Stability of equilibrium and periodic solutions of a delay equation modeling leukemia

© Anca-Veronica Ion[1], Raluca-Mihaela Georgescu[2]

Annotation. We consider a delay differential equation that occurs in the study of chronic myelogenous leukemia. The equation was investigated numerically in [8], [9], where also some conclusions regarding the stability of equilibria are given. In [6] the first author studied in detail the stability of the two equilibrium points and obtained results that do not agree to those of [8], [9]. In the present work, we shortly remind the results of [6] and then concentrate on the study of stability of periodic solutions emerged by Hopf bifurcation from the non-trivial equilibrium point. We give the algorithm for the construction of a center manifold at a typical point (in the parameter space) of Hopf bifurcation, and of a unstable manifold in the vicinity of such a point (where such a manifold exists). Then we find the normal form of the equation restricted to the center manifold, by computing the first Lyapunov coefficient. The normal form allows us to establish the stability properties of the periodic solutions occurred by Hopf bifurcation.
Acknowledgement. Work supported by Grant 11/05.06.2009 within the framework of the Russian Foundation for Basic Research - Romanian Academy collaboration.
AMS MSC 2000: 65L03, 37C75, 37G05, 37G15.
Key words: delay differential equations; stability; Hopf bifurcation; normal forms.

1. The problem

We consider the delay differential equation that occurs in the study of periodic chronic myelogenous leukemia [8], [9]

$$\dot{x}(t) = -\left[\frac{\beta_0}{1+x(t)^n} + \delta\right] x(t) + k\frac{\beta_0 x(t-r)}{1+x(t-r)^n}. \tag{1.1}$$

Here $\beta_0, n, \delta, \gamma, r$ are positive parameters and $k = 2e^{-\gamma r}$. The unknown function, $x(\cdot)$, should also be nonnegative, being a non-dimensional density of cells. We do not insist more on the significance of the function $x(.)$ or in that of the parameters, since these are extensively presented in [8], [9]. Anyway, inasmuch as the equation represents a good model for the periodic chronic myelogenous leukemia, both the equilibrium solutions and the periodic solutions are important, as are their stability properties.

In the following we use the space $\mathcal{B} = C([-r,0],\mathbb{R})$ (the space of continuous, real valued functions defined on $[-r,0]$, with the supremum norm, denoted by $|x|_0$). Given a function $x : [-r,T) \mapsto \mathbb{R}, T > 0$ and a $0 \le t < T$, we define the function $x_t \in \mathcal{B}$ by $x_t(s) = x(t+s)$.

Equation (1.1) may be written as

$$\dot{x} = h(x_t), \tag{1.2}$$

where $h : \mathcal{B} \mapsto \mathbb{R}$, and we impose to this equation the initial condition

$$x_0 = \varphi \in \mathcal{B}. \tag{1.3}$$

In [6] we proved that problem (1.2), (1.3) has an unique, defined on $[-r,\infty)$ bounded solution.

[1]"Gh. Mihoc-C. Iacob" Institute of Mathematical Statistics and Applied Mathematics of the Romanian Academy, Bucharest, Romania.
[2]University of Piteşti, Romania.

1.1. Equilibrium solutions

As shown in [8], the equilibrium points of the problem are

$$x_1 = 0, \;\; x_2 = (\frac{\beta_0}{\delta}(k-1) - 1)^{1/n}.$$

The second one is acceptable from the biological point of view if and only if is strictly positive that is, if and only if

$$\frac{\beta_0}{\delta}(k-1) - 1 > 0. \tag{1.4}$$

In terms of r, the above inequality may be written as

$$r < r_{max} := -\frac{1}{\gamma} \ln \frac{1}{2} \left(1 + \frac{\delta}{\beta_0}\right),$$

and since the delay r is positive, the condition $\delta/\beta_0 < 1$ follows.

The biological interpretation of function β [8] shows that the condition $\beta(x_2) = \delta/(k-1) > 0$ should be fulfilled. This is equivalent to $k > 1$.

The linearized equation around one of the equilibrium points is

$$\dot{z}(t) = -[B_1 + \delta]z(t) + kB_1 z(t-r), \tag{1.5}$$

with $B_1 = \beta'(x^*)x^* + \beta(x^*)$, $x^* = x_1$ or $x^* = x_2$.

The eigenvalues of the infinitesimal generator of the semigroup of operators generated by equation (1.5) are the solutions of the characteristic equation

$$\lambda + \delta + B_1 = kB_1 e^{-\lambda r}. \tag{1.6}$$

2. Stability of equilibrium solution

The study in [6] has lead us to the following conclusions (obtained by using the results in [1]).

2.1. Stability of x_1

In this case $B_1 = \beta_0$. The equilibrium point x_1 is stable as long as it is the single equilibrium point, that is when $\frac{\beta_0}{\delta}(k-1) \leq 1$. When the second equilibrium point occurs ($\frac{\beta_0}{\delta}(k-1) > 1$), x_1 becomes unstable. For $\frac{\beta_0}{\delta}(k-1) = 1$, equation (1.6) admits the solution $\lambda = 0$. Hence the change of stability occurs by traversing the eigenvalue $\lambda = 0$.

2.2. Stability of x_2

In this case,

$$B_1 = \beta_0[n - (n-1)A]/A^2 \tag{2.1}$$

where $A = \beta_0(k-1)/\delta$.

We still rely on [6] in this subsection. Let us define for future use

$$r_n = -\frac{1}{\gamma} \ln \left\{ \frac{1}{2} \left(\frac{\delta}{\beta_0} \frac{n}{n-1} + 1 \right) \right\}.$$

We have the following distinct situations.

I. $B_1 < 0$ that is equivalent to $\frac{\beta_0}{\delta}(k-1) > \frac{n}{n-1}$, and, in terms of r, equivalent to $0 \le r \le r_n$. Two subcases are to be considered.

I.A. $B_1 < 0$ and $\delta + B_1 < 0$. In this case $Re\lambda < 0$ for all eigenvalues λ if and only if $|\delta + B_1| < |kB_1|$ and

$$\frac{\arccos\left((\delta + B_1)/kB_1\right)}{\omega_0} < r < \frac{1}{|\delta + B_1|}, \tag{2.2}$$

where ω_0 is the solution in $(0, \pi/r)$ of the equation $\omega\cot(\omega r) = -p$. Hence when the above conditions are satisfied, the equilibrium solution x_2 is stable.

When $r|\delta + B_1| = 1$, the solution x_2 is unstable [6].

I.B. $B_1 < 0$ and $\delta + B_1 > 0$.

In this case, $Re\lambda < 0$ for all eigenvalues λ if and only if

$$\delta + B_1 > |kB_1| \text{ or } \left\{\delta + B_1 \le |kB_1| \text{ and } r < \frac{\arccos\left((\delta + B_1)/kB_1\right)}{\omega_0}\right\} \tag{2.3}$$

where ω_0 is defined as above.

Remarks. a) If $B_1 < 0, \delta + B_1 = 0$, the solution is stable if and only if $-kB_1 r < \pi/2$ while, for this case, the point $kB_1 r = -\pi/2$ is a Hopf bifurcation point.

b) Assume that we vary r and keep all the other parameters fixed. The conditions (2.2) or (2.3) for r are not as simple as they seem, because B_1 is itself a function of r, (being a function of k). Let us consider the function

$$h(r) = T^{-1}(-(\delta + B_1(r))r) - \arccos\left(\frac{\delta + B_1(r)}{k(r)B_1(r)}\right). \tag{2.4}$$

If for a certain r^* we have $h(r^*) = 0$ (that is the condition for the change of stability), in order to find whether a value r_1 in a neighborhood of r^* is in the stability zone or not, we have to know the sign of $h(r_1)$, hence we have to study the monotony properties of function h in a neighborhood of r^*. This will be done in the last section for an example.

II. $B_1 > 0$ that is equivalent to $\frac{\beta_0}{\delta}(k-1) < \frac{n}{n-1}$, and, in terms of r, equivalent to $r_n \le r \le r_{max}$.

In this case, we can only have $\delta + B_1 > 0$, and, by [1], $Re\lambda < 0$ for all eigenvalues λ if and only if $kB_1 < \delta + B_1$.

By using (2.1) we see the above inequality is equivalent to $\frac{\beta_0(k-1)}{\delta} > 1$ that is already satisfied, since x_2 exists is positive. It follows that if $B_1 > 0$ then x_2 is stable.

3. Hopf bifurcation points

By denoting $\lambda = \mu + i\omega$, and by equating the real, respectively the imaginary part of the characteristic equation (1.6), we obtain

$$\mu + \delta + B_1 = kB_1 e^{-\mu r}\cos(\omega r), \tag{3.1}$$

$$\omega = -kB_1 e^{-\mu r}\sin(\omega r).$$

It is useful to consider the case $\mu = 0$ in the above equations,

$$\delta + B_1 = kB_1\cos(\omega r), \tag{3.2}$$

$$\omega = -kB_1\sin(\omega r).$$

In the above stability discussion, in **I.**, the case

$$r = \frac{\arccos((\delta + B_1)/(kB_1))}{\omega_0} \tag{3.3}$$

occurs on the frontier of the stability domain. This relation, together with $\omega_0 \cot(\omega_0 r) = -(\delta + B_1)$ imply that $\omega_0 = \sqrt{(kB_1)^2 - (\delta + B_1)^2}$ and that the pair $\mu^* = 0$, $\omega^* = \omega_0$ represents a solution of (3.1).

Hence a point in the parameter space, where relation (3.3) is satisfied, might be a Hopf bifurcation point when one of the parameters is varied. The Hopf bifurcation may be either a non-degenerated or a degenerated one.

To be more precise, we consider the vector of parameters $(\beta_0, n, \delta, \gamma, r)$ and denote it by $\mathbf{a} = (a_i)_{1 \le i \le 5}$.

We choose a point in the parameter space, $\mathbf{a}^* = (a_i^*)_{1 \le i \le 5}$, such that, for this choice of parameters, there are two pure imaginary eigenvalues $\widetilde{\lambda}_{1,2}(\mathbf{a}^*) = \pm i\omega^*$, $\omega^* := \omega(\mathbf{a}^*) > 0$ and all other eigenvalues λ have strictly negative real parts (i.e. a point where condition (3.3) holds).

In the following we keep fixed all parameters excepting one, a_j, that we vary (j fixed, $1 \le j \le 5$,). For further simplicity, we denote $a_j := \alpha$, such that $\widetilde{\lambda}_{1,2}(\mathbf{a})$ becomes $\widetilde{\lambda}_{1,2}(\alpha)$ and such that $Re\widetilde{\lambda}_{1,2}(\alpha^*) = 0$.

If $\frac{\partial Re\lambda_i}{\partial \alpha}(\alpha^*) \neq 0$, $i = 1, 2$, then at α^* a Hopf bifurcation occurs and, in a neighborhood U^* of α^*, either to the left or to the right of α^* we have $Re\widetilde{\lambda}_{1,2}(\alpha) < 0$, while $Re\widetilde{\lambda}_{1,2}(\alpha) > 0$ at the opposite side of α^*. We assume that the neighborhood U^* is such that for all $\alpha \in U_j^*$ all other eigenvalues besides $\widetilde{\lambda}_{1,2}$ have real parts less than a fixed negative value.

4. On the stability properties of the periodic solutions emerged by Hopf bifurcation

We consider a periodic solution occured by Hopf bifurcation, as described in the previous section. In order to establish whether or not such a periodic solution is stable, we have to compute the normal form of the reduced to the center manifold (or to the unstable manifold) problem. In this section we present the algorithm for obtaining this normal form and the consequences on the stability of periodic solutions.

Since we study local bifurcations around x_2, throughout this section we work with eq. (1.1) translated by x_2, that is the new unknown function $z = x - x_2$ is considered.

4.1. The delay equation as an equation in a Banach space

We assume that we are in one of the situations, mentioned in Section 3, where a Hopf bifurcation occurs. In order to construct the center (or the unstable) manifold at the equilibrium point x_2 we need to write our equation as a differential equation in a Banach space. We use the method of Teresa Faria, from [2], as we did also in [4], [5]. We consider the space

$$\mathcal{B}_0 = \left\{ \psi : [-r, 0] \mapsto \mathbb{R},\ \psi \,\text{is continuous on}\, [-r, 0) \wedge \exists \lim_{s \to 0} \psi(s) \in \mathbb{R} \right\},$$

that is formed of functions $\psi = \varphi + \sigma d_0$, where $\varphi \in \mathcal{B}$, $\sigma \in \mathbb{R}$ and $d_0 : [-r, 0] \mapsto \mathbb{R}$,

$$d_0(s) = \begin{cases} 0, & s \in [-r, 0), \\ 1, & s = 0. \end{cases}$$

The space $\mathcal{B}_0$ is normed by $\|\psi\| = |\varphi|_0 + |\sigma|$. The linearized equation (1.5) can be written as

$$\dot{z} = Lz_t, \tag{4.1}$$

$$L\varphi = \int_{-r}^{0} d\eta(\theta)\varphi(\theta),$$

(the integral is a Stieljes one) with

$$\eta(s) = \begin{cases} -kB_1, & s = -r; \\ 0, & s \in (-r, 0); \\ -(B_1 + \delta), & s = 0. \end{cases}$$

Nonlinear equation (1.1) may be written as

$$\dot{z}(t) = L(z_t) + f(z(t), z(t-r)), \tag{4.2}$$

where $f(\cdot,\cdot)$ comprises the nonlinear terms of the equation. Since $z(t)$ and $z(t-r)$ are functions of z_t, eq. (4.2) may be written as

$$\dot{z}(t) = L(z_t) + \widetilde{f}(z_t). \tag{4.3}$$

In [2], the linear operator $A : C^1([-r, 0], \mathbb{R}) \subset \mathcal{B}_0 \mapsto \mathcal{B}_0$

$$A(\varphi) = \dot{\varphi} + d_0[L(\varphi) - \dot{\varphi}(0)] \tag{4.4}$$

is defined and it is proved that this is the infinitesimal generator of the semigroup of operators $\{S(t)\}_{t\geq 0}$ given by $S(t)(\varphi) = z_t(\varphi)$, where $z(t, \varphi)$ is the solution of equation (4.1) with the initial condition $z_0 = \varphi$. Then the nonlinear equation may be written as an equation in $\mathcal{B}_0$, that is

$$\frac{dz_t}{dt} = A(z_t) + d_0\widetilde{f}(z_t). \tag{4.5}$$

4.2. Space of eigenfunctions corresponding to $\widetilde{\lambda}_{1,2}$, the projector on this space

We return for the moment to the linear equation (1.5). The eigenfunctions corresponding to the two eigenvalues $\widetilde{\lambda}_{1,2} = \mu(\alpha) \pm i\omega(\alpha)$ are given by $\varphi_{1,2}(s) = e^{\widetilde{\lambda}_{1,2}s}$, $s \in [-r, 0]$. Since the eigenfunctions are complex functions, we need to use the complexification of the space $\mathcal{B}$, $\mathcal{B}_0$ that we denote by $\mathcal{B}_C$, $\mathcal{B}_{0C}$, respectively. We denote by $\mathcal{M}$ the subspace of $\mathcal{B}_C$ generated by $\varphi_{1,2}(\cdot)$.

In [2] a projector defined on $\mathcal{M}$ is constructed. For its construction we need a bilinear form that is defined by using the transposed equation of the linearized equation. The transposed equation is

$$\dot{y}(s) = -\int_{-r}^{0} y(s-\theta)d[\eta(\theta)],$$

hence

$$\dot{y}(s) = (B_1 + \delta)y(s) - kB_1 y(s + r).$$

The characteristic equation for the adjoint problem is

$$\lambda = B_1 + \delta - kB_1 e^{\lambda r},$$

that admits the solutions $\lambda_{1,2} = -\mu(\alpha) \pm i\omega(\alpha)$. The corresponding eigenfunctions are $\psi_1(\zeta) = e^{(-\mu+i\omega)\zeta}$, $\psi_2(\zeta) = e^{(-\mu-i\omega)\zeta}$, $\zeta \in [0, r]$.

In order to construct the projector defined on $\mathcal{B}_{0C}$ with values on $\mathcal{M}$, we define the bilinear form [3]

$$\langle \psi, \varphi \rangle = \psi(0)\varphi(0) - \int_{-r}^{0}\int_{0}^{\theta} \psi(\zeta-\theta)d\eta(\theta)\varphi(\zeta)d\zeta =$$
$$= \psi(0)\varphi(0) + kB_1\int_{-r}^{0}\psi(\zeta+r)\varphi(\zeta)d\zeta,$$

where $\psi : [0, r] \to \mathbb{R}$.

We look for linear combinations of the vectors ψ_j, that we will denote Ψ_i, $i = 1, 2$, such that $\langle \Psi_i,\, \varphi_j\rangle = \delta_{ij}$. For this we determine the 2×2 matrix E, with elements $e_{ij} = \langle \psi_i,\, \varphi_j\rangle$.

$$e_{11} = (\psi_1, \varphi_1) = \psi_1(0)\varphi_1(0) + kB_1\int_{-r}^{0} e^{(-\mu+i\omega)(\theta+r)}e^{(\mu+i\omega)\theta}d\theta = 0,$$

$$e_{12} = (\psi_1, \varphi_2) = \psi_1(0)\varphi_2(0) + kB_1\int_{-r}^{0} e^{(-\mu+i\omega)(\theta+r)}e^{(\mu-i\omega)\theta}d\theta = 1 + (\delta + B_1 + \mu - i\omega)r,$$

$$e_{21} = (\psi_2, \varphi_1) = \psi_2(0)\varphi_1(0) + kB_1\int_{-r}^{0} e^{(-\mu-i\omega)(\theta+r)}e^{(\mu+i\omega)\theta}d\theta = 1 + (\delta + B_1 + \mu + i\omega)r,$$

$$e_{22} = (\psi_2, \varphi_2) = \psi_2(0)\varphi_2(0) + kB_1\int_{-r}^{0} e^{(-\mu-i\omega)(\theta+r)}e^{(\mu-i\omega)\theta}d\theta = 0.$$

We have $\det E = e_{11}e_{22} - e_{12}e_{21} = -[(1 + (\delta + B_1 + \mu)r)^2 + \omega^2 r^2]$. Since

$$\begin{pmatrix}\Psi_1\\ \Psi_2\end{pmatrix} = E^{-1}\begin{pmatrix}\psi_1\\ \psi_2\end{pmatrix},$$

we obtain

$$\Psi_1 = \frac{1}{\det E}[e_{22}\psi_1 - e_{12}\psi_2] = \frac{-e_{12}}{\det E}\psi_2, \quad \Psi_2 = \overline{\Psi}_1.$$

We can now write the projector defined on $\mathcal{B}_{0C}$ and with values on $\mathcal{M}$. It is given, for $\psi = \varphi + d_0\sigma \in \mathcal{B}_{0C}$ by

$$\mathcal{P}(\psi) = (\langle \Psi_1, \varphi\rangle + \Psi_1(0)\sigma)\,\varphi_1 + (\langle \Psi_2, \varphi\rangle + \Psi_2(0)\sigma)\,\varphi_2. \tag{4.6}$$

If $\sigma = 0$ and, thus, $\psi = \varphi \in \mathcal{B}_C$, we have $\mathcal{P}(\varphi) = \langle \Psi_1, \varphi\rangle\varphi_1 + \langle \Psi_2, \varphi\rangle\varphi_2$.

Now, for the solution $z(\cdot, \varphi)$ of (4.5) we can write

$$z_t = \varphi_1 u_1(t) + \varphi_2 u_2(t) + \mathbf{v}(t),$$

with $u_1(t) = \langle \Psi_1,\, z_t\rangle$, $u_2(t) = \langle \Psi_2,\, z_t\rangle$, $\mathbf{v} = (I - \mathcal{P})z_t$.

We project now the equation (4.5) by $\mathcal{P}$, to obtain,

$$\frac{d\mathbf{u}}{dt} = B\mathbf{u} + \Psi(0)\widetilde{f}(\varphi_1 u_1 + \varphi_2 u_2 + \mathbf{v}), \tag{4.7}$$

where

$$\mathbf{u} = \begin{pmatrix}u_1\\ u_2\end{pmatrix},\ B = \begin{pmatrix}\widetilde{\lambda}_1 & 0\\ 0 & \widetilde{\lambda}_2\end{pmatrix},\ \Psi = \begin{pmatrix}\Psi_1\\ \Psi_2\end{pmatrix}.$$

Remark that u_1, u_2 are complex functions, but, since our initial problem is formulated in terms of real functions, we have $u_1 = \overline{u}_2$, and the two scalar equations comprised in (4.7) are complex conjugated one to the other. Hence it suffices to study one of the them, let us say the equation for u_1. We denote $u_1 = u$ and the equation to be studied in the following is

$$\frac{du}{dt} = (\mu + i\omega)u + \Psi_1(0)\widetilde{f}(\varphi_1 u + \varphi_2 \overline{u} + \mathbf{v}), \tag{4.8}$$

where, as the above computations show,

$$\Psi_1(0) = \frac{1 + (\delta + B_1 + \mu - i\omega)r}{[1 + (\delta + B_1 + \mu)r]^2 + \omega^2 r^2}. \tag{4.9}$$

4.3. The equation restricted to the invariant (center or unstable) manifold

For those $\alpha \in U^*$ where $Re\widetilde{\lambda}_{1,2}(\alpha) \geq 0$, since all other eigenvalues have negative real part, there is a local invariant manifold, the local unstable manifold, W^u_{loc}, for $Re\widetilde{\lambda}_{1,2}(\alpha) > 0$, or the local center manifold, W^c_{loc}, for α^* ($Re\widetilde{\lambda}_{1,2}(\alpha^*) = 0$).

The local invariant manifold is an at least C^1 invariant manifold, tangent to the space $\mathcal{M}$ at the point $z = 0$ (that is $x = x_2$), and it is the graph of a function $w(\alpha)(\cdot)$ defined on a neighborhood of zero in $\mathcal{M}$ and taking values in $(I - \mathcal{P})\mathcal{B}_{\mathcal{C}}$. A point on the local invariant manifold has the form $u\,\varphi_1 + \overline{u}\,\varphi_2 + w(\alpha)(u\,\varphi_1 + \overline{u}\,\varphi_2)$. Since it is an invariant manifold, if the initial condition is taken on the manifold, then its image through the semigroup $\{\widetilde{T}(t)\}_{t\geq 0}$, $\widetilde{T}(t)(\varphi) = z_t(\varphi)$, is still on it ($\widetilde{T}(t)(\varphi) = T(t)(\varphi) - x_2$, where $T(t)$ is defined at the end of Subsection 1.1). Hence

$$\widetilde{T}(t)(\varphi) = u(t)\varphi_1 + \overline{u(t)}\varphi_2 + w(\alpha)(u(t)\varphi_1 + \overline{u(t)}\varphi_2), \tag{4.10}$$

with $u(\cdot)$, solution of the equation

$$\frac{du}{dt} = \widetilde{\lambda}_1(\alpha)u + \Psi_1(0)\widetilde{f}(\varphi_1 u + \varphi_2\overline{u} + w(\alpha)(u\varphi_1 + \overline{u}\varphi_2)), \tag{4.11}$$

with the initial condition $u(0) = u_0$, where $\mathcal{P}(\varphi) = u_0\varphi_1 + \overline{u}_0\varphi_2$. The real and the imaginary parts of this complex equation, represent the two-dimensional restricted to the center manifold problem. We can study this problem with the tools of planar dynamical systems theory (see, e.g. [7]).

4.4. The normal form of the reduced equation

In order to find the normal form of equation (4.11) we must consider the series of powers of $u, \overline{u}$ for $w(\alpha)$ and for $\widetilde{f}(z_t)$. We set

$$\widetilde{w}(\alpha)(u, \overline{u}) = \sum_{j+k\geq 2} \frac{1}{j!k!} w_{jk}(\alpha) u^j \overline{u}^k, \tag{4.12}$$

where $\widetilde{w}(\alpha)(u, \overline{u}) := w(\alpha)(u(t)\varphi_1 + \overline{u(t)}\varphi_2)$, $w_{jk}(\alpha) \in \mathcal{B}$, $u : [0, \infty) \mapsto \mathbb{C}$.

$\widetilde{f}(z_t)$ is, due to (4.10), a function of u, $\overline{u}$, and we develop it in a series of powers

$$\widetilde{f}(z_t) = \sum_{j+k\geq 2} \frac{1}{j!k!} f_{jk}(\alpha) u^j \overline{u}^k. \tag{4.13}$$

Equation (4.11) becomes

$$\frac{du}{dt} = \widetilde{\lambda}_1(\alpha)u + \sum_{j+k\geq 2} \frac{1}{j!k!} g_{jk}(\alpha) u^j \overline{u}^k, \tag{4.14}$$

where $g_{jk}(\alpha) = \Psi_1(0) f_{jk}(\alpha)$. If the first Lyapunov coefficient at α^*, [7],

$$l_1(\alpha^*) = \frac{1}{2\omega^{*2}} Re(i g_{20}(\alpha^*) g_{11}(\alpha^*) + \omega^* g_{21}(\alpha^*)) \tag{4.15}$$

is not equal to zero, at $\alpha = \alpha^*$ our equation presents a non-degenerated Hopf bifurcation.

We assume that the initial function, φ, is on the invariant manifold. We give the algorithm for computing the first Lyapunov coefficient. We are interested in the nonlinear part of our equation. We consider the function $\beta(x)x$, compute its derivatives of higher order than one at the point x_2, and denote them B_n

$$B_n = \beta^{(n)}(x_2)x_2 + n\beta^{(n-1)}(x_2).$$

Let F be the function $F(z) = \frac{1}{2!}B_2 z^2 + \frac{1}{3!}B_3 z^3 + \frac{1}{4!}B_4 z^4 + \dots$. The nonlinear part of the RHS of (4.2) is $f(z(t), z(t-r)) = -F(z(t)) + kF(z(t-r))$, or, in terms of z_t, the function $\widetilde{f}$ of (4.3) is $\widetilde{f}(z_t) = -F(z_t(0)) + kF(z_t(-r))$.

The normal form of the restriction of the problem to the unstable manifold is [7]

$$\frac{d}{dt}u = (\beta(\alpha) + i)u + su|u|^2, \tag{4.16}$$

where $\beta(\alpha) = \mu(\alpha)/\omega(\alpha)$, $s = sign(l_1(\alpha^*))$. For $\alpha = \alpha^*$, $\beta(\alpha^*) = 0$, and the normal form on the center manifold is obtained. The existence and stability properties of the cycle emerged by Hopf bifurcation are given by the signs of $\beta(\alpha)$ (for $\alpha \in U^*$) and $l_1(\alpha^*)$. We must compute $l_1(\alpha^*)$, given by (4.15).

In order to identify the coefficients $g_{jk}(\alpha^*)$ we must find the coefficients for the series of $\widetilde{f}$. The following computations are done at $\alpha = \alpha^*$, but for simplicity, the parameter will not be written.

We have (by denoting $\varphi_1 = \varphi$)

$$\widetilde{f}(z_t) = -F([\widetilde{T}(t)\varphi](0)) + kF([\widetilde{T}(t)\varphi](-r)) = \tag{4.17}$$

$$= -\frac{1}{2!}B_2[u\varphi(0) + \overline{u\varphi}(0) + \frac{1}{2}w_{20}(0)u^2 + w_{11}(0)u\overline{u} + \frac{1}{2}w_{02}(0)\overline{u}^2 + ...]^2 -$$

$$-\frac{1}{3!}B_3[u\varphi(0) + \overline{u\varphi}(0) + \frac{1}{2}w_{20}(0)u^2 + w_{11}(0)u\overline{u} + \frac{1}{2}w_{02}(0)\overline{u}^2 + ...]^3 - .... +$$

$$+\frac{1}{2!}kB_2[u\varphi(-r) + \overline{u\varphi}(-r) + \frac{1}{2}w_{20}(-r)u^2 + w_{11}(-r)u\overline{u} + \frac{1}{2}w_{02}(-r)\overline{u}^2 + ...]^2 +$$

$$+\frac{1}{3!}kB_3[u\varphi(-r) + \overline{u\varphi}(-r) + \frac{1}{2}w_{20}(-r)u^2 + w_{11}(-r)u\overline{u} + \frac{1}{2}w_{02}(-r)\overline{u}^2 + ...]^3 + ... =$$

$$= \sum_{j+k\geq 2} \frac{1}{j!k!} f_{jk} u^j \overline{u}^k.$$

The second order terms are

$$-\frac{1}{2}B_2(u^2 + 2u\overline{u} + \overline{u}^2) + \frac{kB_2}{2}(u^2\varphi^2(-r) + 2u\overline{u} + \overline{u}^2\overline{\varphi}^2(-r)),$$

and the coefficients

$$f_{20} = B_2(k\varphi^2(-r) - 1) = -B_2(1 - ke^{-2\omega^* ir});$$

$$f_{11} = B_2(k-1);$$

$$f_{02} = B_2(k\overline{\varphi}^2(-r) - 1) = -B_2(1 - ke^{2\omega^* ir})$$

follow. From here, we already find $g_{ij} = \Psi_1(0)f_{ij},\ i+j=2,$ with $\Psi_1(0)$ given in (4.9).

In order to determine l_1 we still need to compute the coefficient g_{21}. From (4.17) we obtain

$$f_{21} = -\frac{1}{2}B_2[w_{11}(0) + \frac{1}{2}w_{20}(0) - ke^{-i\omega^* r}w_{11}(-r) - \frac{1}{2}ke^{i\omega^* r}w_{20}(-r)] - \frac{1}{2}B_3(1 - ke^{-i\omega^* r}), \quad (4.18)$$

hence we have to determine $w_{20}(0),\ w_{20}(-r),\ w_{11}(0),\ w_{11}(-r)$.

The functions $w_{jk} \in \mathcal{B}_C$ are determined from [10], [4]

$$\frac{\partial}{\partial s}\sum_{j+k\geq 2}\frac{1}{j!k!}w_{jk}(s)u^j\overline{u}^k = \sum_{j+k\geq 2}\frac{1}{j!k!}g_{jk}u^j\overline{u}^k\varphi_1(s) +$$

$$+\sum_{j+k\geq 2}\frac{1}{j!k!}\overline{g}_{jk}\overline{u}^j u^k\varphi_2(s) + \frac{\partial}{\partial t}\sum_{j+k\geq 2}\frac{1}{j!k!}w_{jk}(s)u^j\overline{u}^k,$$

and the integration constants are determined from

$$\frac{d}{dt}\sum_{j+k\geq 2}\frac{1}{j!k!}w_{jk}(0)u^j\overline{u}^k + \sum_{j+k\geq 2}\frac{1}{j!k!}g_{jk}u^j\overline{u}^k\varphi_1(0) + \sum_{j+k\geq 2}\frac{1}{j!k!}\overline{g}_{jk}\overline{u}^j u^k\varphi_2(0) =$$

$$-\sum_{j+k\geq 2}\frac{1}{j!k!}w_{jk}(-r)u^j\overline{u}^k + \sum_{j+k\geq 2}\frac{1}{j!k!}f_{jk}u^j\overline{u}^k.$$

Hence, the function $w_{20}(\cdot)$ is solution of the differential equation,

$$w_{20}'(s) = 2\omega^* i w_{20}(s) + g_{20}\varphi(s) + \overline{g}_{02}\overline{\varphi}(s).$$

We integrate between $-r$ and 0 and obtain

$$w_{20}(0) - w_{20}(-r)e^{2\omega^* ir} = \frac{g_{20}i}{\omega^*}(1 - e^{\omega^* ir}) + \overline{g}_{02}\frac{i}{3\omega^*}(1 - e^{3\omega^* ir}).$$

We also have the relation

$$2\omega^* i w_{20}(0) + g_{20} + \overline{g}_{02} = -w_{20}(-r) + f_{20}.$$

From the two relations above, we get

$$w_{20}(0) = c\left[e^{2\omega^* ir}f_{20} + g_{20}\left(\frac{i}{\omega^*} - \frac{i}{\omega^*}e^{i\omega^* r} - e^{2i\omega^* r}\right) + \right.$$

$$\left. +\overline{g}_{02}\left(\frac{i}{3\omega^*} - \frac{i}{3\omega^*}e^{3i\omega^* r} - e^{2i\omega^* r}\right)\right],$$

$$w_{20}(-r) = c\left[f_{20} + g_{20}(1 - 2e^{\omega^* ir}) - \frac{1}{3}\overline{g}_{02}(1 + 2e^{3\omega^* ir})\right],$$

where $c = [1 + 2\omega^*\sin(2\omega^* r) - 2i\omega^*\cos(2\omega^* r)]/(1 - 4\omega^*\sin(2\omega^* r) + 4\omega^{*2})$.

We now compute w_{11}. It is the solution of

$$\frac{d}{ds}w_{11}(s) = g_{11}e^{\omega^* is} + \overline{g}_{11}e^{-\omega^* is}.$$

By integrating between $-r$ and 0, we obtain

$$w_{11}(0) = w_{11}(-r) - \frac{i}{\omega^*} g_{11}(1 - e^{-\omega^* ir}) + \frac{i}{\omega^*} \overline{g}_{11}(1 - e^{\omega^* ir}).$$

The second relation is here

$$g_{11} + \overline{g}_{11} = -w_{11}(-r) + f_{11} \quad \Leftrightarrow \quad w_{11}(-r) = -g_{11} - \overline{g}_{11} + f_{11}.$$

It follows that

$$w_{11}(0) = g_{11} + \overline{g}_{11} - f_{11} - \frac{i}{\omega^*} g_{11}(1 - e^{-\omega^* ir}) + \frac{i}{\omega^*} \overline{g}_{11}(1 - e^{\omega^* ir}).$$

Now we have all the elements for determining f_{21} by formula (4.18), and then we can compute

$$g_{21} = \Psi_1(0) f_{21}.$$

and after that, the first Lyapunov coefficient, that determines the stability properties of the periodic orbit emerged by Hopf bifurcation.

The above indicated computations, are easy to perform with a computing program (Maple e.g.), for a given Hopf bifurcation point, i.e. if all the parameters are known. If we try to make the computations with all parameters non-determined, we are lead to very complicated expressions that can not be handled even by the program Maple itself, and that can not be analyzed theoretically.

4.5. An example

In order to provide an example, we choose the following "strategy"for finding Hopf bifurcation points. We choose n^*, β_0^*, δ^*, k^*, in a zone of parameters acceptable from biological point of view. With this values of the parameters we can compute B_1^*, (the value of B_1 at these parameters values), $p^* = \delta^* + B_1^*$, $q^* = k^* B_1^*$, and determine ω^* and r^* such that a Hopf bifurcation actually takes place. That is we set $\omega^* = \sqrt{(q^*)^2 - (p^*)^2}$, $r^* = \arccos(p^*/q^*)/\omega^*$. Once r^* determined, we can also compute γ^*.

As above, we choose one of the parameters a_j to be the variable one and check the condition that the curve $\lambda_1(a_j)$ actually crosses the imaginary axis in the complex plane, when a_j varies around a_j^*. This can be done by example by differentiating relations (3.1) with respect to a_j and by solving the obtained system of equations with respect to $\mu'(a_j^*)$, $\omega'(a_j^*)$.

The example. We consider the following selection of parameters:

$$n^* = 12,\ \beta_0^* = 1.77,\ \delta^* = 0.05,\ k^* = 1.180746972\,(\Leftrightarrow \gamma^* r^* = 0.527).$$

These parameters were chosen in the zone of biological interest, as can be seen in [8].

We find then $x_2 = 1.150859618$, $B_1^* = -2.524121872$, $p^* = \delta^* + B_1^* = -2.474121872$, $q^* = k^* B_1^* = -2.980349005$, $\omega^* = \sqrt{q^{*2} - p^{*2}} = 1.661686238$,
$r^* = \arccos(p^*/q^*)/\omega^* = .3559207407$, $\gamma^* = 1.48067$.

We choose to vary r and, by differentiating the relations (3.1) with respect to r find that $\mu'(r^*) = 25.66$.

The first Lyapunov coefficient is easily computed since all the parameters are known, by following the algorithm in the previous subsection. We get

$$1_1(r^*) = -87.387.$$

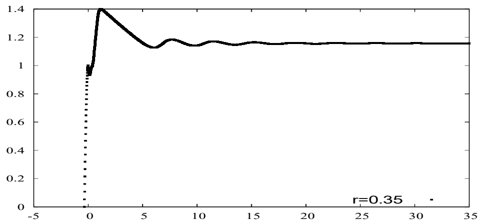
Thus the normal form of the restriction of the equation to the unstable and to the center manifold is (by (4.16))

$$\frac{d}{dt}u = (\beta(r) + i)u - u|u|^2,$$

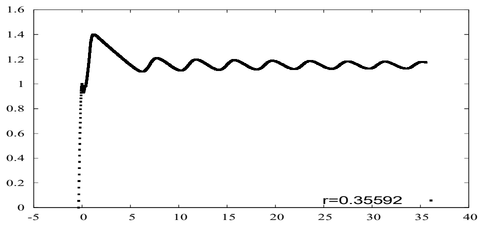
with $\beta(r) = \frac{\mu(r)}{\omega(r)}$ and $\beta(r^*) = 0$. The normal form in polar coordinates is

$$\begin{cases} \dot{\rho} = (\beta(r) - \rho^2)\rho, \\ \dot{\theta} = 1. \end{cases}$$

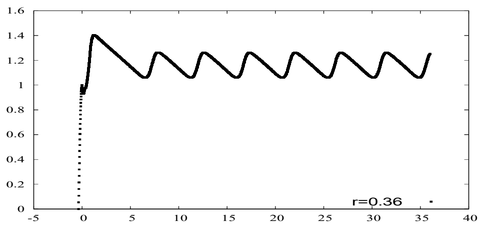
We are interested in the behavior of the solutions on a small neighborhood of r^*. Since $\mu'(r^*) > 0$, on such a neighborhood $r < r^* \Rightarrow \mu(r) < 0 \Rightarrow \beta(r) < 0$, and only the equilibrium solution $z = 0 \Leftrightarrow x = x_2$ exists, and it is stable, while $r > r^* \Rightarrow \mu(r) > 0 \Rightarrow \beta(r) > 0$. Thus a stable periodic solution exists for $r > r^*$.



a) r=0.35.



b) r=0.35592.



c) r=0.36.

Fig.1) Trajectories obtained by numerical integration of eq. (1.1) for initial condition $\varphi(s) = cos(\frac{\pi}{2r}s)$ for r around the Hopf bifurcation value r^*.

These assertions seem in contradiction with the condition of stability (2.2). Actually there is no contradiction. The function h defined in (2.4) satisfies, for the chosen parameters values, $h(r^*) = 0$ and $\frac{dh}{dr}(r^*) = -20.236$. Thus, $r < r^* \Rightarrow h(r) > 0$ and the equilibrium point x_2 is stable, while for $r > r^*$, $h(r) < 0$ and the equilibrium point is unstable.

The numerical integration confirms our theoretical analysis, as the figures above show.

References

1. N. D. Hayes, Roots of the transcendental equation associated with a certain difference-differential equation, J. London Math. Soc., 1950, 226-232.

2. T. Faria, Normal forms for RFDE in finite dimensional spaces -section 8.3 of J. Hale, L.T. Magalhaez, W. Oliva, Dynamics in infinite dimensions, Applied Mathematical Sciences, 47, Springer, 2002.

3. J. Hale, S. M. Verduyn Lunel, Introduction to functional differential equation, Springer, Berlin, 2003.

4. A. V. Ion, On the Bautin bifurcation for systems of delay differential equations, Acta Univ. Apulensis, 8(2004), 235-246 (Proc. of ICTAMI 2004, Thessaloniki, Greece);

5. A. V. Ion, An example of Bautin-type bifurcation in a delay differential equation, J. Math. Anal. Appl., 329(2007), 777-789.

6. A. V. Ion, New results concerning the stability of equilibria of a delay differential equation modeling leukemia, submitted to publication.

7. Y. A. Kuznetsov, Elements of applied bifurcation theory, Springer, New York, 1995.

8. L. Pujo-Menjouet, M. C. Mackey, Contribution to the study of periodic chronic myelogenous leukemia, C. R. Biologies, 327(2004), 235-244.

9. L. Pujo-Menjouet, S. Bernard, M. C. Mackey, Long period oscillations in a G_0 model of hematopoietic stem cells, SIAM J. Applied Dynamical Systems, 2, 4(2005), 312-332.

10. G. Mircea, M. Neamţu, D. Opriş, Dynamical systems from economy, mechanics, biology, described by delay equations, Mirton, Timişoara, 2003 (in Romanian).

Accepted: 17.08.2009