t)} + b(\mu) \int_{-\tau_0}^{0} e^{-i\omega_0 (s + \tau_0)} y(t + s) ds \]
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z and \( \bar{z} \) will be used as local coordinates in the directions \( q^* \) and \( \bar{q}^* \).

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

\[
w(t, s) = \frac{w(t) - z(t)q(s) - \bar{z}(t)\bar{q}(s)}{s} = y(t) - 2Re [z(t)q(s)] = W[z(t), \bar{z}(t), s]
\]

where

\[
W(z, \bar{z}, s) = w_{20}(s)\frac{z^2}{2} + w_{11}(s)z\bar{z} + w_{02}(s)\frac{\bar{z}^2}{2} + \ldots \not= w(s).
\]

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

\[
\langle q^*, w \rangle = \langle q^*, y(t) \rangle - \langle q^*, zq \rangle - \langle q^*, \bar{z}\bar{q} \rangle = \quad z(t) - z(t)\langle q^*, q \rangle - \bar{z}(t)\langle q^*, \bar{q} \rangle = 0
\]

(recall \( \langle q^*, q \rangle = 1, \langle q^*, \bar{q} \rangle = 0 \)). Since \( C_0 \) is locally invariant under (3.8) (see [18], [9]), for \( y(t) \in C_0 \) one has

\[
\dot{z}(t) = \langle q^*, \dot{y}(t) \rangle = \langle q^*, \bar{A}_0y(t) + X_0F_0(y(t)) \rangle = \langle \bar{A}_0q^*, y(t) \rangle + \langle q^*, X_0F_0(y(t)) \rangle = i\omega_0\langle q^*, y(t) \rangle + \quad \bar{d}F_0[W(z(t), \bar{z}(t), \cdot) + 2Re [z(t)q(\cdot)]]|_{s=0} = \quad i\omega_0z(t) + g[z(t), \bar{z}(t)]
\]

where \( g \) is defined by

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

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

\[
F_0(\varphi) = -(1-\eta_1-\eta_2)\beta_0\frac{h''(x_2^*)}{2}\varphi^2(0) + e^{-\gamma\tau_0}2(1-\eta_1-\eta_2)\beta_0\frac{h''(x_2^*)}{2}\varphi^2(-\tau_0) + \quad +\frac{1}{6}[-(1-\eta_1-\eta_2)\beta_0h''(x_2^*), \varphi^3(0) + e^{-\gamma\tau_0}2(1-\eta_1-\eta_2)\beta_0h''(x_2^*)\varphi^3(-\tau_0)] + \ldots
\]

It is convenient to introduce the following notations:

\[
\beta_2 = h''(x_2^*), \quad \beta_3 = h'''(x_2^*)
\]

\[
c_{12} = -(1-\eta_1-\eta_2)\frac{\beta_0\beta_2}{2}, \quad c_{22} = e^{-\gamma\tau_0}2(1-\eta_1-\eta_2)\beta_0\beta_2 \quad (3.15)
\]

\[
C_{13} = -\frac{1}{6}\beta_0\beta_3, \quad c_{23} = \frac{1}{3}e^{-\gamma\tau_0}2(1-\eta_1-\eta_2)\beta_0\beta_3
\]
With these notations $F_0$ becomes
\[ F_0(\phi) = c_{12}\phi^2(0) + c_{22}\phi_{\tau_0}^2(0) + c_{13}\phi^3(0) + c_{23}\phi_{\tau_0}^3(0) + \ldots \] (3.16)

(3.14) and (3.16) imply that
\[
g(z, \overline{z}) = \overline{d}(c_{12}[w(0) + z + \overline{z}]^2 + c_{13}[w(0) + z + \overline{z}]^3 + O(\|w(0) + z + \overline{z}\|^4) + c_{22}[w(-\tau_0) + ze^{-i\omega_0\tau_0} + \overline{z}e^{i\omega_0\tau_0}]^2 +
\]
\[ + c_{23}[w(-\tau_0) + ze^{-i\omega_0\tau_0} + \overline{z}e^{i\omega_0\tau_0}]^3 + O(\|w(-\tau_0) + ze^{-i\omega_0\tau_0} + \overline{z}e^{i\omega_0\tau_0}\|^4) :=
\]
\[
= \frac{g_{20}}{2}z^2 + g_{11}z\overline{z} + \frac{g_{02}}{2}\overline{z}^2 + \frac{1}{2}g_{21}z^2\overline{z} + \ldots
\] (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
\[
\frac{1}{2}g_{20} = \overline{d}(c_{12} + c_{22}e^{-i\omega_0\tau_0})
\]
\[
g_{11} = 2\overline{d}(c_{12} + c_{22})
\]
\[
\frac{1}{2}g_{02} = \overline{d}(c_{12} + c_{22}e^{i\omega_0\tau_0})
\]
\[
\frac{1}{2}g_{21} = \overline{d}[c_{12}(2w_{11}(0) + w_{20}(0))3c_{13} + c_{22}(2w_{11}(-\tau_0) + w_{20}(-\tau_0)e^{i\omega_0\tau_0}) + 3c_{23}e^{-i\omega_0\tau_0}]
\]

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 $w(s) = w_0(s) + \frac{z^2}{2} + w_{11}(s)z\overline{z} + w_{02}(s)\overline{z}^2 + \ldots$ Taking the derivative with respect to $t$ in (3.11) and taking into account (3.8) and (3.11) it follows that
\[
\frac{d}{dt}w(t, \cdot) = \frac{d}{dt}y_t - \frac{d}{dt}[z(t)q(\cdot) + \overline{z}(t)\overline{q}(\cdot)] =
\]
\[ = \tilde{A}_0y_t + X_0F_0(y_t) - 2\text{Re} \left[ \dot{z}(t)q(\cdot) \right] =
\]
\[ = \tilde{A}_0[w(t, \cdot) + 2\text{Re} z(t)q(\cdot)] + X_0F_0[w(t, \cdot) +
\]
\[ + 2\text{Re} (z(t)q(\cdot)) - 2\text{Re} [\dot{z}(t)q(\cdot)].
\]
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

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

Finally

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

where

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

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

$$H(z, \bar{z}, s) = -2\text{Re}[g(z, \bar{z})q(s)] =$$

$$= -\left( g_{20} \frac{z^2}{2} + g_{11}z\bar{z} + g_{02} \frac{\bar{z}^2}{2} + \ldots \right) q(s) -$$

$$- \left( \bar{g}_{20} \frac{z^2}{2} + \bar{g}_{11}z\bar{z} + \bar{g}_{02} \frac{\bar{z}^2}{2} + \ldots \right) \bar{q}(s) =$$

$$= H_{20}(s) \frac{z^2}{2} + H_{11}(s)z\bar{z} + H_{02}(s) \frac{\bar{z}^2}{2} + \ldots$$

It follows that

$$H_{20}(s) = -g_{20}q(s) - \bar{g}_{02} \bar{q}(s)$$

$$H_{11}(s) = -g_{11}q(s) - \bar{g}_{11} \bar{q}(s)$$

$$H_{02}(s) = H_{20}(s)$$

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

$$\tilde{A}_0 w(t, \cdot) + H[z(t), \bar{z}(t), \cdot] = w_{20}(\cdot)z(t)\dot{z}(t) +$$

$$+ w_{11}(\cdot)[\dot{z}(t)\bar{z}(t) + z(t)\ddot{z}(t)] + w_{02}(\cdot)\bar{z}(t)\ddot{z}(t) + \ldots =$$

$$= w_{20}(\cdot)z(t)[i\omega_0 z(t) + g(z(t), \bar{z}(t))] +$$

$$+ w_{11}(\cdot)\bar{z}(t)[i\omega_0 z(t)] + g(z(t), \bar{z}(t))] +$$

$$+ w_{11}(\cdot)z(t)[-i\omega_0 \bar{z}(t) + g(z(t), \bar{z}(t))] +$$

$$+ w_{02}(\cdot)\bar{z}(t)[-i\omega_0 \bar{z}(t) + g(z(t), \bar{z}(t))].$$

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

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

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

\[ w_{20}(s) = -\frac{g_{20}}{i\omega_0}e^{i\omega_0 s} - \frac{\overline{g}_{02}}{3i\omega_0}e^{-i\omega_0 s} + C_1e^{2i\omega_0 s}. \]

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

\begin{align*}
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_1e^{2i\omega_0 \tau_0} \right) &= -H_{20}(0).
\end{align*}

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

\[ H(z, \bar{z}, 0) = -2\mathrm{Re} \left[ g(z, \bar{z}) \right] + F_0[W(z, \bar{z}, s) + 2\mathrm{Re} (zq(s))]|_{s=0} = \\
= -g(z, \bar{z}) - \overline{g}(z, \bar{z}) + \frac{1}{d} g(z, \bar{z}) \]

so

\[ H_{20}(0) = -g_{20} - \overline{g}_{02} + \frac{1}{d} \overline{g}_{20} \]

\[ H_{11}(0) = -g_{11} - \overline{g}_{11} + \frac{1}{d} \overline{g}_{11} \quad (3.24) \]

and it follows that

\begin{align*}
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}{d} g_{20} + \\
&+ 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{align*}

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

(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 \(g_{21}\)
\[
\frac{g_{21}}{2} = \overline{\chi} \left[ c_{12} (2w_{11}(0) + w_{20}(0)) + 3c_{13} + c_{22} (2w_{11}(-\tau_0) e^{-i\omega_0 \tau_0} + w_{20}(-\tau_0) e^{i\omega_0 \tau_0}) + 3c_{23} e^{-i\omega_0 \tau_0} \right].
\]

(3.27)

The Lyapunov coefficient is given by
\[ l_1(0) = \text{Re} L_1(0) \]
with
\[
L_1(0) = \frac{1}{2\omega_0} \left( g_{20} g_{11} - 2|g_{11}|^2 - \frac{1}{3} |g_{02}|^2 \right) + \frac{1}{2} g_{21}
\]
(3.28)

Introduce also
\[
\mu_2 = -\frac{l_1(0)}{\text{Re} \lambda'(\tau_0)}
\]
\[
T_2 = -\frac{\text{Im} L_1(0) + \mu_2 \text{Im} \lambda(\tau_0)}{\omega_0}.
\]

(3.29)
The following theorem sums up the information 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 approximately \( \frac{2\pi}{\omega_0} \) 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

\[
x(t) = x_2^*(\tau_0) + 2 \left( \frac{\tau - \tau_0}{\mu_2} \right)^{1/2} \text{Re} \left( e^{i\omega_0 t} \right) + \\
+ \frac{\tau - \tau_0}{\mu_2} \text{Re} \left( C_1 e^{2i\omega_0 t} + C_2 \right) + O(\varepsilon^3)
\]

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

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 inducing complete hematological remission in almost all patients 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

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

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

$$
\dot{x} = -\gamma Q x - (\eta_1 + \eta_2)k_0 x - (1 - \eta_1 - \eta_2) \beta_0 h(x) - \tilde{k} \theta^q x^{q+1} + 2e^{-\gamma \tau} [2(1 - \eta_1 - \eta_2) \beta_0 h(x_\tau) + k_0 \eta_1 x_\tau].
$$

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

\[
\dot{V} = 2x(t)\dot{x}(t) + 2\alpha x(t)^2 - 2\alpha x(t - \tau)^2 =
\]

\[
= 2x(t)\{-c_1 x(t) - c_2 h[x(t)] + c_3 x(t - \tau) + c_4 h[x(t - \tau)] - kx(t)^{q+1}\} + 2\alpha x(t)^2 - 2\alpha x(t - \tau)^2 =
\]

\[
= -2[(c_1 - \alpha)x(t)^2 - c_3 x(t)x(t - \tau) + \alpha x(t - \tau)^2] - 2x(t)\{c_2 h[x(t)] - c_4 h[x(t - \tau)]\} - 2kx(t)^{q+2}.
\]

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

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

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 \( \omega_0 \) and \( \tau_0 \) verify

\[ \omega_0 \tau_0 = \arccos \left( -\frac{a(\tau_0)}{b(\tau_0)} \right) \]
Stability analysis in a model for stem-like hematopoietic cells dynamics

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

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

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

\[ - \frac{1}{6}(q + 1)q(q - 1)x^{g-2}\varphi(0)^3 - \frac{1}{3}e^{-\gamma Q \tau_0}(1 - \eta_1 - \eta_2) \beta_0 h'''(x^*) \varphi(-\tau_0)^3 + \ldots \]

so

\[ c_{12} = -(1 - \eta_1 - \eta_2) \frac{\beta_0 \beta_2}{2} - \frac{1}{2}(q + 1)qx^{g-1} \]

\[ c_{13} = -\frac{1}{6}(1 - \eta_1 - \eta_2) \beta_0 \beta_3 - \frac{1}{6}(q + 1)q(q - 1)x^{g-2}. \]

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 \( l_1(0), \mu_2 \) 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 \( \tau \) 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>
<thead>
<tr>
<th>Name</th>
<th>Values</th>
<th>Units</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of SC population with asymmetric division</td>
<td>0.1, 0.2, 0.4</td>
<td></td>
<td>The percent of SC population with asymmetric division</td>
</tr>
<tr>
<td>% of SC population with symmetric division</td>
<td>0.1, 0.2, 0.4</td>
<td></td>
<td>The percent of SC population with symmetric division</td>
</tr>
<tr>
<td>% of mature cells (M)</td>
<td>0.1, 0.2, 0.4</td>
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<td>The percent of mature cells (M)</td>
</tr>
<tr>
<td>% of early stage self-renewal cells</td>
<td>0.1, 0.2, 0.4</td>
<td></td>
<td>The percent of early stage self-renewal cells</td>
</tr>
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<td>Maximal self-renewal rate</td>
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<td>Maximal self-renewal rate</td>
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<tr>
<td>Parameter controlling the sensitivity of the self renewal</td>
<td>4</td>
<td></td>
<td>Parameter controlling the sensitivity of the self renewal</td>
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<tr>
<td>Rate to changes in the size of the SC compartment</td>
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<td>Rate to changes in the size of the SC compartment</td>
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<tr>
<td>Value for which β(0) and negative feedback function for SC</td>
<td>0.5*10^6 cells kg^-1</td>
<td></td>
<td>Value for which β(0) and negative feedback function for SC</td>
</tr>
<tr>
<td>SC attains half of its maximum value</td>
<td>2.8 days</td>
<td></td>
<td>SC attains half of its maximum value</td>
</tr>
<tr>
<td>Maximal rate of differentiation / symmetric division</td>
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<td></td>
<td>Maximal rate of differentiation / symmetric division</td>
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<tr>
<td>SC proliferation time</td>
<td>0.0412</td>
<td></td>
<td>SC proliferation time</td>
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<tr>
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<td>SC proliferation time</td>
</tr>
<tr>
<td>Initial number of SC</td>
<td>2.5*10^6 cells kg^-1</td>
<td></td>
<td>Initial number of SC</td>
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<tr>
<td>Resistance to treatment (imatinib)</td>
<td>0.01*10^6 cells kg^-1</td>
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<td>The influence of treatment on SC</td>
<td>0.01*10^6 cells kg^-1</td>
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<td>The influence of treatment on SC</td>
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<td>The effect of resistance to treatment (imatinib)</td>
<td>0.01*10^6 cells kg^-1</td>
<td></td>
<td>The effect of resistance to treatment (imatinib)</td>
</tr>
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</table>
Table 2. The results of calculation for a constant influence of imatinib treatment $k=0.15$

<table>
<thead>
<tr>
<th>Case</th>
<th>$\eta_1$</th>
<th>$k_0$</th>
<th>$k_0$</th>
<th>$L_{1(0)}$</th>
<th>$m_0$</th>
<th>$a_0$</th>
<th>$a_1$</th>
<th>$a_2$</th>
<th>$\beta_1$</th>
<th>$\tau_1$</th>
<th>$T_2$</th>
<th>$T_3$</th>
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<th>$\rho_3$</th>
<th>$\omega_0$</th>
<th>$\delta$</th>
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<td>0.1</td>
<td>0.5</td>
<td>0.15</td>
<td>1.0939</td>
<td>-0.451</td>
<td>0.3225</td>
<td>-1.142</td>
<td>-0.451</td>
<td>5.7419</td>
<td>5.9012</td>
<td>5.9012</td>
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<td>-1.142</td>
<td></td>
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<td>0.1</td>
<td>0.5</td>
<td>0.15</td>
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<td>0.3225</td>
<td>-1.142</td>
<td>-0.451</td>
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<td></td>
<td></td>
</tr>
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<td>0.1</td>
<td>0.5</td>
<td>0.15</td>
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<td>0.3225</td>
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</tr>
<tr>
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<td>0.1</td>
<td>0.1</td>
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Figure 1. Simulation of LSC population (case 2 in the table 2) for $\tau=\tau_0$, starting near steady state point $x_*$;
CML conditions simulated by a percent of asymmetric division small ($\eta_1=0.10$) and a rate of differentiation small ($k_9=0.5$); A represents simulations for the model without treatment, B represents simulations for the model with treatment.
Stability analysis in a model for stem-like hematopoietic cells dynamics

Figure 2. Simulation of LSC population (case 34 in the table 2) for $\tau = \tau_0$, starting near steady state point $x_*$: CML conditions simulated by a percent of asymmetric division small ($\eta_1=0.10$) and a rate of differentiation medium ($k_0=1.0$); 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 $\tau=\tau_0$, starting near steady state point $x^*$; CML conditions simulated by a percent of asymmetric division small ($\eta_1=0.10$) and a rate of differentiation big ($\eta_2=1.5$); A represents simulations for the model without treatment, B represents simulations for the model with treatment.
Stability analysis in a model for stem-like hematopoietic cells dynamics

Figure 4. Simulation of LSC population (case 3 in the table 2) for $\tau = \tau_0$, starting near steady state point $x_*$; CML conditions simulated by a percent of asymmetric division small ($\eta_1=0.10$) and a rate of differentiation small ($k_0=0.1$); $A$ 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 point \( x_* \); CML conditions simulated by a percent of asymmetric division small \( \eta_1=0.10 \) and a rate of differentiation small \( k_0=0.1 \); A represents simulations for the model without treatment, B represents simulations for the model with treatment.
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A. \( \tau > \tau_0 \), case=3, \( \eta_1=0.10, \eta_2=0.30, \tau_0=1.52, x_*=1.3633, \text{Osc.Per.}=\text{7.42, k0}=0.50, k=0 \)

B. \( \tau > \tau_0 \), case=3, \( \eta_1=0.10, \eta_2=0.30, \tau_0=1.32, x_*=1.1251, \text{Osc.Per.}=\text{5.97, k0}=0.50, k=0.15 \)

Figure 6. Simulation of LSC population (case 3 in the table 2) for \( \tau > \tau_0 \), starting near steady state point \( x_* \); CML conditions simulated by a percent of asymmetric division small (\( \eta_1=0.10 \)) and a rate of differentiation small (\( k=0.1 \)); 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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This work was supported by CNCS-ROMANIA Grant ID-PCE-2011-3-0198. The authors express their gratitude to the referee for useful suggestions

References


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