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Existence and Stability of Limit Cycles in a Two-delays Model of Hematopoiesis Including Asymmetric Division

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Abstract. A two dimensional two-delays differential system modeling the dynamics of stem-like cells and white-blood cells in Chronic Myelogenous Leukemia is considered. All three types of stem cell division (asymmetric division, symmetric renewal and symmetric differentiation) are present in the model. Stability of equilibria is investigated and emergence of periodic solutions of limit cycle type, as a result of a Hopf bifurcation, is eventually shown. The stability of these limit cycles is studied using the first Lyapunov coefficient.

Keywords and phrases: leukemia, asymmetric division, stability, Hopf bifurcation, limit cycle,

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1. Introduction

Hematopoiesis is the process of production, multiplication and development of all the different cell lineages that form the blood and the immune system. It takes place in the bone marrow and it begins with the hematopoietic stem cells (HSCs). These cells are pluripotential and self-replicating and can differentiate into each of the three major cell lines: white blood (leucocytes), red blood (erythrocytes) and platelets. While normal hematopoiesis is characterized by the production of healthy blood cells controlled by complex feedback mechanisms, pathological hematopoiesis involves some abnormal functioning of the hematopoietic system and consequently, can lead to blood disease. The ratio between annual deaths to annual new cases for leukemia is 58% [19]. A very common and intensively studied type of blood disease is Chronic Myelogenous Leukemia (CML). The cause of this disease is a chromosomal abnormality believed to appear in a hematopoietic cell in one of the earliest stage of blood cell development ([35], [15], [20]). The importance of the study of mathematical models of CML resides on two major facts: the molecular mechanisms involved in the disease initiation are well known and understood and the current treatment scheme with Imatinib is maybe the most efficient cancer therapy. Because of these particularities, many authors studied and modeled the evolution of leukemia, using different mathematical tools and various biological hypotheses: ordinary differential equations (ODEs); delay differential equations (DDEs) with

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a constant time delay that consider the resting stem cell population [26], [32], [6]; DDEs with distributed parameters: it is taken into consideration the fact that the cells do not divide at the same age and it is supposed that the delays (proliferating phase time duration) obey a low of uniform distribution on an interval [2], [3], [6], [31] and DDE with state dependent delay [6].Models that involve partial differential equations for tumors are described in[19],[4]. Previous mathematical models of hematopoietic stem cell dynamics are analyzed in [7], [11], [12], [24], [26], [27], [37]. Other approaches that do not use the resting phase model are also studied: in [30] the authors used a four-compartment model consisting of stem cells, progenitor cells, differentiated cells, and terminally differentiated cells and involving both normal and leukemic cells to explain the kinetics of the molecular response to Imatinib in a 169-patient data set. More recently, the competition between the healthy and leukemic population was addressed [16], [37]. Moreover, models involving the treatment of CML were developed: in [29], a mathematical model were designed to analyze the in vivo kinetics of CML during treatment with Imatinib; in [34], a model involving Imatinib therapy was investigated, under the assumption that only the proliferating leukemia stem cells are affected by Imatinib. A different approach was used in [25], where a model that takes into consideration the drug resistance of leukemic cells is studied, with the assumption that Imatinib affects all leukemic cells.

Most of the papers investigating CML dynamics through DDEs, did not considered the process of asymmetric division of proliferating HSCs. The model analyzed here takes into account all types of HSCs division that have been experimentally observed (see [38]), namely:

− asymmetric division, when a stem cell divides into one progenitor cell and one stem cell,

− symmetric differentiation, when the cell divides into two progenitors,

− symmetric renewal, when a stem cell divides into two stem cells.

The diagram from Figure 1 illustrates the process of leukopoiesis incorporating also the asymmetric division.

The hematopoietic stem cells that will be considered are supposed to be in the proliferative phase or to spend a short time into the resting phase. These cells will be called, following [28], Short Term Hematopoietic Stem cells (ST-HSC). The density of ST-HSC cells will be denoted by Q (units 10^6 cells/kg) and the density of circulating leukemic cells by N (units 10^9 cells/kg). A percentage η_1 of ST-HSC is supposed to undergo asymmetric division, a percentage η_2 goes to differentiation through symmetric division while the $(1-\eta_1-\eta_2)$ percentage represents cells that self-renew through symmetric division.

Following the approach in [9], [32], [33], [12] and taking into consideration the scheme in Figure 1, the dynamics is given by

$$\begin{aligned}\dot{Q} &= -\gamma_Q Q - KQ - \eta_1\tilde{k}(N)Q - \eta_2\tilde{k}(N)Q \\ &\quad - (1-\eta_1-\eta_2)\tilde{\beta}(Q)Q + 2e^{-\gamma_Q\tau_1}(1-\eta_1-\eta_2)\tilde{\beta}(Q_{\tau_1})Q_{\tau_1} + \\ &\quad + \eta_1\tilde{k}(N_{\tau_1})e^{-\gamma_Q\tau_1}Q_{\tau_1} \\ \dot{N} &= -\gamma_N N + A_N\tilde{k}(N_{\tau_2})Q_{\tau_2}.\end{aligned} \tag{1.1}$$

In this system $\tilde{\beta}(Q)$ is the rate of self-renewal and is given by a Hill function (see [12])

$$\tilde{\beta}(Q) = \beta_0\frac{\theta_1^m}{\theta_1^m + Q^m}$$

$\tilde{k}(N)$ is the rate of differentiation, through symmetric or asymmetric division, and is supposed to be given by a feedback law expressed again by a Hill function

$$\tilde{k}(N) = k_0\frac{\theta_2^n}{\theta_2^n + N^n}.$$

The time necessary for a ST-HSC to complete a cycle of self-renewal, asymmetric division or differentiation is supposed to be the same, τ_1. The time necessary for the maturation of leukocytes is denoted by

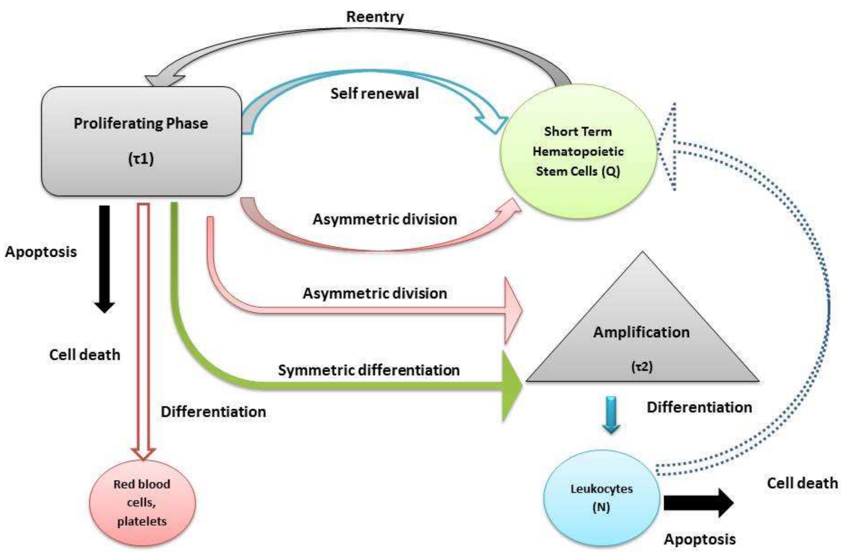

FIGURE 1. The model of leukopoiesis incorporating also the asymmetric division.

τ_2. γ_Q and γ_N stand for the rates of instant mortality of ST-HSC and respectively white blood cells and K denotes the rate of loss of stem-like cells due to differentiation in erythrocyte or thrombocyte lines. $Q_\tau(t) = Q(t-\tau)$, $N_\tau(t) = N(t-\tau)$, A_N is an amplification factor: $A_N = 2^p(\eta_1 + 2\eta_2)C_N$, where p is the number of divisions in the maturation process and C_N a correction due to mortality. $e^{-\gamma_Q \tau_1}$ comes from mortality during the cell cycle.

Denote $\tilde{\gamma}_Q = \gamma_Q + K$, and perform an adimensionalization of (1.1) through the variables

$$x_1 = \frac{Q}{\theta_1}, \quad x_2 = \frac{N}{\theta_2}.$$

Introducing $\tilde{A}_N = A_N \dfrac{\theta_1}{\theta_2}$, $\beta(x_1) = \beta_0 \dfrac{1}{1 + x_1^m}$, $k(x_2) = k_0 \dfrac{1}{1 + x_2^n}$ the following system results from (1.1)

$$\begin{aligned} \dot{x}_1 &= -\tilde{\gamma}_Q x_1 - \eta_1 k(x_2) x_1 - \eta_2 k(x_2) x_1 - (1 - \eta_1 - \eta_2)\beta(x_1) x_1 + \\ &\quad + 2e^{-\gamma_Q \tau_1}(1 - \eta_1 - \eta_2)\beta(x_{1\tau_1}) x_{1\tau_1} + \\ &\quad + \eta_1 e^{-\gamma_Q \tau_1} k(x_{2\tau_1}) x_{1\tau_1} \\ \dot{x}_2 &= -\gamma_N x_2 + \tilde{A}_N k(x_{2\tau_2}) x_{1\tau_2}. \end{aligned} \tag{1.2}$$

The system (1.2) has as an equilibrium point $x_1 = 0$, $x_2 = 0$ that corresponds to the extinction of the population of leukemia cells.

Another equilibrium point can be found as a solution of the system of equations

$$\gamma_N x_2 = \tilde{A}_N k(x_2) x_1$$

$$\tilde{\gamma}_Q + (\eta_1 + \eta_2) k(x_2) + (1 - \eta_1 - \eta_2)\beta(x_1) = e^{-\gamma_Q \tau_1}[2(1 - \eta_1 - \eta_2)\beta(x_1) + \eta_1 k(x_2)].$$

Thus

$$x_1 = \frac{\gamma_N x_2}{\tilde{A}_N k(x_2)} \tag{1.3}$$

and, if the right-hand member is positive, the following equation gives $x_2^* > 0$

$$\tilde{\gamma}_Q + \frac{k_0}{1 + x_2^n}(\eta_1 + \eta_2 - \eta_1 e^{-\gamma_Q \tau_1}) = (2e^{-\gamma_Q \tau_1} - 1)(1 - \eta_1 - \eta_2)\beta(x_1) \tag{1.4}$$

and $x_1^* > 0$ is then obtained from (1.3).

2. Stability of the nontrivial equilibrium

Suppose that (1.3) and (1.4) have a solution (x_1^*, x_2^*) with $x_1^* > 0$, $x_2^* > 0$. Perform a translation to zero through $y = x_1 - x_1^*$, $y_2 = x_2 - x_2^*$ and define $h(x) = \dfrac{x}{1 + x^m}$. Then (1.2) implies that

$$\begin{aligned}
\dot{y}_1 &= -[\tilde{\gamma}_Q + \eta_1 k(y_2 + x_2^*) + \eta_2 k(y_2 + x_2^*)](y_1 + x_1^*) - \\
&\quad - (1 - \eta_1 - \eta_2)\beta_0 h(y_1 + x_1^*) + 2e^{-\gamma_Q \tau_1}(1 - \eta_1 - \eta_2)\beta_0 h(y_{1\tau_1} + x_1^*) + \\
&\quad + \eta_1 e^{-\gamma_Q \tau_1} k(y_{2\tau_1} + x_2^*)(y_{1\tau_1} + x_1^*) \\
\dot{y}_2 &= -\gamma_N y_2 - \gamma_2 x_2^* + \hat{A}_N k(y_{2\tau_2} + x_2^*)(y_{1\tau_2} + x_1^*).
\end{aligned} \tag{2.1}$$

The linearization of (2.1) about (0,0) gives

$$\begin{aligned}
\dot{y}_1 &= -[\tilde{\gamma}_Q + (\eta_1 + \eta_2) k(x_2^*) + (1 - \eta_1 - \eta_2)\beta_0 h'(x_1^*)] y_1 - \\
&\quad - (\eta_1 + \eta_2) x_1^* k'(x_2^*) y_2 + [2e^{-\gamma_Q \tau_1}(1 - \eta_1 - \eta_2)\beta_0 h'(x_1^*) + \\
&\quad + \eta_1 e^{-\gamma_Q \tau_1} k(x_2^*)] y_{1\tau_1} + \eta_1 e^{-\gamma_Q \tau_1} x_1^* k'(x_2^*) y_{2\tau_1} \\
\dot{y}_2 &= -\gamma_N y_2 + \tilde{A}_N k(x_2^*) y_{1\tau_2} + \tilde{A}_N k'(x_2^*) x_1^* y_{2\tau_2}.
\end{aligned} \tag{2.2}$$

In the matrix form, with $y = \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}$, (2.2) becomes

$$\dot{y} = A_2 y + B_{2\tau_1} y_{\tau_1} + B_{2\tau_2} y_{\tau_2}$$

where $A_2 = [a_{ij}]_{1 \le i,j \le 2}$, $B_{2\tau_1} = [b_{ij}]_{1 \le i,j \le 2}$, $B_{2\tau_2} = [c_{ij}]_{1 \le i,j \le 2}$

$$\begin{aligned}
a_{11} &= -[\tilde{\gamma}_Q + (\eta_1 + \eta_2) k(x_2^*) + (1 - \eta_1 - \eta_2) h'(x_1^*)\beta_0] \\
a_{12} &= -(\eta_1 + \eta_2) x_1^* k'(x_2^*), \quad a_{21} = 0, \quad a_{22} = -\gamma_N \\
b_{11} &= 2e^{-\gamma_Q \tau_1}(1 - \eta_1 - \eta_2)\beta_0 h'(x_1^*) + \eta_1 e^{-\gamma_Q \tau_1} k(x_2^*) \\
b_{12} &= \eta_1 e^{-\gamma_Q \tau_1} x_1^* k'(x_2^*), \quad b_{21} = b_{22} = 0 \\
c_{11} &= 0,\ c_{12} = 0,\ c_{21} = \tilde{A}_N k(x_2^*),\ c_{22} = \tilde{A}_N x_1^* k'(x_2^*).
\end{aligned}$$

The characteristic equation is

$$\Delta_2(\lambda, \tau_1, \tau_2) = \det(\lambda I_2 - A_2 - B_{2\tau_1} e^{-\lambda \tau_1} - B_{2\tau_2} e^{-\lambda \tau_2}) = 0$$

so

$$(\lambda - a_{11})(\lambda + \gamma_N) - (\lambda c_{22} - a_{11}c_{22} + c_{21}a_{12})e^{-\lambda\tau_2} - \\ -(\lambda + \gamma_N)b_{11}e^{-\lambda\tau_1} + (b_{11}c_{22} - c_{21}b_{12})e^{-\lambda(\tau_1+\tau_2)} = 0. \tag{2.3}$$

To study stability we follow the approach in [4]. Consider first the case $\tau_1 = \tau_2 = 0$. Then (2.3) becomes

$$\lambda^2 + \lambda(\gamma_N - a_{11} - c_{22} - b_{11}) - a_{11}\gamma_N + a_{11}c_{22} - c_{21}a_{12} - \gamma_N b_{11} + b_{11}c_{22} - c_{21}b_{12} = 0 \tag{2.4}$$

Then, if

$$\gamma_N - a_{11} - c_{22} - b_{11} > 0 \tag{2.5}$$

and

$$a_{11}(c_{22} - \gamma_N) - c_{21}a_{12} - c_{21}b_{12} + b_{11}(c_{22} - \gamma_N) > 0 \tag{2.6}$$

the solutions of (2.4) are in the left half-plane and the zero solution of the linear system (2.2) with $\tau_1 = \tau_2 = 0$ is asymptotically stable thus, by the theorem of stability in the first approximation, the equillibrium (x_1^*, x_2^*) is locally asymptotically stable for the nonlinear system in this case.

In order to simplify the discussion we make the following assumption:

$$h'(x_1^*) < 0 \tag{H1}$$

Obviously

$$k'(x) = -nk_0\frac{x^{n-1}}{(1+x^n)^2} < 0$$

Since

$$a_{11} + b_{11} = -\tilde{\gamma}_Q - (\eta_1 + \eta_2)k(x_2^*) - (1 - \eta_1 + \eta_2)\beta_0 h'(x_1^*) + 2(1 - \eta_1 - \eta_2)\beta_0 h'(x_1^*) + \\ +\eta_1 k(x_2^*) = -\tilde{\gamma}_Q - \eta_2 k(x_2^*) + (1 - \eta_1 - \eta_2)\beta_0 h'(x_1^*) < 0.$$

and

$$c_{22} = \tilde{A}_N k'(x_2^*) < 0$$

condition (2.5) is verified. Concerning (2.6), remark that

$$a_{11}c_{22} - c_{21}a_{12} + b_{11}c_{22} - c_{21}b_{12} = \tilde{A}_N k'(x_2^*)x_1^*(-\tilde{\gamma}_Q + (1 - \eta_1 - \eta_2)\beta_0 h'(x_1^*)) > 0$$

and, since $a_{11} + b_{11} < 0$,condition (2.6) is also verified.

Suppose now that $\tau_1 = 0$ and $\tau_2 > 0$. Then (2.3) becomes

$$(\lambda + \gamma_N)(\lambda - a_{11} - b_{11}) - (\lambda c_{22} - a_{11}c_{22} + c_{21}a_{12} - b_{11}c_{22} + c_{21}b_{12})e^{-\lambda\tau_2} = 0 \tag{2.7}$$

The equation of the steady-state, (1.4), becomes

$$\tilde{\gamma}_Q + \frac{k_0\eta_2}{1 + x_2^n} = \frac{(1 - \eta_1 - \eta_2)\beta_0}{1 + x_1^m}$$

so (x_1^*, x_2^*) does not depend on τ_2. Since (2.7) reduces to (2.4) for $\tau_2 = 0$, if (2.5) and (2.6) hold then (x_1^*, x_2^*) is locally asymptotically stable for $\tau_2 = 0$ and the stability can be lost with the increase of τ_2 if a pair of pure imaginary roots verifies (2.7). Equation (2.7) can be analysed following [14]. So, define

$$P(z) = (z + \gamma_N)(z - a_{11} - b_{11}) = z^2 + z(\gamma_N - a_{11} - b_{11}) - \gamma_N(a_{11} + b_{11})$$
$$Q(z) = -(zc_{22} - b_{11}c_{22} - a_{11}c_{22} + a_{12}c_{21} + b_{12}c_{21}).$$

Suppose the conditions of Theorem 1 in [14] are fulfiled ((ii), (iv) and (v) are obvious and (i), (iii) are most likely to hold). Then the stability of (2.7) depends on the roots of the equation

$$|P(iy)|^2 = |Q(iy)|^2 \tag{2.8}$$

If (2.8) has no $y > 0$ as a root (thus, by (ii), no $y \neq 0$ as a root), since (2.7) is stable for $\tau_2 = 0$ it will be stable for all $\tau_2 > 0$.

If (2.8) has at least one positive root and all the positive roots are simple, stability will change as τ_2 increases and (2.7) will become unstable after a threshold $\hat{\tau}_2$ is depassed ($\tau_2 > \hat{\tau}_2$). If, following [11], one sets

$$P(iy) = P_R(y) + iP_I(y), \quad Q(iy) = Q_R(y) + iQ_I(y)$$

with P_R, P_I, Q_R, Q_I real-valued, $i\omega$ verifies (2.7) if and only if

$$Q_R(\omega)\cos\omega\tau_2 + Q_I(\omega)\sin\omega\tau_2 = -P_R(\omega)$$

$$Q_I(\omega)\cos\omega\tau_2 - Q_R(\omega)\sin\omega\tau_2 = -P_I(\omega)$$

and this gives

$$\begin{aligned} \cos\omega\tau_2 &= -\frac{P_R(\omega)Q_R(\omega) + P_I(\omega)Q_I(\omega)}{Q_R^2(\omega) + Q_I^2(\omega)} \\ \sin\omega\tau_2 &= \frac{P_I(\omega)Q_R(\omega) - P_R(\omega)Q_I(\omega)}{Q_R^2(\omega) + Q_I^2(\omega)} \end{aligned} \tag{2.9}$$

while from (2.8) one has

$$P_R^2(\omega) + P_I^2(\omega) = Q_R^2(\omega) + Q_I^2(\omega). \tag{2.10}$$

It follows also from [11] that if $z(\tau_2)$ is a solution of (2.7) then, if τ_2^* verifies (2.9) for a certain solution ω_0 of (2.10), $z'(\tau_2^*) \neq 0$. It is also proved in [10] that

$$s = \operatorname{sgn} \frac{d}{d\tau_2} \operatorname{Re} z(\tau_2)|_{\tau_2 = \tau_2^*} = \operatorname{sgn} F'(\omega_0)$$

with $F(y) := |P(iy)|^2 - |Q(iy)|^2$. Then, if sgn $F'(\omega_0) > 0$ the crossing of the imaginary axix takes place from left to right and a Hopf bifurcation occurs. Remark that to a root ω_0 of (2.10) corresponds an infinite number of $\tau_2^*(\omega_0)$ that verify (2.9) for $\omega = \omega_0$. These are given by

$$\begin{aligned} \omega_0\tau_2 &= \arccos\left[-\frac{P_R(\omega_0)Q_R(\omega_0) + P_I(\omega_0)Q_I(\omega_0)}{Q_R^2(\omega_0) + Q_I^2(\omega_0)}\right] + 2j\pi \\ \omega_0\tau_2 &= 2\pi - \arccos\left[-\frac{P_R(\omega_0)Q_R(\omega_0) + P_I(\omega_0)Q_I(\omega_0)}{Q_R^2(\omega_0) + Q_I^2(\omega_0)}\right] + 2j\pi \end{aligned} \tag{2.12}$$

where $j \in \mathbf{N}$ (see also [8]).

The following result, similar to Theorem 5 in [4], is proved.

Proposition 2.1. *Suppose that Eq. (2.10) has positive roots ω_l and let $\tau_{2j}^*(\omega_l)$ be defined from (2.11), (2.12). Define $\tau_2^* = \min\{\tau_{2j}^*(\omega_l) | \omega_l > 0 verifies (2.10), \tau_{2j}^*(\omega_l) verifies (3.11) or (2.12)\}$. Then, if (2.5) and (2.6) hold, the equilibrium (x_1^*, x_2^*) is locally asymptotically stable for $\tau_2 < \tau_2^*$ and, if $F'(\omega_0) > 0$, a Hopf bifurcation occurs when $\tau_2 = \tau_2^*$ (τ_2^* is defined with respect to ω_0).*

We take now $\tau_1^0 > 0$ and calculate the equilibrium point from (1.4). Suppose such an equilibrium point exists (i.e (1.4) has a positive root). Consider first $\tau_2 = 0$ and write the characteristic equation (2.3).

$$P(z) + Q(z)e^{-z\tau_1^0} = 0. \tag{2.13}$$

Here $P(z) = z^2 + az + c$, $Q(z) = bz + d$.

$$\begin{aligned} a &= -a_{11} + \gamma_N - c_{22}, \\ b &= -b_{11}, \\ c &= -\gamma_N a_{11} + a_{11}c_{22} - c_{21}a_{12} \\ d &= -b_{11}\gamma_N + b_{11}c_{22} - c_{21}b_{12} \end{aligned}$$

Equation (2.13) is completely investigated in [13] and [17].

It has one solution $\lambda = i\omega_0$, $\omega > 0$ if

$$c^2 < d^2. \tag{2.14}$$

It has two solutions $\lambda_1 = i\omega_1$, $\lambda_2 = i\omega_2$, $\omega_2 > \omega_1 > 0$ if

$$c^2 > d^2 \tag{2.15}$$

$$b^2 - a^2 + 2c > 0 \tag{2.16}$$

$$(b^2 - a^2 + 2c)^2 > 4(c^2 - d^2) \tag{2.17}$$

and no pure imaginary solution if (2.15) holds but either (2.16) or (2.17) is violated. For τ_1^0 near zero, nonexistence of purely imaginary solutions implies that (x_1^*, x_2^*) preserves the asymptotic stability that holds for $\tau_1 = \tau_2 = 0$ and one can proceed as in the case $\tau_1 = 0$ to calculate a possible bifurcating value τ_2^0.

3. Stability of the limit cycle

In this section we compute, following [23], the Lyapunov coefficient that gives information on the stability of the cycle when this one exists.

Consider (τ_1^0, τ_2^0) with $\tau_2^0 > \tau_1^0 > 0$ the values where a Hopf bifurcation appears. Take $\mu > 0$, $\tau_2 = \tau_2^0 + \mu, \tau_1 = \tau_1^0$ and introduce

$C_\mu = C([-\tau_2^0 - \mu, 0], \mathbb{C}^2)$. The system (2.1) can be written as

$$\dot{y} = G_\mu(y_t) \tag{3.1}$$

where $y_t(\theta) = y(t+\theta)$ and, for $\varphi \in C_\mu$, G_μ is defined by

$$\begin{aligned} G_\mu^{(1)}(\varphi) &= -\{\tilde{\gamma}_Q + \eta_1 k[\varphi_2(0) + x_2^*] + \eta_2 k[\varphi_2(0) + x_2^*]\}[\varphi_1(0) + x_1^*] \\ &- (1 - \eta_1 - \eta_2)\beta_0 h[\varphi_1(0) + x_1^*] + \\ &+ 2e^{-\gamma_Q \tau_1}(1 - \eta_1 - \eta_2)\beta_0 h[\varphi_1(-\tau_1) + x_1^*] + \\ &+ \eta_1 e^{-\gamma_Q \tau_1} k[\varphi_2(-\tau_1) + x_2^*][\varphi_1(-\tau_1) + x_1^*] \\ G_\mu^{(2)}\varphi &= -\gamma_N[\varphi_2(0) + x_2^*] + \tilde{A}_N k[\varphi_2(-\tau_2) + x_2^*][\varphi_1(-\tau_2) + x_1^*]. \end{aligned} \tag{3.2}$$

The linearized equation that corresponds to (3.1) is

$$\dot{y} = L_\mu y_t \tag{3.3}$$

where

$$L_\mu \varphi = A_2 \varphi(0) + B_{2\tau_1}\varphi(-\tau_1) + B_{2\tau_2}\varphi(-\tau_2) \tag{3.4}$$

Define

$$F_\mu = G_\mu - L_\mu. \tag{3.5}$$

Then $F_\mu(0) = F'_\mu(0) = 0$ and (3.1) can be written as

$$\dot{y}(t) = L_\mu y_t + F_\mu(y_t). \tag{3.6}$$

Following [23], [5], introduce $X_0 : [-\tau_2, 0] \to \mathbb{R}$ through

$$X_0(\theta) = \begin{cases} 0, \ -\tau_2 \le \theta < 0 \\ 1, \ \theta = 0 \end{cases}$$

and, for $c \in \mathbb{C}^2$, define

$$(X_0 c)(\theta) = X_0(\theta)c, \quad \theta \in [-\tau_2, 0]$$

and

$$\langle X_0 \rangle = \{X_0 c | c \in \mathbb{C}^2\}$$

By [22] the linear equation (3.3) defines a C_0-semigroup with generator A_μ defined by

$$\mathcal{D}(A_\mu) = \{\varphi \in C^1([-\tau_2, 0], \mathcal{C}^2),\ \varphi'(0) = L_\mu \varphi\}$$

$$A_\mu \varphi = \varphi' \quad \text{for} \quad \varphi \in \mathcal{D}(A_\mu)$$

Define $\tilde{C}_\mu = C_\mu \oplus \langle X_0 \rangle$ and define the extension $\tilde{A}_\mu$ of A_μ to $\tilde{C}_\mu$ through $\mathcal{D}(\tilde{A}_\mu) = \mathcal{D}(A_\mu)$ and $\tilde{A}_\mu \varphi = \varphi' + X_0(L_\mu \varphi - \varphi'(0))$. Then $(\tilde{A}_\mu \varphi)(\theta) = \varphi'(\theta)$ for $\theta \in [-\tau_2, 0)$ and

$$(\tilde{A}_\mu \varphi)(0) = A_2 \begin{pmatrix} \varphi_1(0) \\ \varphi_2(0) \end{pmatrix} + B_{2\tau_1} \begin{pmatrix} \varphi_1(-\tau_1) \\ \varphi_2(-\tau_1) \end{pmatrix} + B_{2\tau_2} \begin{pmatrix} \varphi_1(-\tau_2) \\ \varphi_2(-\tau_2) \end{pmatrix} \tag{3.7}$$

$\tilde{A}_\mu$ is a Hille-Yoside operator on $\tilde{C}_\mu$ (see [1]) and (3.6) becomes equivalent to the well-posed Cauchy problem for an ODE in Banach spaces (see the details in [5])

$$\begin{aligned} &\frac{d}{dt} y_t = \tilde{A}_\mu y_t + X_0 F_\mu(y_t) \\ &y_0(\theta) = \varphi(\theta), \quad \theta \in [-\tau_2, 0]. \end{aligned} \tag{3.8}$$

Consider the matrix distribution associated to L_μ

$$\eta(\theta) = \eta(\theta, \mu) = A_2 \mathrm{d}_0(\theta) + B_{2\tau_1} \delta{-}\tau_1(\theta) + B_{2\tau_2} \delta{-}\tau_2(\theta) \tag{3.9}$$

(d is the Dirac distribution). If $\varphi \in C_\mu$, $\psi \in C_\mu^0 := C([0, \tau_2], \mathbb{C}^2)$ and dot denotes the scalar product in $\mathbb{C}^2$, define, according to [21], [23], the bilinear form

$$\begin{aligned}
&\langle \psi, \varphi \rangle = \overline{\psi(0)^T} \cdot \varphi(0) - \int_{\theta=-\tau_2}^{0} \int_{\xi=0}^{\theta} \overline{\psi(\xi-\theta)^T} d\eta(\theta) \varphi(\xi) d\xi = \\
&= \overline{\psi(0)^T} \cdot \varphi(0) - \int_{\theta=-\tau_2}^{0} \int_{\xi=0}^{\theta} (\overline{\psi_1(\xi-\theta)}, \overline{\psi_2(\xi-\theta)}) \cdot \\
&\cdot \begin{pmatrix} (a_{11}\mathrm{d}_0(\theta) + b_{11}\delta{-}\tau_1(\theta)\varphi_1(\xi) + (a_{12}\mathrm{d}_0(\theta) + b_{12}\delta{-}\tau_1(\theta)))\varphi_2(\xi) \\ c_{21}\delta{-}\tau_2(\theta)\varphi_1(\xi) + (a_{22}\mathrm{d}_0(\theta) + c_{22}\delta_{-\tau_2}(\theta))\varphi_2(\xi) \end{pmatrix} d\xi d\theta = \\
&= \overline{\psi(0)^T} \cdot \varphi(0) - \int_0^{-\tau_2} \bar{\psi}_2(\xi+\tau_2)[c_{22}\varphi_2(\xi) + c_{21}\varphi_2(\xi)] d\xi + \\
&- \int_0^{-\tau_1} \bar{\psi}_1(\xi+\tau_1)[b_{11}\varphi_1(\xi) + b_{12}\varphi_2(\xi)] d\xi = \\
&= \overline{\psi(0)^T} \cdot \varphi(0) + \int_{-\tau_1}^{0} [b_{11}\varphi_1(\xi)\overline{\psi_1(\xi+\tau_1)} + b_{12}\varphi_2(\xi)\overline{\psi_1(\xi+\tau_1)}] d\xi + \\
&+ \int_{-\tau_2}^{0} [c_{22}\varphi_2(\xi)\overline{\psi_2(\xi+\tau_2)} + c_{21}\varphi_1(\xi)\overline{\psi_2(\xi+\tau_2)}] d\xi.
\end{aligned} \tag{3.10}$$

(3.10) extends to $\tilde{C}_\mu$ through $\langle \psi + X_0 a, \varphi + X_0 b \rangle = \langle \psi, \varphi \rangle + \bar{a} \cdot b$.

The adjoint operator $\tilde{A}^*_\mu$ verifies $\langle \psi, \tilde{A}_\mu \varphi \rangle = \langle \tilde{A}^*_\mu \psi, \varphi \rangle$. Consider $q(\theta) = e^{i\omega_0 \theta} \begin{pmatrix} \gamma_1 \\ \gamma_2 \end{pmatrix}$. Then $\tilde{A}_0 q = i\omega_0 q$ if

$$\gamma_1 = 1, \ \gamma_2 = \frac{c_{21} e^{-i\omega_0 \tau_2^0}}{i\omega_0 - a_{22} - c_{22} e^{-i\omega_0 \tau_2^0}} \tag{3.11}$$

when the characteristic equation (2.3) is used ($i\omega_0$ is a root of (2.3)).

Then $q^*(s) = d(\tilde{\gamma}_1, \tilde{\gamma}_2) e^{i\omega_0 s}$ is an eigenvector of $\tilde{A}^*_0$ when $\tilde{\gamma}_1 = 1$ and

$$\tilde{\gamma}_2 = -\frac{b_{12} e^{i\omega_0 \tau_1^0} + a_{12}}{i\omega_0 + a_{22} + c_{22} e^{i\omega_0 \tau_2^0}}$$

and we choose d such that the norming condition $\langle q^*, q \rangle = 1$ be satisfied.

$$\begin{aligned}
\langle q^*, q \rangle &= \bar{d}(1 + \bar{\tilde{\gamma}}_2 \gamma_2) + \bar{d} \int_{-\tau_1^0}^{0} (b_{11} e^{-i\omega_0(\xi + \tau_1^0)} e^{i\omega_0 \xi} + \\
&+ b_{12} e^{-i\omega_0(\xi + \tau_1^0)} \gamma_2 e^{i\omega_0 \xi}) d\xi + \bar{d} \int_{-\tau_2^0}^{0} (c_{22} \gamma_2 \bar{\tilde{\gamma}}_2 e^{-i\omega_0(\xi + \tau_2^0)} e^{i\omega_0 \xi} + \\
&+ c_{21} \bar{\tilde{\gamma}}_2 e^{-i\omega_0(\xi + \tau_2^0)} e^{i\omega_0 \xi}) d\xi = \bar{d}(1 + \gamma_2 \bar{\tilde{\gamma}}_2) + \\
&+ \bar{d}(b_{11} e^{-i\omega_0 \tau_1^0} \tau_1^0 + b_{12} \gamma_2 e^{-i\omega_0 \tau_1^0} \tau_1^0) + c_{22} \gamma_2 \bar{\tilde{\gamma}}_2 e^{-i\omega_0 \tau_2^0} \tau_2^0 + \\
&+ c_{21} \bar{\tilde{\gamma}}_2 e^{-i\omega_0 \tau_2^0} \tau_2^0) = 1
\end{aligned}$$

so

$$\bar{d} = [1 + \gamma_2 \bar{\tilde{\gamma}}_2 + \tau_1^0 e^{-i\omega_0 \tau_1^0}(b_{11} + b_{12}\gamma_2) + \tau_2^0 \bar{\tilde{\gamma}}_2 e^{-i\omega_0 \tau_2^0}(c_{21} + c_{22}\gamma_2)]^{-1} \tag{3.12}$$

With this d, one has $\langle q^*, \bar{q} \rangle = 0$.

Let now y be a solution of (3.8). The section $\mathcal{C}_0$ of the center manifold corresponding to $\mu = 0$ is described by the local coordinates (see [23]) z and $\bar{z}$ with

$$z(t) = \langle q^*, y_t \rangle. \tag{3.13}$$

For $t \geq 0$ and $s \in [-\tau_2^0, 0]$, define

$$w(t, s) = y_t(s) - 2\mathrm{Re}\,[z(t) q(s)] = W[z(t), \bar{z}(t), s] \tag{3.14}$$

where

$$W(z, \bar{z}, s) = w_{20}(s) \frac{z^2}{2} + w_{11}(s) z\bar{z} + w_{02}(s) \frac{\bar{z}^2}{2} + w_{30}(s) \frac{z^3}{6} + \ldots$$

Since, for y real w is real, it follows that

$$w_{02} = \bar{w}_{20}.$$

Remark also that

$$\langle q^*, w \rangle = \langle q^*, y_t \rangle - \langle q^*, zq \rangle - \langle q^*, \bar{z}\bar{q} \rangle = z(t) - z(t)\langle q^*, q \rangle - \bar{z}(t) \langle q^*, \bar{q} \rangle = 0$$

Since $\mathcal{C}_0$ is locally invariant under (3.8) (see [23], [10]) one has

$$\begin{aligned}
\dot{z}(t) &= \langle q^*, \dot{y}_t \rangle = \langle q^*, \tilde{A}_0 y_t + X_0 F_0(y_t) \rangle = \langle \tilde{A}^*_0 q^*, y_t \rangle + \\
&+ \langle q^*, X_0 F_0(y_t) \rangle = i\omega_0 \langle q^*, y_t \rangle + \bar{d}(1, \bar{\tilde{\gamma}}_2) \cdot F_0[W(z(t), \bar{z}(t), \cdot) + \\
&+ 2\mathrm{Re}\,[z(t) q(\cdot)]]|_{s=0} \stackrel{def}{=} i\omega_0 z(t) + g(z, \bar{z})
\end{aligned} \tag{3.15}$$

where g is defined by

$$\begin{aligned} g(z,\bar{z}) &= \bar{q}^*(0)\cdot F_0[W(z,\bar{z},\cdot)+2\mathrm{Re}\,[zq(\cdot)]]|_{s=0} = \\ &= \frac{g_{20}}{2}z^2+g_{11}z\bar{z}+\frac{g_{02}}{2}\bar{z}^2+\frac{g_{21}}{2}z^2\bar{z}+\dots \end{aligned} \tag{3.16}$$

It follows from (3.2), (3.4) and (3.5) that, with the upper index denoting the components, we have

$$\begin{aligned} &F_0^{(1)}(\varphi_1,\varphi_2) = \frac{1}{2}[-(1-\eta_1-\eta_2)\beta_0 h''(x_1^*)\varphi_1(0)^2- \\ &-(\eta_1+\eta_2)x_1^*k''(x_2^*)\varphi_2(0)^2+2e^{-\gamma_Q\tau_1^0}(1-\eta_1-\eta_2)\beta_0 h''(x_1^*)\varphi_1(-\tau_1^0)^2+ \\ &+\eta_1 e^{-\gamma_Q\tau_1^0}x_1^*k''(x_2^*)\varphi_2(-\tau_1^0)^2- \\ &-2(\eta_1+\eta_2)k'(x_2^*)\varphi_2(0)\varphi_1(0)+2\eta_1 e^{-\gamma_Q\tau_1^0}k'(x_2^*)\varphi_1(-\tau_1^0)\varphi_2(-\tau_1^0)]+ \\ &+\frac{1}{6}[-(1-\eta_1-\eta_2)\beta_0 h'''(x_1^*)\varphi_1(0)^3-3(\eta_1+\eta_2)k''(x_2^*)\varphi_1(0)\varphi_2(0)^2- \\ &-(\eta_1+\eta_2)x_1^*k'''(x_2^*)\varphi_2(0)^3+2e^{-\gamma_Q\tau_1^0}(1-\eta_1-\eta_2)\beta_0 h'''(x_1^*)\varphi_1(-\tau_1^0)^3+ \\ &+3\eta_1 e^{-\gamma_Q\tau_1^0}k''(x_2^*)\varphi_1(-\tau_1)\varphi_2(-\tau_1)^2+\eta_1 e^{-\gamma_Q\tau_1^0}x_1^*k'''(x_2^*)\varphi_2(-\tau_1^0)^3]+\dots \end{aligned}$$

$$\begin{aligned} &F_0^{(2)}(\varphi_1,\varphi_2) = \frac{1}{2}[2\tilde{A}_N k'(x_2^*)x_1^*\varphi_1(-\tau_2^0)\varphi_2(-\tau_2^0)+ \\ &+\tilde{A}_N k''(x_2^*)x_1^*\varphi_2(-\tau_2^0)^2]+\frac{1}{6}[3\tilde{A}_N k''(x_2^*)\varphi_1(-\tau_2^0)\varphi_2(-\tau_2^0)^2+A_N k'''(x_2^*)x_1^*\varphi_2(-\tau_2^0)^3]+\dots \end{aligned}$$

In order to simplify the presentation it is convenient to introduce the following notations

$$\begin{aligned} \alpha_{20}^{(1)} &= -\frac{1}{2}(1-\eta_1-\eta_2)\beta_0 h''(x_1^*), \quad \alpha_{11}^{(1)} = -(\eta_1+\eta_2)k'(x_2^*), \\ \alpha_{02}^{(1)} &= -\frac{1}{2}(\eta_1+\eta_2)x_1^*k''(x_2^*), \quad \eta_{20}^{(1)} = e^{-\gamma_Q\tau_1^0}(1-\eta_1-\eta_2)\beta_0 h''(x_1^*), \\ \eta_{11}^{(1)} &= \eta_1 e^{-\gamma_Q\tau_1^0}k'(x_2^*), \quad \eta_{02}^{(1)} = \frac{1}{2}\eta_1 e^{-\gamma_Q\tau_1^0}x_1^*k''(x_2^*) \\ \alpha_{30}^{(1)} &= -\frac{1}{6}(1-\eta_1-\eta_2)\beta_0 h'''(x_1^*)), \quad \alpha_{12}^{(1)} = -\frac{1}{2}(\eta_1+\eta_2)k''(x_2^*) \\ \alpha_{03}^{(1)} &= -\frac{1}{6}(\eta_1+\eta_2)x_1^*k'''(x_2^*)), \quad \eta_{30}^{(1)} = \frac{1}{3}e^{-\gamma_Q\tau_1^0}(1-\eta_1-\eta_2)\beta_0 h'''(x_1^*) \\ \eta_{12}^{(1)} &= \frac{1}{2}\eta_1 e^{-\gamma_Q\tau_1^0}k''(x_2^*) \\ \eta_{03}^{(1)} &= \frac{1}{6}\eta_1 e^{-\gamma_Q\tau_1^0}x_1^*k'''(x_2^*), \quad \eta_{11}^{(2)} = \tilde{A}_N k'(x_2^*)x_1^* \\ \eta_{02}^{(2)} &= \frac{1}{2}\tilde{A}_N k''(x_2^*)x_1^*, \quad \eta_{12}^{(2)} = \frac{1}{2}\tilde{A}_N k''(x_2^*) \\ \eta_{03}^{(2)} &= \frac{1}{6}\tilde{A}_N k'''(x_2^*)x_1^*. \end{aligned} \tag{3.17}$$

Then, the expression of F_0 is

$$
\begin{aligned}
&F_0^{(1)}(\varphi_1,\varphi_2)=\alpha_{20}^{(1)}\varphi_1(0)^2+\alpha_{11}^{(1)}\varphi_1(0)\varphi_2(0)+\alpha_{02}^{(1)}\varphi_2(0)^2+\\
&+\eta_{20}^{(1)}\varphi_1(-\tau_1^0)^2+\eta_{11}^{(1)}\varphi_1(-\tau_1^0)\varphi_2(-\tau_1^0)+\eta_{02}^{(1)}\varphi_2(-\tau_1^0)^2+\\
&+\alpha_{30}^{(1)}\varphi_1(0)^3+\alpha_{12}^{(1)}\varphi_1(0)\varphi_2(0)^2+\alpha_{03}^{(1)}\varphi_2(0)^3+\\
&+\eta_{30}^{(1)}\varphi_1(-\tau_1^0)^3+\eta_{12}^{(1)}\varphi_1(-\tau_1^0)\varphi_2(-\tau_1^0)^2+\eta_{03}^{(1)}\varphi_2(-\tau_1^0)^3+\ldots\\
&F_0^{(2)}(\varphi_1,\varphi_2)=\eta_{11}^{(2)}\varphi_1(-\tau_2^0)\varphi_2(-\tau_2^0)+\eta_{02}^{(2)}\varphi_2(-\tau_2^0)^2+\\
&+\eta_{12}^{(2)}\varphi_1(-\tau_2^0)\varphi_2(-\tau_2^0)^2+\eta_{03}^{(2)}\varphi_2(-\tau_2^0)^3\ldots
\end{aligned}
\tag{3.18}
$$

From (3.16) and (3.18) we infer that

$$
\begin{aligned}
&g(z,\bar z)=\bar d F_0^{(1)}[W(z,\bar z,\cdot)+2\mathrm{Re}\,(zq(\cdot))]|_{s=0}+\\
&+\bar d\bar{\bar\gamma}_2F_0^{(2)}[W(z,\bar z,\cdot)+2\mathrm{Re}\,(zq(\cdot))]|_{s=0}=\\
&=\bar d\{\alpha_{20}^{(1)}[W^{(1)}(0)+z+\bar z]^2+\alpha_{11}^{(1)}[W^{(1)}(0)+z+\bar z]\cdot\\
&\cdot[W^{(2)}(0)+z\gamma_2+\bar z\bar\gamma_2]+\alpha_{02}^{(1)}[W^{(2)}(0)+z\gamma_2+\bar z\bar\gamma_2]^2+\\
&+\eta_{20}^{(1)}[W^{(1)}(-\tau_1^0)+ze^{-i\omega_0\tau_1^0}+\bar ze^{i\omega_0\tau_1^0}]^2+\\
&+\eta_{11}^{(1)}[W^{(1)}(-\tau_1^0)+ze^{-i\omega_0\tau_1^0}+\bar ze^{i\omega_0\tau_1^0}]\cdot\\
&\cdot[W^{(2)}(-\tau_1^0)+z\gamma_2e^{-i\omega_0\tau_1^0}+\bar z\bar\gamma_2e^{i\omega_0\tau_1^0}]+\\
&+\eta_{02}^{(1)}[W^{(2)}(-\tau_1^0)+z\gamma_2e^{-i\omega_0\tau_1^0}+\bar z\bar\gamma_2e^{i\omega_0\tau_1^0}]^2+\\
&+\alpha_{30}^{(1)}[W^{(1)}(0)+z+\bar z]^3+\alpha_{12}^{(1)}[W^{(1)}(0)+z+\bar z]\cdot\\
&\cdot[W^{(2)}(0)+z\gamma_2+\bar z\bar\gamma_2]^2+\alpha_{03}^{(1)}[W^{(2)}(0)+z\gamma_2+\bar z\bar\gamma_2]^3+\\
&+\eta_{30}^{(1)}[W^{(1)}(-\tau_1^0)+ze^{-i\omega_0\tau_1^0}+\bar ze^{i\omega_0\tau_1^0}]^3+\\
&+\eta_{12}^{(1)}[W^{(1)}(-\tau_1^0)+ze^{-i\omega_0\tau_1^0}+\bar ze^{i\omega_0\tau_1^0}]\cdot\\
&\cdot[W^{(2)}(-\tau_1^0)+z\gamma_2e^{-i\omega_0\tau_1^0}+\bar z\bar\gamma_2e^{i\omega_0\tau_1^0}]^2+\eta_{03}^{(1)}[W^{(2)}(-\tau_1^0)+z\gamma_2e^{-i\omega_0\tau_1^0}+\bar z\bar\gamma_2e^{i\omega_0\tau_1^0}]^3\}+\\
&+\bar d\bar{\bar\gamma}_2\{\eta_{11}^{(2)}[W^{(1)}(-\tau_2^0)+ze^{-i\omega_0\tau_2^0}+\bar z\bar e^{i\omega_0\tau_2^0}]\cdot\\
&\cdot[W^{(2)}(-\tau_2^0)+z\gamma_2e^{-i\omega_0\tau_2^0}+\bar z\bar\gamma_2e^{i\omega_0\tau_2^0}]+\\
&+\eta_{02}^{(2)}[W^{(2)}(-\tau_2^0)+z\gamma_2e^{-i\omega_0\tau_2^0}+\bar z\bar\gamma_2e^{i\omega_0\tau_2^0}]^2+\\
&+\eta_{12}^{(2)}[W^{(1)}(-\tau_2^0)+ze^{-i\omega_0\tau_2^0}+\bar ze^{i\omega_0\tau_2^0}]\cdot\\
&\cdot[W^{(2)}(-\tau_2^0)+z\gamma_2e^{-i\omega_0\tau_2^0}+\bar z\bar\gamma_2e^{i\omega_0\tau_2^0}]^2\}+\\
&+\eta_{03}^{(2)}[W^{(2)}(-\tau_2^0)+z\gamma_2e^{-i\omega_0\tau_2^0}+\bar z\bar\gamma_2e^{i\omega_0\tau_2^0}]^3\ldots
\end{aligned}
\tag{3.19}
$$

Identification of coefficients in (3.16) and (3.19) gives

$$
\begin{aligned}
&\frac{g_{20}}{2} = \bar{d}[\alpha_{20}^{(1)} + \alpha_{11}^{(1)}\gamma_2 + \alpha_{02}^{(1)}\gamma_2^2 + \eta_{20}^{(1)}e^{-2i\omega_0\tau_0^1} + \eta_{11}^{(1)}\gamma_2 e^{-2i\omega_0\tau_1^0} + \eta_{02}^{(1)}\gamma_2^2 e^{-2i\omega_0\tau_1^0}] \\
&+\bar{d}\bar{\bar{\gamma}}_2[\eta_{11}^{(2)}\gamma_2 e^{-2i\omega_0\tau_2^0} + \eta_{02}^{(2)}\gamma_2^2 e^{-2i\omega_0\tau_2^0}] \\
&g_{11} = \bar{d}[2\alpha_{20}^{(1)} + \alpha_{11}^{(1)}(\gamma_2+\bar{\gamma}_2) + \alpha_{02}^{(1)}2\gamma_2\bar{\gamma}_2 + 2\eta_{20}^{(1)} + \eta_{11}^{(1)}(\gamma_2+\bar{\gamma}_2) + \eta_{02}^{(1)}2\gamma_2\bar{\gamma}_2]+ \\
&+\bar{d}\bar{\bar{\gamma}}_2[\eta_{11}^{(2)}(\gamma_2+\bar{\gamma}_2) + \eta_{02}^{(2)}2\gamma_2\bar{\gamma}_2] \\
&\frac{1}{2}g_{02} = \bar{d}[\alpha_{20}^{(1)} + \alpha_{11}^{(1)}\bar{\gamma}_2 + \alpha_{02}^{(1)}\bar{\gamma}_2^2 + \eta_{20}^{(1)}e^{2i\omega_0\tau_1^0}+ \\
&+\eta_{11}^{(1)}\bar{\gamma}_2 e^{2i\omega_0\tau_1^0} + \eta_{02}^{(1)}\bar{\gamma}_2^2 e^{2i\omega_0\tau_1^0}] + \bar{d}\bar{\bar{\gamma}}_2[\eta_{11}^{(2)}\bar{\gamma}_2 e^{2i\omega_0\tau_2^0} + \eta_{02}^{(2)}\bar{\gamma}_2^2 e^{2i\omega_0\tau_2^0}] \\
&\frac{1}{2}g_{21} = \bar{d}[\alpha_{20}^{(1)}(w_{20}^{(1)}(0) + 2w_{11}^{(1)}(0)) + \alpha_{11}^{(1)}\left(\frac{w_{20}^{(1)}}{2}(0)\bar{\gamma}_2 + w_{11}^{(1)}(0)\gamma_2 + w_{11}^{(2)}(0) + \frac{w_{20}^{(2)}}{2}(0)\right)+ \\
&+\alpha_{02}^{(1)}(w_{20}^{(2)}(0)\bar{\gamma}_2 + 2\gamma_2 w_{11}^{(2)}(0)) + \eta_{20}^{(1)}(w_{20}^{(1)}(-\tau_1^0)e^{i\omega_0\tau_1^0}+ \\
&+2w_{11}^{(1)}(-\tau_1^0)e^{-i\omega_0\tau_1^0}) + \eta_{11}^{(1)}\left(\frac{w_{20}^{(1)}(-\tau_1^0)}{2}\bar{\gamma}_2 e^{i\omega_0\tau_1^0} + w_{11}^{(1)}(-\tau_1^0)\gamma_2 e^{-i\omega_0\tau_1^0}+\right. \\
&\left.+\,w_{11}^{(2)}(-\tau_1^0)e^{-i\omega_0\tau_1^0} + \frac{w_{20}^{(2)}(-\tau_1^0)}{2}e^{i\omega_0\tau_1^0}\right) + \eta_{02}^{(1)}(w_{20}^{(2)}(-\tau_1^0)\bar{\gamma}_2 e^{i\omega_0\tau_1^0} + 2w_{11}^{(2)}(-\tau_1^0)\gamma_2 e^{-i\omega_0\tau_1^0})+ \\
&+3\alpha_{30}^{(1)} + \alpha_{12}^{(1)}(\gamma_2^2 + 2\gamma_2\bar{\gamma}_2) + 3\alpha_{03}^{(1)}\gamma_2^2\bar{\gamma}_2 + 3\eta_{30}^{(1)}e^{-i\omega_0\tau_1^0} + \eta_{12}^{(1)}(2\gamma_2\bar{\gamma}_2 e^{-i\omega_0\tau_1^0} + \gamma_2^2 e^{-i\omega_0\tau_1^0})+ \\
&+3\eta_{03}^{(1)}\gamma_2^2\bar{\gamma}_2 e^{-i\omega_0\tau_1^0}] + \bar{d}\bar{\bar{\gamma}}_2\left[\eta_{11}^{(2)}\left(\frac{w_{20}^{(1)}(-\tau_2^0)}{2}\bar{\gamma}_2 e^{i\omega_0\tau_2^0}+\right.\right. \\
&\left.+\,w_{11}^{(2)}(-\tau_2^0)e^{-i\omega_0\tau_2^0} + \frac{w_{20}^{(2)}(-\tau_2^0)}{2}e^{i\omega_0\tau_2^0} + w_{11}^{(1)}(-\tau_2^0)\gamma_2 e^{-i\omega_0\tau_2^0}\right) \\
&+\eta_{02}^{(2)}(w_{20}^{(2)}(-\tau_2^0)\bar{\gamma}_2 e^{i\omega_0\tau_2^0} + 2w_{11}^{(2)}(-\tau_2^0)\gamma_2 e^{-i\omega_0\tau_2^0})+ \\
&\left.+\,\eta_{12}^{(2)}\left(\gamma_2^2 e^{-i\omega_0\tau_2^0} + 2\gamma_2\bar{\gamma}_2 e^{-i\omega_0\tau_2^0}\right) + 3\eta_{03}^{(2)}\gamma_2^2\bar{\gamma}_2 e^{-i\omega_0\tau_2^0}\right]
\end{aligned}
\tag{3.20}
$$

In order to compute g_{21} one must find the expressions of $w_{20}(0)$, $w_{20}(-\tau_1^0)$, $w_{20}(-\tau_2^0)$, $w_{11}(0)$, $w_{11}(-\tau_1^0)$ and $w_{11}(-\tau_2^0)$.

From (3.13), (3.14) and (3.8) it follows that

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

But

$$
\begin{aligned}
\tilde{A}_0[2\mathrm{Re}\,z(t)q(\cdot)] = 2\mathrm{Re}\,[i\omega_0 z(t)q(\cdot)] \\
\mathrm{Re}\,[\dot{z}(t)q(\cdot)] = \mathrm{Re}\,i\omega_0 z(t)q(\cdot) + \mathrm{Re}\,[g(z(t),\bar{z}(t))q(\cdot)]
\end{aligned}
$$

so

$$
\frac{d}{dt}w(t,\cdot) = \tilde{A}_0 w(t,\cdot) + H(z,\bar{z},\cdot) \tag{3.21}
$$

where

$$\begin{aligned} H(z,\bar{z},s) &= -2\mathrm{Re}\,[g(z,\bar{z})q(s)] + X_0(s)F_0[w(z,\bar{z},s) + 2\mathrm{Re}\,(zq(s))] \\ &= H_{20}(s)\frac{z^2}{2} + H_{11}(s)z\bar{z} + H_{02}(s)\frac{\bar{z}^2}{2} + \dots \end{aligned} \tag{3.22}$$

For $s \in [-\tau_2^0, 0)$

$$\begin{aligned} H(z,\bar{z},s) = &-\left(\frac{g_{20}}{2}z^2 + g_{11}z\bar{z} + \frac{g_{02}}{2}\bar{z}^2 + \dots\right)q(s) - \\ &-\left(\frac{\bar{g}_{20}}{2}\bar{z}^2 + \bar{g}_{11}z\bar{z} + \frac{\bar{g}_{02}}{2}z^2 + \dots\right)\overline{q(s)} = \\ &= H_{20}(s)\frac{z^2}{2} + H_{11}(s)z\bar{z} + H_{02}(s)\frac{\bar{z}^2}{2} + \dots \end{aligned} \tag{3.23}$$

Then

$$\begin{aligned} H_{20}(s) &= -g_{20}q(s) - \bar{g}_{02}\overline{q(s)} \\ H_{11}(s) &= -g_{11}q(s) - \bar{g}_{11}\overline{q(s)} \\ H_{02}(s) &= \overline{H_{20}(s)} \end{aligned} \tag{3.24}$$

From (3.14), (3.15) and (3.21) it follows that

$$\begin{aligned} &\tilde{A}_0 w(t,\cdot) + H[z(t),\bar{z}(t),\cdot] = w_{20}(\cdot)\dot{z}(t)z(t) + \\ &+ w_{11}(\cdot)[\dot{z}(t)\bar{z}(t) + z(t)\dot{\bar{z}}(t)] + w_{02}(\cdot)\bar{z}(t)\dot{\bar{z}}(t) + \dots \\ &= w_{20}(\cdot)z(t)[i\omega_0 z(t) + g(z(t),\bar{z}(t))] + \\ &+ w_{11}(\cdot)\bar{z}(t)[i\omega_0 z(t) + g(z(t),\bar{z}(t))] + \\ &+ w_{11}(\cdot)z(t)[-i\omega_0\bar{z}(t) + \overline{g(z(t),\bar{z}(t))}] + \\ &+ w_{02}(\cdot)\bar{z}(t)[-i\omega_0 z(t) + \overline{g(z(t),\bar{z}(t))}]. \end{aligned} \tag{3.25}$$

Identification of coefficients in (3.25) gives, due to (3.23),

$$\begin{aligned} (\tilde{A}_0 - 2i\omega_0)w_{20}(s) &= -H_{20}(s) \\ \tilde{A}_0 w_{11}(s) &= -H_{11}(s) \\ (\tilde{A}_0 + 2i\omega_0)w_{02}(s) &= -H_{02}(s). \end{aligned} \tag{3.26}$$

so, for $s \in [\tau_2^0, 0)$, (3.24) gives

$$\dot{w}_{20}(s) = 2i\omega_0 w_{20}(s) + g_{20}q(s) + \bar{g}_{02}\bar{q}(s)$$

thus

$$\begin{aligned} \dot{w}_{20}^{(1)}(s) &= 2i\omega_0 w_{20}^{(1)}(s) + g_{20}e^{i\omega_0 s} + \bar{g}_{02}e^{-i\omega_0 s} \\ \dot{w}_{20}^{(2)}(s) &= 2i\omega_0 w_{20}^{(2)}(s) + g_{20}\gamma_2 e^{i\omega_0 s} + \bar{g}_{02}\bar{\gamma}_2 e^{-i\omega_0 s} \end{aligned}$$

whence

$$\begin{aligned} w_{20}^{(1)}(s) &= C_1^{(1)}e^{2i\omega_0 s} - g_{20}\frac{e^{i\omega_0 s}}{i\omega_0} - \bar{g}_{02}\frac{e^{-i\omega_0 s}}{3i\omega_0} \\ w_{20}^{(2)}(s) &= C_1^{(2)}e^{2i\omega_0 s} - g_{20}\gamma_2\frac{e^{i\omega_0 s}}{i\omega_0} - \bar{g}_{02}\bar{\gamma}_2\frac{e^{-i\omega_0 s}}{3i\omega_0} \end{aligned} \tag{3.27}$$

Recall that, for $s = 0$, from the definition of $\tilde{A}_0$ it folows that

$$\tilde{A}_0\begin{pmatrix}\varphi_1\\ \varphi_2\end{pmatrix} = \begin{pmatrix} a_{11}\varphi_1(0) + a_{12}\varphi_2(0) + b_{11}\varphi_1(-\tau_1^0) + b_{12}\varphi_2(-\tau_1^0) \\ a_{22}\varphi_2(0) + c_{21}\varphi_1(-\tau_2^0) + c_{22}\varphi_2(-\tau_2^0) \end{pmatrix} \tag{3.28}$$

Then (3.26), (3.27) and (3.28) give

$$\begin{aligned}&a_{11}\left(C_1^{(1)}-\frac{g_{20}}{i\omega_0}-\frac{\bar g_{02}}{3i\omega_0}\right)+a_{12}\left(C_1^{(2)}-\frac{g_{20}\gamma_2}{i\omega_0}-\frac{\bar g_{02}\bar\gamma_2}{3i\omega_0}\right)+\\&+b_{11}\left(C_1^{(1)}e^{-2i\omega_0\tau_1^0}-g_{20}\frac{e^{-i\omega_0\tau_1^0}}{i\omega_0}-\bar g_{02}\frac{e^{i\omega_0\tau_1^0}}{3i\omega_0}\right)+\\&+b_{12}\left(C_1^{(2)}e^{-2i\omega_0\tau_1^0}-g_{20}\frac{\gamma_2e^{-i\omega_0\tau_1^0}}{i\omega_0}-\bar g_{02}\frac{\bar\gamma_2e^{i\omega_0\tau_1^0}}{3i\omega_0}\right)-2i\omega_0C_1^{(1)}+2g_{20}+\frac{2\bar g_{02}}{3}=-H_{20}^{(1)}(0)\end{aligned}\tag{3.29}$$

$$\begin{aligned}&a_{22}\left(C_1^{(2)}-\frac{g_{20}\gamma_2}{i\omega_0}-\frac{\bar g_{02}\bar\gamma_2}{3i\omega_0}\right)+\\&+c_{21}\left(C_1^{(1)}e^{-2i\omega_0\tau_2^0}-g_{20}\frac{e^{-i\omega_0\tau_2^0}}{i\omega_0}-\bar g_{02}\frac{e^{i\omega_0\tau_2^0}}{3i\omega_0}\right)+\\&+c_{22}\left(C_1^{(2)}e^{-2i\omega_0\tau_2^0}-g_{20}\frac{\gamma_2e^{-i\omega_0\tau_2^0}}{i\omega_0}-\bar g_{02}\frac{\bar\gamma_2e^{i\omega_0\tau_2^0}}{3i\omega_0}\right)-2i\omega_0C_1^{(2)}+2g_{20}\gamma_2+\frac{2\bar g_{02}\bar\gamma_2}{3}=-H_{20}^{(2)}(0)\end{aligned}\tag{3.30}$$

$s=0$ in (3.22) gives

$$\begin{aligned}H^{(1)}(z,\bar z,0)&=-2\mathrm{Re}\,[g(z,\bar z)]+F_0^{(1)}[W(z,\bar z,s)+2\mathrm{Re}\,[zq(s)]]|_{s=0}\\H^{(2)}(z,\bar z,0)&=-g(z,\bar z)\gamma_2-\overline{g(z,\bar z)}\bar\gamma_2+F_0^{(2)}[w(z,\bar z,s)+\\&\qquad+2\mathrm{Re}\,[zq(s)]]|_{s=0}\end{aligned}\tag{3.31}$$

so (see (3.19))

$$\begin{aligned}\frac{H_{20}^{(1)}(0)}{2}&=-\frac{g_{20}}{2}-\frac{\bar g_{02}}{2}+\alpha_{20}^{(1)}+\alpha_{11}^{(1)}\gamma_2+\alpha_{02}^{(1)}\gamma_2^2+\eta_{20}^{(1)}e^{-2i\omega_0\tau_1^0}+\\&\quad+\eta_{11}^{(1)}\gamma_2e^{-2i\omega_0\tau_1^0}+\eta_{02}^{(1)}\gamma_2^2e^{-2i\omega_0\tau_1^0}\\\frac{H_{20}^{(2)}(0)}{2}&=-\frac{g_{20}}{2}\gamma_2-\frac{\bar g_{02}}{2}\bar\gamma_2+\eta_{11}^{(2)}\gamma_2e^{-2i\omega_0\tau_2^0}+\eta_{02}^{(2)}\gamma_2^2e^{-2i\omega_0\tau_2^0}\end{aligned}\tag{3.32}$$

and from the system (3.29), (3.30), (3.32) one can calculate $C_1^{(1)}$ and $C_2^{(2)}$. In the same vein, for $s\in[-\tau_1^0,0)$

$$\dot w_{11}(s)=g_{11}q(s)+\bar g_{11}\overline{g(s)}$$

thus

$$\begin{aligned}\dot w_{11}^{(1)}(s)&=g_{11}e^{i\omega_0s}+\bar g_{11}e^{-i\omega_0s}\\\dot w_{11}^{(2)}(s)&=(g_{11}e^{i\omega_0s}+\bar g_{11}e^{-i\omega_0s})\gamma_2.\end{aligned}$$

Then

$$\begin{aligned}w_{11}^{(1)}(s)&=\frac{g_{11}}{i\omega_0}(e^{i\omega_0s}-1)-\frac{\bar g_{11}}{i\omega_0}(e^{-i\omega_0s}-1)+C_2^{(1)}\\w_{11}^{(2)}(s)&=\gamma_2\left[\frac{g_{11}}{i\omega_0}(e^{i\omega_0s}-1)-\frac{\bar g_{11}}{i\omega_0}(e^{-i\omega_0s}-1)\right]+C_2^{(2)}.\end{aligned}$$

For $s = 0$ one has

$$\begin{aligned}
&a_{11}C_2^{(1)} + a_{12}C_2^{(2)} + b_{11}\left[\frac{g_{11}}{i\omega_0}(e^{-i\omega_0\tau_1^0} - 1) - \frac{\bar{g}_{11}}{i\omega_0}(e^{i\omega_0\tau_1^0} - 1) + C_2^{(1)}\right] + \\
&+b_{12}\left\{\gamma_2\left[\frac{g_{11}}{i\omega_0}(e^{-i\omega_0\tau_1^0} - 1) - \frac{\bar{g}_{11}}{i\omega_0}(e^{i\omega_0\tau_1^0} - 1)\right] + C_2^{(2)}\right\} = \\
&= -H_{11}^{(1)}(0) \\
&a_{22}C_2^{(2)} + c_{21}\left[\frac{g_{11}}{i\omega_0}(e^{-i\omega_0\tau_2^0} - 1) - \frac{\bar{g}_{11}}{i\omega_0}(e^{i\omega_0\tau_2^0} - 1) + C_2^{(1)}\right] + \\
&+c_{22}\left\{\gamma_2\left[\frac{g_{11}}{i\omega_0}(e^{-i\omega_0\tau_2^0} - 1) - \frac{\bar{g}_{11}}{i\omega_0}(e^{i\omega_0\tau_2^0} - 1)\right] + C_2^{(2)}\right\} = \\
&= -H_{11}^{(2)}(0)
\end{aligned} \tag{3.33}$$

From (3.22) it follows that

$$\begin{aligned}
H_{11}^{(1)}(0) &= -g_{11} - \bar{g}_{11} + 2\alpha_{20}^{(1)} + \alpha_{11}^{(1)}(\gamma_2 + \bar{\gamma}_2) + 2\alpha_{02}^{(1)}\gamma_2\bar{\gamma}_2 + \\
&+2\eta_{20}^{(1)} + \eta_{11}^{(1)}(\gamma_2 + \bar{\gamma}_2) + 2\eta_{02}^{(1)}\gamma_2\bar{\gamma}_2 \\
H_{11}^{(2)}(0) &= -g_{11}\gamma_2 - \bar{g}_{11}\bar{\gamma}_2 + 2\eta_{02}^{(2)}\gamma_2\bar{\gamma}_2 + \eta_{11}^{(2)}(\gamma_2 + \bar{\gamma}_2)
\end{aligned} \tag{3.34}$$

(3.33) and (3.34) give a system for $C_2^{(1)}$ and $C_2^{(2)}$ and now (3.20) can be used to compute g_{21}.

Calculate next

$$\begin{aligned}
L_1(0) &= \frac{1}{2\omega_0}(g_{20}g_{11} - 2|g_{11}|^2 - \frac{1}{3}|g_{02}|^2) + \frac{1}{2}g_{21} \\
l_1(0) &= \text{Re } L_1(0) \\
\mu_2 &= -\frac{l_1(0)}{\text{Re }(\lambda'(\tau_2^0))} \\
T_2 &= -\frac{\text{Im }(L_1(0)) + \mu_2 \text{Im } \lambda'(\tau_2^0)}{\omega_0}.
\end{aligned}$$

If the Lyapunov coefficient $l_1(0)$ is negative, bifurcating periodic solutions exist for $\tau_2 > \tau_2^0$ and are orbitally stable. The period of the cycle can be approximated using T_2 (see [23]).

4. Numerical results and simulations

In this section we illustrate through numerical simulations the switch of stability as different parameters considered to be important for disease initiation and progress are varied. The values of parameters involved in the equations of ST-HSC and mature cells are taken from [9] and [12].

Stem cell compartment parameters are:

– the maximal self renewal rate β_0=1.77 day^{-1}.

– the parameter controlling the sensitivity of the self renewal rate to changes in the size of HSC compartment, m=3.

– the rate of instant mortality/apoptosis for ST-HSC,$\gamma_Q = 0.05$ day^{-1}.

– the value for which $\tilde{\beta}$, the negative feedback function for ST-HSC, attains half of its maximum value of stem cells population density, $\theta_1 = 0.5 \cdot 10^6$ cells kg^{-1}.

– the rate of loss of stem like cells due to differentiation in erythrocytes or trombocytes lines, K=0.1.

Mature cells compartment (leukocytes line) parameters are:

– the maximal rate of differentiation and of asymmetric division for leukocytes line $k0 = 0.1$ day^{-1}.

– the parameter controlling the sensitivity of the differentiation rate to changes in the size of mature cells compartment, n=4.

– the rate of instant mortality/apoptosis for leukocyte cells, $\gamma_N = 2.4\ day^{-1}$.

– the value for which the negative feedback function for mature cells, $\hat{k}$, attains half of its maximum value of mature cells population density, $\theta_2 = 0.6 \cdot 10^8\ cells \cdot kg^{-1}$.

For numerical simulations the following parameters considered to reflect the main features of the CML population are varied:

– η_1 percent of ST-HSC undergo asymmetric division is small (for example=0.1 for leukemic cells, but 0.8 for healthy cells)

– $(1 - \eta_1 - \eta_2)$ percent of ST-HSC self-renew through symmetric division is big (for example=0.8 for leukemic cells, but 0.1 for healthy cells) and η_2 (for example=0.2)

– the number of divisions in the maturation process (p=[10, 12, 15]) corresponding to different values for the amplification factor A_N (small, medium, big) used in simulations.

– τ_1 - duration of ST-HSC cells' cycle

– τ_2 - time necessary for the maturation of the leukocytes

The study of the stability of non trivial equilibria is based on the approach from [4]. In order to determine switches of stability for the two delays in a specific configuration of parameters, the following procedure is applied. First consider that τ_2 =0 and that τ_1' belongs to some interval $[0,\ \tau_1^{max}]$ taken discretely with some small step. For each such τ_1' we calculate the non trivial equilibrium and if it exists we build the corresponding P(z), Q(z) associated to (2.13). P(z) and Q(z) are used to determine the roots of (2.8) and then formulas similar to (2.11), (2.12) are used to determine switches of stabilities in τ_1^0. If $\tau_1' > \tau_1^0$ and if substitution of $\lambda = i\omega_0$, τ_2, τ_1^0 verifies (2.3) with an error smaller than a predefined threshold (10^{-5}) we consider that τ_1^0 is a good approximation for the switch value of τ_1. Repeat this procedure for τ_2' which belongs to some interval $[0,\ \tau_2^{max}]$ taken discretely with some small step and determine corresponding values of switch of stability for τ_1.

The switches of stability determined for the two delays τ_1 and τ_2 are used to:

– check if, for some switches of stability, phenomena as bifurcations appear for this model.

– build charts of stability of the equilibrium when τ_1 and τ_2 are varied for different configurations of parameters.

The formulas from section 3 are used to compute the first Lyapunov coefficient and the other parameters related to the bifurcation formulae. In the figures the values of the parameters of the system that are varied, the values of τ_1 and τ_2 where bifurcation occur and the values of the nontrivial equilibrium.

In order to illustrate the appearance of Hopf bifurcations and the stability of the limit cycles in some cases, phase portraits with bifurcation parameters τ_1 and τ_2 are shown in figures 2, 3, 4. In these figures τ_1^0 is the first switch of stability from stable to unstable equilibrium and τ_1 is varied. The first row represents the situation with τ_1 near 0, the second row represents the situation with $\tau_1 < \tau_1^0$ (before the switch of stability, a stable equilibrium), the third row represents the situation with $\tau_1 = \tau_1^0$ (first switch of stability; the value of Lyapunov coefficient is displayed) and the last row illustrates the situation with $\tau_1 > \tau_1^0$ (after the first switch of stability, an unstable equilibrium).

One of the main ideas of this model was the consideration of asymmetric division in the evolution of stem cell population. In the following charts of stability, one can observe the influence of asymmetric division parameters η_1 and η_2 to the stability of the equilibria (Figures 5, 6, 7). The normal leukopoiesis seems to be characterized by a big value of η_1 (or more generally $1 - \eta_1 - \eta_2$ small) and a small value of A_N . One can observe that stability is prevalent for healthy cells (for example for η_1 =0.8). In this situation there are no limit cycles and bifurcation phenomena. The influence of A_N is also very important and the charts for A_N medium and big show small islands of stability (7).

The numerical results are obtained using dde23, a Matlab solver for DDEs written by Shampine and Thompson [36]. The history used in examples is constant and is taken in a neighborhood of the non trivial steady state and we use the default values of accuracy and step size of dde23. In the figures, the dynamics and phase portraits for the population of stem cells cells x_1 and mature cells x_2 are shown.

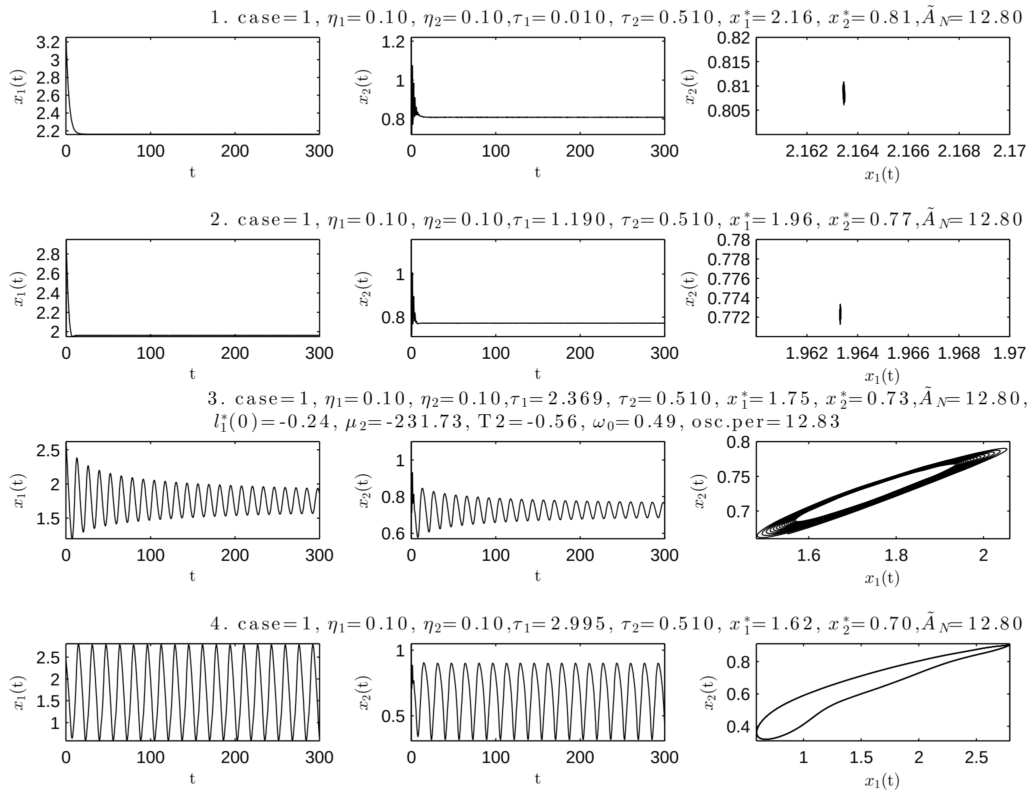

FIGURE 2. A switch of stability with respect to τ_1 for a case with $\eta_1 = 0.1$, $\tau_2 = 0.51$ and an amplification factor A_N small (corresponding to p=10).

Our results are confirmed using DDE-BIFTOOL - a Matlab package for bifurcation analysis of delay differential equations [18].

5. Conclusions

The evolution of a healthy or pathological hematopoietic system is described through a DDEs system including asymmetric division. The healthy or leukemic state of the system is determined by the configuration of the model parameters. The stability of the equilibrium is analyzed using the Stability in the First Approximation Theorem and numerical simulations illustrate the switch of stability as a variety of parameters considered essential for the disease onset and evolution are varied.

From the point of view of medical interpretation, it is of great importance to find those parameter configurations that are responsible for the appearance of stable steady states or of stable limit cycles. In this way, a desirable state, where there are no big fluctuations (as in the case of a blast crisis), is attained. The analysis of the stability of the limit cycles is performed using the computation of the first Lyapunov coefficient.The formulae obtained are used to study the influence of different parameters on the stability of the periodic solutions that result in the case of a Hopf bifurcation.

Even so, in real systems, the dynamical evolution can be significantly complicated. For example, simple oscillations were observed in many biological systems. These oscillations appear when the equilibrium become unstable, the system moves away from it and then often burst into persistent oscillations around the equilibrium. Into the phase space this corresponds to the evolution to a limit cycle, although evolution to a limit cycle is not the only scenario possible when a steady state becomes unstable. The system may

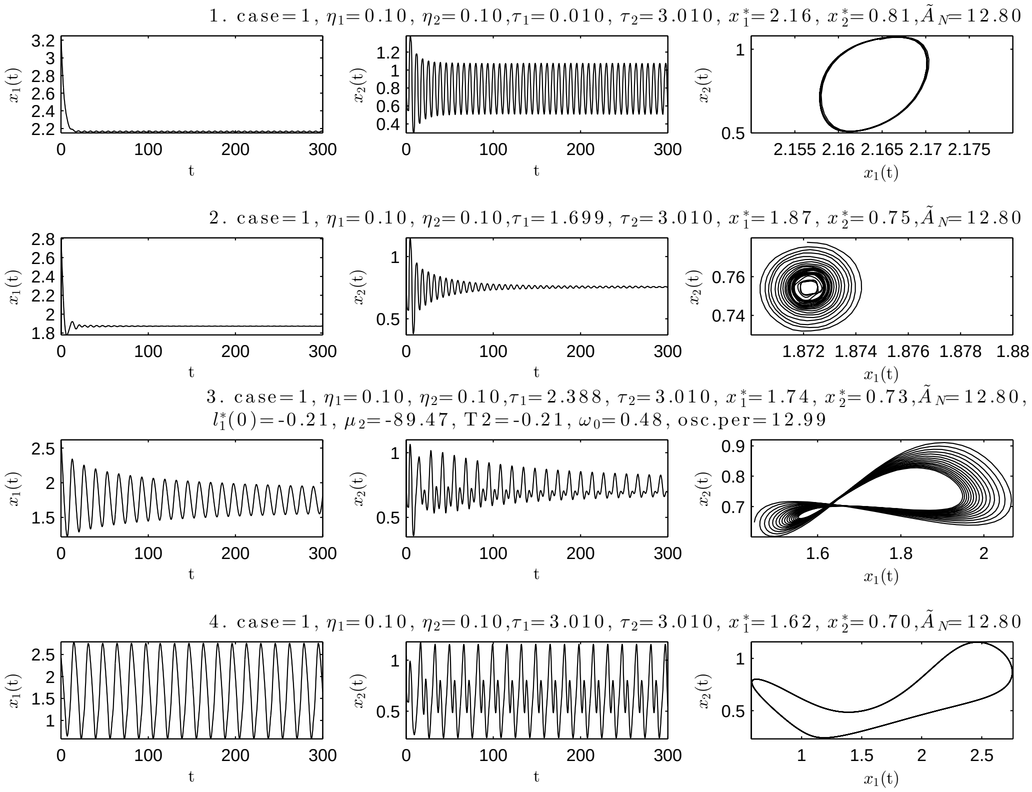

FIGURE 3. A switch of stability with respect to τ_1 for a case with $\eta_1 = 0.1$, $\tau_2 = 3.01$ and an amplification factor A_N small (corresponding to p=10), the case 1.7 from the table 1. One can observe that for τ_1 near 0 the system is unstable and the first switch to instability appears after a switch to stability.

evolve to another steady state, a process called bistability. However, from an intuitive point of view, in the case of a healthy cell population, we expect to find stable steady states or stable limit cycles, while in the case of a cancerous cell population, unstable steady states or unstable limit cycles are more likely to appear.

For the model studied in this paper, one can notice from the stability charts, that an increase of the percentage of asymmetric division η_1 has as a result a larger area of stability. Another interesting, although expected, fact is that with the increase of the amplification factor A_N, the stability domain of the steady state becomes smaller. As a larger percentage of asymmetric division corresponds to a healthy hematopoietic system, while a larger amplification factor corresponds to a pathological one, these conclusions are in accord with medical evidence.

In order to derive more pertinent and medically sound conclusions, a future goal for all the scientific researchers in the field is to find the configuration of parameters for every different patient, in order to be able to personalize the treatment approach. There is no need to say, that, particularly for stem cell populations, this is a difficult and challenging task.Hopefully, future medical discoveries might bring us closer to this goal.

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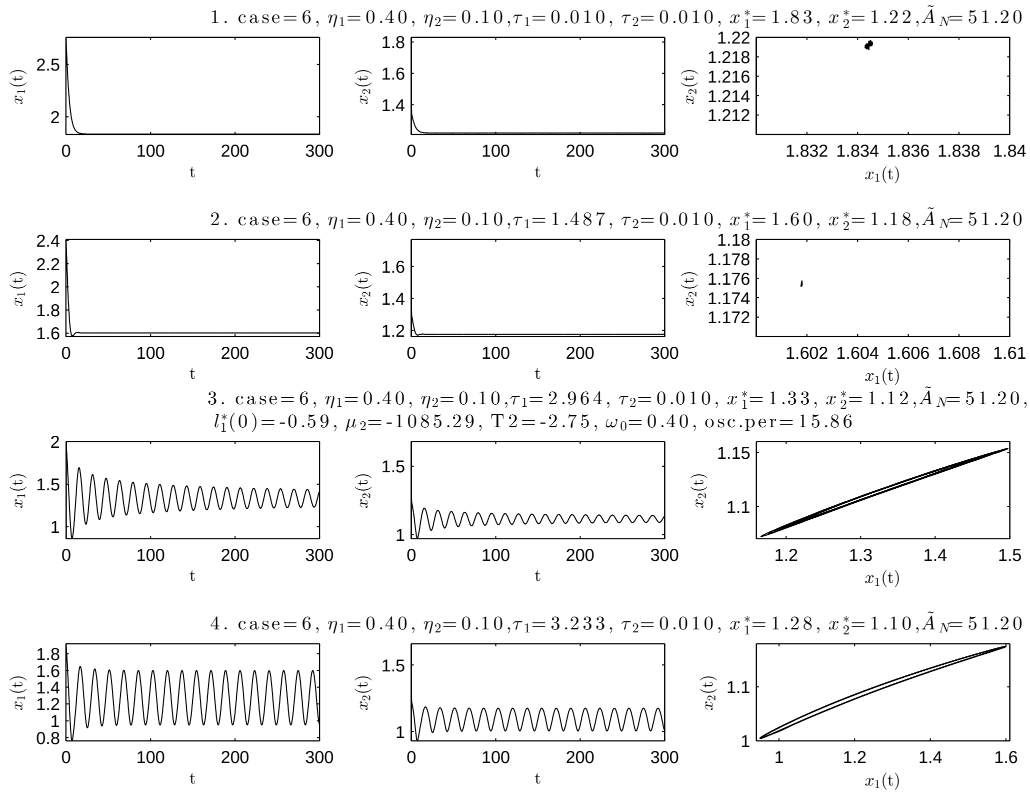

FIGURE 4. A switch of stability with respect to τ_1 for a case with $\eta_1 = 0.4$, $\tau_2 = 2.51$ and an amplification factor A_N medium (corresponding to p=12)

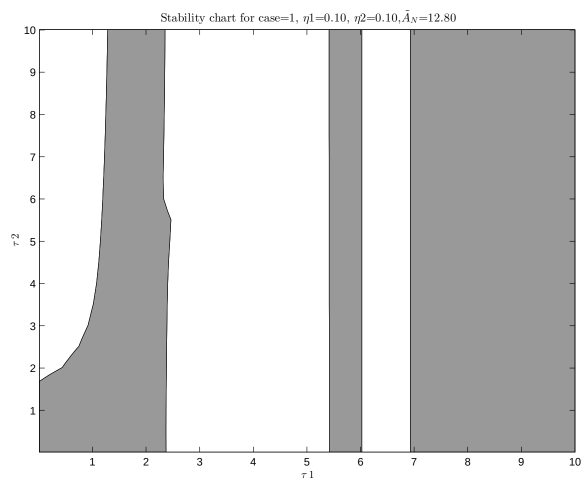

FIGURE 5. A stability chart of stationary point with respect to τ_1 and τ_2 for a case with $\eta_1 = 0.1$ (leukemic leukopoiesis characterized by a small value of η_1) and an amplification factor A_N small (corresponding to p=10); the gray colour is associated with stable equilibria.

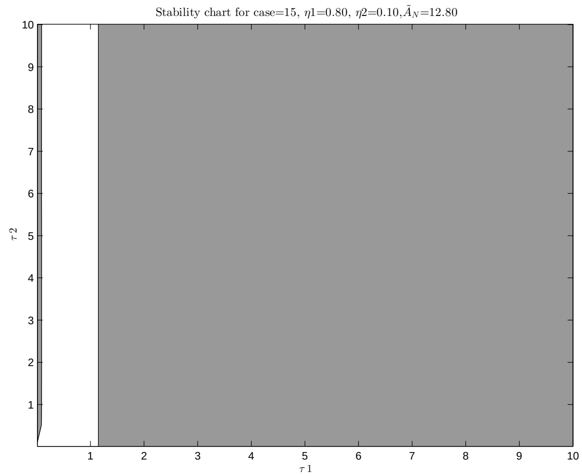

FIGURE 6. A stability chart of stationary point with respect to τ_1 and τ_2 for a case with $\eta_1 = 0.8$ (normal leukopoiesis characterized by a big value of η_1) and an amplification factor A_N small (corresponding to p=10)

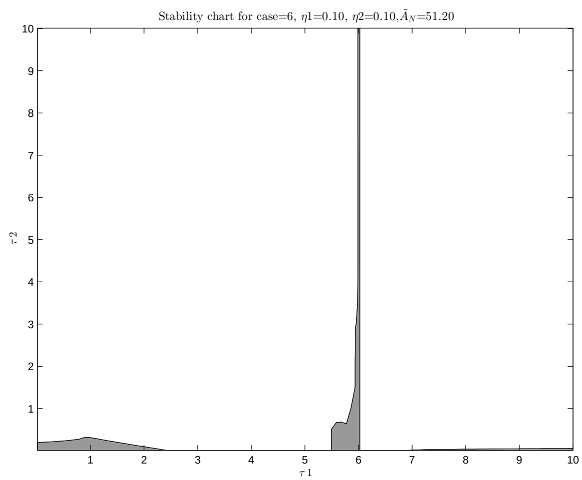

FIGURE 7. A stability chart of stationary point with respect to τ_1 and τ_2 for a case with $\eta_1 = 0.1$ (leukemic leukopoiesis characterized by a small value of η_1) and an amplification factor A_N medium (corresponding to p=12); the gray colour is associated with stable state

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