Research Article

Physical Manipulation of Calcium Oscillation in Shen-Larter Cell System

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Experimental observations show that calcium signals in response to external stimuli encode information via frequency modulation or alternatively via amplitude modulation. Here, by arguments of bifurcation theory and bifurcation control theorem, the amplitude and frequency manipulation of limit cycle in Shen-Larter cell system are investigated. A nonlinear feedback controller is then applied to the system, in order to assign the peak frequency to a prescribed value, such that bifurcation is minimized or eliminated in the closed-loop system. And numerical simulations are presented in order to illustrate the theoretical analysis.

1. Introduction

Biological cells draw on intracellular and extracellular calcium sources to generate signals that transduce stimulation into physiological output. Changes in cellular calcium concentration control a wide range of physiological processes [1, 2]. The complex behavior can be understood through bifurcation analysis. A bifurcation is a qualitative change in the number of candidate operating conditions of a nonlinear system when the parameters are quasistatically varied [3]. One important attribute of a bifurcation is the direction, or stability, of the bifurcation. It is known that bifurcation properties of nonlinear system can be modified via various feedback control method, thereby achieving some desirable dynamical behaviors.

In general, bifurcation control deals with using a control input to modify the characteristics of a parameterized nonlinear system. The control can be static or dynamic feedback control or open loop control law. The bifurcation control objective can be delaying the onset of an inherent bifurcation, optimization of performance index near bifurcation, stabilization or reduction of the amplitude of some limit cycle emerging from bifurcation, changing the parameter value of an existing bifurcation point, reshaping of the bifurcation diagram, or a combination of these [4–6]. The work has been applied to control problems in engineering, biological, and physicochemical systems.

Representative approaches employing linear or nonlinear state-feedback controls were proposed by Abed and Fu in [7]. In [4], Wang and Abed apply a washout filter-aided dynamic feedback controller to bifurcation control. Harmonic balance approximations method was used to design the controller by Berns et al. Kang [8] investigated the bifurcation control with quadratic invariants in normal forms. In this paper, we focus on the analysis and control of the amplitudes of limit cycle in Shen-Larter cell system, and the control law is achieved by computing the stability index (or curvature coefficient).

The organization of the paper is as follows. Section 2 introduces the nonlinear system under study and shows all equilibrium points [9]. In Section 3, we use bifurcation control theory [10–12] to analyze the amplitude of limit cycle in the original system. Section 4 gives the amplitude control for limit cycle in Shen-Larter cell system. Some numerical simulations are presented for illustrating the theory in Section 5. Finally, our conclusions are presented in Section 6.

2. Model

The Shen-Larter model is considered in this paper as a typical example of calcium oscillation in nonexcitable cells [13]. The mechanisms of this model are based on the calcium-induced calcium release (CICR) as well as the inositol trisphosphate cross coupling (ICC), which contains three variables, namely,

the concentrations of free calcium in the cytosol (x) and in the internal pool (y) and IP_3 concentration (z):

$$\begin{aligned}\frac{dx}{dt} &= J_{\text{ch}} + J_{\text{leak}} - J_{\text{pump}} + J_{\text{in}} - J_{\text{out}}, \\ \frac{dy}{dt} &= J_{\text{pump}} - J_{\text{ch}} - J_{\text{leak}}, \\ \frac{dz}{dt} &= J_+ - J_-, \end{aligned} \quad (1)$$

where

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

Parameters are made as follows if not otherwise stated: $k_{\text{ch}} = 3000 \mu\text{Ms}^{-1}$, $k_{\text{leak}} = 1.0 \text{ s}^{-1}$, $k_{\text{pump}} = 50 \mu\text{Ms}^{-1}$, $k_{\text{in1}} = 4 \mu\text{Ms}^{-1}$, $k_{\text{in2}} = 1 \mu\text{Ms}^{-1}$, $k_{\text{out}} = 10 \text{ s}^{-1}$, $k_+ = 4.0 \mu\text{Ms}^{-1}$, $k_- = 2 \mu\text{Ms}^{-1}$, $K_1 = K_2 = 0.2 \mu\text{Ms}^{-1}$, $K_3 = 1 \mu\text{M}$, and $K_4 = K_5 = 0.69 \mu\text{M}$; we define r as bifurcation parameter.

When $r = 0.2345$, the equilibrium points of system are as follows: $o_1 = (0.1938, 18.4885, 0.0761)$ and o_1 is unstable; when $r = 0.6859$, the equilibrium points of system are as follows: $o_2 = (0.3744, 1.1486, 0.3737)$ and o_2 is unstable. By applying Hopf bifurcation theorem, we obtain subcritical Hopf bifurcation of equilibria which are demonstrated in Figure 1.

3. Amplitude of Limit Cycle in the Original System

We consider the equilibrium point o_1 for $r = 0.2345$ and calculate the eigenvalues of system (1) at $(0.1938, 18.4885, 0.0761)$ that are $\lambda_{1,2}(r) = \alpha(r) \pm i\omega(r)$, $\lambda_3(r)$. It is known that

$$\alpha'(0.2345) = \left. \frac{\partial \alpha(r)}{\partial r} \right|_{r=0.2345} = 0.4160. \quad (3)$$

Suppose that

$$\begin{pmatrix} x \\ y \\ z \end{pmatrix} = \begin{pmatrix} 0.1938 \\ 18.4885 \\ 0.0761 \end{pmatrix} + P \begin{pmatrix} u \\ v \\ w \end{pmatrix}, \quad (4)$$

where $P = \begin{pmatrix} 0 & 1 & 1 \\ 18.7853 & -1.0387 & -0.8918 \\ -0.0817 & 0.3072 & -0.0073 \end{pmatrix}$.

FIGURE 1: The equilibrium curve of $(r, \text{Ca}_{\text{cyt}})$ for system (1).

Substituting (4) into system (1), we obtain

$$\begin{pmatrix} \dot{u} \\ \dot{v} \\ \dot{w} \end{pmatrix} = \begin{pmatrix} 0 & -0.5323 & 0 \\ 0.5323 & 0 & 0 \\ 0 & 0 & -92.4310 \end{pmatrix} \cdot \begin{pmatrix} u \\ v \\ w \end{pmatrix} + \begin{pmatrix} Q_1 \\ Q_2 \\ Q_3 \end{pmatrix}, \quad (5)$$

where

$$\begin{aligned}Q_1 &= -0.09925049u + 0.0471429v - 0.47273156w \\ &\quad + 0.0233562a + 0.275b - 5.4203985c \\ &\quad - 0.10547653, \end{aligned}$$

$$\begin{aligned}Q_2 &= 0.39594975u - 2.33607963v - 0.328835w \\ &\quad + 2.9885618a - 1.085b + 21.3859359c \\ &\quad - 0.08372397, \end{aligned}$$

$$\begin{aligned}Q_3 &= 17.85705025u - 8.70262037v + 81.868035w \\ &\quad - 2.9885618a - 48.915b + 964.141064c \\ &\quad + 18.57222397, \end{aligned}$$

$$a = \frac{\sigma_2}{\sigma_2 + 1},$$

$$b = \frac{\sigma_2^2}{\sigma_2^2 + 0.04},$$

$$c = \frac{\sigma_1 \sigma_2^3 \sigma_3}{(\sigma_1 + 0.0016) \sigma_4},$$

$$\begin{aligned}
\sigma_1 &= (0.0817u - 0.3072v + 0.0073w - 0.0761)^4, \\
\sigma_2 &= v + w + 0.1938, \\
\sigma_3 &= 18.7853u - 1.0387v - 0.8918w + 18.4885, \\
\sigma_4 &= (v + w + 0.8838)^6.
\end{aligned} \tag{6}$$

In order to facilitate discussion, we make the following hypothesis:

$$\begin{aligned}
(t_1, t_2, t_3) &= (u, v, w), \\
L_{jk}^i &= \left. \frac{\partial Q_i}{\partial t_j \partial t_k} \right|_{(t_1, t_2, t_3, r) = (0, 0, 0, 0.2345)}, \\
L_{jks}^i &= \left. \frac{\partial Q_i}{\partial t_j \partial t_k \partial t_s} \right|_{(t_1, t_2, t_3, r) = (0, 0, 0, 0.2345)}.
\end{aligned} \tag{7}$$

We calculate the following characteristic quantities for $r = 0.2345$ and $(u, v, w) = (0, 0, 0)$

$$\begin{aligned}
g_{20} &= 0.25 (L_{11}^1 - L_{22}^1 + 2L_{12}^2 + i(L_{11}^2 - L_{22}^2 - 2L_{12}^1)), \\
g_{11} &= 0.25 (L_{11}^1 + L_{22}^1 + i(L_{11}^2 + L_{22}^2)), \\
G_{110} &= 0.5 (L_{13}^1 + L_{23}^2 + i(L_{13}^2 - L_{23}^1)), \\
G_{101} &= 0.5 (L_{13}^1 - L_{23}^1 + i(L_{13}^2 + L_{23}^1)), \\
w_{11} &= \frac{1}{4 \times 92.43} (L_{11}^3 + L_{22}^3), \\
w_{20} &= \frac{1}{4 \times (2 \times 0.5323i + 92.431)} (L_{11}^3 - L_{22}^3 \\
&\quad - 2iL_{12}^3), \\
G_{21} &= \frac{1}{8} (L_{111}^1 + L_{122}^1 + L_{112}^2 + L_{222}^2 \\
&\quad + i(L_{111}^2 + L_{122}^2 - L_{112}^1 - L_{222}^1))
\end{aligned} \tag{8}$$

and get that

$$\begin{aligned}
g_{20} &= 0.7240 - 12.8285i, \\
g_{11} &= -4.4838 + 16.7853i, \\
G_{110} &= 13.5814 + 2.1357i, \\
G_{101} &= -12.7404 - 5.5436i, \\
w_{11} &= 8.6249, \\
w_{20} &= -8.4743 + 1.8988i, \\
G_{21} &= 91.9212 + 11.9489i.
\end{aligned} \tag{9}$$

Then the curvature coefficient of limit cycle is described by

$$\begin{aligned}
\sigma &= \operatorname{Re} \left\{ \frac{g_{20}g_{11}}{2 \times 0.5323} i + G_{110}w_{11} + \frac{G_{21} + G_{101}w_{20}}{2} \right\} \\
&= 156.8140339.
\end{aligned} \tag{10}$$

For $|r - 0.2345| \ll 1$, the amplitude of limit cycle of system (1) is

$$\begin{aligned}
R &\ll \sqrt{-\frac{\alpha'(0.2345)}{\sigma} (r - 0.2345)} \\
&= 0.0515 \sqrt{r - 0.2345}.
\end{aligned} \tag{11}$$

4. Amplitude Control

For the purpose of not changing the equilibrium and bifurcation parameter of system (1), we assume that the nonlinear feedback controller is $U(X, r) = [k(y - 18.4885)^2 \ 0 \ 0]^T$, and then the model (1) can be rewritten as

$$\begin{aligned}
\frac{dx}{dt} &= J_{\text{ch}} + J_{\text{leak}} - J_{\text{pump}} + J_{\text{in}} - J_{\text{out}} \\
&\quad + k(y - 18.4885)^2, \\
\frac{dy}{dt} &= J_{\text{pump}} - J_{\text{ch}} - J_{\text{leak}}, \\
\frac{dz}{dt} &= J_+ - J_-.
\end{aligned} \tag{12}$$

According to the analysis of AM of limit cycle, we have

$$\begin{aligned}
\begin{pmatrix} \dot{u} \\ \dot{v} \\ \dot{w} \end{pmatrix} &= \begin{pmatrix} 0 & -0.5323 & 0 \\ 0.5323 & 0 & 0 \\ 0 & 0 & -92.4310 \end{pmatrix} \begin{pmatrix} u \\ v \\ w \end{pmatrix} \\
&\quad + \begin{pmatrix} \bar{Q}_1 \\ \bar{Q}_2 \\ \bar{Q}_3 \end{pmatrix},
\end{aligned} \tag{13}$$

where

$$\begin{aligned}
\begin{pmatrix} \bar{Q}_1 \\ \bar{Q}_2 \\ \bar{Q}_3 \end{pmatrix} &= \begin{pmatrix} Q_1 \\ Q_2 \\ Q_3 \end{pmatrix} + \begin{pmatrix} U_1 \\ U_2 \\ U_3 \end{pmatrix}, \\
\begin{pmatrix} U_1 \\ U_2 \\ U_3 \end{pmatrix} &= \begin{pmatrix} 0.0478 & 0.0533 & 0.0249 \\ 0.0356 & 0.0139 & 3.1861 \\ 0.9644 & -0.0139 & -3.1861 \end{pmatrix} U(X, r).
\end{aligned} \tag{14}$$

Similar to previous analysis, we calculate that

$$\begin{aligned}
 \tilde{g}_{20} &= g_{20} + k(7.7136 + 6.9568i), \\
 \tilde{g}_{11} &= g_{11} + k(8.4598 + 6.3006i), \\
 \tilde{G}_{110} &= G_{110} + k(-0.7678 - 0.6407i), \\
 \tilde{G}_{101} &= G_{101} + k(-0.8338 - 0.5521i), \\
 \tilde{w}_{11} &= w_{11} + 1.8466k, \\
 \tilde{w}_{20} &= w_{20} + k(1.8374 + 0.1824i), \\
 \tilde{G}_{21} &= G_{21}.
 \end{aligned} \tag{15}$$

Then we have the curvature coefficient of limit cycle:

$$\begin{aligned}
 \tilde{\sigma} &= \text{Re} \left\{ \frac{\tilde{g}_{20}\tilde{g}_{11}}{2 \times 0.5323} i + \tilde{G}_{110}\tilde{w}_{11} + \frac{\tilde{G}_{21} + \tilde{G}_{101}\tilde{w}_{20}}{2} \right\} \\
 &= \sigma + \text{Re} \left\{ k^2(-103.0668 + 18.3568i) \right. \\
 &\quad \left. + k(16.6443 - 66.7055i) \right\} = 156.8140 \\
 &\quad - 103.0668k^2 + 16.6443k.
 \end{aligned} \tag{16}$$

For $|r - 0.2345| \ll 1$, the amplitude of limit cycle of system (12) is

$$\tilde{R} \ll \sqrt{-\frac{\alpha'(0.2345)}{\tilde{\sigma}}(r - 0.2345)}. \tag{17}$$

Furthermore, define $P = R/\tilde{R}$; then

$$P = \sqrt{1 + 0.1061k - 0.6573k^2}. \tag{18}$$

With these results that are in good agreement with experimental findings, the correct control parameter in the range $-1.1554 < k < 1.3169$ can be accomplished if the appropriate conditions are fulfilled [14]. The goal is to indirectly vary the value of P , thereby controlling the amplitudes of the limit cycles. The results are depicted in Figure 5.

5. Numerical Simulation

Considering the original system (1), Figure 2 indicates time series for $r = 0.2345$ and Figure 3 shows the phase diagram in $(Ca_{\text{cyl}}, Ca_{\text{er}})$ -space of system (1) for $r = 0.2345$. System (1) has a nonhyperbolic equilibrium. It is concluded that system (1) has subcritical Hopf bifurcation at $o_1 = (0.1938, 18.4885, 0.0761)$ for $r = 0.2345$.

As expected the amplitude and frequency of system (1) are changed by the nonlinear feedback controller. Otherwise, the equilibrium and the location of the Hopf bifurcation points remain the same, which can be seen from Figure 4. The green and blue lines of the curves represent the time series with and without control when varying the parameter k .

FIGURE 2: Time course of Ca_{cyl} for $r = 0.2345$.

FIGURE 3: Trajectory in phase space for $r = 0.2345$.

It is concluded that

- (1) for $k = -0.004$ and $k = -0.053$, there are six peaks in blue line graphics comparing to those four peaks and three peaks in green line curve, as shown in Figures 4(a) and 4(b); its effect is to decrease the frequency by the feedback law $U(x, r)$;
- (2) for $k = 0.0066$ and $k = 0.01644$, there are six peaks in blue line graphics comparing to those seven peaks and eight peaks in green line curve, as shown in Figures 4(c) and 4(d); its effect is to increase the frequency by the feedback law $U(x, r)$.

It shows that an increase in frequency was observed for the calcium oscillations, when the concentration of agonist is raised high enough. This phenomenon can also qualitatively reproduce experimental data with appropriate values for parameter [15].

For the sake of comparing the variation of the amplitude of the limit cycles when $r = 0.2345$, in Figure 5, we include

FIGURE 4: Time course of Ca_{cyt} for $r = 0.2345$ under feedback law $U(x, r)$.

the original (without control) oscillatory solution and the one obtained by using the varying controller parameter k . It represents that the limit cycle under feedback law $U(x, r)$ and the predicted solutions are both difficult to be distinguished from the limit cycle for the value of $r = 0.2345$. Figure 5 shows that the amplitude of the limit cycles can be controlled by varying the parameter k . In this case, we have reproduced the temporal sequence similar to those recorded in experiments [16].

6. Conclusion

We investigate the amplitude manipulation of Shen-Larter calcium oscillation model. A nonlinear feedback controller

is designed for the amplitude control of the limit cycle. To ensure the effective control, the formula for amplitude of limit cycle is obtained by calculating the coefficient of curvature, and then the formula is used for the determination of the appropriate values of the control parameter. It is shown that the appropriate values of control parameter can be found through the formula. Simulations confirm our theoretical analysis results. Future studies should be undertaken to study amplitude and frequency control of calcium oscillation with time delay in detail.

Our numerical simulations of intracellular free calcium oscillation approximately reproduce the range of agonist-induced calcium responses via at least two modalities. It shows good agreement with experiments in that these

FIGURE 5: Trajectory in phase space for $r = 0.2345$ under control.

calcium oscillations could persist for as long as receptors are activated at the cell surface. Comparing with experimental observations, we hope that the results may provide a guide for interpreting the previous experimental observations in other cell systems, where different types of calcium channels are possibly thought to be involved in calcium signaling.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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