Complex Dynamics of a Calcium Oscillation Model in Non-excitable Cells

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Abstract. In order to explain the mechanism of the calcium oscillations induced by the calcium-induced calcium release in non-excitable cells, the Kummer-Olsen calcium oscillation model was proposed. In this paper, by using the qualitative theory, bifurcation theorem and the center manifold theory, the nonlinear dynamics of this model is first characterized, including the stability and classification of the equilibrium points with parameter value. It is shown that supercritical Hopf bifurcations play very important roles in calcium oscillations. Furthermore, some new numerical simulations have confirmed the theoretical analysis results. Based on the existing numerical results with the theoretical analysis, complex dynamics of the Kummer-Olsen calcium oscillation model has been described perfectly.

Introduction

The calcium ion, Ca^{2+} plays a very important role in Cellular signal transduction [1]. Since 1980s, calcium oscillations were found experimentally, the role of oscillation for intracellular Ca^{2+} signaling has become of interest. Many researchers, such as Borghans and Marhl etc. established some mathematical models [2-6] to explain the mechanism of Ca^{2+} oscillations from experimental point of view, the other researchers made some theoretic analysis and researches about the appearance and disappearance of calcium oscillations based on numerical simulation[6-8].

In 2000[9], one of the important calcium oscillation models in non-excitable cells, the Kummer-Olsen calcium oscillation model was put forward by Kummer and Olsen. In this paper, by using the qualitative theory, bifurcation theorem and the center manifold theory, the nonlinear dynamics of this model is first characterized, including the stability and classification of the equilibrium points with parameter value. It is shown that supercritical Hopf bifurcations play very important roles in calcium oscillations. Furthermore, some new numerical simulations have confirmed the theoretical analysis results. Based on the existing numerical results with the theoretical analysis, complex dynamics of the Kummer-Olsen calcium oscillation model has been described perfectly.

The mathematical model and main results

The Kummer-Olsen calcium oscillation model is described in [9] as follows:

$$\begin{cases} d\text{Ca}_{\text{cyt}}/dt = k_{10} - k_{11} \text{Ca}_{\text{cyt}} / (\text{Ca}_{\text{cyt}} + k_{12}) \\ dG_{\alpha}/dt = k_1 - k_2 G_{\alpha} - k_3 \text{PLC} G_{\alpha} / (G_{\alpha} + k_4) \\ \quad - k_5 \text{Ca}_{\text{cyt}} G_{\alpha} / (G_{\alpha} + k_6) \\ d\text{PLC}/dt = k_7 G_{\alpha} - k_8 \text{PLC} / (\text{PLC} + k_9) \end{cases} \quad (1)$$

Where $k_1 = 0.212, k_2 = 1.63, k_3 \in [1.13, 3.37], k_4 = 0.19, k_5 = 4.88, k_6 = 1.18, k_7 = 1.24,$
 $k_8 = 32.24, k_9 = 29.09, k_{10} = 13.58, k_{11} = 153, k_{12} = 0.16.$

In the following analysis, we investigate the existence, types, stability and bifurcation of equilibrium of the system (1) when k_3 is changing as bifurcation parameter.

Let $x = Ca_{cvt}$, $y = G_\alpha$, $z = PLC$, $r = k_3$, we rewrite system (1) as follows:

$$\begin{cases} \dot{x} = -153x/(x+0.16) + 13.58y \\ \dot{y} = -4.88xy/(y+1.18) \\ \quad - ryz/(y+0.19) \\ \quad - 1.63y + 0.212 \\ \dot{z} = 1.24y - 32.24z/(z+29.09) \end{cases} \quad (2)$$

The equilibrium of the system (2) is determined by the following equations:

$$\begin{cases} x = 2.1728y/(153-13.58y) \\ f(y, r) = \frac{10.6032y^2}{(y+1.18)(153-13.58y)} \\ \quad - \frac{78.3763ry^2}{(y+0.19)(153-13.58y)(32.24-12.4y)} \\ \quad - 1.63y + 0.212 \\ z = 36.0716y/(32.24-1.24y) \end{cases} \quad (3)$$

Obviously, $f(0, r) > 0$ and $f(1, r) < 0$, there exist an equilibrium (x_0, y_0, z_0) of system (2) for $x_0 > 0, y_0 > 0, z_0 > 0$ when $r \in [1.13, 3.37]$.

Base on the above analysis and the qualitative theory and stability theory, we obtain: When $r < 1.4017$, the system (2) has a stable node; When $r = 1.4017$, the system (2) has a non-hyperbolic equilibrium O_1 ; When $1.4017 < r < 3.3615$, the system (2) has equilibrium (saddle); When $r = 3.3615$, the system (2) has a non-hyperbolic equilibrium O_2 ; When $r > 3.3615$, the system (2) has a stable node. It infer that system (2) have two non-hyperbolic equilibriums $O_1(r'_1)$ and $O_2(r'_2)$, for $r'_1 = 1.4017$ and $r'_2 = 3.3615$ respectively.

Now, by using the center manifold theorem and bifurcation theory, we analyzed dynamics around these two equilibriums.

We suppose that (x_0, y_0, z_0) is the corresponding equilibrium of system (2) when $r = r_0$. In order to apply the center manifold theorem with parameters of a continuous dynamical system, r_1 is regard as a new dynamical variable. Let $x_1 = x - x_0$, $y_1 = y - y_0$, $z_1 = z - z_0$, $r_1 = r - r_0$, under the consideration of $\dot{r}_1 = 0$ and system (2), we get a new system as follows:

$$\begin{cases} \dot{x}_1 = -153(x_0 + x_1)/(x_0 + x_1 + 0.16) \\ \quad + 13.58(y_0 + y_1) \\ \dot{y}_1 = -4.88(x_0 + x_1)(y_0 + y_1)/(y_0 + y_1 + 1.18) \\ \quad - (r_0 + r_1)(z_0 + z_1)(y_0 + y_1)/(y_0 + y_1 + 0.19) \\ \quad - 1.63(y_0 + y_1) + 0.212 \\ \dot{z}_1 = 1.24(y_0 + y_1) \\ \quad - 32.24(z_0 + z_1)/(z_0 + z_1 + 29.09) \\ \dot{r}_1 = 0 \end{cases} \quad (4)$$

It is widely know that the origin $O_1(x_1, y_1, z_1, r_1) = (0, 0, 0, 0)$ is the equilibrium of system (4) when $r_1 = 0$ Which has same characteristics with equilibrium (x_0, y_0, z_0) of system (3) in types, stability and bifurcation types. The characteristic equation associated with the equilibrium $(0, 0, 0, 0)$ is given by $P(\rho) = \rho(\rho^3 + Q_1\rho^2 + Q_2\rho + Q_3) = 0$

Where $Q_1 = -(A + E + I)$, $Q_2 = AE + AI + EI - BD$, $Q_3 = BDI + CEG - AEI - BFG$;

$$A = -24.48/(x_0 + 0.16)^2, B = 13.58, C = 0, D = -4.88y_0/(y_0 + 1.18),$$

$$E = -1.63 - 5.7584x_0/(y_0 + 1.18)^2 - 0.19r_0z_0/(y_0 + 0.19)^2, F = -r_0y_0/(y_0 + 0.19)$$

$$I = -937.8616/(z_0 + 29.09)^2, G = 0, H = 1.24$$

When $r = 1.40172563$, the equilibrium $O_1(0, 0, 0, 0)$ of system (4) have characteristic Roots $\xi_1 = 0.2060i$, $\xi_2 = -0.2060i$, $\xi_3 = -228.0827$ and $\xi_4 = 0$.

Let: $X = UY$, with $X = (x, y, z, r)'$ $Y = (u, v, w, s)'$

$$U = \begin{pmatrix} 1 & 0 & 0.1142 & 0.0214 \\ 0.0035 & 0 & 0.6117 & 0.8013 \\ 0 & 0.2160 & 0.738 & 0.8301 \\ 0 & 0 & 0 & 0.3553 \end{pmatrix}$$

System (4) can be rewritten as: $\dot{Y} = VY + W$ (4)

Where $\dot{Y} = (\dot{u}, \dot{v}, \dot{w}, \dot{s})'$ $W = (g_1, g_2, g_3, g_4)'$

$$V = \begin{pmatrix} -228.0827 & 0 & 0 & 0 \\ 0 & 0 & -0.2060 & 0 \\ 0 & 0.2060 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

$$g_1 = 7.3834s + 228.0823u + 3.618w - \sigma_2/(\sigma_4 + 0.16) - 0.0261(0.3143s + 1.3163)\sigma_1$$

$$+ 1.7620\sigma_1\sigma_3/(\sigma_1 + 0.1906) - 3.8053\sigma_1(\sigma_4 + 0.16)/(\sigma_1 + 1.1806) + 12.8125$$

$$g_2 = 0.8139s + 0.1083u + 2.9081w - 0.0026\sigma_2/(\sigma_4 + 0.1906)$$

$$- 1.9042(0.1103s + 3.3103)\sigma_1 - 22.1401\sigma_5/(\sigma_3 + 39.13)$$

$$+ 3.0702\sigma_1\sigma_3/(\sigma_1 + 0.1906) + 1.5796\sigma_1\sigma_4/(\sigma_1 + 1.1896) + 2.6331$$

$$g_3 = 1.2037\sigma_2/(\sigma_4 + 0.16) + 0.1301u - 0.6325v - 0.1371w - 0.0415s +$$

$$1.9833(0.4043s + 1.0167)\sigma_1 - 6.1027\sigma_1\sigma_3/(\sigma_1 + 1.1476) -$$

$$3.7272\sigma_1\sigma_4/(\sigma_1 + 3.1509) + 0.3448;$$

$$g_4 = 0$$

$$\sigma_1 = 1.7042s + 0.2016u + 0.8117w + 1.253;$$

$$\sigma_2 = 1.0154s + 12.33u + 1.2768w + 2.5982;$$

$$\sigma_3 = 0.9221s + 0.518v + 0.2672w + 1.6851;$$

$$\sigma_4 = 0.0214s + u + 0.3012w + 0.2051;$$

$$\sigma_5 = 11.6135s + 10.9161v + 16.8103w + 39.0417$$

The existence theorem of centre manifold tells us that system (4) has a centre manifold as:

$$W_{loc}^c(O_1) = \{(u, v, w, s) \in R^4 | u = h^*(v, w, s), h^*(0, 0, 0) = 0, Dh^*(0, 0, 0) = 0\}$$

Let $h^*(v, w, s) = a'v^2 + bw^2 + cs^2 + d'vw + evs + fws + \dots$,

we get $a' = 0.0003082517011, b = 0.000001385080502, c = 0.002383628106,$

$d' = 0.00000002147422404, e = 0.000002926062736, f = 0.0007443617052$

So, the system confined by this centre manifold of system (5) is:

$$\begin{pmatrix} \dot{v} \\ \dot{w} \end{pmatrix} = \begin{pmatrix} & -0.2060 \\ 0.2060 & \end{pmatrix} \begin{pmatrix} v \\ w \end{pmatrix} + \begin{pmatrix} f_1(v, w) \\ f_2(v, w) \end{pmatrix}$$

where $f_1(v, w) = 0.0027v^2 + 0.0016w^2 + 0.2424vw + \dots$;

$f_2(v, w) = 0.0101v^2 + 0.0103w^2 + 0.0618vw + \dots$.

The following statements are easily obtained base on the bifurcation theory:

$$\begin{aligned} a &= 1/16 [f_{uuu}^1 + f_{uuv}^1 + f_{uuv}^1 + f_{vvv}^1] \big| (0, 0, 0) + 1/16 \times 0.2060 [f_{uv}^1 (f_{uu}^1 + f_{vv}^1) - f_{uv}^2 (f_{uu}^2 + f_{vv}^2) \\ &\quad - f_{uu}^1 f_{uu}^2 + f_{vv}^1 f_{vv}^2] \big| (0, 0, 0) = 0.201705 > 0, \\ d &= d \operatorname{Re}(\lambda(s)) / ds \big| (0, 0, 0) = -0.112178 < 0. \end{aligned}$$

Hence, we can obtain: When $r = 1.40172563$, the supercritical Hopf bifurcation in system (2) occurs at O_1 . When $r > 1.4017$, the stability of Equilibrium O_1 changes. A limit cycle will occur around the area of O_1 , and system (1) can generate the calcium oscillations.

When $r = 3.3615$, the system confined by the center manifold of system (2) is:

$$\begin{pmatrix} \dot{v} \\ \dot{w} \end{pmatrix} = \begin{pmatrix} & -1.2075 \\ 1.2075 & \end{pmatrix} \begin{pmatrix} v \\ w \end{pmatrix} + \begin{pmatrix} f_1(v, w) \\ f_2(v, w) \end{pmatrix}$$

where $f_1(v, w) = 0.0037v^2 + 0.3034w^2 + 0.0489vw + \dots$;

$f_2(v, w) = -0.0019v^2 - 1.0762w^2 - 0.2312vw + \dots$.

The following statements are easily obtained base on the bifurcation theory:

$$\begin{aligned} a &= 1/16 [f_{uuu}^1 + f_{uuv}^1 + f_{uuv}^1 + f_{vvv}^1] \big| (0, 0, 0) + 1/16 \times 1.2075 [f_{uv}^1 (f_{uu}^1 + f_{vv}^1) - f_{uv}^2 (f_{uu}^2 + f_{vv}^2) \\ &\quad - f_{uu}^1 f_{uu}^2 + f_{vv}^1 f_{vv}^2] \big| (0, 0, 0) = 0.2061 > 0, \\ d &= d \operatorname{Re}(\lambda(s)) / ds \big| (0, 0, 0) = -0.1250 < 0. \end{aligned}$$

Base on the bifurcation theorem, we can get: When $r = 3.36150211$, the supercritical Hopf bifurcation in system (2) occurs at O_2 . For $r > 3.36150211$, the equilibrium O_2 become stable. A limit cycle will occur around the area of O_2 become unstable, and the oscillatory phenomenon disappears.

Numerical Simulation

Fig.1 The equilibrium points curve of $r - y$ for system (2).

The Fig.1 shows that the equilibrium $O(r)$ undergoes bifurcation two times, marked HB1 and HB2 of which the corresponding parameter values are $r_1 = 1.4017$, and $r_2 = 3.3615$ respectively. When $1 < r < r_1$, there exist a stable equilibrium of system (2). When r increases the equilibrium loses its stability at HB1 and returns to be stable at HB2.

Fig. 2(a) Stable periodic orbit for $r = 1.4017$ (b) Time series for $r = 1.4017$

Fig.3 (a) An orbit near a stable equilibrium for $r = 1.413$ (b) Time series for $r = 1.413$

Fig.2 (a) Shows the projection of stable periodic solutions in (x, y, z) -plane for $r = 1.413$, Fig.2 (b) indicates time series of x in system (2) for $r = 1.413$ and its period is $T = 5.17s$. Fig.3 shows a plot of one orbit near HB1 for $r = 1.413$ and sample time behaviors of x for $r = 1.413$.

Conclusions

In this paper, we first analyzed the nonlinear dynamics of the Kummer-Olsen calcium oscillation model in non-excitable cells by using the qualitative theory, bifurcation theorem and the center manifold theory, including the stability and classification of the equilibrium points with parameter value. It is shown that supercritical Hopf bifurcations play very important roles in calcium oscillations. Furthermore, some new numerical simulations have confirmed the theoretical analysis results. Based on the existing numerical results with the theoretical analysis, complex dynamics of has been described perfectly.

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References

- [1] R.E.Dolmetsch,K.Xu and R.S.Lewis,Calcium oscillations increase the efficiency and specificity of gene expression,*Nature*,vol.392,no.6679,pp.933-936,1998.
- [2] Dupont G,Swillens,Clair C,Tordjmann T,Combettes L.Hierarchical organization of calcium signals in hepatocytes:From experiments to models.*Biophys Acta* 2000;1498:134-52.
- [3] J.A.M Borghans, G. Dupont, A. Goldbeter: *Biophys Chem*, Vol. 66 (1997), p.25.
- [4] Schuster S,Marhl M,Hofer T.Modelling of simple and complex calcium oscillations.From single-cell responses to intercellular signaling. *Eur J Biochem*
- [5] P. Shen and R. Larter : *Biophys Chem*, Vol. 66 (1997), p. 25.
- [6] M. Marhl, T. Haberichter, M. Brumen and R. Heinrich: *BioSystems*, Vol. 57 (2000), p.75.
- [7] Z.J. Jing, Y. Chang and G.R. Chen: *Chaos, Solitons and Fractals*, Vol. 22 (2004) No.4, p.831.
- [8] S. Wiggins: *Introduction to Applied Nonlinear Dynamical Systems and Chaos*. (Springer, Germany 1990), p.5.
- [9] U. Kummer, L.F. Olsen, C.J. Dixon, A.K. Green, E. Borhberg-Bauer and G. Baier: *Biophys*, Vol. 79 (2000) No.11, p.88.