LINEAR STABILITY OF DYNAMICAL SYSTEMS IN PHYSIOLOGY

Ileana Rodica Nicola, Vladimir Balan
Department Mathematics I, University Politehnica of Bucharest,
nicola_rodica@yahoo.com, vbalan@mathem.pub.ro

Abstract The SODE-modelled calcium variations in certain cell-types are investigated. The structural stability of hepatocyte physiology time-delayed flow is studied for three distinct cases (bursting, chaotic and quasiperiodic behavior), for the uniform and exponential distributions.

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1. INTRODUCTION

The SODE which describes the intra-cell calcium variation in time exhibits a very rich and complex dynamical behavior. An illustrative fact is the case when a time-delay imposed to one of the state variables leads to structural instability and Hopf bifurcations. In the present work, we investigate the dynamics of a mathematic biological model which describes the calcium variations in time in the living cell, while one of the state variables is delayed in time. The applicative biological aspects represent an important open question in the field, and are subject of further research.

The variables used in the present model for calcium variations are:

Z - the concentration of free Ca^{2+} in the cytosol;

Y - the concentration of free Ca^{2+} in the internal pool;

A - the $InsP_3$ concentration.

The time evolution of these variables is governed by the following SODE

$$\begin{cases} \dfrac{dZ}{dt} = & -k\cdot Z + V_0 + \beta\cdot V_1 + T \\ \dfrac{dY}{dt} = & -T \\ \dfrac{dA}{dt} = & \beta\cdot V_{M_4} - V_{M_5}\cdot \dfrac{A^p}{k_5^p + A^p}\cdot\dfrac{Z^n}{k_d^n + Z^n} - \varepsilon\cdot A, \end{cases} \tag{1}$$

where $T = k_f \cdot Y - V_{M_2} \cdot \dfrac{Z^2}{k_2^2 + Z^2} + V_{M_3} \cdot \dfrac{Z^m}{k_Z^m + Z^m} \cdot \dfrac{Y^2}{k_Y^2 + Y^2} \cdot \dfrac{A^4}{k_A^4 + A^4}$.

The parameters involved are: V_0, V_1, β, V_2, V_3, k_2, k_Y, k_Z, k_A, k_f, k, V_{M4}, V_{M_5}, m, n, p and ε, and are described in detail in [7], [6].

From biological point of view, this SODE is based on the mechanism of calcium release induced by calcium influenced by the inozitol 1,4,5-triphosphate (IP_3) degradation by a 3-kynase. This model may exhibit various types of variations as: explosion, chaos, quasi-periodicity, depending on the values assigned to the parameters.

2. THE TIME-DELAYED EVOLUTION FLOW

We shall study the biological flow when one variable coordinate is subject to time-delay. In our case, we assume this to be A - which denotes the concentration of inozitol, leaving still open the question of biological interpretations to their full extent.

In order to obtain the dynamical system with delayed argument in the dependent variable $A(t)$, it is known that for a given probability density $f : \mathbb{R} \to \mathbb{R}_+$ obeying $\int_0^\infty f(s)ds = 1$, the transformation (perturbation) of the state variable $A(t) \in \mathbb{R}$ dependent on f is the new variable $\tilde{A}(t)$ defined by

$$\tilde{A}(t) = \int_0^\infty A(t-s)f(s)ds = \int_{-\infty}^t A(s)f(t-s)ds. \tag{2}$$

Applying the time-delay process to A, one changes the system (1) into the new SODE

$$\begin{cases} \dfrac{dZ}{dt} = & -k \cdot Z(t) + V_0 + \beta \cdot V_1 + \tilde{T}(t), \\ \dfrac{dY}{dt} = & -\tilde{T}(t), \\ \dfrac{dA}{dt} = & \beta \cdot V_{M_4} - V_{M_5} \cdot \dfrac{\tilde{A}(t)}{k_5 + \tilde{A}(t)} \cdot \dfrac{Z(t)^2}{k_d^2 + Z(t)^2} - \varepsilon \cdot \tilde{A}(t), \end{cases} \tag{3}$$

where

$$\begin{aligned} \tilde{T}(t) = \quad & k_f \cdot Y(t) - V_{M_2} \cdot \frac{Z(t)^2}{k_2^2 + Z(t)^2} + \\ & + V_{M_3} \cdot \frac{Z(t)^4}{k_Z(t)^4 + Z(t)^4} \cdot \frac{Y(t)^2}{k_Y^2 + Y(t)^2} \cdot \frac{\tilde{A}(t)^4}{k_A^4 + \tilde{A}(t)^4}, \end{aligned}$$

with $Z(0) = Z_0, Y(0) = Y_0, A(\theta) = \varphi(\theta), \theta \in [-\tau, 0], \tau \geq 0$, where the transform $\tilde{A}(t)$ is defined by (2) and $\varphi : [-\tau, 0] \to \mathbb{R}$ is a differentiable function which describes the behavior of the flow in the O direction. In other words, the initial SODE is replaced by a differential-functional system.

The equilibrium points of the system (1) are obtained when the right side of the differential system (1) is set to zero. The resulting nonlinear system has in general several solutions; from physiological point of view only the positive ones can be accepted. We denote such a solution as (Z^*, Y^*, A^*). Regarding the linearization of the SODE (3) we have the following statement [7]

Proposition 1. *The following assertions hold:*

a) The linearized SODE of the differential autonomous system with delayed argument (3) at its equilibrium point (Z^*, Y^*, A^*) is $\dot{V}(t) = M_1 V(t) + M_2 V(t-\tau)$, where we have denoted by "dot" the t-differentation, $V(t) = {}^t(Z(t), Y(t), A(t))$ and

$$M_1 = \left.\begin{pmatrix} \frac{\partial f_1}{\partial Z} & \frac{\partial f_1}{\partial Y} & 0 \\ \frac{\partial f_2}{\partial Z} & \frac{\partial f_2}{\partial Y} & 0 \\ \frac{\partial f_3}{\partial Z} & \frac{\partial f_3}{\partial Y} & 0 \end{pmatrix}\right|_{(Z^*,Y^*,A^*)}, \qquad M_2 = \left.\begin{pmatrix} 0 & 0 & \frac{\partial f_1}{\partial A} \\ 0 & 0 & \frac{\partial f_2}{\partial A} \\ 0 & 0 & \frac{\partial f_3}{\partial A} \end{pmatrix}\right|_{(Z^*,Y^*,A^*)}$$

and (f_1, f_2, f_3) are the components of the field which provides the SODE (1).

b) The characteristic equation of the differential autonomous system with delayed argument (3) is

$$\det\left(\lambda I - M_1 - \int_0^\infty e^{-\lambda s} f(s) ds \cdot M_2\right) = 0. \tag{4}$$

Besides the Dirac distribution case, extensively studied in [7], two more notable distributions are worthy to consider: the uniform distribution and the gamma distribution. In these cases, the delayed A-component of the system has respectively the following forms:

1. If f is the *uniform distribution* of $\tau > 0$, i.e., $f(s) = \begin{cases} \frac{1}{\tau}, & 0 \le s \le \tau \\ 0, & s > 0 \end{cases}$, then $\tilde{A}(t) = \frac{1}{\tau}\int_{-\tau}^{0} A(t+s)ds$.

2. If f is the *gamma distribution* of $\tau > 0$, i.e., $f(s) = \frac{d^m}{\Gamma(m)} s^{m-1} e^{-ds}, s \ge 0, d > 0$, then $\tilde{A}(t) = \frac{d^m}{\Gamma(m)}\int_{-\infty}^{t} A(s)(t-s)^{m-1} e^{-d(t-s)} ds$. For $m = 1$, we obtain the *exponential distribution* and the delayed function respectively

$$f(s) = \frac{d}{\Gamma(1)} e^{-ds}, s \ge 0, d > 0, \text{ and } \widetilde{A}(t) = \frac{d}{\Gamma(1)}\int_{-\infty}^{t} A(s) e^{-d(t-s)} ds.$$

3. STABILITY RESULTS REGARDING THE DELAYED FLOW

Further we study the subcases when the SODE leads to explosion, chaos and quasiperiodicity. The first one was thoroughly investigated in [7], in the case of the Dirac distribution. For the three cases of parameter sets and for the two types of distributions described above, we further develop the basic results regarding the stability and bifurcation of the considered delayed SODE.

The three sets of values for parameters, corresponding to the subcases (explosion, chaos and quasiperiodicity) are provided in detail in the works [6], [7].
a) Explosion. In this case is known the following [7]

Proposition 2. *i) The only non-negative equilibrium point is*

$$(Z^*, Y^*, A^*) = (0.2916496701;\ 0.2344675015;\ 0.1989819160).$$

ii) The eigenvalues of the Jacobian matrix of the field at this point are

$$\{-0.07285104555, 0.02709536609 \pm i\ 0.2468748453\}; \tag{5}$$

iii) The constitutive matrices of the linearized delayed SODE (4) are

$$M_1 = \begin{pmatrix} 0.3886052798 & 0.3240919299 & 0 \\ -0.5553052794 & -0.3240919299 & 0 \\ -0.08796881783 & 0 & 0 \end{pmatrix}, \qquad M_2 = \begin{pmatrix} 0 & 0 & 0.103140906 \\ 0 & 0 & -0.103140906 \\ 0 & 0 & -0.08317366327 \end{pmatrix}.$$

b) Chaos. In this case we obtain:

Proposition 3. *i) The only non-negative equilibrium point is*

$$(Z^*, Y^*, A^*) = (0.3296040792; 0.7830862038; 0.1365437815);$$

ii) The eigenvalues of the Jacobian matrix of the field at this point are

$$\{-0.1767271957, 0.2753920311 \pm i0.9217492250\};$$

iii) The constitutive matrices of the linearized delayed SODE (4) are

$$M_1 = \begin{pmatrix} 0.1523424612 & 0.0423568326 & 0 \\ -0.3190424612 & -0.0423568326 & 0 \\ -0.03491470092 & 0 & 0 \end{pmatrix}, \quad M_2 = \begin{pmatrix} 0 & 0 & 0.513718989 \\ 0 & 0 & -0.513718989 \\ 0 & 0 & -0.2316344181 \end{pmatrix};$$

c) Quasiperiodicity. We obtain

Proposition 4. *i) The only equilibrium point of the SODE is*

$$(Z^*, Y^*, A^*) = (0.3016376725; 0.6476260612; -0.5077053483);$$

We obtained a negative solution which can not be acceptable from a physiological point of view.

ii) The eigenvalues of the Jacobian matrix of the field at this point are

$$\{-0.1767271957, 0.2753920311 \pm i0.9217492250\}.$$

In the following we examine the two distribution cases with the parameter sets corresponding to the subcases a) and b).

1-a) The uniform distribution-explosion subcase. In this case $\widetilde{A}(t) = \frac{1}{\tau}\int_{-\tau}^{0} A(t+s)ds$, and the equation (4) becomes

$$\det\left(\lambda I - M_1 - \frac{1-e^{-\lambda\tau}}{\lambda\tau}M_2\right) = 0. \tag{6}$$

Following the same steps like in the case of Dirac distribution, we obtain that there exist no solutions for the bifurcation parameter τ_0.

1-b) The uniform distribution-chaos subcase. In this case $\widetilde{A}(t) = \frac{1}{\tau}\int_{-\tau}^{0} A(t+s)ds$ and the equation (4) becomes (6). Following the same steps like in the case of the Dirac distribution, we obtain that there exists no solution for the equation (6) for $u = 0$ in terms of τ_0 and ω_0.

2-a) The exponential distribution-explosion subcase. In this case the equation (4) becomes

$$\det\left(\lambda I - M_1 - \frac{d}{\lambda + d}M_2\right) = 0. \tag{7}$$

Using the graphic package Maple 8, we obtain that there exists no solution for the equation (7) for $u = 0$ in terms of τ_0 and ω_0.

2-b) The case of exponential distribution-chaos subcase. In this case the equation (4) becomes (7). Using the graphic package Maple 8, we obtain that there exists no solution for the equation (6) for $u = 0$ in terms of τ_0 and ω_0.

In the cases pointed out by Propositions 2 and 3, the initial dynamical SODE becomes subject to the Hopf bifurcation theorem ([13]). Further considerations on this issue can be found in [6] and [7].

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