Synchronization Feature of Coupled Cell-Cycle Oscillators

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***Abstract*—Based on the model of the Xenopus embryonic cell cycle proposed in literature [1], which can exhibit sustained limit cycle oscillations, we first build a multi-cell system of these oscillators that are coupled through a common complex protein that plays an important role in the core regulation of cell-cycle oscillators, and then show synchronization features in this coupled multi-cell system. Through bifurcation analysis and numerical simulations, we give synchronization intervals of the sensitive parameters in the individual oscillator and the coupling parameters in the coupled oscillators. Then, we analyze the effects of these parameters on synchronization time, period and amplitude, and find interesting phenomena, e.g., there are two synchronization intervals of activation coefficient in the Hill function of the activated CDK1 that activates the Plk1, and different synchronization intervals have distinct influences on synchronization time, period and amplitude. More interestingly, we find that the coupled system can switch between a stable state and a stable periodic orbit. These results suggest that the reaction process that the activated cyclin-CDK1 activates the Plk1 has very important influence on the synchronization ability of the coupled system. Our work not only can be viewed as an important step toward the comprehensive understanding for mechanisms of Xenopus embryonic cell cycle and but also can provide the guide for further biological experiments.**

Keywords- Synchronization; Cell cycle oscillators; Coupled system; Period; Amplitude

I. INTRODUCTION

Synchronization is a kind of typical collective behaviors and basic motions in nature which can explain many natural phenomena ([2, 3]). Recent studies have shown that cellular communication is accomplished by synchronization, and a number of simulations and fundamental experiment works have also confirmed synchronization mechanisms in some interacting or independent biological systems ([4-7]). The revealing synchronization mechanisms and dynamics control in multi-cellular systems are essential for understanding rhythmicity of living organisms at both molecular and cellular levels ([8-10]).

Oscillations play an important role in many dynamic cellular processes and two typical examples of genetic oscillators are the cell cycle oscillators [11] and circadian clocks [12].The synchronization analysis of these oscillators have been presented to understand how and why the cell cycle works and explain some inherent phenomena ([13-16]). Although existing detailed models confirm that the known interactions in the cell cycle can produce oscillations and predict behaviors such as hysteresis, there are still some problems that deserve exploring. These include asking how the various elaborations and collective behaviors of the basic oscillator affect the robustness of the system and how cells use the information to control the cell cycle [17].

To elucidate various synchronization mechanisms from the viewpoint of dynamics by investigating the effects of various biologically plausible couplings and external stimuli, in this paper, we use the three-order ordinary differential equation(ODE) model of the Xenopus embryonic cell cycle that exhibits sustained limit cycle oscillations that was presented in literature [1] as a basic model for one oscillator and study the synchronization for a network of N oscillators that all units are indirectly coupled by interacting to a common environment.

The paper is organized as follows. In Section Ⅱ, we describe the coupled model of cell cycle oscillators and present the synchronization of the coupled system. Section III makes a detailed sensitivity analysis for all parameters. Through the bifurcation analysis and numerical simulations, the synchronization intervals of system parameters are presented in Section III. In Section Ⅳ we analyze the effects of parameters on synchronization time, period and amplitude when achieved synchronization. Finally some conclusions are addressed in Section V.

II. MODEL OF COUPLED CELL CYCLE OSCILLATORS AND SYNCHRONIZATION ANALYSIS

A. Model of coupled cell cycle regulatory oscillators

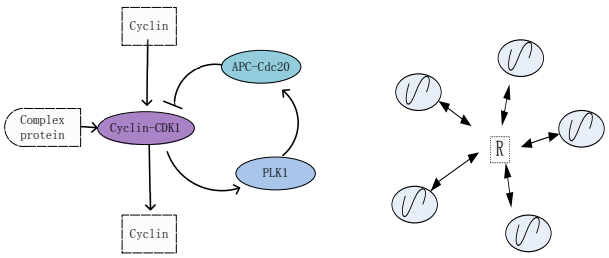

Figure 1. (a) The simplified diagram of the Embryonic cell cycle (redrawed from [1]), (b) global coupling between N oscillators.

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The simplified reaction diagram of the Embryonic cell cycle is depicted in Fig.1 (a). The cyclin-dependent protein kinase CDK1 is activated by the rapid, high-affinity binding of cyclin, and form the synthesized protein Cyclin-CDK1, which is the master regulator of mitosis. A protein like Polo-like kinase (Plk1) cooperates with cyclin-CDK1 to activate the E3 ubiquityl ligase APC-Cdc20, and APC-Cdc20 inactivates cyclin-CDK1.

For cell *i*, we assume that CDK1 is activated by a constant rate of cyclin synthesis (α_1), and the inactivation rate is proportional to the concentration of CDK1* (C_i) times a Hill function of APC*(A_i). The activation of Plk1 (P_i) by CDK1* is proportional to the concentration of inactive Plk1 (we also assume the total concentration of active and inactive Plk1 to be constant, we take to be 1-P_i) times a Hill function of CDK1*(C_i), and the inactivation is proportional to Plk1*(P_i). The activation of APC (A_i) by Plk1 is proportional to the concentration of inactive APC (1- Ai) times a Hill function of Plk1 (Pi), and the rate of inactivation of APC is described by simple mass action kinetics. The resulting three-ODE model is as follows.

$$\begin{aligned}
\frac{dC_i}{dt} &= \alpha_1 - \beta_1 C_i \frac{A_i^{n1}}{K1^{n1} + A_i^{n1}} \\
\frac{dP_i}{dt} &= \alpha_2 (1 - P_i) \frac{C_i^{n2}}{K2^{n2} + C_i^{n2}} - \beta_2 P_i \qquad (1) \\
\frac{dA_i}{dt} &= \alpha_3 (1 - A_i) \frac{P_i^{n3}}{K3^{n3} + P_i^{n3}} - \beta_3 A_i
\end{aligned}$$

The experiments indicated that the cyclin-dependent kinases (CDKs) are not solely responsible for establishing the global cell-cycle transcription programme although they have a function in the regulation of cell cycle transcription and precise cell cycle could be controlled by coupling a transcription factor network oscillator with the cyclin-CDK oscillator [11]. In order to reveal the internal mechanism of Xenopus embryonic cell cycle, we assume that all cells are coupled indirectly through the common extracellular medium, that is, they are coupled through a complex protein (R) which excites the protein of Cyclin-CDK1 in the core cell cycle regulatory pathway. The diagram for global coupling of the cell cycle oscillators is shown as Fig. 1(b).

The ODE equations for N cell oscillators (denoted by i=1, 2,.., N) are written as follows.

$$\begin{aligned}
\frac{dC_i}{dt} &= \alpha_1 - \beta_1 C_i \frac{A_i^{n1}}{K1^{n1} + A_i^{n1}} + k \frac{R^n}{KL^n + R^n} \\
\frac{dP_i}{dt} &= \alpha_2 (1 - P_i) \frac{C_i^{n2}}{K2^{n2} + C_i^{n2}} - \beta_2 P_i \qquad (2) \\
\frac{dA_i}{dt} &= \alpha_3 (1 - A_i) \frac{P_i^{n3}}{K3^{n3} + P_i^{n3}} - \beta_3 A_i \\
\frac{dR}{dt} &= \frac{k_0}{N} \sum_{i=1}^{N} \frac{C_i^n}{K_a^n + C_i^n} - k_m R
\end{aligned}$$

□

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B. *Synchronization of a population of N-cell cycle oscillators*

The synchronization error is defined as follows.

$$E = \sum_{i=2}^{N} [(C_i - C_1)^2 + (P_i - P_1)^2 + (A_i - A_1)^2] \qquad (3)$$

Assume that the coupled system can achieve synchronization when the E reaches to zero in a limit time.

For simplicity, we analysis the case of ten identical oscillators (N=10) and the same results can be obtained when N is set to be greater than 10. Through the numerical simulation, the parameter settings that the coupled system can reach synchronization are listed at Table1, and the synchronization diagram is depicted in Fig.2. The oscillation period of the coupled system is about 4.315 min when achieved synchronization and the period of single oscillator is about 3.78min.

Table 1 The parameter settings of the coupled system

α_1	α_2	α_3	β_1	β_2	β_3	$K1$	$K2$	$K3$
0.1	3	3	3	1	1	0.5	0.5	0.5
$n1$	$n2$	$n3$	n	k_0	K_a	k_m	k	KL
4	4	4	3	2	0.5	1.5	1	0.5

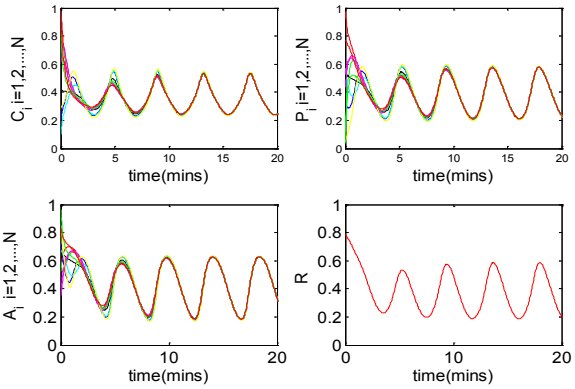

Figure 2. The synchronization behavior of the coupled oscillators.

III. PARAMETER SENSITIVITY ANALYSIS OF THE COUPLED SYSTEM

To investigate the effects of parameter changes on the amount of all variables in the coupled system, we make the sensitivity analysis of parameters by using an approach proposed in [18]. For the continuous state equation that has continuous first-order partial derivatives with parameters λ_0.

$$\begin{aligned}
\dot{x} &= f(t, x, \lambda_0) \\
x(t_0) &= x_0
\end{aligned} \qquad (4)$$

The solution can be approximated by expanding Taylor series about the nominal solution $x(t, \lambda_0)$.

$$x(t, \lambda) \approx x(t, \lambda_0) + S(t)(\lambda - \lambda_0) \qquad (5)$$

Sensitivity function *S(t)* provides the first-order estimates of the effects of parameter variations on solutions. When the all values λ are in a small ball centered at λ_0, the sensitivity

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function suffices to approximate the solution. Then we can calculate the sensitivity of the system parameters by solving the following sensitivity equation (See [18] for details).

$$\dot{S}(t) = [\frac{\partial f(t,x,\lambda)}{\partial x}]|_{\lambda=\lambda_0} S + [\frac{\partial f(t,x,\lambda)}{\partial \lambda}]|_{\lambda=\lambda_0}, S(t_0) = 0 \qquad (6)$$

The range of the parameter distributions is set to be a random number between [0, 1] and get an average running for 100 times. All results are normalized and the effects of parameter changes on the amount of three variables and complex protein R in equation (2) are showed in Figs.3-6.

From Figs.3-6, we can see that the most sensitive parameter is K1, in turn, is α_1, Ka, K2, K3, β_2, β_3, α_3, km, et al.

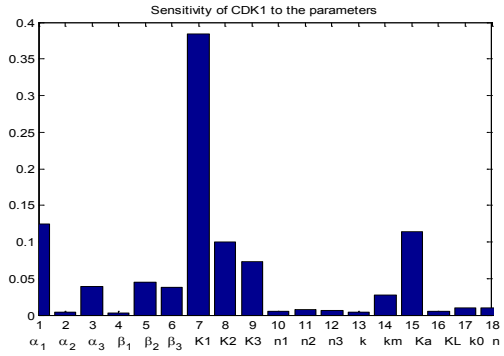

Figure 3. Sensitivity of CDK1 to the perturbation of parameters

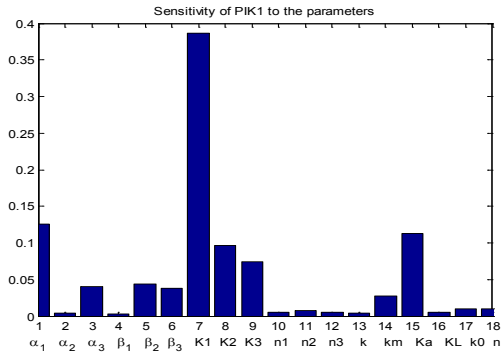

Figure 4. Sensitivity of PIK1 to the perturbation of parameters

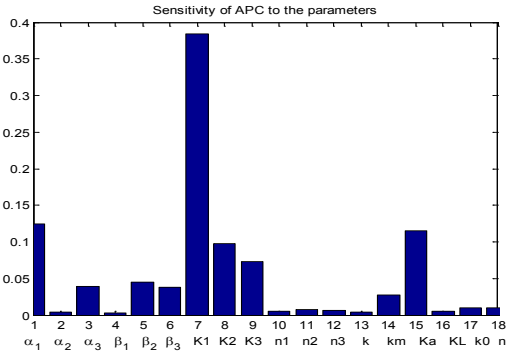

Figure 5. Sensitivity of APC to the perturbation of parameters

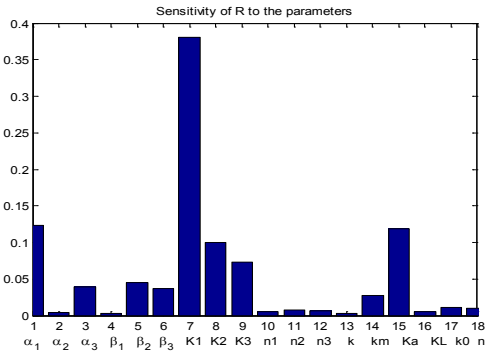

Figure 6. Sensitivity of R to the perturbation of parameters

IV. IDENTIFICATION OF SYNCHRONIZATION INTERVALS FOR THE SELECTED PARAMETERS

In order to analyze the effects on the synchronization when parameters change, we make bifurcation analysis for the sensitive parameters and the coupling parameters by varying the chosen parameter and fixing other parameters. The bifurcation diagram for the parameters to the varieties of the complex protein CDK1 (C_1) of the first oscillator in the coupled system are shown in Figs.7-12, respectively.

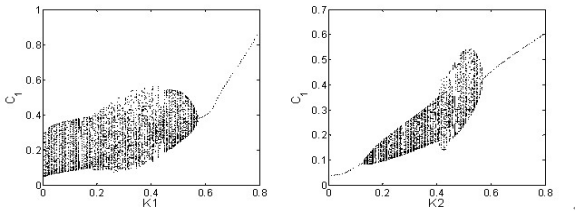

Figure 7. The bifurcation diagrams of the activation coefficients K1 and K2 in Hill functions.

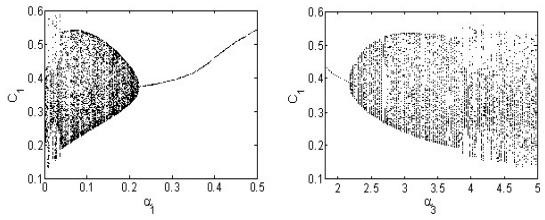

Figure 8. The bifurcation diagram of active constants α_1 and α_3.

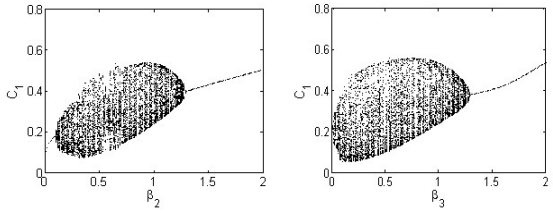

Figure 9. The bifurcation diagram of degradation rates β_2 and β_3.

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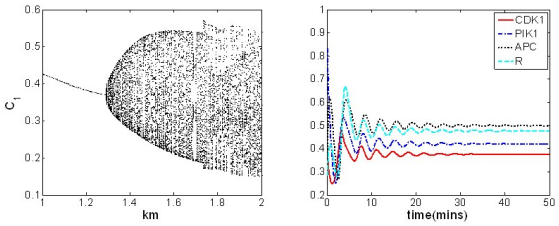

Figure 10. Bifurcation diagram for degradation rate (Left) and the system achieves asymptotically steady state when k_m=1.25 (Right).

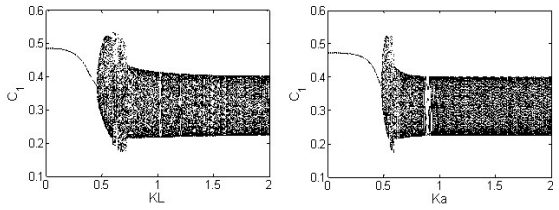

Figure 11. Bifurcation diagram for the activation coefficients KL and Ka in Hill functions.

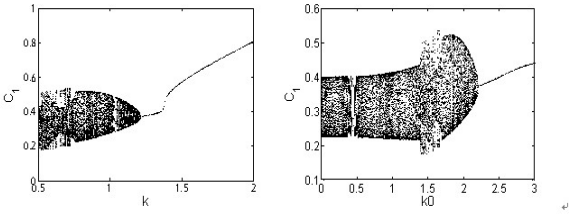

Figure 12. Bifurcation diagram for coupling strength k and active constant k0.

From these figures we find an interesting phenomena, that is, there are two stable states for parameters K2 (Fig.7) and β_2 (Fig.9) when K2 varies in [0, 0.8] and β_2 varies in [0, 2], respectively.

Furthermore, we search for the synchronization intervals of these parameters through numerical simulations. We assume that the system achieves synchronization when the synchronization error is small than 1e-4. The obtained synchronization intervals for parameters are shown in Table 2.

From Table 2, we can see that there are two synchronization intervals for K2 and other parameters only have one synchronization interval. Although there are two stable states for the degradation rate β_2, there is only one synchronization interval. We can also observe that the more sensitive parameters have the smaller synchronization intervals

Table 2 the synchronization intervals for the sensitive parameters

K1	***K2***	***K3***	***α1***	***α3***	***β2***
[0.48,0.57]	[0.185,0.22] [0.48,0.57]	[0.48,0.57]	[0.09,0.21]	[2.2,3.5]	[0.9,1.3]
β3	***km***	***KL***	***Ka***	***k***	***k0***
[0.89,1.3]	[1.3,1.6]	[0.44,0.55]	[0.46,0.52]	[0.92,1.3]	[1.85,2.3]

V. THE EFFECTS OF SENSITIVE PARAMETERS ON THE SYNCHRONIZATION TIME, PERIOD AND AMPLITUDE

In order to analysis the effects of parameters on synchronization time (the time when the synchronization error of coupled system is smaller than 1e-4), period and amplitude, we let all parameters vary in their synchronization intervals listed at Table 2 and randomly select one initial value for each system variable in [0, 1].The average results for 20 independent runs are shown in the following subsections.

A. The effects of activation coefficients K1,K2,K3 in Hill functions

From Fig.13 and Fig.14, we can observe that activation coefficients K1 and K3 have the same influence on period and amplitude, that is, the oscillation period and amplitude are almost linearly decreased with the increasing of K1 and K3.

However, activation coefficient K2 has distinct influences on period and amplitude of synchronization system in different synchronization intervals (Fig.15). In the first interval [0.185, 0.22], the period is increasing and amplitude is not changed, but in the second interval, period and amplitude are decreasing.

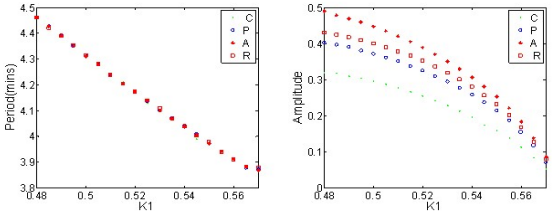

Figure 13. The effects of K1on period and amplitude.

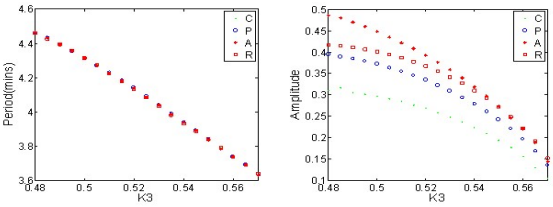

Figure 14. The effects of K3 on period and amplitude.

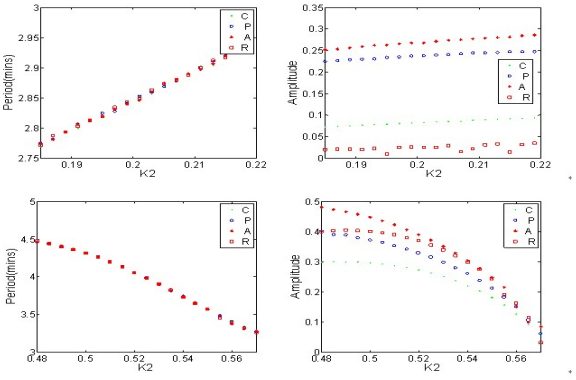

Figure 15. The effects of K2 on period and amplitude in two different synchronization intervals.

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Especially, we analyze the effect of K2 on synchronization time (Fig.16), we find that the synchronization time is increasing with the increase of K2 in the first interval and the synchronization time is decreasing with the increase of K2 in the second interval. We also observe that the synchronization time in the first interval is quite shorter than that in the second interval, but the synchronization is very sensitive to the change of initial values.

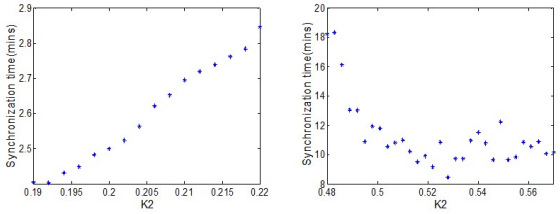
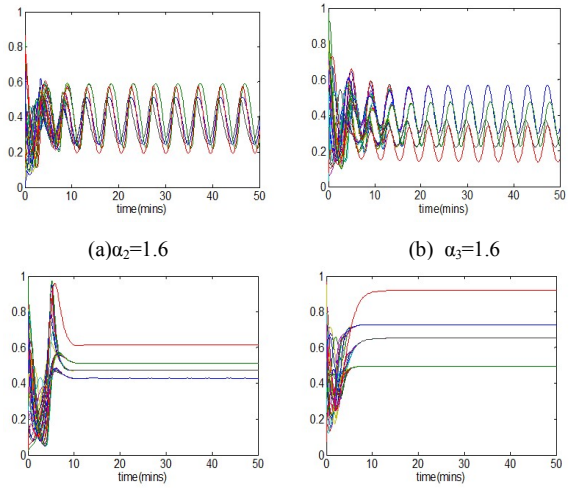


Figure 16. The effects of K2 on synchronization time in two different synchronization intervals.



(a)α_2=1.6 (b) α_3=1.6

(c) α_2=1 (d) α_3=1.2

Figure 17. The coupled system switch from stable period oscillations to stable steady state when K2 is between two different synchronization intervals.

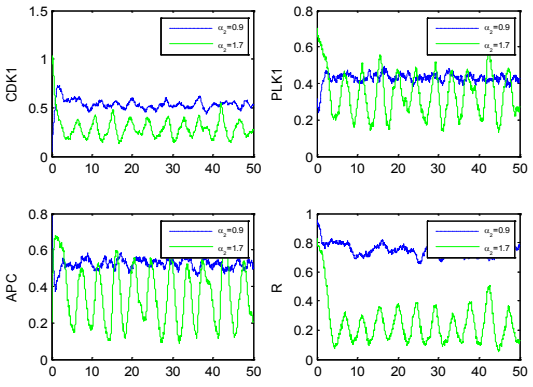


Figure 18. The coupled system switch from stable steady state to stable period oscillations if inner noises are introduced when K2 is between two different synchronization intervals (The intensity of inner noise is 0.001, the parameter α2 changes from 0.9 to 1.7)

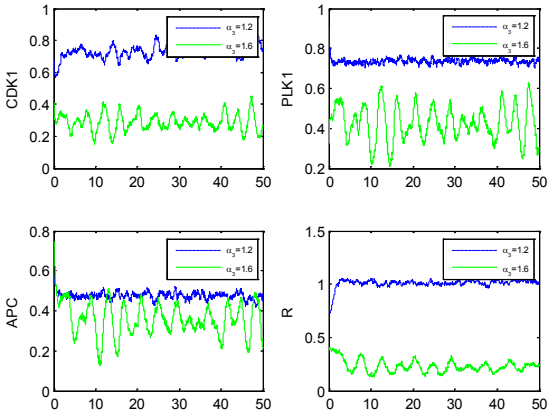


Figure 19. The coupled system switch from stable steady state to stable period oscillations if inner noises are introduced when K2 is between two different synchronization intervals (The intensity of inner noise is 0.001, the parameter α3 changes from 1.2 to 1.6)

When K2 varies in the interval [0.35, 0.42] and the parameter α2 changes from 1.6 to 1.0 (Fig.17 (a) and Fig.17(c)), or α3 changes from 1.6 to 1.2 (Fig.17 (b) and Fig.17 (d)), the coupled system switches from stable period oscillations to stable steady state (Fig.17).

In order to consider the influence of random factors on the feature of the system, we introduce the inner noise in system (2). Fig.18 and Fig.19 show stochastic transitions between the stable steady state and the stable limit cycle when intensity of inner noise is 0.001 and the parameter α2 changes from 0.9 to 1.7 or the parameter α3 changes from 1.2 to 1.6, respectively.

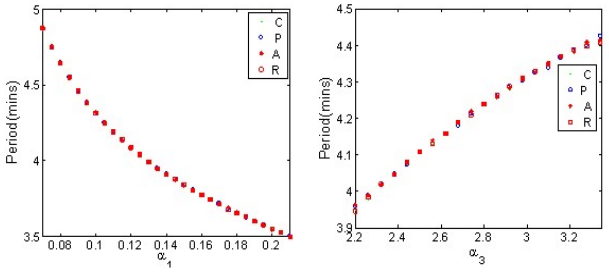


Figure 20. The effects of α_1 and α_3 on period.

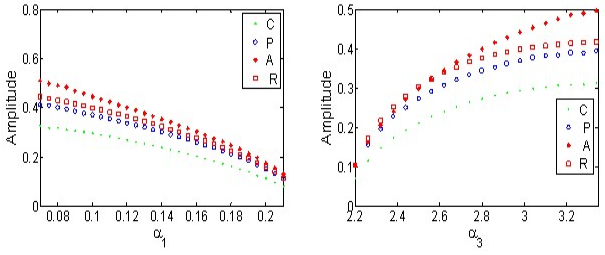


Figure 21. The effects of α_1 and α_3 on amplitude.

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B. *The effects of α_1 and α_3 on the period and amplitude when achieved synchronization*

The effects of α_1 and α_3 on period and amplitude are depicted in Fig.20 and Fig.21, respectively. From Fig.20 and Fig.21, we can see that the oscillation period and amplitude are decreased with the increasing of α_1, but the effects of α_3 are reverse.

C. *The effects of coupling parameters on period and amplitude when achieved synchronization*

The effects of coupling strength k, ratio coefficient k0 and activation coefficients KL and Ka on the period and amplitude are shown in Fig.22 and Fig.23, respectively.

With the increasing of these parameters, the oscillation periods for parameters KL, Ka and K are increasing, but the oscillation period for parameter K0 is decreasing. The trend of the oscillation amplitudes is similar to the periods except the coupling strength k.

Because we find that the oscillation period is very sensitive to the changes of Ka (Fig.22), we further examine the Ka. When Ka is smaller than 0.46, the system runs into stable state asymptotically, like the right sub-figure in Fig.10. With the increasing of Ka, the coupled system has two clusters (Fig.24), or stays in anti-phase state (Fig.25).

In addition, from above figures we also observe that the synchronized oscillator periods of all variables are almost the same but the oscillator amplitudes of all variables are not.

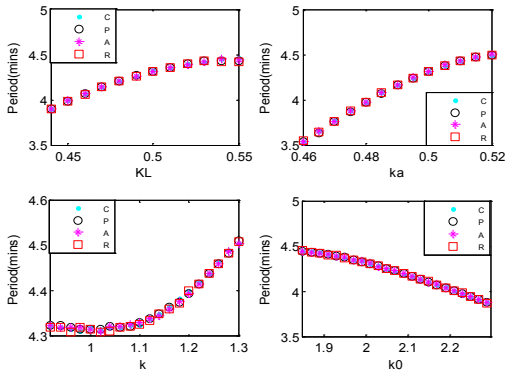

Figure 22. The effect of parameters KL, Ka, K and K0 on period when achieved synchronization.

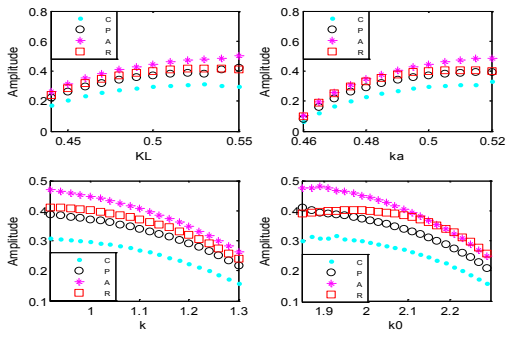

Figure 23. The effect of parameters KL, Ka, K and K0 on amplitude when achieved synchronization.

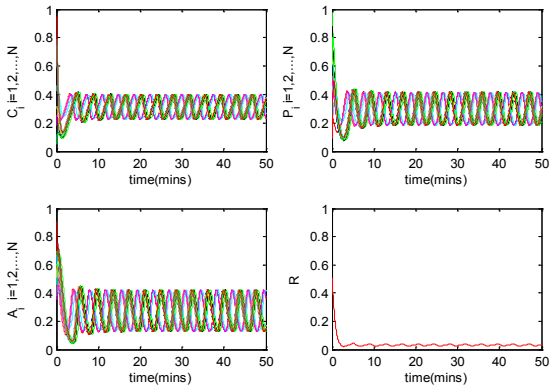

Figure 24. There are two clusters, each contains five oscillators synchronized in phase (Ka=1.1).

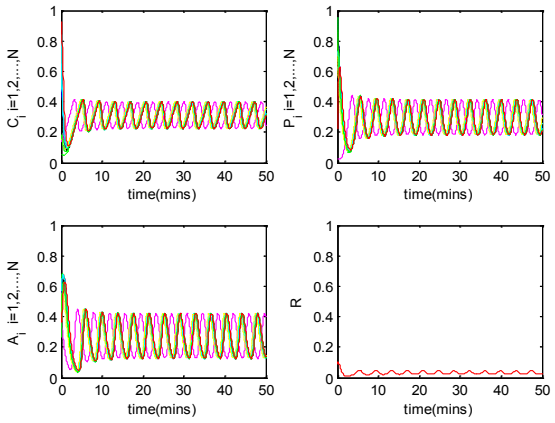

Figure 25. The coupled system stays in anti-phase state.

VI. CONCLUSIONS

In this paper, a new dynamical global coupled model for the oscillators is presented. Through bifurcation analysis and numerical simulations, we determine synchronization intervals of the coupled system. Our simulation results show that the more sensitive parameters have the smaller synchronization intervals. Furthermore, we find that there are two synchronization intervals of activation coefficient in the Hill function of activated CDK1 which activate the Plk1, and different synchronization intervals have distinct influences on synchronization time, period and amplitude of synchronization system. Afterwards, when this parameter shifts from two different synchronization intervals, the coupled system switches from stable period oscillations to stable steady state. These results suggest that the reaction process that the activated cyclin-CDK1 activates the Plk1 has very important influence on the synchronization ability of the coupled system. Our approaches help to gain insight into internal mechanisms of cell cycle system and to generate hypotheses for further research.

Although we have mainly examined effects of most sensitive parameters and coupled parameters on the cellular dynamics, there are also other important factors which may

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act important roles in biological processes and should be further investigated from theoretical viewpoints. The effect of internal and external noise on synchronization will be our further work.

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