STABILITY OF LIMIT CYCLES IN A CALCIUM OSCILLATIONS DYNAMICS MODEL

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Abstract The stability of the limit cycles of a nonlinear delay system of ordinary differential equations is studied. The system is a model proposed by Borghans in 1997 [2] describing calcium oscillations in nonexcitable cells. The unique positive equilibrium point of the associated dynamical system can lose its stability on the account of a Hopf bifurcation. We then investigate the stability of the bifurcating limit cycles by using the center manifold theorem.

Keywords: dynamical system, time delay, bifurcation, limit cycle.

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1. INTRODUCTION

This paper is devoted to the analysis of the nonlinear delay system of ordinary differential equations (SODE)

\[
\begin{align*}
\frac{dZ}{dt} &= -kZ(t) + V_0 + \beta V_1 + k_f Y(t) - V M_2 \frac{(Z(t))^2}{k_2^2 + (Z(t))^2} + V M_3 \frac{(Z(t))^m}{k_2^m(Z(t))^m} \frac{(Y(t))^2}{k_1^2 + (Y(t))^2} \frac{(A(t - \tau_0))^4}{k_A^4} \frac{(A(t - \tau_0))^4}{k_A^4} \\
\frac{dY}{dt} &= -k_f Y(t) + V M_2 \frac{(Z(t))^2}{k_2^2 + (Z(t))^2} - V M_3 \frac{(Z(t))^m}{k_2^m(Z(t))^m} \frac{(Y(t))^2}{k_1^2 + (Y(t))^2} \frac{(A(t - \tau_0))^4}{k_A^4} \frac{(A(t - \tau_0))^4}{k_A^4} \\
\frac{dA}{dt} &= \beta V M_4 - V M_3 \frac{(A(t - \tau_0))^p}{k_2^p(A(t - \tau_0))^p} \frac{(Z(t))^n}{k_3^n(A(t - \tau_0))^n} - \varepsilon A(t - \tau_0).
\end{align*}
\]

With the autonomous SODE (1.1) we associate the initial condition

\[Z(0) = Z_0, Y(0) = Y_0, A(\theta) = \varphi(\theta), \theta \in [-\tau, 0], \tau \geq 0,\]

where \(\varphi : [-\tau, 0] \to \mathbb{R}\) is a differentiable function which describes the behavior of the flow in the \(O\) direction.
These equations arise from a model of calcium oscillations dynamics. The non-delayed model was previously proposed and investigated by Houart et al. in [6]; it is based on the mechanism of Ca^{2+}-induced Ca^{2+}-release, that takes into account the Ca^{2+}-stimulated degradation of inositol 1,4,5-trisphosphate (InsP_3) by a 3-kinase. In the vast majority of cells, an external stimulus initiates the synthesis of InsP_3, starting an intracellular chain reaction, which culminates with the release of Ca^{2+} from an internal store of the cell, in the cytosol. Two mechanisms are responsible for calcium oscillation: the autocatalitic nature of Ca^{2+} release in the cytosol and the increased InsP_3 degradation, due to the Ca^{2+}-stimulated of the InsP_3 3-kinase.

The variables involved in the process are Z, Y and A, representing the concentration of free Ca^{2+} in the cytosol, in a certain internal pool of the cell, respectively the InsP_3 concentration.

The biological interpretation of the parameters is as follows: \( V_0 \) refers to a constant input of Ca^{2+} from the extracellular medium and \( V_1 \) is the maximum rate of stimulus-induced influx of Ca^{2+} from the extracellular medium. Parameter \( \beta \) reflects the degree of stimulation of the cell by an agonist. The rates \( V_2 \) and \( V_3 \) refer, respectively, to pumping of cytosolic Ca^{2+} into the internal stores and to the release of Ca^{2+} from these stores into the cytosol in a process activated by citosolic calcium (CICR); \( V_{M2} \) and \( V_{M3} \) denote the maximum values of these rates. Parameters \( k_2 \), \( k_Y \), \( k_z \) and \( k_A \) are threshold constants for pumping, release, and activation of release by Ca^{2+} and by InsP_3; \( k_f \) is a rate constant measuring the passive, linear leak of Y into Z; \( k \) relates to the assumed linear transport of citosolic calcium into the extracellular medium; \( V_{M4} \) is the maximum rate of stimulus-induced synthesis of InsP_3. \( V_5 \) is the rate of phosphorylation of InsP_3 by the 3-kinase; \( V_{M5} \) is the maximum value of this rate, while \( k_5 \) is a half-saturation constant. \( m \), \( n \) and \( p \) are Hill coefficients related to the cooperative processes and \( \varepsilon \) is the phosphorylation rate of InsP_3 by the 5-phosphatase.

The study of the Hopf bifurcation was previously performed in [13] for three sets of values of the parameters, namely the set for which the oscillations exhibit chaotic behaviour, bursting behaviour, respectively birithmetic. We proved that in the case when the perturbation \( A(t - \tau) \) is obtained via the Dirac distribution, the calcium oscillations model may undergo a Hopf bifurcation for some critical value of the time delay \( \tau = \tau_0 \). We further develop only the "bursting" case, that is, we consider the following values of the parameters

\[
\begin{align*}
\beta &= 0.46, \quad n = 2, \quad m = 4, \quad p = 1, \quad K_2 = 0.1\mu M, \quad k_5 = 1\mu M, \\
k_A &= 0.1\mu M, \quad k_d = 0.6\mu M, \quad k_Y = 0.2\mu M, \\
k_z &= 0.3\mu M, \quad k = 0.1667s^{-1}, \quad k_f = 0.0167s^{-1}, \quad \varepsilon = 0.0167s^{-1}, \\
V_0 &= 0.0333\mu Ms^{-1}, \quad V_1 = 0.0333\mu Ms^{-1}, \quad V_{M2} = 0.1\mu Ms^{-1}, \\
V_{M3} &= 0.3333\mu Ms^{-1}, \quad V_{M4} = 0.0417\mu Ms^{-1}, \quad V_{M5} = 0.5\mu Ms^{-1}.
\end{align*}
\]
We mention that, in this case, using the Maple 8 software package, we find the equilibrium point \((Z^*, Y^*, A^*)=(0.2916496701; 0.2344675015; 0.1989819160)\), the eigenvalues \(\pm i\omega = \pm 0.08289718923\) and the bifurcation parameter \(\tau_0 = 21.25439515\). The existence of a Hopf bifurcation leads to the existence of a limit cycle when the bifurcation occurs; herein our aim is to show the stability of this limit cycle following the approach in [7].

2. STABILITY OF LIMIT CYCLES

Denote by \(\Lambda = \{\pm i\Omega_0\}\) the simple eigenvalues of the characteristic equation associated with the delayed SODE (for details, see [13]). Denote \(x(t) = (z(t), y(t), a(t))\). By the translation \(Z = z + Z^*, Y = y + Y^*, A = a + A^*\) the autonomous delay differential system (1) changes to

\[
\dot{x}(t) = X_i(z(t), y(t), a(t - \tau)),
\]

\(z(0) = Z_0 - Z^*, y_0 = Y_0 - Y^*, \varphi(\theta) = \varphi(0) - A^*, \tau \geq 0\), with the equilibrium point \((0,0,0)\). In order to characterize the orbits of the linearized delay-differential system, we can use the standard form

\[
\dot{x}_t(\theta) = Lx_t = \begin{cases} \frac{d}{dt}x_t(\theta), & \theta \in [-\tau, 0) \\ \int_{-\tau}^{0} [d\eta(\theta)]x_t(\theta), & \theta = 0 \end{cases}
\]

where

\[x_t \in \mathcal{B} = C'([-\tau, 0], \mathbb{R}^3), \quad x_t(\theta) = x(t + \theta), \theta \in [-\tau, 0).\]

The mapping \(\eta : [-\tau, 0] \rightarrow \mathbb{R}^3 \times \mathbb{R}^3\) is a matrix whose elements are functions with bounded variation and the Lebesgue-Stieltjes integral can be written as

\[
\int_{-\tau}^{0} [d\eta(\theta)]x_t(\theta) = N_1x(0) + N_2x(-\tau).
\]

The spectrum of the linear operator \(L\) coincides with the set of eigenvalues of the characteristic equation associated to the equilibrium point of the SODE.

Consider the linear operator \(L : \mathcal{B} \rightarrow \mathcal{B}, L\varphi = N_1\varphi(0) + N_2\varphi(-\tau)\), \(\varphi \in \mathcal{B}\), where

\[
N_1 = \begin{pmatrix} n_1 & n_1^4 & 0 \\ n_1^2 & -n_1^4 & 0 \\ n_1^3 & 0 & 0 \end{pmatrix}, \quad N_2 = \begin{pmatrix} 0 & 0 & n_2^1 \\ 0 & 0 & -n_2^1 \\ 0 & 0 & n_2^2 \end{pmatrix}
\]

and

\(n_1^1 = 0.38860527, \quad n_2^1 = -0.55530527, \quad n_2^3 = -0.08796881\),
\[ n_1^1 = 0.324091, \quad n_2^1 = -0.10314090, \quad n_2^2 = -0.08317366 \]

are the constitutive matrices of the linearized system. The operator \( A : B \to B^* \)
\[ A \phi(\theta) = \begin{cases} \frac{d\phi(\theta)}{d\theta}, & \theta \in [-\tau, 0] \\ N_1 \phi(0) + N_2 \phi(-\tau), & \theta = 0 \end{cases}, \phi \in B \]  
(4)
determines the adjoint operator \( A^* \psi(s) = \)
\[ \begin{cases} \frac{d\psi(s)}{ds}, & s \in [0, \tau] \\ \psi(0)N_1 + \psi(\tau_0)N_2, & s = 0 \end{cases}, \psi \in B^*, \]  
(5)
with respect to the bilinear form ("scalar product")
\[(\phi^*(s), \phi(\theta)) = \bar{\phi}^*(0)\phi(0) - \bar{\phi}^*(\tau)N_2 \int_0^\tau e^{-\xi \Omega_0} \phi(\xi) d\xi, \quad \theta \in [-\tau, 0], \quad s \in [0, \tau].\]

**Proposition 2.1** The following statements are true:

(i) the generalized eigenvectors of the infinitesimal generators \( A \) and \( A^* \),
corresponding to the proper eigen \( \Lambda \), are
\[
\phi(\theta) = (f_1, f_2, f_3)^T e^{i\Omega_0 \theta}, \quad \bar{\phi}(\theta) = (\bar{f}_1, \bar{f}_2, \bar{f}_3)^T e^{-i\Omega_0 \theta}, \quad \theta \in [0, \tau_0] \]
(6)

\[ f_1 = 0.151551 - i 0.172126, \quad f_2 = 0.497684 - i 0.132631, \]
\[ f_3 = -0.763963 - i 1.018165 \]
respectively,
\[
\phi^*(s) = (f_1^*, f_2^*, f_3^*) e^{i\Omega_0 s}, \quad \bar{\phi}^*(s) = (\bar{f}_1^*, \bar{f}_2^*, \bar{f}_3^*) e^{-i\Omega_0 s}, \quad s \in [0, \tau_0], \]
(7)

\[ f_1^* = -0.536353 + i 0.373245, \quad f_2^* = -0.413810 + i 0.479090, \]
\[ f_3^* = 0.594553 - i 0.870017; \]

(ii) the bilinear form \((\cdot, \cdot) : M_\Lambda(A^*) \times B \to C\), with \( \Lambda = \{ \pm i \Omega_0 \} \) is defined by
\[
(\phi^*(s), \phi(\theta)) = \bar{f}_1^* \phi_1(0) + \bar{f}_2^* \phi_2(0) + \bar{f}_3^* \phi_3(0) - \alpha_0 F(\phi_3)(-\tau_0),
\]
\[
(\bar{\phi}^*(s), \phi(\theta)) = f_1^* \phi_1(0) + f_2^* \phi_2(0) + f_3^* \phi_3(0) - \bar{\alpha}_0 F(\phi_3)(-\tau_0),
\]
\[ s \in [0, \tau_0], \quad \phi \in B, \quad \theta \in [-\tau_0, 0], \alpha_0 = 0.072121 - i 0.049286, \]
(8)

where \( M_\Lambda(A^*) \) is the generalized vector space of \( A^* \) and
\[ F(\phi_3)(-\tau_0) = \int_0^{-\tau_0} e^{-i \Omega_0 \xi} \phi(\xi) d\xi; \]
(9)
(iii) the generalized eigenvectors of $\phi^*(s), \bar{\phi}^*(s)$ and $\phi(\theta), \bar{\phi}(\theta)$ satisfy the relations

\[
\begin{align*}
(\phi^*(s), \phi(\theta)) &= r_1, \\
(\bar{\phi}^*(s), \phi(\theta)) &= r_2, \\
(\phi^*(s), \bar{\phi}(\theta)) &= \bar{r}_2, \\
(\phi^*(s), \bar{\phi}(\theta)) &= \bar{r}_1, 
\end{align*}
\] (10)

where $r_1 = -2.058522 - i 2.065137$, $r_2 = -1.441408 - i 1.972671$;

(iv) the vectors

\[
\begin{align*}
\psi(s) &= f_{11} \phi^*(s) + \bar{f}_{12} \bar{\phi}^*(s) \\
\bar{\psi}(s) &= f_{12} \phi^*(s) + \bar{f}_{11} \bar{\phi}^*(s), \quad s \in [0, \tau_0],
\end{align*}
\] (11)

are generalized eigenvectors of the operator $A^*$. They satisfy the relations

\[
\begin{align*}
(\psi(s), \phi(\theta)) &= 1, \quad (\psi(s), \bar{\phi}(\theta)) = 0, \\
(\bar{\psi}(s), \phi(\theta)) &= 0, \quad (\bar{\psi}(s), \bar{\phi}(\theta)) = 1, \quad \theta \in [-\tau, 0], \quad s \in [0, \tau_0].
\end{align*}
\] (12)

The bilinear form is associated to the linearized delay differential system. The numbers $f_{ij}$ are the entries of the matrix $F$, the inverse of the matrix $E = (e_{ij})_{i,j=1,2}$, where

\[
e_{11} = (\phi^*(s), \phi(\theta)), \quad e_{12} = (\bar{\phi}^*(s), \phi(\theta)), \quad e_{21} = \bar{e}_{12}, \quad e_{22} = \bar{e}_{11}.
\]

**Proof.** (i) The generalized eigenvectors of $A$, corresponding to $\Lambda$ are

\[
\phi(\theta) = \phi(0) e^{i \Omega_0 \theta}, \quad \bar{\phi}(\theta) = \bar{\phi}(0) e^{-i \Omega_0 \theta},
\] (13)

where $\phi(0)$ is a nonzero solution of the following linear system

\[
(i \Omega_0 I - N_1 - e^{i \Omega_0 \tau_0} N_2) \phi(0) = 0.
\] (14)

Replacing $N_1$ and $N_2$ by their expressions (2) and using the software package Maple 8, we find

\[
\phi(0) = (f_1, f_2, f_3)^T,
\] (15)

where $f_1 = -0.151551 - i 0.172126$, $f_2 = 0.497684 - i 0.132631$ and $f_3 = -0.763963 - i 1.018165$.

From (14) and (12) it follows (5). For the operator $A^*$, the generalized eigenvectors corresponding to $\Lambda$ are

\[
\phi^*(s) = \phi^*(0) e^{i \Omega_0 s}, \quad \bar{\phi}^*(s) = \bar{\phi}^*(0) e^{-i \Omega_0 s}, \quad s \in [0, \tau_0],
\] (16)
where $\phi^*(0)$ is a nonzero solution of the following linear system
\begin{equation}
\phi^*(0)(i\Omega_0 I - N_1 - e^{i\Omega_0 \tau_0} N_2) = 0.
\end{equation}

After computations we get
\begin{equation}
\phi^*(0) = (f_1^*, f_2^*, f_3^*),
\end{equation}
where $f_1^* = -0.536353 + i 0.373245$, $f_2^* = -0.413810 + i 0.479090$ and $f_3^* = 0.594553 - i 0.870017$.

(ii) The definition of the bilinear form implies
\begin{align}
(\phi^*(s), \varphi(\theta)) &= \bar{f}_1^* \varphi_1(0) + \bar{f}_2^* \varphi_2(0) + \bar{f}_3^* \varphi_3(0) - \\
&- e^{i\Omega_0 \tau_0}[(f_1^* - \bar{f}_2^*) n_1^2 + f_3^* n_2^2] F(\varphi_3)(-\tau_0) \\
&= \bar{f}_1^* \varphi_1(0) + \bar{f}_2^* \varphi_2(0) + \bar{f}_3^* \varphi_3(0) - \alpha_0 F(\varphi_3)(-\tau_0), \\
&\alpha_0 = 0.072121 - i 0.049286,
\end{align}
\begin{align}
(\bar{\phi}^*(s), \varphi(\theta)) &= \bar{f}_1^* \varphi_1(0) + \bar{f}_2^* \varphi_2(0) + \bar{f}_3^* \varphi_3(0) - \\
&- e^{-i\Omega_0 \tau_0}[(f_1^* - \bar{f}_2^*) n_1^2 + f_3^* n_2^2] F(\varphi_3)(-\tau_0) \\
&= f_1^* \varphi_1(0) + f_2^* \varphi_2(0) + f_3^* \varphi_3(0) - \alpha_0 F(\varphi_3)(-\tau_0).
\end{align}

In conclusion, we get the relation (7).

(iii) From (7), for $\varphi(\theta) = \phi(\theta)$, we have
\begin{align}
(\phi^*(s), \phi(\theta)) &= \bar{f}_1^* \phi_1(0) + \bar{f}_2^* \phi_2(0) + \bar{f}_3^* \phi_3(0) - \alpha_0 \int_0^{-\tau_0} e^{-i\Omega_0 \xi} f_2 e^{i\Omega_0 \xi} d\xi = \\
&= \bar{f}_1^* f_1 + \bar{f}_2^* f_2 + \bar{f}_3^* f_3 + \alpha_0 \tau_0 f_3 = r_1, \quad r_1 = -2.058522 - i 2.065137.
\end{align}

\begin{align}
(\bar{\phi}^*(s), \phi(\theta)) &= f_1^* \bar{f}_1 + f_2^* \bar{f}_2 + f_3^* \bar{f}_3 + \alpha_0 \tau_0 \bar{f}_3 = r_2, \quad r_2 = -1.441408 - i 1.972671.
\end{align}

\begin{align}
(\phi^*(s), \bar{\phi}(\theta)) &= \bar{f}_1^* \bar{f}_1 + \bar{f}_2^* \bar{f}_2 + \bar{f}_3^* \bar{f}_3 + \alpha_0 \tau_0 \bar{f}_3 = (\phi^*(s), \phi(\theta)) \\
(\bar{\phi}^*(s), \bar{\phi}(\theta)) &= f_1^* f_1 + f_2^* f_2 + f_3^* f_3 + \alpha_0 \tau_0 f_3 = (\bar{\phi}^*(s), \phi(\theta)).
\end{align}

These lead to the relation (9).

(iv) Because the function $(\cdot, \cdot)$ is bilinear and $EF = I$, we have the relations
\begin{align}
(\psi^*(s), \phi(\theta)) &= f_{11}(\phi^*(s), \phi(\theta)) + \bar{f}_{12}(\bar{\phi}^*(s), \bar{\phi}(\theta)) = f_{11} e_{11} + f_{21} e_{12} = 1 \\
(\bar{\psi}^*(s), \bar{\phi}(\theta)) &= f_{11}(\phi^*(s), \bar{\phi}(\theta)) + \bar{f}_{12}(\bar{\phi}^*(s), \bar{\phi}(\theta)) = f_{11} e_{21} + f_{21} e_{22} = 0 \\
(\bar{\psi}^*(s), \phi(\theta)) &= (\psi^*(s), \phi(\theta)) = 0 \\
(\bar{\psi}^*(s), \bar{\phi}(\theta)) &= (\psi^*(s), \bar{\phi}(\theta)) = 1.
\end{align}
Let $N = M_A(A)$ be the vector space generated by the generalized eigenvectors $\Phi, \bar{\Phi}$.

**Definition 2.1** A submanifold $W_{\text{loc}}^r(0) = W^r(0, V)$ in the Banach space $B$, tangent at $0 \in B$ to the vector space $N$ and invariant with respect to the semigroup of operators $T(t)$ of the delayed system (1), where $V$ is an open set with $0 \in V \subset B$, is called stable-unstable local centre manifold of the system (1).

In the sequel, let us denote the nonlinear part of the system (1) by $F(x(t), x(t-\tau)) = X(x(t), x(t-\tau)) - N_1x(t) - N_2x(t-\tau)$, where $\dot{x} = X(x)$, $x = (z, y, a)^T$ is the vector field given by the relation (1). Using the Taylor formula of order three at the point $(0,0,0)$, the autonomous delay differential system (1) can be written as

$$
\begin{align*}
\dot{x}(t) &= N_1x(t) + N_2x(t-\tau_0) + P(x(t), x(t-\tau_0)) + O_1(|x(t)|^4), \\
x(t) &= (z(t), y(t), a(t)),
\end{align*}
(19)
$$

where $P$ is the vector whose components are Taylor polynomials of degrees two or three of the vector $F$ and has the form $P(x(t), x(t-\tau)) = (P_1(z(t), y(t), a(t-\tau)), P_2(z(t), y(t), a(t-\tau)), P_3(z(t), a(t-\tau)))^T$, where

$$
\begin{align*}
P_1(z(t), y(t), a(t-\tau)) &= -0.537512z(t)^2 + 2.226838z(t)y(t) + \\
&+ 0.747183a(t-\tau)z(t) - 0.862223y(t)^2 + 0.3708534a(t-\tau)y(t) - \\
&- 1.171530a(t-\tau)^2 - 9.088956z(t)^2 - 2.956420z(t)^2y(t) - \\
&- 0.991983a(t-\tau)z(t)^2 - 6.246203z(t)y(t)^2 + 2.684263a(t-\tau)z(t)y(t) - \\
&- 8.486912a(t-\tau)^2z(t) + 1.020635y(t)^3 - 1.039337a(t-\tau)y(t)^2 - \\
&- 4.208734a(t-\tau)^2y(t) + 10.050654a(t-\tau)^3 \\
P_2(z(t), y(t), a(t-\tau)) &= -P_1(z(t), y(t), a(t-\tau)), \\
P_3(z(t), a(t-\tau)) &= -0.035519z(t) - 0.368724a(t-\tau)z(t) + \\
&+ 0.05541a(t-\tau)^2 - 0.244208z(t)^3 - 0.148882a(t-\tau)z(t) + \\
&+ 0.307531a(t-\tau)^2z(t) - 0.046240a(t-\tau)^3
\end{align*}
$$

Introduce the function

$$
\begin{align*}
w(\theta, z_c, \bar{z}_c) &= w_{20}(\theta) \frac{z_c^2}{2} + w_{11}(\theta)z_c\bar{z}_c + w_{02}(\theta)\frac{\bar{z}_c^2}{2} + O_1(|z_c|^3), \\
w_{02} &= \bar{w}_{20}(\theta), w_{11}(\theta) \in \mathbb{R}, \theta \in [-\tau, 0].
\end{align*}
$$

Replacing, in $P(x(t), x(t-\tau))$, by $z_c\phi(0) + \bar{z}_c\bar{\phi}(0) + w(0, z_c, \bar{z}_c)$ and $x(t-\tau)$
by 

\[ z_c \phi(-\tau) + \bar{z}_c \bar{\phi}(-\tau) + w(-\tau, z_c, \bar{z}_c), \]

we find

\[ F(z_c, \bar{z}_c) = F_{20} \frac{z_c^2}{2} + F_{11} z_c \bar{z}_c + F_{02} \frac{z_c^2}{2} + F_{21} \frac{z_c^2 \bar{z}_c^2}{2}, \]

where

\[
\begin{align*}
F_{20} &= \begin{pmatrix} F_{20}^1 \\ -F_{20}^2 \\ F_{20}^3 \end{pmatrix}, \\
F_{11} &= \begin{pmatrix} F_{11}^1 \\ -F_{11}^2 \\ F_{11}^3 \end{pmatrix}, \\
F_{02} &= \begin{pmatrix} F_{02}^1 \\ -F_{02}^2 \\ F_{02}^3 \end{pmatrix}, \\
F_{21} &= \begin{pmatrix} F_{21}^1 \\ -F_{21}^2 \\ F_{21}^3 \end{pmatrix}.
\end{align*}
\]

By extracting from expansion of \( F \) the coefficients of the terms \( \frac{z_c^2}{2}, \frac{z_c \bar{z}_c}{2}, \frac{z_c^2}{2} \) respectively \( \frac{z_c^2 \bar{z}_c^2}{2} \), we find

\[
\begin{align*}
F_{20}^1 &= -1.137957 + i 3.464395, & F_{20}^3 &= -0.010181 + i 0.041143, \\
F_{11}^1 &= -3.981737 - i 1.600830, & F_{11}^3 &= 0.035900 - i 0.014433, \\
F_{02}^1 &= 1.576785 - i 3.287968, & F_{02}^3 &= 0.021130 - i 0.036741, \\
F_{21}^1 &= -108.851161 + i 11.064876 - (1.444304 + i 1.706172) w_{11}^2 - (1.606180 - i 2.701638) w_{11}^2 + (5.042470 + i 2.815720) w_{11}^2 - (0.988250 - i 0.522131) w_{20}^2 - (0.241235 + i 1.552891) w_{20}^2 + (1.814090 + i 2.246725) w_{20}^2, \\
F_{21}^3 &= -0.068091 + i 0.020966 + (0.872300 - i 0.426980) w_{11}^2 - (0.108014 - i 0.037829) w_{20}^2 + (0.325032 - i 0.360775) w_{20}^2 + (0.043053 + i 0.037695) w_{20}^2.
\end{align*}
\]

**Proposition 2.2** The following statements are true:

(i) the central manifold \( W^c_{loc}(0) \) of the system (1) has the elements \( \tilde{\phi} \in B \),

where

\[
\tilde{\phi}(\theta) = z_c \phi(\theta) + \bar{z}_c \bar{\phi}(\theta) + w_{20}(\theta) \frac{z_c^2}{2} + w_{11}(\theta) z_c \bar{z}_c + w_{02}(\theta) \frac{z_c^2}{2} + \ldots, \theta \in [-\tau, 0]
\]

where \( z_c = x_1 + i y_1 \), \( (x_1, y_1) \in V_1 \subset \mathbb{R}^2 \), \( V_1 \) is a neighborhood of zero and

\[
\begin{align*}
w_{20}(\theta) &= -\frac{g_{20}}{i \Omega} \phi(0) e^{i \Omega \theta} - \frac{g_{02}}{3 i \Omega} \phi(0) e^{-i \Omega \theta} + E_1 e^{2i \Omega \theta}, \\
w_{11}(\theta) &= \frac{g_{11}}{i \Omega} \phi(0) e^{i \Omega \theta} - \frac{g_{11}}{i \Omega} \bar{\phi}(0) e^{-i \Omega \theta} + E_2, \quad \theta \in [-\tau_0, 0], \\
w_{02}(\theta) &= w_{20}(\theta),
\end{align*}
\]
$g_{20} = 0.302874 + i 0.912785$
$g_{11} = -1.079822 + i 0.272609$
$g_{02} = -0.171742 - i 0.947895$
$g_{21} = -40.208575 + i 35.475448 + (0.032165 - i 1.7317770)w_{11} +
+0.064066 + i 0.764149)w_{12} + (0.514234 - i 1.094785)w_{13} +
+(0.722945 + i 0.294077)w_{20} - (0.268046 + i 0.274150)w_{21} +
+(0.579122 + i 0.194816)w_{22}$, \hspace{1cm} \hspace{1cm} (22)

where
$$w_{20} = (w_{20}^1, w_{20}^2, w_{20}^3)^T, \quad w_{11} = (w_{11}^1, w_{11}^2, w_{11}^3)^T,$$
$$E_1 = \begin{pmatrix}
-22.833534 - i 15.188009 \\
38.104506 - i 7.770249 \\
2.614298 - i 11.178749
\end{pmatrix}, \hspace{1cm} (23)$$
$$E_2 = \begin{pmatrix}
12.423192 + i 4.994660 \\
-0.431636 - i 0.173536
\end{pmatrix}.$$

(ii) if the initial condition of (1) is
$$\hat{\phi}(\theta) = (\psi, \varphi_1)\phi(\theta) + (\psi, \varphi_1)\phi(\theta) + w_{20}(\theta)^2 + 
\frac{w_{11}(\theta)(\psi, \varphi_1)^2}{2} + w_{02}(\psi, \varphi_1)^2,$$ \hspace{1cm} (24)

then the solution of autonomous delay differential system (1) in a neighborhood of the equilibrium point $(0,0,0)$ is (25):
$$\begin{cases}
z'(\theta) = 2x_1 Re (f_1) - 2y_1 Im (f_1) + r_{20}^1 (x_1^2 - y_1^2) - i_{20}^1 x_1 y_1 + r_{11}^1 (x_1^2 + y_1^2) \\
y'(\theta) = 2x_1 Re (f_2) - 2y_1 Im (f_2) + r_{20}^2 (x_1^2 - y_1^2) - i_{20}^2 x_1 y_1 + r_{11}^2 (x_1^2 + y_1^2) \\
a'(\theta) = 2x_1 Re (f_3) - 2y_1 Im (f_3) + r_{20}^3 (x_1^2 - y_1^2) - i_{20}^3 x_1 y_1 + r_{11}^3 (x_1^2 + y_1^2)
\end{cases}\hspace{1cm}\hspace{1cm}(25)$$

where
$$r_{20}^k = Re (w_{20}^k(0)), \quad i_{20}^k = Im (w_{20}^k(0)), \quad r_{11}^k = w_{11}^k(0), \quad \forall k = 1, 3 \hspace{1cm} (26)$$

and $(x_1(t), y_1(t))$ is the solution of the differential equation
$$\begin{cases}
\dot{z}_c(t) = i\Omega_0 z_c(t) + \frac{g_{20}}{2} z_c(t)^2 + g_{11} z_c(t)\tilde{z}_c(t) + \frac{g_{02}}{2} \tilde{z}(t)^2 + \frac{g_{21}}{2} z(t)^2 z(t) \\
z_c(0) = x_1(0) + iy_1(0)\hspace{1cm}\hspace{1cm}(27)
\end{cases}$$
where
\[ x(0) = \text{Re}(\psi, \varphi_1), \quad y(0) = \text{Im}(\psi, \varphi_1) \]
\[ \varphi_1(t) = (Z_0 - Z^*, Y - Y^*, \varphi(\theta) - A^*)^T. \] (28)

**Proof.** (i) We use the following relations
\[ E_1 = -(N_1 + e^{-2i\Omega_0}N_2 - 2i\Omega_0 I)^{-1}F_{20}, \quad E_2 = -(N_1 + N_2)^{-1}F_{11}. \]
\[ g_{20} = \bar{\psi}(0)F_{20}, \quad g_{11} = \bar{\psi}(0)F_{11}, \quad g_{02} = \bar{\psi}(0)F_{02}, \quad g_{21} = \bar{\psi}(0)F_{21}, \]
where
\[ \bar{\psi}(0) = f_{12}\phi_x(0) + f_{22}\phi_y(0) \]
is one of the eigenvectors of $A^*$ (see Proposition 2.1 (iv))
(ii) The solution of autonomous delay differential system (1) in a neighborhood of the equilibrium point $(0,0,0)$ is
\[
\begin{align*}
(z(\tilde{\phi}))(t) &= z_c(t)f_1 + \tilde{z}_c(t)f_1 + \frac{1}{2}z_c(t)^2\omega^1_{20}(0) + z_c(t)\tilde{z}_c(t)\omega^1_{11}(0) + \frac{1}{2}\tilde{z}_c(t)^2\omega^1_{02}(0) \\
y(\tilde{\phi}))(t) &= z_c(t)f_2 + \tilde{z}_c(t)f_2 + \frac{1}{2}z_c(t)\omega^2_{20}(0) + z_c(t)\tilde{z}_c(t)\omega^2_{11}(0) + \frac{1}{2}\tilde{z}_c(t)\omega^2_{02}(0) \\
a(\tilde{\phi}))(t) &= z_c(t)f_3 + \tilde{z}_c(t)f_3 + \frac{1}{2}z_c(t)\omega^3_{20}(0) + z_c(t)\tilde{z}_c(t)\omega^3_{11}(0) + \frac{1}{2}\tilde{z}_c(t)\omega^3_{02}(0),
\end{align*}
\]
where $f_i, i = 1, 2, 3$ are given by (5). Replacing $z_c$ by $x_1 + iy_1$, we find (24).

**Remark 2.1.** Let $R_{20} = \text{Re}(g_{20}), I_{20} = \text{Im}(g_{20}), R_{11} = \text{Re}(g_{11}), I_{11} = \text{Im}(g_{21}), R_{21} = \text{Re}(g_{21}), I_{21} = \text{Im}(g_{21})$. The autonomous delay differential system (1) can be rewritten in the form
\[
\begin{align*}
\dot{x}_1(t) &= -\Omega_0x_1(t) + \frac{1}{2}(R_{20} + 2R_{11} + R_{02})x_1^2(t) - \\
&\quad - \frac{1}{2}(R_{20} - 2R_{11} + R_{02})y_1(t) + (I_{02} - I_{20})x_1(t)y_1(t) + \\
&\quad + R_{21}x_1(t)(x_1(t)^2 + y_1(t)^2) - I_{21}y_1(t)(x_1(t)^2 + y_1(t)^2), \\
\dot{y}_1(t) &= -\Omega_0x_1(t) + \frac{1}{2}(I_{20} + 2I_{11} + I_{02})y_1(t)^2 - \\
&\quad - \frac{1}{2}(I_{20} - 2I_{11} + I_{02})x_1(t)^2 + (R_{20} - R_{02})x_1(t)y_1(t) + \\
&\quad + R_{21}y_1(t)(x_1(t)^2 + y_1(t)^2) - I_{21}x_1(t)(x_1(t)^2 + y_1(t)^2), \\
x_1(0) &= \text{Re}(\psi, \varphi_1), \quad y_1(0) = \text{Im}(\psi, \varphi_1),
\end{align*}
\]
where $\varphi_1$ is given by (27).
Remark 2.2. The term $g_{21}$ depends explicitly on $w_{11}^1(0)$, $w_{11}^2(0)$, $w_{11}^3(0)$, $w_{20}^1(0)$, $w_{20}^2(0)$ and $w_{20}^3(\tau)$: using this and the relations (20) we find $g_{21} = -55.129357 + 4.070772$.

Remark 2.3. The limit cycle can be characterized by the following numbers

$$\mu_2 = -\frac{\text{Re}(C_1)}{\text{Re}(M)}, \quad T_2 = -\frac{-\text{Im}(C_1) + \mu_2 \text{Im}(M)}{\Omega_0}, \quad \beta_2 = 2\text{Re}(C_1), \quad (30)$$

where

$$C_1 = \frac{i}{2\Omega_0} \left(g_{20}g_{11} - 2|g_{11}|^2 - \frac{1}{3}|g_{02}|^2\right) + \frac{g_{21}}{2}$$

$$M = \left(\frac{d}{d\tau}\right)_{\tau = \tau_0, \omega = i\Omega_0}. \quad (31)$$

One knows from [5] that the following properties hold: if $\mu_2 > 0$ ($< 0$) then the Hopf bifurcation is supercritical (subcritical) and the bifurcating periodic solution exists for $\tau > \tau_0$ ($\tau < \tau_0$); the solutions are orbitally stable (unstable) if $\beta_2 > 0$ ($< 0$), and the bifurcating periodic solution increases (decreases) if $T_2 > 0$ ($< 0$).

Consider the values of the parameters as in the case of "bursting". Using Maple 8 programming techniques, we find $\mu_2 = 10587.6533$, $\beta_2 = -44.2353$ and $T_2 = -180.9126$. Hence, the unique Hopf bifurcation of the equation (1.1) seems to be supercritical and the solutions orbitally stable, with decreasing period.

Remark 2.4. The cycle of the dynamics of calcium oscillations with time-delay around the equilibrium point $(Z^*, Y^*, A^*)$ is given by

$$Z(\tilde{\varphi})(t) = z(\tilde{\varphi})(t) + Z^*, \quad Y(\tilde{\varphi})(t) = y(\tilde{\varphi})(t) + Y^*, \quad A(\tilde{\varphi})(t) = a(\tilde{\varphi})(t) + A^*,$$

where $z(\tilde{\varphi})(t), y(\tilde{\varphi})(t), a(\tilde{\varphi})(t)$ are given by Proposition 2.2.

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References


