Hopf bifurcations for time-delayed intra-cell Calcium variation models

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Abstract

The paper investigates the Hopf bifurcations of hepatocyte physiology time-delayed flow for three distinct cases: bursting (explosive), chaotic and quasiperiodic behavior, for three distributions (Dirac, uniform and exponential).In the first section we describe a three-dimensional system which models the Ca oscillations in the living cells. This model was proposed by Borghans et. al in[2]. In the second section, it is shown that the system obtained from the initial dynamical system by incorporating time-delay in one of the state variables, exhibits Hopf bifurcations only in the case of Dirac distribution, for explosive and chaotic behaviour of the system.

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1 Introduction.

It is well known that the SODE (system of ordinary diferential equations) which describes the intra-cell calcium variation in time exhibit 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 unstability 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.

Incorporating time-delay in one of the state variables could induce unstability and Hopf bifurcation. The calcium variations in time model is based on the mechanism of Ca^{2+}- induced Ca^{2+} release (CICR). This model takes into account Ca^{2+}-stimulated degradation of inositol 1,4,5- triphosphate ($InsP_3$) by a 3-kinase ([2]).

In certain cell types, particularly in hepatocytes, complex calcium variations in time have been observed in response to stimulation by specific agonists. As these cells are not electrically excitable, it is likely that these complex calcium variations

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rely on the interplay between two intracellular mechanisms capable of destabilizing the steady state. Two antagonistic effects are indeed at play: an increase in $InsP_3$ is expected to lead to an increase in the frequency of Ca^{2+} spikes, but at the same time the $InsP_3$ induced rise in Ca^{2+} will also lead to increased $InsP_3$ metabolisis due to the Ca^{2+} activation of the $InsP_3$ 3-kinase.

The model for calcium variations used in the present study, was also studied in [8], and containes three variables, namely the concentration of free Ca^{2+} in the cytosol (Z) and in the internal pool (Y), and the $InsP_3$ concentration (A). The time evolution of these variables is governed by the following SODE

$$\tag{1.1} \begin{cases} \dfrac{dZ}{dt} = & -k \cdot Z + V_0 + \beta \cdot V_1 + T \\ \dfrac{dY}{dt} = & -T \\ \dfrac{dA}{dt} = & \beta \cdot V_{M_4} - V_{M_5} \cdot \dfrac{A^p}{k_5^p + A^p} \cdot \dfrac{Z^n}{k_d^n + Z^n} - \varepsilon \cdot A, \end{cases}$$

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

- V_0 refers to a constant input of Ca^{2+} from the extracellular medium;
- V_1 is the maximum rate of stimulus-induced influx of Ca^{2+} from the extracellular medium;
- β reflects the degree of stimulation of the cell by an agonist and thus only varies between 0 and 1;
- 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 treshold 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_{M_5} is the rate of phosphorylation of $InsP_3$ by the 3-kinase;
- m, n and p are Hill coefficients related to the cooperative processes;
- ε is the phosphorilation rate of $InsP_3$ by the 5-phosphatase.

We remind that 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 (for details, please see [4]).

2 Biologic flow with time-delayed evolution

In the following we are interested in the study of 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.

To obtain the dynamical system with delayed argument in the dependent variable $A(t)$ we recollect that for any 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

$$\tilde{A}(t) = \int_0^\infty A(t-s)f(s)ds = \int_{-\infty}^t A(s)f(t-s)ds. \tag{2.2}$$

After the time-delay process applied to A, the system (1.1) becomes

$$\begin{cases} \dfrac{dZ}{dt} = & -k \cdot Z(t) + V_0 + \beta \cdot V_1 + k_f \cdot Y(t) - V_{M_2} \cdot \dfrac{Z(t)^2}{k_2^2 + Z(t)^2} + \\ & +V_{M_3} \cdot \dfrac{Z(t)^m}{k_Z(t)^m + Z(t)^m} \cdot \dfrac{Y(t)^2}{k_Y^2 + Y(t)^2} \cdot \dfrac{\tilde{A}(t)^4}{k_A^4 + \tilde{A}(t)^4} \\ \dfrac{dY}{dt} = & -k_f \cdot Y(t) + V_{M_2} \cdot \dfrac{Z(t)^2}{k_2^2 + Z(t)^2} - \\ & -V_{M_3} \cdot \dfrac{Z(t)^m}{k_Z(t)^m + Z(t)^m} \cdot \dfrac{Y(t)^2}{k_Y^2 + Y(t)^2} \cdot \dfrac{\tilde{A}(t)^4}{k_A^4 + \tilde{A}(t)^4} \\ \dfrac{dA}{dt} = & \beta \cdot V_{M_4} - V_{M_5} \cdot \dfrac{\tilde{A}(t)^p}{k_5^p + \tilde{A}(t)^p} \cdot \dfrac{Z(t)^n}{k_d^n + Z(t)^n} - \varepsilon \cdot \tilde{A}(t). \end{cases} \tag{2.3}$$

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 (2.2) 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 (1.1) are solutions of the nonlinear system

$$\begin{cases} -kZ + V_0 + \beta V_1 = 0 \\ -V_{M_3} \dfrac{Z^m}{k_Z^m + Z^m} \cdot \dfrac{Y^2}{k_Y^2 + Y^2} \cdot \dfrac{A^4}{k_A^4 + A^4} + V_{M_2} \dfrac{Z^2}{k_Z^2 + Z^2} - k_f Y = 0 \\ \beta V_{M_4} - V_{M_5} \cdot \dfrac{A^p}{k_5^p + A^p} \cdot \dfrac{Z^n}{k_d^n + Z^n} - \varepsilon A = 0, \end{cases} \tag{2.4}$$

where we shall consider the three sets of parameters corresponding to bursting, chaotic and quasiperiodic behavior of the SODE.

The system above has in general several solutions; only the positive ones can be accepted from physiological point of view. We denote such a solution as (Z^*, Y^*, A^*). From the first equation of the system above we get $Z^* = \dfrac{(V_0 + \beta \cdot V_1)}{k}$ which is positive, because of the positivity of the parameters. For $p = 1$ (this happens in the cases of explosion and chaos), from the third (respectively the second) equation of the system (2.4) and the Viété relations we have at least one positive solution for A^* (respectively for Y^*). In conclusion, in the case, we have at least a positive equilibrium point (Z^*, Y^*, A^*). For $p = 2$ (the case of quasiperiodicity) we have a positive equilibrium point if the inequality

$$V_{M_5} \cdot \frac{(V_0 + \beta \cdot V_1)^n}{(k \cdot k_d)^n (V_0 + \beta \cdot V_1)^n} - \beta \cdot V_{M_4} > 0$$

holds always true.

Regarding the linearization of the SODE (2.3) we have the following statement ([8])

Proposition 1. *The following assertions hold true:*

a) The linearized SODE of the differential autonomous system with delayed argument (2.3) at its equilibrium point (Z^*, Y^*, A^*) *is*

$$\begin{pmatrix} \dot{Z}(t) \\ \dot{Y}(t) \\ \dot{A}(t) \end{pmatrix} = M_1 \begin{pmatrix} Z(t) \\ Y(t) \\ A(t) \end{pmatrix} + M_2 \begin{pmatrix} Z(t-\tau) \\ Y(t-\tau) \\ A(t-\tau), \end{pmatrix}$$

where

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

and (f_1, f_2, f_3) *are the components of the field which provides the SODE (1.1).*

b) The characteristic equation of the differential autonomous system with delayed argument (2.3) is

$$\det\left(\lambda I - M_1 - \int_0^\infty e^{-\lambda s} f(s) ds \cdot M_2\right) = 0. \tag{2.5}$$

Remark 1. By noting $\left.\frac{\partial T}{\partial Z}\right|_{(Z^*,Y^*,A^*)} = T_z$, $\left.\frac{\partial T}{\partial Y}\right|_{(Z^*,Y^*,A^*)} = T_y$, $\left.\frac{\partial T}{\partial A}\right|_{(Z^*,Y^*,A^*)} = T_A$, $\left.\frac{\partial f_3}{\partial Z}\right|_{(Z^*,Y^*,A^*)} = \alpha$ and $\left.\frac{\partial f_3}{\partial A}\right|_{(Z^*,Y^*,A^*)} = \gamma$ the constitutive matrices of the linearized delayed SODE (2.4) become

$$M_1 = \begin{pmatrix} T_z - k & T_y & 0 \\ -T_z & -T_y & 0 \\ \alpha & 0 & 0 \end{pmatrix}, \quad M_2 = \begin{pmatrix} 0 & 0 & T_A \\ 0 & 0 & -T_A \\ 0 & 0 & \gamma \end{pmatrix}.$$

Besides the Dirac distribution case, extensively studied in [8], 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:

A. If f is the *Dirac distribution* of $\tau \geq 0$, i.e.,

$$f(s) = \delta_\tau(s) = \begin{cases} 1, & s = \tau \\ 0, & s \neq \tau, \end{cases}$$

then the transform $\tilde{A}(t) = A(t-\tau)$ denotes the variable A with delayed argument.

In this case, the equation (2.5) becomes

$$det(\lambda I - M_1 - e^{-\lambda\tau} M_2) = 0. \tag{2.6}$$

which explicitely rewrites

$$\begin{aligned} &\lambda^3 + a_1\lambda^2 \cdot e^{-\lambda\tau} + a_2\lambda^2 + a_3\lambda \cdot e^{-\lambda\tau} + a_4\lambda + a_5 e^{-\lambda\tau} = 0 \Leftrightarrow \\ &\lambda^3 + a_2\lambda^2 + a_4\lambda + (a_1\lambda^2 + a_3\lambda + a_5)e^{-\lambda\tau} = 0, \end{aligned} \tag{2.7}$$

where $a_1 = \gamma$, $a_2 = T_y - T_z + k$, $a_3 = \gamma(-T_y + T_z - k) - \alpha \cdot T_A$, $a_4 = k \cdot T_y$, $a_5 = -k \cdot T_y \cdot \gamma$.

We denote the characteristic polynomial function in (2.7) by $J(\lambda)$. The existence of $\tau-$independent solutions of (2.7) would require the condition

$$a_5[(a_1a_2 - a_3)^2 + a_2^2(a_5 - a_1a_4)^2] = 0.$$

In our case, we note that there exist no such solutions. Looking for the critical values of the parameter τ at which there is an exchange of stability, we note that the solutions of the characteristic equation (2.7) are of the form $\lambda = \lambda(\tau) = u(\tau) \pm i\omega(\tau) \in \mathbb{C}$, and that the equation (2.7) is equivalent to

$$\operatorname{Re} J(\lambda) = \operatorname{Im} J(\lambda) = 0. \tag{2.8}$$

In order to study the Hopf bifurcation, the critical values of the parameter τ can be obtained, imposing $u(\tau) = 0$ and $\omega(\tau) \neq 0$. Under these assumptions, we infer the nonlinear system in terms of ω and τ,

$$\begin{cases} (a_5 - a_1\omega^2)\cos\omega\tau + a_3\omega\sin\omega\tau = a_2\omega^2 \\ a_3\omega\cos\omega\tau - (a_5 - a_1\omega^2)\sin\omega\tau = \omega^3 - a_4\omega; \end{cases} \tag{2.9}$$

solving (2.9) for $\cos\omega\tau$ and $\sin\omega\tau$ the relation $\cos^2\omega\tau + \sin^2\omega\tau = 1$ leads to the six-degree equation in ω

$$\omega^6 + (-a_1^2 + a_2^2 - 2a_4)\omega^4 + (2a_1 - a_3^2 + a_4)\omega^2 - a_5^2 = 0. \tag{2.10}$$

By noting $\omega^2 = x$, we obtain a third-degree equation in x with positive product of the solutions and hence the equation (2.10) provides at least two real solutions for ω, $\omega = \pm\omega_0$.

In order to find solutions for τ from the system (2.9), the following inequalities have to be satisfied

$$\begin{cases} (a_2\omega^2)^2 \leq (a_5 - a_1\omega^2)^2 + (a_3\omega)^2 \\ \omega^2(\omega^2 - a_4)^2 \leq (a_5 - a_1\omega^2)^2 + (a_3\omega)^2. \end{cases} \tag{2.11}$$

But, from system (2.9) we have $(a_5 - a_1\omega^2)^2 + (a_3\omega)^2 = \omega^2(\omega^2 - a_4)^2$ and hence, the inequalities (2.11) always hold true.

In conclusion, in the case of Dirac distribution, the system (2.9) always provides a set of solutions $(\omega, \tau) = (\pm\omega_0, \tau_0)$.

In order to exibit Hopf bifurcation, the transversality condition $Re\,(\lambda'(\tau_0)) \neq 0$ has to be satisfied; this is equivalent to

$$[2a_1a_2\omega_0^2 - a_3(\omega_0^2 - a_4)]\cos\omega_0\tau_0 - [a_2a_3\omega_0 + 2a_1\omega_0(\omega_0^2 - a_4)]\sin\omega_0\tau_0 +$$

$$+2a_2\omega_0^4 + (3\omega_0^2 - a_4)(\omega_0^2 - a_4) \neq 0$$

which takes place if and only if

$$[2a_1a_2\omega_0^2 - a_3(\omega_0^2 - a_4)]^2 + [a_2a_3\omega_0 + 2a_1\omega_0(\omega_0^2 - a_4)]^2 <$$

$$< [2a_2\omega_0^4 + (3\omega_0^2 - a_4)(\omega_0^2 - a_4)]^2$$

B. If f is the *uniform distribution* of $\tau > 0$, i.e.,

$$f(s) = \begin{cases} \frac{1}{\tau}, & 0 \leq s \leq \tau \\ 0, & s > 0 \end{cases},$$

then $\tilde{A}(t) = \frac{1}{\tau}\int_{-\tau}^{0} A(t+s)ds$.

In this case, the equation (2.5) becomes

$$\det\left(\lambda I - M_1 - \frac{1 - e^{-\lambda\tau}}{\lambda\tau}M_2\right) = 0, \tag{2.12}$$

which explicitely rewrites

$$\lambda^3 + a_1\lambda^2 + a_4\lambda + (a_1\lambda^2 + a_3\lambda + a_5)\frac{1 - e^{-\lambda\tau}}{\lambda\tau} = 0$$

with a_i, $i = \overline{1,5}$ the same as in the case of Dirac distribution.

In order to study the Hopf bifurcation and imposing the conditions $Re\,(\lambda(\tau)) = 0$ and $Im\,(\lambda(\tau)) \neq 0$, the characteristic equation is equivalent to the nonlinear system

$$\begin{cases} (a_5 - a_1\omega^2)\cos\omega\tau + a_3\omega\sin\omega\tau = \tau\omega^4 - (a_4\tau + a_1)\omega^2 + a_5 \\ -a_3\omega\cdot\cos\omega\tau + (a_5 - a_1\omega^2)\sin\omega\tau = (a_2\omega - a_3)\omega. \end{cases} \tag{2.13}$$

C. If f is the *gamma distribution* of $\tau > 0$, i.e.,

$$f(s) = \frac{d^m}{\Gamma(m)}s^{m-1}e^{-ds}, s \geq 0, d > 0,$$

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*

$$f(s) = \frac{d}{\Gamma(1)} e^{-ds}, s \geq 0, d > 0,$$

and $\widetilde{A}(t) = \frac{d}{\Gamma(1)} \int_{-\infty}^{t} A(s) e^{-d(t-s)} ds$. In this case the equation (2.5) becomes

$$\det\left(\lambda I - M_1 - \frac{d}{\lambda + d} M_2\right) = 0. \tag{2.14}$$

which explicitely rewrites

$$\lambda^3 + a_2\lambda^2 + a_4\lambda + (a_1\lambda^2 + a_3\lambda + a_5)\frac{d}{\lambda + d} = 0$$

with the constants a_5, $i = \overline{1,5}$, the same as in the case of Dirac distribution.

Following the same steps as in the cases of Dirac and uniform distribution, we note that in this case the vanishing of the real and the imaginar parts of the characteristic polynomial function is equivalent to

$$\begin{cases} \omega^4 - (da_1 + da_2 + a_4)\omega^2 + a_5 d = 0 \\ (d + a_2)\omega^2 - d(a_3 + a_4) = 0 \end{cases} \tag{2.15}$$

system which has real solutions for ω if and only if $\dfrac{d(a_3 + a_4)}{d + a_2} > 0$ and

$$[(a_1 + a_2)(a_3 + a_4) + a_5]d^2 + [(a_3 + a_4)(a_1 a_2 + a_2^2 + a_3 + 2a_4) + 2a_2 a_5]d +$$
$$+[(a_3 + a_4)a_2 a_4 + a_2^2 a_5] = 0.$$

We shall point out the cases when the SODE leads to explosion, chaos and quasi-periodicity. The first one was thoroughly investigated in [8], in the case of the Dirac distribution. For the three cases of parameter sets and for the three types of distributions we further develop the basic results regarding the stability and bifurcation of the considered delayed SODE.

I. The case of explosion. The values of the parameters which lead to the event called "explosion" are:

$$\beta = 0.46,\ n = 2,\ m = 4,\ p = 1,\ K_2 = 0.1\mu M,\ k_5 = 1\mu M,$$
$$k_A = 0.1\mu M,\ k_d = 0.6\mu M,\ k_Y = 0.2\mu M,$$
$$k_Z = 0.3\mu M,\ k = 0.1667 s^{-1},\ k_f = 0.0167 s^{-1},\ \varepsilon = 0.0167 s^{-1},$$
$$V_0 = 0.0333\mu M \cdot s^{-1},\ V_1 = 0.0333\mu M \cdot s^{-1},\ V_{M_2} = 0.1\mu M \cdot s^{-1},$$
$$V_{M_3} = 0.3333\mu M \cdot s^{-1},\ V_{M_4} = 0.0417\mu M \cdot s^{-1},\ V_{M_5} = 0.5\mu M \cdot s^{-1}.$$

We attach to the autonomous SODE (1.1) the initial condition $Z(0) = Z_0, Y(0) = Y_0, A(0) = A_0$. In this case is known the following ([8]):

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

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

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

$$\{-0.07285104555, 0.02709536609 \pm i\, 0.2468748453\}; \tag{2.16}$$

c) The constitutive matrices of the liniarized delayed SODE (2.5) are

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

I.A. The Dirac distribution case. In this case

$$a_1 = 0.08317366327, \quad a_2 = -0.0645133499 \quad a_3 = 0.0037073737193,$$
$$a_4 = 0.0540261246 \qquad a_5 = 0.00449355070.$$

Using the Maple 8 software package, we detect that the only real solutions are (ω_0, τ_0) with

$$\omega_0 \in \{\pm 0.08289718923\},\ \tau_0 = 21.25439515.$$

Since $\lambda(\tau) = \pm i\omega(\tau)$, it follows that $\lambda'(\tau_0) = 0.002089008054 - 0.003141707558i$, hence the transversality condition $\operatorname{Re}\lambda'(\tau_0) = 0.002089008054 > 0$ is satisfied.

While τ passes through τ_0, the function $u(\tau)$ changes from negative to positive values. It follows that the critical value of τ for which the Hopf bifurcation appears is exactly $\tau = \tau_0$.

Based on Maple computations is known the following ([8])

Proposition 3. *a) For $\tau = 0$, the equation (2.7) has just three roots, which are the eigenvalues (2.16) of the Jacobian matrix of the vector field at the considered equilibrium point.*

b) For $\tau = \tau_0$ the equation (2.7) has two imaginary conjugate roots $\lambda = \pm i\omega$, an infinity of roots with negative real part and no root with positive real part.

I.B. The uniform distribution case. In this case, the equation (2.5) becomes

$$0.0540261246\lambda + 0.00449355070\tfrac{(1-e^{-\lambda\tau})}{\lambda\tau} - 0.0645133499\lambda^2 +$$
$$+0.003707371930\tfrac{(1-e^{-\lambda\tau})}{\tau} + \lambda^3 + 0.08317366327\lambda\tfrac{(1-e^{-\lambda\tau})}{\tau} = 0.$$

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

I.C. The Gamma distribution case. In this case, the equation (2.5) becomes (2.14), which explicitely rewrites

$$0.540261246\lambda + 0.00449355070\tfrac{d}{\lambda+d} - 0.0645133499\lambda^2 +$$
$$+0.003707371930\tfrac{d\lambda}{\lambda+d} + \lambda^3 + 0.08317366327\lambda^2\tfrac{d}{\lambda+d} = 0.$$

Using the graphic package Maple 8, we obtain that there exists no solution for the equation (2.15) for $u = 0$ in terms of τ_0 and ω_0.

II. The case of Chaos. The parameters which lead to the event called "explosion" are:

$$\beta = 0.65,\ n=4,\ m=2, p=1,\ k_2 = 0.1\mu M, k_5 = 0.3194\mu M,\ k_A = 0.1\mu M,$$
$$k_d = 1\mu M,\ k_Y = 0.3\mu M,\ k_Z = 0.6\mu M,\ k = 0.1667 s^{-1},\ k_f = 0.0167 s^{-1},$$
$$\varepsilon = 0.2167 s^{-1},\ V_0 = 0.0333\mu M s^{-1},\ V_1 = 0.0333\mu M s^{-1}, V_{M_2} = 0.1\mu M s^{-1},$$
$$V_{M_3} = 0.5\mu M s^{-1},\ V_{M_4} = 0.05\mu M s^{-1},\ V_{M_5} = 0.8333\mu M s^{-1}.$$

We attach to the autonomous SODE (1.1) the initial condition $Z(0) = Z_0, Y(0) = Y_0, A(0) = A_0$. In this case we obtain the following:

Proposition 4. *a) The only non-negative equilibrium point*

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

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

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

c) The constitutive matrices of the liniarized delayed SODE (2.5) are

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

II.A. The Dirac distribution case. For the Dirac distribution, the equation (2.5) becomes (2.7), where

$$a_1 = 0.2316344181, \quad a_2 = -0.1099856286, \quad a_3 = -0.00754011222,$$
$$a_4 = 0.007060883993, \quad a_5 = 0.001635543755.$$

Following the same steps as in the precedent case, we obtain

$$\tau_0 = 24.86935346, \omega_0 = \pm 0.07612239751$$

and Proposition 3 holds true.

II.B. The uniform distribution case. In this case $\widetilde{A}(t) = \frac{1}{\tau}\int_{-\tau}^{0} A(t+s)ds$ and the equation (2.5) becomes (2.12), which explicitely rewrites

$$0.007060883993\lambda + 0.001635543755\frac{(1-e^{-\lambda\tau})}{\lambda\tau} - 0.1099856286\lambda^2 -$$
$$-0.00754011222\frac{(1-e^{-\lambda\tau})}{\tau} + \lambda^3 + 0.2316344181\frac{\lambda(1-e^{-\lambda\tau})}{\tau} = 0.$$

Following the same steps like in the case of Dirac distribution, we obtain that there exists no solution for the equation (2.13) for $u = 0$ in terms of τ_0 and ω_0.

II.C. The case of Gamma distribution. In this case we have

$$\widetilde{A}(t) = \frac{d}{\Gamma(1)}\int_{-\infty}^{t} A(s)e^{-d(t-s)}ds,$$

and the equation (2.5) becomes (2.14), which explicitely rewrites

$$0.007060883993\lambda + 0.001635543755 d/(\lambda+d) - 0.1099856286\lambda^2 -$$
$$-0.00754011222 d\lambda/(\lambda+d) + \lambda^3 + 0.2316344181\lambda^2 d/(\lambda+d) = 0.$$

Using the graphic package Maple 8, we obtain that there exists no solution for the equation (2.15) for $u = 0$ in terms of τ_0 and ω_0.

III. The case of quasiperiodicity. In the following we shall use the values of the parameters which lead to the event called "quasiperiodicity", namely:

$$\beta = 0.51,\ n = 4,\ m = 2, p = 2,\ k_2 = 0.1\mu M, k_5 = 0.3\mu M,\ k_A = 0.2\mu M,$$
$$k_d = 0.5\mu M,\ k_Y = 0.2\mu M,\ k_Z = 0.5\mu M,\ k = 0.1667 s^{-1},\ k_f = 0.0167 s^{-1},$$
$$\varepsilon = 0.0017 s^{-1},\ V_0 = 0.0333\mu M s^{-1},\ V_1 = 0.0333\mu M s^{-1}, V_{M_2} = 0.1\mu M s^{-1},$$
$$V_{M_3} = 0.3333\mu M s^{-1},\ V_{M_4} = 0.0833\mu M s^{-1},\ V_{M_5} = 0.5\mu M s^{-1}.$$

We obtain the following:

Proposition 5. *a) 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.

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

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

In the cases of * explosion-Dirac distribution subcase and * chaos-Dirac distribution , the initial dynamical SODE becomes subject to the following result, known as the Hopf bifurcation theorem ([14])

Theorem 1. Let $X \in \mathcal{X}(\mathbb{R}^n \times \mathbb{R}) \ni (x, \tau),\quad n \geq 2$ be a $\mathcal{C}^\infty$ vector field, which differentiably depends on the parameter τ and obeys the property that the set $E : X(x, \tau) = 0$ contains the isolated point $x = x(\tau), \tau \in I \subset \mathbb{R}$. Consider in a neighborhood of the stationary point $x = x(\tau)$ the linear approximation

$$\frac{dx}{dt} = A(\tau)x,\ A(\tau) = \left[\frac{\partial X_i}{\partial x_j}(x(\tau), \tau)\right]$$

of the system $\frac{dx}{dt} = X(x, \tau)$. Denote by $\lambda_1(\tau), \ldots, \lambda_n(\tau)$ the eigenvalues of $A(\tau)$ and assume that

$$\lambda_1(\tau) = \mu(\tau) + i\omega(\tau), \quad \lambda_2(\tau) = \mu(\tau) - i\omega(\tau) = \bar{\lambda}_1(\tau).$$

For $n > 2$, additionally assume that $Re(\lambda_k(\tau)) < 0, k = 3, \ldots n$ and that exists an isolated value $\tau_0 \in I$ such that $u(\tau_0) = 0, \omega(\tau_0) \neq 0$ and $\frac{du}{d\tau} > 0$. Under these hypotheses, one of the following assertions holds true:

a) The stationary point $x = x(\tau_0)$ is a center; for $\tau \neq \tau_0$ neighbor to τ_0, there exists no periodic orbit around $x(\tau)$;

b) There exists a number $b > \tau_0$ s.t. for each $\tau \in (\tau_0, b)$ there exists an unique induced orbit around the stationary point $x(\tau)$ in a neighborhood of this point. This 1-parameter family of closed orbits split at the stationary point $x(\tau_0)$, i.e., for $\tau \to \tau_0$, the diameter of the closed orbit varies with $|\tau - \tau_0|^{1/2}$. In this case, for $\tau \leq \tau_0,\ \tau \in I$, there exist no closed orbit neighbor to $x(\tau)$.

c) There exists a number $a < \tau_0$ s.t. for each $\tau \in (a, \tau_0)$ there exists an unique closed orbit around the stationary point $x(\tau_0)$ in one of its neighborhoods. This 1-parameter family of closed orbits split at the stationary point $x(\tau_0)$, i.e., for $\tau \to \tau_0$, the diameter of the closed orbit varies with $|\tau - \tau_0|^{1/2}$. In this case, for $\tau \geq \tau_0$, $\tau \in I$, there exist no closed orbit neighbor to $x(\tau)$.

We note that though in the case $\tau = 0$, in a certain neighborhood of the singular point there exist no closed orbits, for the delayed system at a certain delay $\tau \neq 0$, the SODE may exhibit one of the situations b) or c) in the Theorem, hence the presence of closed orbits arbitrarily close to the singular point may occur; their complete characterization of these cases is subject of further research.

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