frontiers in Physics

BRIEF RESEARCH REPORT
published: 14 August 2020
doi: 10.3389/fphy.2020.00258

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# Bifurcation and Numerical Simulations of $Ca^{2+}$ Oscillatory Behavior in Astrocytes

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In this paper, the dynamical analysis of $Ca^{2+}$ oscillations in astrocytes is theoretically investigated by the center manifold theorem and the stability theory of equilibrium point. The global structure of bifurcation and evoked $Ca^{2+}$ dynamics are presented in a human astrocyte model from a mathematical perspective. Results show that the difference in appearance and disappearance of $Ca^{2+}$ oscillations is partly due to two subcritical Hopf bifurcation points. In addition, the numerical simulations are performed to further verify the effectiveness of the proposed method.

**Keywords: astrocyte, equilibrium, Hopf bifurcation, center manifold, stability**

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**Specialty section:**
*This article was submitted to Mathematical and Statistical Physics, a section of the journal Frontiers in Physics*

**Received:** *02 May 2020*
**Accepted:** *10 June 2020*
**Published:** *14 August 2020*

**Citation:**
*Zuo H and Ye M (2020) Bifurcation and Numerical Simulations of $Ca^{2+}$ Oscillatory Behavior in Astrocytes. Front. Phys. 8:258. doi: 10.3389/fphy.2020.00258*

## INTRODUCTION

$Ca^{2+}$ as an important second messenger in the cytosol is critical for synaptic neurons and glia cells in the brain [1]. The oscillatory changes in concentration of $Ca^{2+}$ are called $Ca^{2+}$ oscillations and play an active part in the transmission of chemical and electrical signaling process [2]. Astrocytes comprise approximately 50% of the volume of human brain and exhibit not only neuron-dependent $Ca^{2+}$ oscillations but also spontaneous $Ca^{2+}$ waves [3]. It was demonstrated that the frequencies and amplitudes of $Ca^{2+}$ oscillations play key roles in $Ca^{2+}$ signal transduction in the nervous system [4]. Recent results from experiment calcium release-activated calcium channel (CRAC) have shown that it is effective for the control in inhibiting neuronal excitability by enhancing calcium release from astrocytes [5].

It was generally considered that $Ca^{2+}$ oscillations in astrocyte take place in response to external stimuli, inducing the release of neuro-active chemicals [6, 7]. This view began to change as several lines of evidence indicate that these oscillations can also be formed spontaneously [8]. Nevertheless, the mechanism and functional role involved in these stochastic spontaneous $Ca^{2+}$ waves are still not well-understood. Basically, $Ca^{2+}$ signal transmission of astrocytes in the brain may vary owing to certain bifurcation principles, and different chemical information is typically characterized by frequency, amplitude, and spatial $Ca^{2+}$ propagation [9]. Dynamical mechanisms that underlie the $Ca^{2+}$ waves have been investigated from both theoretical and experimental points of view in recent years [10–18]. Therefore, the stability and bifurcation analysis are fundamental to investigate the appearance and disappearance of spontaneous $Ca^{2+}$ oscillations in astrocytes. In the last decades, existing mathematical models helped explore the possible dynamical mechanism of these oscillatory activities in neuronal excitability [19–23].

## STABILITY OF EQUILIBRIUM POINT AND BIFURCATION ANALYSIS

In the present work, we apply an extension of the one-pool model proposed by Lavrentovich and Hemkin as a specific example of the stability of equilibrium point and the bifurcation scenario. This model consists of three main variables: cytosol $Ca^{2+}$ concentration ($Ca_{\text{cyt}}$), $Ca^{2+}$ concentration in the endoplasmic reticulum ($Ca_{\text{er}}$), and $IP_3$ concentration in cell ($IP_3$). The equations and meanings of each expression in the model are given as follows:

$$\begin{cases} \frac{dCa_{\text{cyt}}}{dt} = v_{in} - k_{\text{out}}Ca_{\text{cyt}} + v_{\text{CICR}} - v_{\text{serca}} + k_f\left(Ca_{\text{er}} - Ca_{\text{cyt}}\right), \\ \frac{dCa_{\text{er}}}{dt} = v_{\text{serca}} - v_{CICR} - k_f\left(Ca_{\text{er}} - Ca_{\text{cyt}}\right), \\ \frac{dIP_3}{dt} = v_{\text{PLC}} - k_{\text{deg}}IP_3, \end{cases} \tag{1}$$

where

$$\begin{aligned} v_{\text{serca}} &= v_{M2}\left(\frac{Ca_{\text{cyt}}^2}{Ca_{\text{cyt}}^2 + k_2^2}\right), \\ V_{\text{PLC}} &= v_p\left(\frac{Ca_{\text{cyt}}^2}{Ca_{\text{cyt}}^2 + k_p^2}\right), \\ v_{\text{CICR}} &= 4v_{M3}\left(\frac{k_{\text{CaA}}^n Ca_{\text{cyt}}^n}{\left(Ca_{\text{cyt}}^n + k_{\text{CaA}}^n\right)\left(Ca_{\text{cyt}}^n + k_{\text{CaI}}^n\right)}\right) \\ &\times \left(\frac{IP_3^m}{IP_3^m + k_{\text{ip3}}^m}\right)\left(Ca_{\text{er}} - Ca_{\text{cyt}}\right). \end{aligned}$$

The details of each parameter can be found in **Table 1** and [4].

**TABLE 1** | Model parameters for which all results are computed unless otherwise stated.

| | | | | | |
|---|---|---|---|---|---|
| $v_{M2}$ | 15 μM/s | $v_{M3}$ | 40.0 $s^{-1}$ | $k_{out}$ | 0.5 $s^{-1}$ |
| $k_{deg}$ | 0.08 $s^{-1}$ | $k_2$ | 0.1 μM | $m$ | 2.2 |
| $k_{CaA}$ | 0.15 μM | $k_{CaI}$ | 0.15 μM | $n$ | 2.02 |
| $k_{ip3}$ | 0.1 μM | $k_p$ | 0.3 μM | $k_f$ | 0.5 $s^{-1}$ |

## ANALYSIS OF STABILITY AND BIFURCATION OF EQUILIBRIA

In the following, $v_{\text{in}}$ is chosen as the bifurcation parameter, corresponding to $Ca^{2+}$ inflow into the cytosol through the astrocyte's membrane.

For convenience, let $x = Ca_{\text{cyt}}$, $y = Ca_{\text{er}}$, $z = \text{IP}_3$, and $r = v_{\text{in}}$, we first rewrite model (1) as the following form:

$$\begin{cases} \dot{x} = r - x + 0.5y - \frac{15x^2}{x^2+0.01} - \frac{3.466x^{2.02}z^{2.2}(x-y)}{(x^{2.02}+0.022)(z^{2.2}+0.0063)}, \\ \dot{y} = 0.5x - 0.5y + \frac{15x^2}{x^2+0.01} + \frac{3.466x^{2.02}z^{2.2}(x-y)}{(x^{2.02}+0.022)(z^{2.2}+0.0063)}, \\ \dot{z} = \frac{0.05x^2}{x^2+0.09} - 0.08z. \end{cases} \tag{2}$$

The equilibrium of system (2) meets the following equations:

$$\begin{cases} x = \frac{r}{k_{\text{out}}} \\ z = \frac{v_{\text{p}}x^2}{\left(x^2+k_{\text{p}}^2\right)k_{\text{deg}}} \\ y = \frac{v_{\text{serca}} - v_{\text{CICR}} + k_{\text{f}}x}{k_{\text{f}}} \end{cases} \tag{3}$$

Let $x_0$, $y_0$, and $z_0$ be the roots of Equation (2) and $x_1 = x - x_0$, $y_1 = y - y_0$, and $z_1 = z - z_0$, we have the following representations:

$$\begin{cases} \dot{x}_1 = r - (x_1 + x_0) + 0.5\left(y_1 + y_0\right) - \frac{15(x_1+x_0)^2}{(x_1+x_0)^2+0.01} - \\ \qquad \frac{3.466(x_1+x_0)^{2.02}(z_1+z_0)^{2.2}(x_1+x_0-y_1-y_0)}{\left((x_1+x_0)^{2.02}+0.022\right)\left((z_1+z_0)^{2.2}+0.0063\right)}, \\ \dot{y}_1 = 0.5(x_1 + x_0) - 0.5\left(y_1 + y_0\right) + \frac{15(x_1+x_0)^2}{(x_1+x_0)^2+0.01} \\ \qquad + \frac{3.466(x_1+x_0)^{2.02}(z_1+z_0)^{2.2}(x_1+x_0-y_1-y_0)}{\left((x_1+x_0)^{2.02}+0.022\right)\left((z_1+z_0)^{2.2}+0.0063\right)}, \\ \dot{z}_1 = \frac{0.05(x_1+x_0)^2}{(x_1+x_0)^2+0.09} - 0.08(z_1 + z_0). \end{cases} \tag{4}$$

The corresponding equilibrium is (0, 0, 0), and system (4) has the same properties with the equilibrium of system (2). With simple calculation, it is easy to calculate the Jacobian matrix of system (4),

$$\text{A} = (a_{ij})_{3\times3} = \begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix},$$

where

$$\begin{aligned} a_{11} &= \frac{30x^3}{\left(x^2+0.01\right)^2} - \frac{30}{x^2+0.01} - \frac{3.465966x^{2.02}z^{2.2}}{\sigma} \\ &- \frac{7.0012517x^{1.02}z^{2.2}\left(x-y\right)}{\sigma} + \frac{14.002503x^{3.04}z^{2.2}\left(x-y\right)}{\sigma\left(x^{2.02}+0.021622\right)} - 1, \\ a_{12} &= \frac{3.465966x^{2.02}z^{2.2}}{\sigma} + 0.5, \\ a_{13} &= \frac{7.6251256x^{2.02}z^{3.4}\left(x-y\right)}{\sigma\left(z^{2.2}+0.00630957\right)} - \frac{7.625125x^{2.02}z^{1.2}\left(x-y\right)}{\sigma}, \\ a_{21} &= -\frac{30x^3}{\left(x^2+0.01\right)^2} + \frac{30}{x^2+0.01} + \frac{3.465966x^{2.02}z^{2.2}}{\sigma} \\ &+ \frac{7.0012517x^{1.02}z^{2.2}\left(x-y\right)}{\sigma} - \frac{14.002503x^{3.04}z^{2.2}\left(x-y\right)}{\sigma\left(x^{2.02}+0.021622\right)} + 0.5, \end{aligned}$$

$$
\begin{aligned}
a_{22} &= -\frac{3.465966x^{2.02}z^{2.2}}{\sigma} - 0.5,\\
a_{23} &= -\frac{7.6251256x^{2.02}z^{3.4}\left(x-y\right)}{\sigma\left(z^{2.2}+0.00630957\right)} + \frac{7.625125x^{2.02}z^{1.2}\left(x-y\right)}{\sigma},\\
a_{31} &= \frac{0.1x}{x^2+0.09} - \frac{0.1x^3}{\left(x^2+0.09\right)^2},\\
a_{32} &= 0,\\
a_{33} &= -0.8,\\
\sigma &= \left(x^{2.02}+0.02166228\right)^2\left(z^{2.2}+0.0063095\right).
\end{aligned}
$$

And one can easily obtain the following characteristic equation:

$$\lambda^3 + Q_3\lambda^2 + Q_2\lambda + Q_1 = 0,$$

where

$$
\begin{aligned}
Q_1 &= -\left(a_{11}+a_{22}+a_{33}\right),\\
Q_2 &= a_{11}a_{22}+a_{11}a_{33}+a_{22}a_{33}-a_{13}a_{31}-a_{12}a_{21}-a_{32}a_{23},\\
Q_3 &= a_{31}a_{13}a_{22}+a_{12}a_{21}a_{33}+a_{32}a_{23}a_{11}-a_{11}a_{22}a_{33}\\
&\quad - a_{12}a_{23}a_{31}-a_{13}a_{21}a_{32}.
\end{aligned}
$$

After a simple calculation, we have the following equations:

$$
\begin{aligned}
Q_1 &= \frac{30x}{x^2+0.01} - \frac{30x^3}{\left(x^2+0.01\right)^2} + \frac{6.93193x^{2.02}z^{2.2}}{\sigma_{11}}\\
&+\frac{7.00125x^{1.02}z^{2.2}\left(x-y\right)}{\sigma_{11}} - \frac{14.0025x^{3.04}z^{2.2}\left(x-y\right)}{\left(x^{2.02}+0.02166\right)^3\left(z^{2.2}+0.0063\right)},\\
Q_2 &= -\left(\frac{0.1x^3}{\left(x^2+0.09\right)^2} - \frac{0.1x}{x^2+0.09}\right)\left(\frac{7.62512x^{2.02}z^{1.2}\left(x-y\right)}{\sigma_{21}}\right.\\
&\left.-\frac{7.62512x^{2.02}z^{3.4}\left(x-y\right)}{\sigma_{22}\left(z^{2.2}+0.0063\right)^2}\right) - \frac{24x^3}{\sigma_{23}} + 0.5\left(\sigma_{22}+0.5\right)\\
&+\frac{0.55455x^{2.02}z^{2.2}}{\sigma_{21}} + \frac{0.5601x^{1.02}z^{2.2}\left(x-y\right)}{\sigma_{22}}\\
&-\frac{1.1202x^{3.04}z^{2.2}\left(x-y\right)}{\sigma_{24}} + \frac{2.4x}{x^2+0.01} + 0.12,\\
Q_3 &= 0.004\left(\frac{3.465966x^{2.02}z^{2.2}}{\left(x^{2.02}+0.02166\right)^2\left(z^{2.2}+0.0063\right)}\right),
\end{aligned}
$$

where

$$
\begin{aligned}
\sigma_{11} &= \left(x^{2.02}+0.02166\right)^2\left(z^{2.2}+0.0063\right),\\
Q_{21} &= \left(z^{2.2}+0.0063\right)\sigma_{22},\\
Q_{22} &= \left(x^{2.02}+0.02166\right)^2,\\
Q_{23} &= \left(x^2+0.01\right)^2,\\
Q_{24} &= \left(x^{2.02}+0.02166\right)^3\left(z^{2.2}+0.006309\right),
\end{aligned}
$$

Owing to the meaning of $x$, $y$, $z$ and $r$, special conditions meet the needs whether there exists equilibrium of system (4) when $r \in [0.02, 0.06]$.

We consider the Hurwitz matrix using coefficients $Q_i$ of the characteristic polynomial:

$$H_1 = \left(Q_1\right),\ H_2 = \begin{pmatrix} Q_1 & 1 \\ Q_3 & Q_2 \end{pmatrix},\ H_3 = \begin{pmatrix} Q_1 & 1 & 0 \\ Q_3 & Q_2 & 1 \\ 0 & 0 & Q_3 \end{pmatrix}.$$

It is easy to verify that the eigenvalues of the linearized system are negative or have a negative real part if the determinants of the three Hurwitz matrices are positive:

$$\det\left(H_i\right) > 0,\ i = 1, 2, 3,$$

Consider the stability and bifurcations of system (4) for varying parameter $v_{\text{in}}$ in the case of the following Routh–Hurwitz criteria:

$$Q_1 > 0,\ Q_3 > 0,\ Q_1Q_2 > Q_3.$$

The corresponding two values can be obtained:

$$r_1 = 0.02383, r_2 = 0.05944.$$

After the computation based on the Routh–Hurwitz criteria, when we choose $r_1 = 0.02383$,

$$
\begin{aligned}
Q_1 &= 68.4381 > 0,\ Q_3 = 0.02838 > 0,\ Q_1Q_2\\
&- Q_3 = 0.775418 > 0.
\end{aligned}
$$

As $r_2 = 0.05944$,

$$
\begin{aligned}
Q_1 &= 60.5333804 > 0,\ Q_3 = 0.64149 > 0,\ Q_1Q_2\\
&- Q_3 = 0.027890411 > 0.
\end{aligned}
$$

It can be seen that all the two values satisfy the Routh–Hurwitz criteria. After using the normal form method, one can easily obtain the following conclusions:

(1) $r < 0.02383$, there is a stable node of system (4);
(2) $r = 0.02383$, and system (4) has a non-hyperbolic equilibrium $O_1 = (0.04766, 3.96096098, 0.0153858)$;
(3) $0.02383 < r < 0.05944$, system (4) has an equilibrium (saddle);
(4) $r = 0.05944$, and there exists a non-hyperbolic equilibrium $O_2 = (0.11886, 0.6665221778, 0.0847979)$;
(5) $r > 0.05944$, there is a stable node.

Let $r = r_0$, $x_1 = x - x_0$, $y_1 = y - y_0$, $z_1 = z - z_0$, and $r_1 = r - r_0$, the equilibrium of system (4) is $(x_0, y_0, z_0)$. In order to apply the center manifold theorem with bifurcation parameter $v_{\text{in}}$, a new variable $r_1$ is introduced in the original model. On the basis of $dr_1/dt = 0$, we have the following:

$$\begin{cases} \dot{x}_1 = (r_1 + r_0) - \frac{3.466(x_1+x_0)^{2.02}(z_1+z_0)^{2.2}(x_1+x_0-y_1-y_0)}{((x_1+x_0)^{2.02}+0.02166)((z_1+z_0)^{2.2}+0.00631)} \\ \quad - \frac{15(x_1+x_0)^2}{(x_1+x_0)^2+0.01} - (x_1+x_0) + 0.5\left(y_1+y_0\right), \\ \dot{y}_1 = \frac{15(x_1+x_0)^2}{(x_1+x_0)^2+0.01} + \frac{3.466(x_1+x_0)^{2.02}(z_1+z_0)^{2.2}(x_1+x_0-y_1-y_0)}{((x_1+x_0)^{2.02}+0.02166)((z_1+z_0)^{2.2}+0.00631)} \\ \quad +0.5\left(x_1+x_0-y_1-y_0\right), \\ \dot{z}_1 = \frac{0.05(x_1+x_0)^2}{(x_1+x_0)^2+0.09} - 0.08\left(z_1+z_0\right), \\ \dot{r}_1 = 0. \end{cases} \quad (5)$$

$r_1 = 0$, $O(x_1, y_1, z_1, r_1) = (0, 0, 0, 0)$ is the equilibrium of system (5), which has a same conclusion as the one of system (2) in stability and bifurcations.

For $r_0 = 0.02383$, the Jacobian matrix of system (4) has the following form:

$$\begin{pmatrix} -67.6083 & 0.71022 & 115.6304 & 1 \\ 67.1083 & -0.71022 & -115.6304 & 0 \\ 0.05041 & 0 & -0.08 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

We have the eigenvalues of equilibrium point $O_1 = (0, 0, 0, 0)$ of system (5): $\xi_1 = -68.3987$, $\xi_2 = 0.0204i$, $\xi_3 = -0.0204i$, $\xi_4 = 0$, and the eigenvectors have met the following matrix:

$$\begin{pmatrix} -0.7097 & -0.0018-0.0406i & -0.0018+0.0406i & 0.1217 \\ 0.7045 & 0.9989 & 0.9989 & -0.9877 \\ 0.0005 & -0.0072-0.0238i & -0.0072+0.0238i & -0.0767 \\ 0 & 0 & 0 & 0.0608 \end{pmatrix}.$$

Suppose

$$\begin{pmatrix} x_1 \\ y_1 \\ z_1 \\ r_1 \end{pmatrix} = U \begin{pmatrix} u \\ v \\ w \\ s \end{pmatrix},$$

where

$$U = \begin{pmatrix} -0.7097 & -0.0018 & 0.0406 & 0.1217 \\ 0.7045 & 0.9989 & 0 & -0.9877 \\ 0.0005 & -0.0072 & 0.0238 & 0.0767 \\ 0 & 0 & 0 & 0.0608 \end{pmatrix}.$$

System (5) has the following form

$$\begin{pmatrix} \dot{u} \\ \dot{v} \\ \dot{w} \\ \dot{s} \end{pmatrix} = \begin{pmatrix} -68.3987 & 0 & 0 & 0 \\ 0 & 0 & -0.0204 & 0 \\ 0 & 0.0204 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} u \\ v \\ w \\ s \end{pmatrix} + \begin{pmatrix} g_1 \\ g_2 \\ g_3 \\ g_4 \end{pmatrix}, \quad (6)$$

and

$$\begin{pmatrix} \dot{x}_1 \\ \dot{y}_1 \\ \dot{z}_1 \\ \dot{r}_1 \end{pmatrix} = U \begin{pmatrix} \dot{u} \\ \dot{v} \\ \dot{w} \\ \dot{s} \end{pmatrix} \Rightarrow \begin{pmatrix} \dot{u} \\ \dot{v} \\ \dot{w} \\ \dot{s} \end{pmatrix} = U^{-1} \begin{pmatrix} \dot{x}_1 \\ \dot{y}_1 \\ \dot{z}_1 \\ \dot{r}_1 \end{pmatrix} = U^{-1} \begin{pmatrix} f_1 \\ f_2 \\ f_3 \\ 0 \end{pmatrix},$$

where

$$\begin{aligned} f_1 &= g_{14} - 15g_{11}^2/\left(g_{11}^2 + 0.01\right) - g_{11} + 0.5g_{12} \\ &- [3.465966222{g_{11}}^{2.02}{g_{13}}^{2.2}\left(g_{11} - g_{12}\right)] \\ &/ \left[\left({g_{11}}^{2.02} + 0.02166228889\right)^2\left({g_{13}}^{2.2} + 0.006309573445\right)\right], \\ f_2 &= 15g_{11}^2/\left(g_{11}^2 + 0.01\right) + 0.5\left(g_{11} - g_{12}\right) \\ &+ [3.465966222{g_{11}}^{2.02}{g_{13}}^{2.2}\left(g_{11} - g_{12}\right)] \\ &/ \left[\left({g_{11}}^{2.02} + 0.02166228889\right)^2\left({g_{13}}^{2.2} + 0.006309573445\right)\right], \\ f_3 &= 0.05g_{11}^2/\left(g_{11}^2 + 0.09\right) - 0.08g_{13}, \\ g_{11} &= x_1 + x_0 = -0.7097u - 0.0018v + 0.0406w + 0.1217s \\ &+ 0.04766, \\ g_{12} &= y_1 + y_0 = 0.7045u + 0.9989v - 0.9877s + 3.96096, \\ g_{13} &= z_1 + z_0 = 0.0005u - 0.0072v + 0.0238w + 0.0767s \\ &+ 0.01538, \\ g_{14} &= 0.0608s + 0.02383. \end{aligned}$$

Furthermore,

$$\begin{pmatrix} g_1 \\ g_2 \\ g_3 \\ g_4 \end{pmatrix} = U^{-1} \begin{pmatrix} f_1 \\ f_2 \\ f_3 \\ 0 \end{pmatrix} - \begin{pmatrix} -68.3987 & 0 & 0 & 0 \\ 0 & 0 & -0.0204 & 0 \\ 0 & 0.0204 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} u \\ v \\ w \\ s \end{pmatrix},$$

where

$$U^{-1} = \begin{pmatrix} -1.3929 & 0.0146 & 2.3761 & 0.0280 \\ 0.9824 & 0.9908 & -1.6758 & 16.2432 \\ 0.3264 & 0.2994 & 41.4599 & -48.0914 \\ 0 & 0 & 0 & 16.4474 \end{pmatrix}.$$

Through calculation, we have the following equations:

$$\begin{aligned} g_1 &= -1.3928f_1 + 0.0146f_2 + 2.3761f_3 + 68.3987u, \\ g_2 &= 0.9823f_1 + 0.9907f_2 - 1.6757f_3 + 0.0204w, \\ g_3 &= 0.3264f_1 + 0.2994f_2 + 41.4599f_3 - 0.0204v, \\ g_4 &= 0. \end{aligned}$$

On the basis of the center manifold theory, one can conclude that there exists a center manifold of system (5), and its form can be expressed as

$$W_{loc}^{c}(O_1) = \left\{(u, v, w, s) \in R^4 \middle| u = h^*(v, w, s), h^*(0,0,0) = 0, Dh^*(0,0,0) = 0\right\}. \quad (7)$$

Substituting Equation (7) into Equation (6), the following equations can be derived as:

$$\begin{pmatrix} \dot{h^*(v, w, s)} \\ \dot{v} \\ \dot{w} \\ \dot{s} \end{pmatrix} = \begin{pmatrix} -68.3987 & 0 & 0 & 0 \\ 0 & 0 & -0.0204 & 0 \\ 0 & 0.0204 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} h^*(v, w, s) \\ v \\ w \\ s \end{pmatrix} + \begin{pmatrix} g_1 \\ g_2 \\ g_3 \\ g_4 \end{pmatrix}.$$

Let $h(v, w, s) = av^2 + bw^2 + cs^2 + dvw + evs + fws + \ldots$, and the center manifold of system (5) is

$$N(h) = Dh \cdot \begin{bmatrix} \dot{v} \\ \dot{w} \\ \dot{s} \end{bmatrix} + 68.3987h - g_1 \equiv 0. \quad (8)$$

Using the method of high-order partial derivatives, one can obtain the following equations:

$$\begin{pmatrix} 136.79775 & 0 & 0 & 0.0406996 & 0 & 0 \\ 0 & 136.7975 & 0 & -0.04082 & 0 & 0 \\ 0 & 0 & 136.7973 & 0 & -0.000102 & -0.00002 \\ -0.040825 & 0.040699 & 0 & 68.39882 & 0 & 0 \\ -0.000102 & 0 & 0 & -0.000011 & 68.3987 & 0.020349 \\ 0 & -0.0000226 & 0 & -0.000051 & -0.02031 & 68.39873 \end{pmatrix} \begin{pmatrix} a \\ b \\ c \\ d \\ e \\ f \end{pmatrix} = 0.$$

Based on the center manifold theory, one can compute $a = -0.00094$, $b = -0.12224$, $c = -1.15703$, $d = 0.03634$, $e = 0.10863$, and $f = -0.75265$. So the system that is confined to this center manifold is as follows:

$$\begin{pmatrix} \dot{v} \\ \dot{w} \end{pmatrix} = \begin{pmatrix} 0 & -0.0204 \\ 0.0204 & 0 \end{pmatrix} \begin{pmatrix} v \\ w \end{pmatrix} + \begin{pmatrix} f^1(v, w) \\ f^2(v, w) \end{pmatrix}, \quad (9)$$

where

$$\begin{aligned} f^1(v, w) &= 0.014915s - 0.004304v + 0.00382w + 0.037228sv \\ &\quad - 0.257924sw + 0.012455vw + \cdots, \\ f^2(v, w) &= 0.017292v - 0.269399s - 0.086114w + 0.014479sv \\ &\quad - 0.100315sw + 0.004844vw + \cdots. \end{aligned}$$

Hence, it is easy to verify that

$$\begin{aligned} a &= \frac{1}{16}\left[f_{vvv}^1 + f_{vww}^1 + f_{vvw}^2 + f_{www}^2\right]\Big|_{(0,0)} \\ &+ \frac{1}{16 \times 0.0204}\left[f_{vw}^1(f_{vv}^1 + f_{ww}^1)\right. \\ &- \left. f_{vw}^2(f_{vv}^2 + f_{ww}^2) - f_{vv}^1 f_{vv}^2 + f_{ww}^1 f_{ww}^2)\right]\Big|_{(v=0,w=0,s=0)} \\ &= 0.1014870557 > 0, \\ d &= \frac{d(\mathrm{Re}(\xi(s)))}{ds}\Big|_{(v=0,w=0,s=0)} = -0.0189 < 0. \end{aligned}$$

From the discussion above, we summarize the following conclusions.

**Conclusion 1:** A subcritical Hopf bifurcation occurs when $r$ passes through $r_0 = 0.02383$ of system (2). $r < r_0$, and the equilibrium $O_1$ is stable. $r > r_0$, and the equilibrium loses its stability; meanwhile, a stable periodic solution occurs, and system (2) begins to oscillate.

$r_0 = 0.05944$, eigenvalues of equilibrium point $O_2 = (0, 0, 0, 0)$ of system (3) are $\xi_1 = -60.5573$, $\xi_2 = 0.1029i$, $\xi_3 = -0.1029i$, and $\xi_4 = 0$, respectively. System (5) has the following form:

$$\begin{pmatrix} \dot{u} \\ \dot{v} \\ \dot{w} \\ \dot{s} \end{pmatrix} = \begin{pmatrix} -60.5573 & 0 & 0 & 0 \\ 0 & 0 & -0.1029 & 0 \\ 0 & 0.1029 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} u \\ v \\ w \\ s \end{pmatrix} + \begin{pmatrix} g_1 \\ g_2 \\ g_3 \\ g_4 \end{pmatrix}, \quad (10)$$

$$\begin{pmatrix} \dot{u} \\ \dot{v} \\ \dot{w} \\ \dot{s} \end{pmatrix} = U^{-1} \begin{pmatrix} f_1 \\ f_2 \\ f_3 \\ 0 \end{pmatrix},$$

where

$$U = \begin{pmatrix} -0.71 & 0.0393 & 0.1915 & 0.1341 \\ 0.7042 & -0.9695 & 0 & -0.9748 \\ 0.0012 & 0.1328 & 0.0654 & 0.1654 \\ 0 & 0 & 0 & 0.067 \end{pmatrix},$$

$$\begin{aligned} f_1 &= g_{14} - \frac{15g_{11}^2}{(g_{11}^2 + 0.01)} - g_{11} + 0.5g_{12} \\ &- \frac{\left[3.465966222{g_{11}}^{2.02}{g_{13}}^{2.2}\left(g_{11} - g_{12}\right)\right]}{\left[\left({g_{11}}^{2.02} + 0.02166228889\right)^2\left({g_{13}}^{2.2} + 0.006309573445\right)\right]}, \end{aligned}$$

$$f_2 = \frac{15g_{11}^2}{\left(g_{11}^2+0.01\right)} + 0.5\left(g_{11}-g_{12}\right) + \frac{\left[3.465966222 g_{11}{}^{2.02} g_{13}{}^{2.2}\left(g_{11}-g_{12}\right)\right]}{\left[\left(g_{11}{}^{2.02}+0.02166228889\right)^2\left(g_{13}{}^{2.2}+0.006309573445\right)\right]},$$

$$f_3 = \frac{0.05g_{11}^2}{\left(g_{11}^2+0.09\right)} - 0.08g_{13}.$$

And $g_{1j}\ \left(j=1,\ \ldots,4\right)$ have the following different formulae:

$$\begin{aligned} g_{11} &= x_1 + x_0 = -0.71u + 0.0393v + 0.1915w + 0.1341s \\ &\quad + 0.1189, \\ g_{12} &= y_1 + y_0 = 0.7042u - 0.9695v - 0.9748s + 0.6664, \\ g_{13} &= z_1 + z_0 = 0.0012u + 0.1328v + 0.0654w + 0.1654s \\ &\quad + 0.0848, \\ g_{14} &= 0.067s + 0.05944, \end{aligned}$$

$$\begin{pmatrix} g_1 \\ g_2 \\ g_3 \\ g_4 \end{pmatrix} = U^{-1}\begin{pmatrix} f_1 \\ f_2 \\ f_3 \\ 0 \end{pmatrix} - \begin{pmatrix} -60.5573 & 0 & 0 & 0 \\ 0 & 0 & -0.1029 & 0 \\ 0 & 0.1029 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}\begin{pmatrix} u \\ v \\ w \\ s \end{pmatrix}, \tag{11}$$

which reduce to the following equations:

$$\begin{aligned} g_1 &= -1.0337f_1 + 0.3727f_2 + 3.0268f_3 + 60.5573u, \\ g_2 &= -0.7508f_1 - 0.7607f_2 + 2.1985f_3 + 0.1029w, \\ g_3 &= 1.5436f_1 + 1.5379f_2 = 10.7708f_3 - 0.1029v, \\ g_4 &= 0. \end{aligned}$$

The center manifold of system (5) is

$$N(h) = Dh \cdot \begin{bmatrix} \dot{v} \\ \dot{w} \\ \dot{s} \end{bmatrix} + 60.5573h - g_1 \equiv 0,$$

where

$$u = h^*(v,w,s), h^*(0,0,0) = 0, Dh^*(0,0,0) = 0.$$

And thus, the following equation can be obtained:

$$\begin{pmatrix} 105.4628 & 0 & 0 & 0.04089 & 0 & 0 \\ 0 & 105.462 & 0 & 0.04077 & 0 & 0 \\ 0 & 0 & 105.4628 & 0 & 0.00001678 & -0.0001493 \\ 0.040771 & -0.0408 & 0 & 52.7313 & 0 & 0 \\ 0.000067 & 0 & 0 & -0.0000746 & 652.73142 & -0.02044 \\ 0 & -0.00014 & 0 & 0.0000339 & 0.0203859 & 52.7313498 \end{pmatrix}\begin{pmatrix} a \\ b \\ c \\ d \\ e \\ f \end{pmatrix} = 0.$$

We compute $a = 1.073869652$, $b = 0.3254214051$, $c = 1.590904144$, $d = 0.8641549$, $e = 2.5838022$, and $f = 1.1901543$. So the system confined to the center manifold of system (5) is

$$\begin{pmatrix} \dot{v} \\ \dot{w} \end{pmatrix} = \begin{pmatrix} 0 & -0.1029 \\ 0.1029 & 0 \end{pmatrix}\begin{pmatrix} v \\ w \end{pmatrix} + \begin{pmatrix} f^1(v,w) \\ f^2(v,w) \end{pmatrix}, \tag{12}$$

where

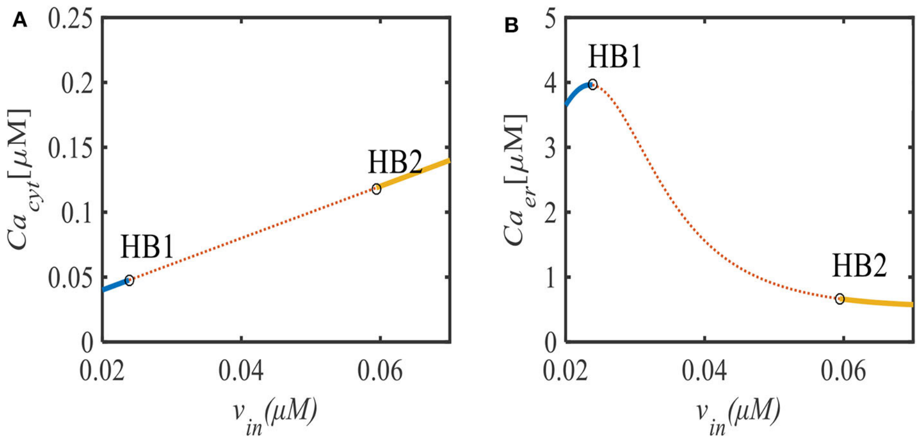


**FIGURE 1 | (A)** Bifurcation diagram of the equilibrium of system (2) in the ($v_{in}$, $Ca_{cyt}$)-plane. **(B)** Bifurcation diagram of the equilibrium of system (2) in the ($v_{in}$, $Ca_{er}$)-plane. Points HB1 and HB2 are the Hopf bifurcation points.

$$\begin{aligned} f^1(v,w) &= 0.079838w - 0.013612v - 0.034559\,s - 0.671091sv \\ &\quad - 0.309119sw - 0.224447vw + \cdots, \\ f^2(v,w) &= 1.423469sv - 0.168005v - 0.204689w - 0.145723s \\ &\quad + 0.655680sw + 0.476081vw + \cdots. \end{aligned}$$

By computation, Conclusion 2 can be inferred as follows:

$$\begin{aligned} a &= \frac{1}{16}\,[f^1_{vvv} + f^1_{vww} + f^2_{vvw} + f^2_{www}]|_{(0,0)} \\ &\quad + \frac{1}{16\times 0.1029}[f^1_{vw}(f^1_{vv} + f^1_{ww}) \\ &\quad - f^2_{vw}(f^2_{vv} + f^2_{ww}) - f^1_{vv}f^2_{vv} + f^1_{ww}f^2_{ww})]|_{(v=0,w=0,s=0)} \\ &= 0.2483398204 > 0, \\ d &= \frac{d(\mathrm{Re}(\xi(s)))}{ds}\Big|_{(v=0,w=0,s=0)} = -0.00069 < 0. \end{aligned}$$

**Conclusion 2**: A subcritical Hopf bifurcation occurs when $r$ passes through $r_0 = 0.05944$ of system (2). $r < r_0$, the equilibrium $O_2$ is unstable, and system (2) begins to oscillate. $r > r_0$, the equilibrium $O_2$ is stable, and the global oscillations of system (2) vanish.

## NUMERICAL SIMULATIONS

In order to investigate the bifurcation phenomenon in different $Ca^{2+}$ oscillation patterns, we study the generation process with respect to the parameter $v_{\mathrm{in}}$. The bifurcation diagram of the equilibrium of system (2) in the ($Ca_{\mathrm{cyt}}$, $v_{\mathrm{in}}$)-plane [($Ca_{\mathrm{cyt}}$, $v_{\mathrm{in}}$)-plane)] is shown in **Figures 1A,B**. Each point of the curve (solid line) represents a stable equilibrium, and the dashed line represents an unstable equilibrium. The equilibrium undergoes the Hopf bifurcation twice, marked by points HB1 and HB2 with respect to the bifurcation parameter $v^1_{\mathrm{in}} = 0.0238$ μM/s and $v^2_{\mathrm{in}} = 0.0594$ μM/s. When $v_{\mathrm{in}} < v^1_{\mathrm{in}}$, there exists stable equilibrium of system (2). As $v_{\mathrm{in}}$ increases, the stable equilibrium loses its stability at the point HB1 and returns to being stable at HB2.

In **Figure 2**, we shall present the time evolutions of cytosol $Ca^{2+}$ concentration in this model for different values of the parameter $v_{\mathrm{in}}$ by numerical simulation. The left panels represent time series of $Ca_{\mathrm{cyt}}$ comparison of parameter $v_{\mathrm{in}}$, and the right panels are the corresponding $Ca_{\mathrm{cyt}}$-$Ca_{\mathrm{er}}$-$IP_3$ phase portrait. For example, there is a single peak in this type of oscillation for $v_{\mathrm{in}} = 0.024$ μM/s in **Figure 2A**, and the corresponding 3D phase-space is shown in **Figure 2B**. Around $v_{\mathrm{in}} = 0.033$ μM/s, it is seen that the number of peak counts and peak magnitude begin to increase, as shown in **Figures 2C,D**. Similarly, when $v_{\mathrm{in}} = 0.052$ μM/s, five peaks were obtained (**Figures 2E,F**). Moreover, it should be mentioned in **Figures 2G,E**, although the results for peak magnitude look very similar and in agreement with the peak counts, that the oscillatory vibration is significantly different (**Figures 2G,H**).

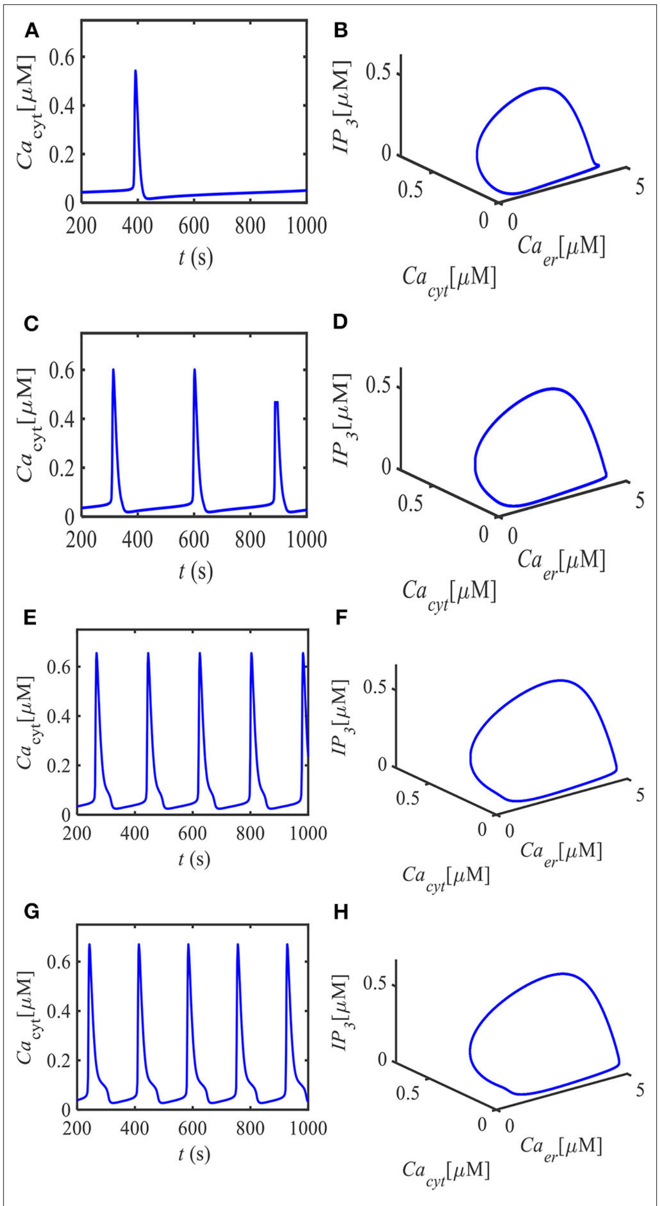


**FIGURE 2 |** Spontaneous $Ca^{2+}$ oscillations in astrocytes emerged at different parts of the curve in **Figure 1** relative to points HB1 and HB2. The left panels denote the time evolution of $Ca_{\mathrm{cyt}}$ for different sets of parameter $v_{\mathrm{in}}$, and the right panels denote the corresponding $Ca_{\mathrm{cyt}}$-$Ca_{\mathrm{er}}$-$IP_3$ phase portrait. **(A)** $v_{\mathrm{in}} = 0.024$ μM/s, **(B)** portrait diagram as $v_{\mathrm{in}} = 0.024$ μM/s, **(C)** $v_{\mathrm{in}} = 0.033$ μM/s, **(D)** portrait diagram as $v_{\mathrm{in}} = 0.033$ μM/s, **(E)** $v_{\mathrm{in}} = 0.052$ μM/s, **(F)** portrait diagram as $v_{\mathrm{in}} = 0.052$ μM/s, **(G)** $v_{\mathrm{in}} = 0.0593$ μM/s, and **(H)** portrait diagram as $v_{\mathrm{in}} = 0.0593$ μM/s.

## CONCLUSION

In this paper, we have theoretically investigated the stability of equilibrium and bifurcation of spontaneous $Ca^{2+}$ oscillations with a mathematical model in astrocytes. By choosing the flow of $Ca^{2+}$ from the extracellular vesicles through the membrane and into the cytosol as the bifurcation parameter, we conclude that two subcritical Hopf bifurcation points play an important role in the occurrence of $Ca^{2+}$ oscillations. By combining the theoretical analysis results in this paper, we numerically gave the Hopf bifurcations, which agree with the theoretical results. Our results may be instructive for better understanding the role of spontaneous $Ca^{2+}$ oscillations in astrocytes. Because synchronization of different oscillatory patterns may relate to bifurcation, we will give detailed research in future.

## DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

## AUTHOR CONTRIBUTIONS

HZ and MY contributed to the conception and design of the study. HZ organized the literature and wrote the first draft of the manuscript. MY performed the design of figures. All authors contributed to the manuscript revision and read and approved the submitted version.

## FUNDING

This work was supported by the Natural Science Foundation of China under Grant No. 11872084 and the Natural Science Foundation of the Anhui Higher Education Institutions of China under Grant Nos. KJ2016SD54 and KJ2017A460.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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