Available online at www.tjnsa.com
J. Nonlinear Sci. Appl. 9 (2016), 309–315
Research Article

Journal of Nonlinear Science and Applications
Print: ISSN 2008-1898 Online: ISSN 2008-1901

Computation and stability analysis of Hopf Bifurcation in biophysical system model of cells

Yi Zhou

School of Mathematical and Computational Science, Huainan Normal University, Huainan 232038, Anhui, P. R. China.

Communicated by Martin Bohner

Abstract

Dynamics of the Shen-Larter calcium oscillation model is investigated based on the theory of the center manifold and bifurcation, including the classification and stability of equilibrium. The existence of two subcritical Hopf bifurcations is derived in this case. More precisely, it is shown that the subcritical Hopf bifurcations play a great role in the study of this calcium oscillation model. In addition, numerical simulations are provided to verify our theoretical analysis and to display new phenomena. Based on the theoretical analysis results and the numerical results, an effective mechanism explaining the Shen-Larter calcium oscillation model is obtained.

Keywords: Calcium ion, Hopf, equilibrium.
2010 MSC: 37G10, 37J20.

1. Introduction

In non-excitable eukaryotic cell types, including hepatocytes, oscillatory changes in concentration of free cytosolic calcium (Ca^{2+}) generate extracellular agonists acting through the phospho-inositide signalling pathway. Ca^{2+} oscillations play a vital role in intra- and intercellular signaling [1]. When simple self-sustained Ca^{2+} oscillations were first discovered experimentally during the 1980s, many theoretical studies have been conducted to describe the complex mechanism of Ca^{2+} oscillations [10]

To explain the mechanism of complex calcium oscillations, a variety of mathematical models for complex Ca^{2+} oscillations were proposed in non-excitable as well as in excitable cells [5, 6]. Based on calcium-induced calcium release (CICR) and the inositol trisphosphate cross-coupling (ICC), Shen et al. gave an

Email address: zhouyi3280@163.com (Yi Zhou)

Received 2015-02-04

early theoretical study of complex Ca^{2+} oscillations trying to describe bursting Ca^{2+} oscillations in non-excitable cells [11]. A more detailed study of different mechanisms explaining the Ca^{2+} oscillations in non-excitable cells have been given by Borghans [2] and further mathematically analyzed by Houart, *et al.* [3, 4, 7, 12]. Synchronization behaviors of non-excitable cells by gap junction coupling were explored by Huo and Zhou, and the threshold values of synchronization for identical and un-identical oscillators were computed numerically [8].

The mathematical models for Ca^{2+} oscillations in non-excitable cells were presented for several years. Many analytical methods were reported for the estimation of Hopf bifurcation of Shen-Larter model. In this paper, the existence and stability of equilibrium is derived by using the qualitative and stability theory. The theoretical analysis shows that it will display Hopf bifurcation at equilibrium o_1, o_2, which are non-degenerate and subcritical. Theoretical predictions from this model are confirmed numerically. It is shown that this system has complex dynamics with some interesting characteristics.

2. Model

Consider the system suggested by Shen *et al.*:

$$\begin{aligned} dCa_{cyt}/dt &= J_{ch} + J_{leak} - J_{pump} + J_{in} - J_{out}, \\ dCa_{er}/dt &= J_{pump} - J_{ch} - J_{leak}, \\ dIP_3/dt &= J_+ - J_-, \end{aligned} \tag{2.1}$$

where three dynamical variables are Ca_{cyt} (the free concentration of Ca^{2+} in the cytosol), Ca_{er} (the free concentration of Ca^{2+} in ER) and IP_3 (IP_3 concentration). The explicit expressions for J can be written generally as:

$$\begin{aligned} J_{ch} &= k_{ch}\left(\frac{IP_3^4}{IP_3^4 + K_1^4}\right)\left(\frac{K_4 Ca_{cyt}}{(Ca_{cyt}+K_4)(Ca_{cyt}+K_5)}\right)^3 Ca_{er}, \\ J_{leak} &= k_{leak} Ca_{er}, \\ J_{pump} &= k_{pump}\frac{Ca_{cyt}^2}{Ca_{cyt}^2 + K_2^2}, \\ J_{in1} &= k_{in1} r + k_{in2}, \quad J_{out} = k_{out} Ca_{cyt}, \\ J_+ &= \frac{k_+ r Ca_{cyt}}{(Ca_{cyt}+K_3)}, \quad J_- = k_- IP_3. \end{aligned}$$

Therefore we propose some hypothesis to facilitate the following discussion:

$$x = Ca_{cyt}, \quad y = Ca_{er}, \quad z = IP_3.$$

Parameters are made if not otherwise stated:

$$\begin{aligned} &k_{ch} = 2500\mu M s^{-1}, \quad k_{leak} = 1.1 s^{-1}, \quad k_{pump} = 40\mu M s^{-1}, \\ &k_{in1} = 4\mu M s^{-1}, \quad k_{in2} = 1\mu M s^{-1}, k_{out} = 2 - -12 s^{-1}, \quad k_+ = 4.0\mu M s^{-1}, \\ &k_- = 2\mu M s^{-1}, \quad K_1 = K_2 = 0.2\mu M s^{-1}, K_3 = 1\mu M, \quad K_4 = K_5 = 0.69\mu M, r = 0.25. \end{aligned}$$

We will investigate the variations of the equilibrium with changing the parameter k_{out}, including the existence, number, type and bifurcation.

3. Results

Let the equilibrium of system (2.1) is (x_0, y_0, z_0) and $x_1 = x - x_0, y_1 = y - y_0, z_1 = z - z_0$. We rewrite system (2.1) as:

$$\begin{aligned}\frac{dx_1}{dt} &= 1.1(y_0+y_1) - k_{out}(x_0+x_1) + \frac{821.2725(x_0+x_1)^3(y_0+y_1)(z_0+z_1)^4}{((z_0+z_1)^4+0.0016)(x_0+x_1+0.69)^6}\\ &\quad - \frac{40(x_0+x_1)^2}{(x_0+x_1)^2+0.04}+2,\\ \frac{dy_1}{dt} &= \frac{40(x_0+x_1)^2}{(x_0+x_1)^2+0.04} - 1.1(y_1+y_0) - \frac{821.2725(x_0+x_1)^3(y_0+y_1)(z_0+z_1)^4}{((z_0+z_1)^4+0.0016)(x_0+x_1+0.69)^6},\\ \frac{dz_1}{dt} &= \frac{(x_0+x_1)}{x_0+x_1+1} - 2(z_0+z_1).\end{aligned} \tag{3.1}$$

It is easily seen that the system (3.1) has the equilibrium $(0,0,0)$, which has the same properties as the equilibrium of (2.1). One can calculate the jacobian matrix $(a_{ij})_{33}$ of system (3.1), and obtain the following characteristic equation:

$$\begin{aligned}&\lambda^3 + Q_1\lambda^2 + Q_2\lambda + Q_1 = 0,\\ &Q_1 = -(a_{11}+a_{22}+a_{33}),\\ &Q_2 = a_{11}a_{22} + a_{11}a_{33} + a_{22}a_{33} - a_{13}a_{31} - a_{12}a_{21} - a_{32}a_{23},\\ &Q_3 = a_{31}a_{13}a_{22} + a_{12}a_{21}a_{33} + a_{32}a_{23}a_{11} - a_{11}a_{22}a_{33} - a_{12}a_{23}a_{31} - a_{13}a_{21}a_{32}.\end{aligned}$$

Based on the above results, we have the following conclusions by using the qualitative and stability theory of differential equation:

1) When $k_{out} < 2.9548$, there is a stable node of system (2.1);
2) If $k_{out} = 2.9548$, system (2.1) has a non-hyperbolic equilibrium;
3) When $2.9548 < k_{out} < 10.1658$, there is an equilibrium (saddle);
4) If $k_{out} = 10.1658$, system (2.1) has a non-hyperbolic equilibrium;
5) There is a stable node of system (2.1) for $k_out > 10.1658$.

As above, one has the equilibrium $o_1 = (0.6769, 1.7534, 0.2018)$ for $r = 2.9548$, and let $n = k_{out} - 2.9548$, system (3.1) can be rewritten as:

$$dx_1/dt = f_1(x_1,y_1,z_1,n),\ dy_1/dt = f_2(x_1,y_1,z_1,n),\ dz_1/dt = f_3(x_1,y_1,z_1,n),\ dn/dt = 0. \tag{3.2}$$

$o_1'(0,0,0,0)$ is the equilibrium of (3.2), and the characteristic roots of (3.2) are: $\xi_1 = -33.1792$, $\xi_2 = 1.9331i, \xi_3 = -1.93313i, \xi_4 = 0$.

Suppose

$$\begin{pmatrix} x_1\\ y_1\\ z_1\\ n\end{pmatrix} = U\begin{pmatrix} u\\ v\\ w\\ s\end{pmatrix}, U = \begin{bmatrix} 0.7392 & -0.2624 & 0.4011 & 0.1943\\ -0.6734 & 0.8755 & 0 & -0.4914\\ -0.0084 & -0.0598 & 0.0136 & 0.0346\\ 0 & 0 & 0 & 0.8482\end{bmatrix}.$$

The (3.2) has the following form:

$$\begin{pmatrix}\dot u\\ \dot v\\ \dot w\\ \dot s\end{pmatrix} = \begin{pmatrix} -33.1792 & 0 & 0 & 0\\ 0 & 0 & -1.9331 & 0\\ 0 & 1.9331 & 0 & 0\\ 0 & 0 & 0 & 0\end{pmatrix}\begin{pmatrix} u\\ v\\ w\\ s\end{pmatrix} + \begin{pmatrix} g_1\\ g_2\\ g_3\\ g_4\end{pmatrix},$$

where

$$\begin{aligned}g_1 &= 0.4699g_{11} - 0.8007g_{21} - 13.7710g_{31},\\ g_2 &= 0.3591g_{11} + 0.5264g_{21} - 10.5921g_{31},\end{aligned}$$

$$
\begin{aligned}
g_3 =&1.8676g_{11}+1.8199g_{21}+18.4497g_{31},\\
g_4 =&0,\\
g_{11} =&0.96305v-0.74074u-0.54054s-\frac{40\sigma_1^2}{\sigma_1^2+0.04}-(0.8482s+2.9548)\sigma_1\\
&+\frac{821.2725\sigma_1^3\sigma_2^4\sigma_3}{(\sigma_2^4+0.0016)(\sigma_1+0.69)^6}+3.92874,\\
g_{21} =&0.54054s+0.74074u-0.96305v-\frac{40\sigma_1^2}{\sigma_1^2+0.04}\\
&+\frac{821.2725\sigma_3\sigma_2^4\sigma_1^3}{(\sigma_2^4+0.0016)(\sigma_1+0.69)^6}-1.92874,\\
g_{31} =&0.0168u+0.1196v-0.0692s-0.0272w+\frac{\sigma_1}{\sigma_1+0.69}-0.4036,\\
\sigma_1 =&0.1943s+0.7392u-0.2624v+0.4011w+0.6769,\\
\sigma_2 =&0.0346s-0.0084u-0.0598v+0.0136w+0.2018,\\
\sigma_3 =&0.6734u+0.4914s-0.8755v-1.7534.
\end{aligned}
$$

By using the theory of the existence theorem of center manifold, (3.2) has center manifold:

$$
W_{loc}^c(o_1)=\left\{(u,v,w,s)\in R^4 | u=h(v,w,s),\ h(0,0,0)=0,\ Dh(0,0,0)=0\right\}. \tag{3.3}
$$

Let $h(v,w,s)=av^2+bw^2+cs^2+dvw+evs+fws+\cdots$, therefore $a=-0.6115821885, b=-0.240776026, c=-0.2199609268, d=0.4510853689, e=-0.7303394098, f=0.3043974495$.

The center manifold is founded to be

$$
\begin{pmatrix} v\\ w\end{pmatrix}=\begin{pmatrix} 0 & -1.9331\\ 1.9331 & 0\end{pmatrix}\begin{pmatrix} v\\ w\end{pmatrix}+\begin{pmatrix} f^1(v,w)\\ f^2(v,w)\end{pmatrix},
$$

where

$$
\begin{aligned}
f^1(v,w)&=0.03303857374v^2+0.01300707679w^2-0.02436829833vw\cdots,\\
f^2(v,w)&=-0.1679537171v^2-0.06612231243w^2+0.1238778137vw\cdots.
\end{aligned}
$$

The following conclusions can be derived from the bifurcation theory:

$$
\begin{aligned}
&\frac{1}{16}\{(f^1_{vvv}+f^1_{vww}+f^2_{vvw}+f^2_{www})+\frac{1}{1.9331}[f^1_{vw}(f^1_{vv}+f^1_{ww})\\
&\quad -f^2_{vw}(f^2_{vv}+f^2_{ww})-f^1_{vv}f^2_{vv}+f^1_{ww}f^2_{ww}]\}\,|_{(0,0,0)}=2.161580721>0,\\
&\frac{dRe(\xi(s))}{ds}\,|_{(0,0,0)}=3.942156993>0.
\end{aligned} \tag{3.4}
$$

After computations we include that system (2.1) has a subcritical Hopf bifurcation at $o_1=(0.6769, 1.7534, 0.2018)$ for $k_{out}=2.9548$. If $k_{out}>2.9548$, the stability of equilibrium o_1 changes and a limit cycle occurs around the area of o_1, and system (2.1) will generate the complex Ca^{2+} oscillations.

Let $k_{out}=10.1658$, we have the equilibrium $o_2=(0.1967, 13.5026, 0.0822)$. Similar to the previous analysis, we have the center manifold corresponding $k_{out}=10.1658$:

$$
\begin{pmatrix} v\\ w\end{pmatrix}=\begin{pmatrix} 0 & -0.6310\\ 0.6310 & 0\end{pmatrix}\begin{pmatrix} v\\ w\end{pmatrix}+\begin{pmatrix} f^1(v,w)\\ f^2(v,w)\end{pmatrix},
$$

where

$$f^1(v,w) = 0.0001755106261v^2 + 0.006192521331w^2 - 0.002284032267vw \cdots,$$
$$f^2(v,w) = 0.0009553465592v^2 + 0.03370738331w^2 - 0.01243253709vw \cdots.$$

Hence

$$\begin{aligned} &\frac{1}{16}\{(f^1_{vvv} + f^1_{vww} + f^2_{vvw} + f^2_{www}) + \frac{1}{0.631}[f^1_{vw}(f^1_{vv} + f^1_{ww}) \\ &\quad - f^2_{vw}(f^2_{vv} + f^2_{ww}) - f^1_{vv}f^2_{vv} + f^1_{ww}f^2_{ww}]\}\,|_{(0,0,0)} = 0.4615188239 > 0, \\ &\frac{dRe(\xi(s))}{ds}\,|_{(0,0,0)} = -1.312987179 < 0. \end{aligned} \tag{3.5}$$

When $k_{out} = 10.1658$, the subcritical Hopf bifurcation occurs at $o_2 = (0.1967, 13.5026, 0.0822)$. For $k_{out} > 10.1658$, the equilibrium o_2 become stable. A limit cycle around the area of o_2 becomes unstable and the oscillatory phenomenon disappears.

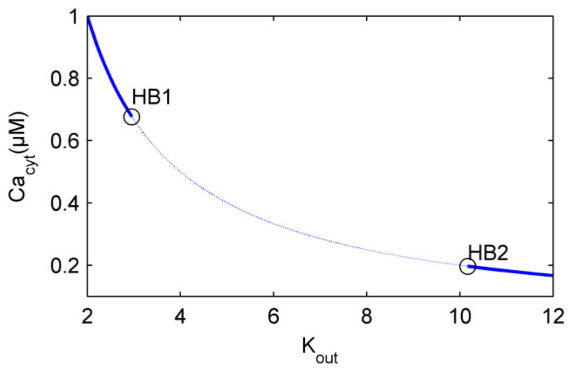
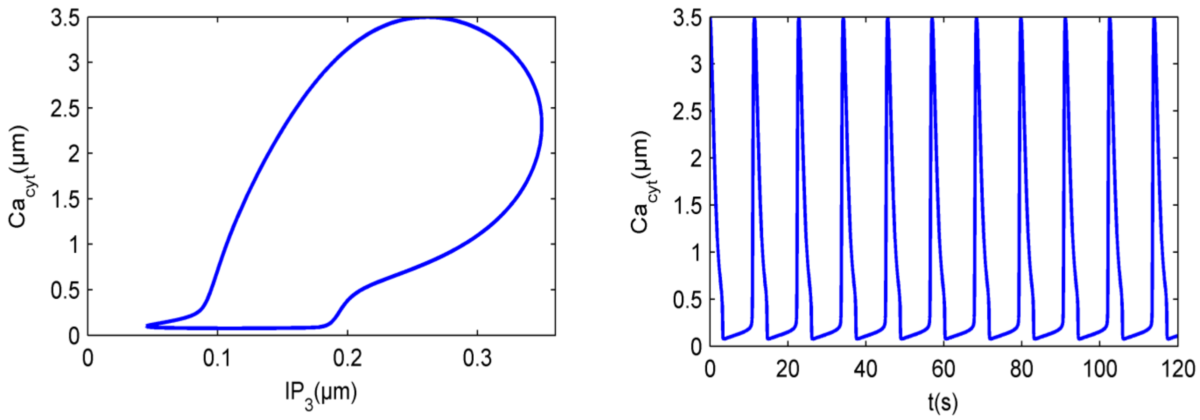


Figure 1: One-parameter bifurcation diagram versus the parameter (k_{out}) for system (1)

The bifurcation diagram of equilibrium of system (2.1) is shown as Fig. 1. The solid line of the curve means the stable equilibrium, and the dashed line unstable equilibrium. It is shown that system (2.1) has two bifurcations, marked HB1 and HB2 of which parameters are $k^1_{out} = 2.9548$ and $k^2_{out} = 10.1658$ respectively. For $k_{out} < k^1_{out}$, there is a stable node of system (2.1), whereas the equilibrium loses its stability when $k^1_{out} < k_{out} < k^2_{out}$. As k_{out} increases, the equilibrium changes its stability at HB2.



(a) (b)

Figure 2: (a) The 2D projection of the trajectory of the system (1) for $k_{out} = 3$; (b) Corresponding time course of Ca_{cyt} .

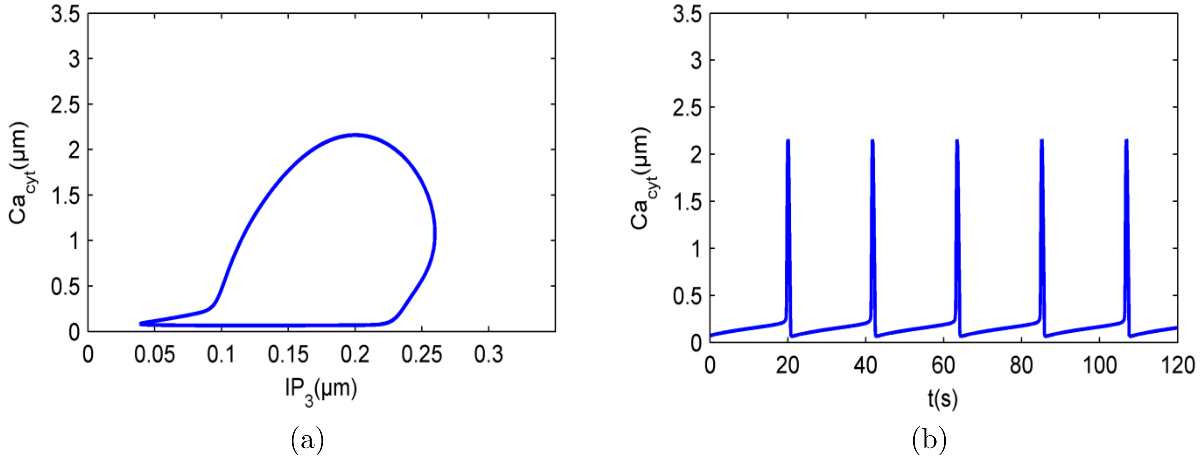


Figure 3: (a) The 2D projection of the trajectory of the system (1) for $k_{out} = 10$; (b) Corresponding time course of Ca_{cyt} .

Fig. 2(a) indicates the phase diagram in (x, z)-plane of system (2.1) for $k_{out} = 3$, and Fig. 2(b) shows time series for $k_{out} = 3$. The phase diagram for $k_{out} = 10$ is plotted in Fig. 3(a), Fig. 3(b) represents time series. We can infer that the frequency decrease with the bifurcation parameter increasing.

The fast subsystem corresponding to Fig. 4(a) has the form:

$$\begin{cases} dCa_{cyt}/dt = J_{ch} + J_{leak} - J_{pump} + J_{in} - J_{out}, \\ dIP_3/dt = J_+ - J_-. \end{cases}$$

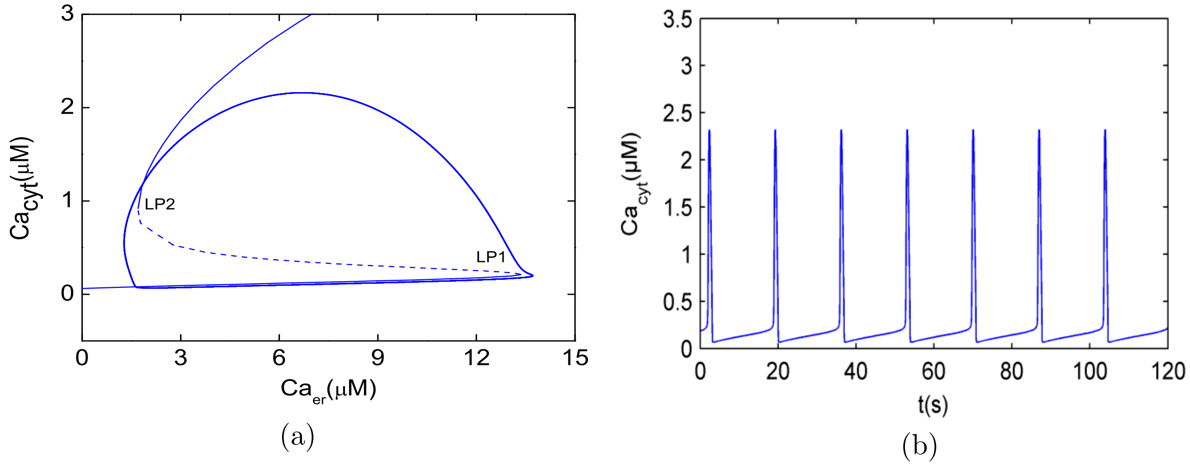


Figure 4: (a) The fast/slow dynamic analysis of fold-fold bursting of point-point type for $k_{out} = 9$; (b) Corresponding time course of Ca_{cyt}.

Fig. 4(b) is the time course for $k_{out} = 9$. The phase plot of system (2.1) is also superposed. LP1 and LP2 represent the fold bifurcations. Solid (dashed) lines represent stable (unstable) steady states. The closed line denotes the limit cycle trajectory. Here we fix $k_{out} = 9$, and the slow variable (Ca_{er}) is used as the bifurcation parameter. According to Izhikevichs classification of bursting [9], this graph shows a point-point bursting of fold-fold type.

The main characteristic of this type of bursting is that the active phase starts with a fold bifurcation $(LP1)$ and ends with another fold bifurcation $(LP2)$. To understand this type of bursting, we start at the silent phase in the anti-clockwise direction. When the trajectory passes the fold bifurcation point $(LP1)$, the lower stable steady state branch loses its stability and turns unstable. As time progresses, the trajectory passes another fold bifurcation $(LP2)$ and becomes closed because of the attraction of the lower stable steady state. The silent phase of bursting starts again.

We obtain different types of calcium oscillations in system (2.1) with the increase of k_{out} for $2.9548 < k_{out} < 10.1658$. The type of calcium oscillations can be determined by the fast-slow dynamic bifurcation analysis.

4. Conclusion

We studied the nonlinear dynamic of the Shen-Larter calcium oscillation model, including the stability, classification and bifurcation of equilibrium points. By choosing the parameter knout as a bifurcation parameter, it is found that two subcritical Hopf bifurcations play a great role in the occurrence of calcium oscillations. Numerical simulations verify our theoretical analysis results. By combining the existing numerical results with the theoretical analysis results in this paper, a complete description of the nonlinear dynamics of the Shen-Larter calcium oscillation model is obtained.

Acknowledgements

This work was supported by the Natural Science Foundation of China under Grant No. 11202083, 11372017, the Natural Science Foundation for the Higher Education Institutions of Anhui Province of China (Grant No. KJ2015A178) and the research foundation of Huainan Normal University (2014xj11zd,2014xk07zd).

References

[1] M. J. Berridge, *Elementary and global aspects of calcium signaling*, J. Physiol., **499** (1997), 291–306. 1
[2] J. A. M. Borghans, G. Dupont, A. Goldbeter, *Complex intracellular calcium oscillations: a theoretical exploration of possible mechanisms*, Biophys. Chem., **66** (1997), 25–41 1
[3] Y. Chang, L. L. Zhou, J. L. Wang, *Hopf bifurcation in a calcium oscillation model and its control: frequency domain approach*, Internat. J. Bifur. Chaos Appl. Sci., **23** (2013), 9 pages. 1
[4] V. A. Gaiko, *Global bifuration analysis of the lorenz system*, J. Nonlinear Sci. Appl., **7** (2014), 429–434. 1
[5] A. Goldbeter, *Biochemical oscillations and cellular rhythms*, Cambridge University press, England, (1996). 1
[6] T. Haberichter, M. Marhlb, R. Heinricha, *Birhythmicity, trihythmicity and chaos in bursting calcium oscillations*, Biophy. Chem., **90** (2001), 17–30. 1
[7] G. Houart, G. Dupont, A. Goldbeter, *Bursting, chaos and birhythmicity originating from self-modulation of the inositol 1, 4, 5-triphosphate signal in a model for intracellular Ca^{2+} oscillations*, Bull. Math. Biol., **61** (1999), 507–530. 1
[8] Y. H. Huo, Y. Zhou, *Bifurcation and Global Synchroniztion Analysis in Diffusively Coupled Calcium Oscillators*, Commun. Comput. Inform. Sci., **472** (2014), 192–197. 1
[9] E. M. Izhikevich, *Neural excitability spiking and bursting*, Int. J. Bifurcation Chaos, **10** (2000), 1171-1226. 3
[10] M. Perc, M. Marhl, *Different types of bursting calcium oscillations in non-excitable cells*, Chaos, Solitons Fractals, **18** (2003), 759–773. 1
[11] P. Shen, R. Larter, *Chaos in intracellure Ca^{2+} oscillations in a new model for non-excitable cells*, Cell Calcium, **17** (1995), 225–232. 1
[12] Y. Zhang, Q. L. Zhang, T. Z. Zhang, *Dynamical Analysis of a Delayed Singular Bioeconomic Model with Stochastic Fluctuations*, J. Comput. Inform. Syst., **6** (2010), 931–938. 1