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Synchronization of two electrically coupled inspiratory pacemaker neurons

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Synchronization is considered to be a crucial mechanism that maintains respiratory rhythm. For understanding the effect of electrical coupling on the transition of the firing patterns and synchronization, we coupled two inspiratory pacemaker neurons together, and studied various synchronous behaviors between them. We firstly compared the bifurcation diagrams between the coupled neurons and single neuron, and found that the coupled neurons had a more complicated bifurcation mode. By increasing the coupling strength, the regular variation of phase differences was illustrated so that asynchronous and some synchronous states could be observed. These synchronous states were also shown in detail by phase portraits and firing series. In addition, we explored the ranges of different synchronous states, which attributed to different ranges of membrane capacitance and coupling strength.

synchronization, inspiratory pacemaker neuron, phase differences, electrical coupling, bifurcation

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1 Introduction

As an important mechanism in neuronal activity, synchronization has been receiving lots of attention since it is related to a great number of central issues in neuroscience, such as neural information processing and neurological diseases [1–8]. Due to the difficulty of experiment, however, computational studies provide essential new insights into the research of neuronal synchronization. Recently, a number of researchers have intensively investigated the synchronous behavior of the coupled neurons. It was common that the studies about synchronization evaluated the effect of coupling between neurons on the firing patterns and synchronization [9,10]. Some numerical results showed that strong coupling could synchronize the coupled neurons [11,12]. In addition, the impact of time delay was also considered in some models for the propagation of the excitement in realistic neuron is not instantaneous [6]. After comparing the behavior of two coupled systems Adhikari et al. found that time delay could induce synchronization change from one state to another state [13]. Similar effect could also be found in the results of Wang et al. [14]. Besides time delay, the noise effect was often taken into account in studies about synchronization. A number of studies uncovered that the synchronization would occur when the noise amplitude was larger than a threshold [15,16]. Zhou et al. [17] even found a saddle point in phase plane, which played an important role in producing the nose-induced synchronization.

In recent years, some researches have reported that synchronization of inspiratory neurons in pre-Bötzinger complex has an effect on respiratory rhythm [18–23]. Nevertheless, experimental studies on the synchronization of inspiratory neurons remain less. In the aspect of numerical researches, although Butera et al. [24] constructed two minimal models of excitatory neurons in pre-Bötzinger complex

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and Smith et al. [25] developed a network model to reproduce and explain the firing patterns, related articles were seldom relative to the neuronal synchronization. The main goal of this paper is to investigate the synchronization of coupled inspiratory neurons using the computational method.

Synchronization usually reveals different states, which are called synchronization states. Based on phase differences between neurons, we could easily classify different synchronization states. With different computational processes, two major methods were developed. By the first method, the synchronization states are divided into spike synchronization and burst synchronization [6,26]. The second one divides synchronization into two states: in-phase synchronization and out-of-phase synchronization [4,27]. In the current research, we have used the second pattern to distinguish the synchrony states.

2 Introduction of model and indexes

2.1 Model description

Based on the model of inspiratory pacemaker neuron in pre-Bötzinger Complex introduced by Butera et al. [24], we developed a coupled model by connecting two pacemaker neurons with a gap junction (Figure 1). Each neuron includes sodium channels, potassium channels, persistent sodium channels, and leakage channels.

Each neuron in coupled model is given as

$$C_m \mathrm{d}V/\mathrm{d}t = I_{\mathrm{ext}} - (I_{Na} + I_K + I_{NaP} + I_{leak} + I_{couple}),$$

where V represents the membrane potential, Cm denotes the membrane capacitance. The current of each ion channel is described by the following equations:

$$\begin{aligned}
I_{Na} &= g_{Na} m_\infty^3 (1-n)(V - E_{Na}),\\
&\quad m_\infty = 1 + \exp(-(V+34.0)/5.0),\\
&\quad \mathrm{d}n/\mathrm{d}t = (n_\infty - n)/\tau_n,\\
&\quad n_\infty = 1 + \exp(-(V+29)/4.0),\\
&\quad \tau_n = 10/\cosh(-(V+29)/4.0),\\
I_K &= g_K n^4 (V - E_K),\\
I_{NaP} &= g_{NaP} a_\infty^3 b (V - E_{NaP}),\\
&\quad a_\infty = 1 + \exp(-(V+40.0)/6.0),\\
&\quad \mathrm{d}b/\mathrm{d}t = (b_\infty - b)/\tau_b,\\
&\quad b_\infty = 1 + \exp((V+48)/6.0),\\
&\quad \tau_b = 10000/\cosh((V+48)/6.0),\\
I_{Leak} &= g_L (V - E_L),\\
I_{Couple} &= g_C (V - V_{neighbor}).
\end{aligned}$$

Some parameters in the equations are fixed to the value g_{Na} = 28 nS, g_K = 11.2 nS, g_{NaP} = 2.8 nS, g_L = 2.8 nS, E_{Na} = 50 mV, E_K = −85 mV, E_{NaP} = 50 mV, E_L =−57.5 mV.

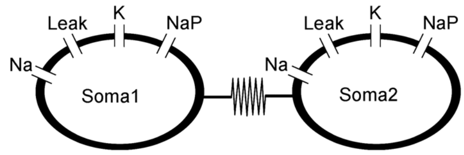

Figure 1 Coupled inspiratory pacemaker neurons.

2.2 Phase differences and index of synchronization

The distribution of phase differences between the spike times of two coupled neurons is considered to be an index that describes the state of synchronization [4]. It is given as

$$\Delta\varphi = 2\pi \frac{t_{\mathrm{in}} - t_2}{t_1 - t_2}, t_2 < t_{\mathrm{in}} \leqslant t_1,$$

where t_1 and t_2 represent the adjacent spike times of the first neuron, t_{in} is the spike time of the second neuron. When $\Delta\varphi$ equals to 0 or 2π, neurons are in in-phase synchronization state. Out-of-phase synchronization is characterized by a pattern with constant phase differences ($0<\Delta\varphi<2\pi$).

Although phase differences can be used to visually represent the synchronization state, we consider that it is not useful enough to tell apart the out-of-phase synchronization and asynchronization. Thus, we use the index of synchronization (*IS*) to supplement the phase differences. Firstly, according to the actual error, a threshold ε=0.004 is defined. We believe that two phase differences $\Delta\varphi 1$ and $\Delta\varphi 2$ are the same when $-\varepsilon \leqslant \Delta\varphi 1 - \Delta\varphi 2 \leqslant \varepsilon$, otherwise, they would be different phase differences. In a stable firing series of about 20000ms, all the phase differences are calculated and classified under the above standard, and then we obtain the number of phase differences (*NPD*). With the modification of some parameters, such as the coupled strength g_C, a series of *NPD* [*NPD*1, *NPD*2,···] are calculated, from which we could obtain the average number of phase differences ($\overline{NPD}$). *IS* is calculated by

$$IS = \frac{NPD}{\overline{NPD}}.$$

It is necessary to note that the phase differences could be the arbitrary value of the range (0, 2π) when neurons are in asynchronization state, while phase differences in out-of-phase synchronization are some fixed values. Thus, NPD in different states have the following relationship:

$$NPD_{\text{out-of-phase synchronization}} < \overline{NPD} < NPD_{\text{asynchronization}}.$$

Let the above inequality divide $\overline{NPD}$, we obtain,

$$IS_{\text{out-of-phase synchronization}} < 1 < IS_{\text{asynchronization}}.$$

Hence, we could conclude that, if $IS > 1.0$, it would be thought to be a state of asynchronization. If $IS \leqslant 1.0$, the synchronization state is out-of-phase synchronization. When phase differences are equal to 0 or 2π, we consider the synchronization state to be in-phase synchronization.

The simulations were performed in Python 2.7.3.

3 Results and discussion

3.1 Comparison of bifurcation patterns between single neuron and coupled neurons

To understand the effect of gap junction on the neurons, we compare the bifurcation diagrams of the maximum of activation variable n, which exhibits the variation of firing patterns in neuron. The results are shown in Figure 2. While membrane capacitance C_m in a single neuron increases from 16 to 18.7 μF, the maximum of state variable n exhibits a period-doubling cascade (Figure 2(a)). As C_m is greater than 18.7 μF, the bifurcation pattern turns into period-adding mode. From the sub-graph of Figure 2(a), a much clearer view is provided in which we can see the bifurcation mode. In contrast, when C_m in the coupled neurons is less than 18.2 μF, the maximum of n reveals a chaotic state other than bifurcation. Once C_m exceeds 18.2 μF, the coupled neurons exhibit both inverse period-doubling and period-adding motions (Figure 2(b)). In this range, when it underwent bifurcation with inverse period-doubing motion, it would be accompanied with chaotic firing. The reasons why chaotic and inverse period-doubling motions did not appear in this range for single neuron may be associated with the respiratory rhythm.

3.2 Effect of coupled strength on phase differences and *IS*

Based on phase differences, we could distinguish different synchronization states. For simplicity, *IS* was developed.

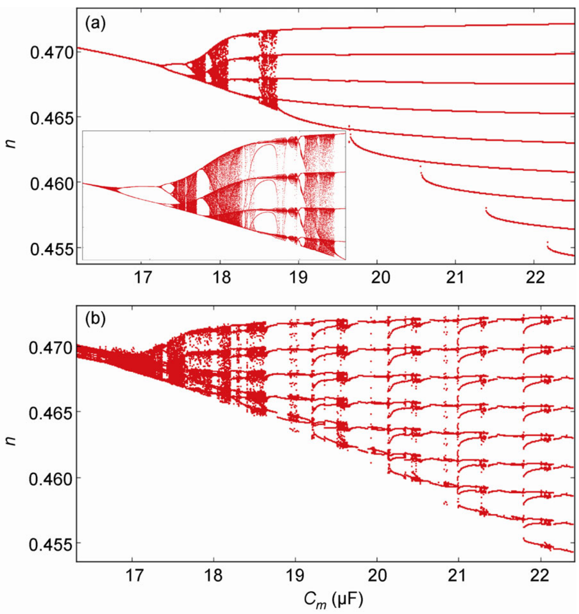

Figure 2 Comparison on the bifurcation patterns between single neuron (a) and coupled neurons (b).

The continuous variation of phase differences and IS provides insight into how synchronization state varies with the increase of coupling strength. Thus, a series of diagrams of different membrane capacitances (C_m) are illustrated in Figures 3–6.

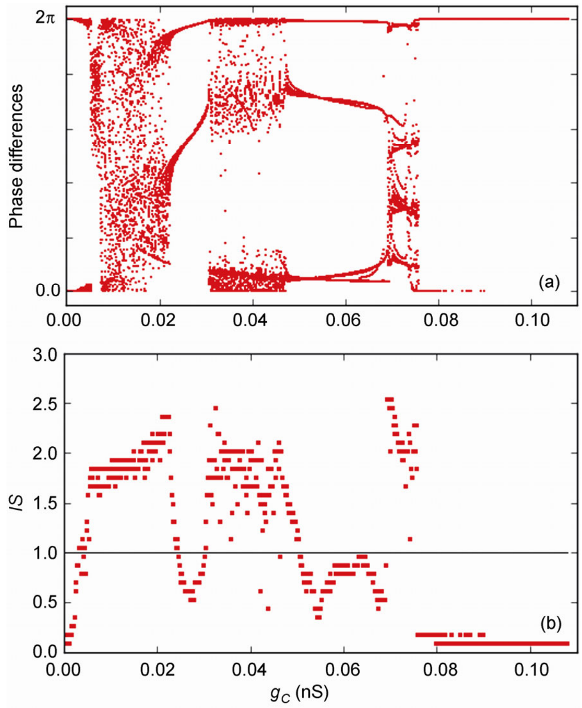

Figure 3 Variation of phase differences (a) and *IS* (b) with increment of coupling strength when C_m = 17.0 μF.

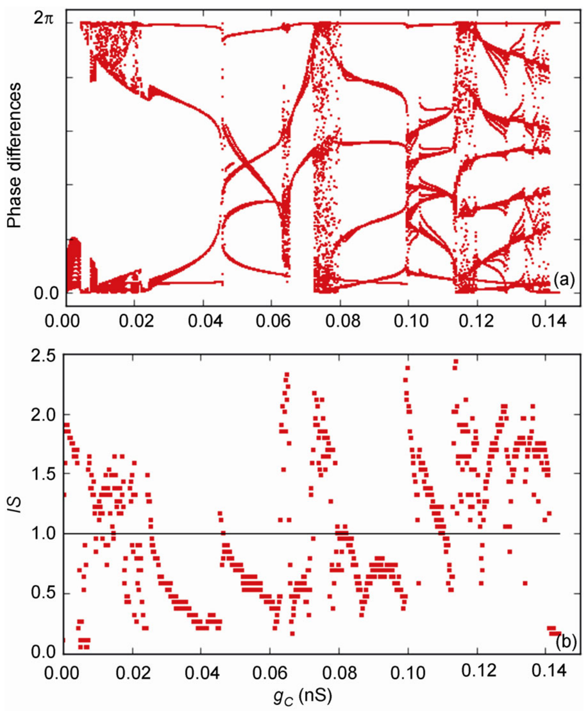

Figure 4 Variation of difference (a) and *IS* (b) with increment of coupling strength when C_m = 17.60 μF.

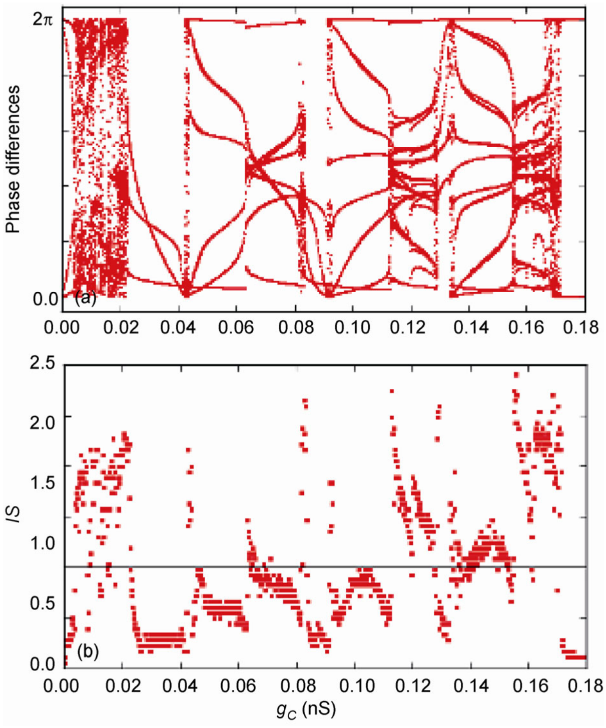

Figure 5 Variation of phase differences (a) and *IS* (b) with increment of coupling strength when C_m = 18.46 μF.

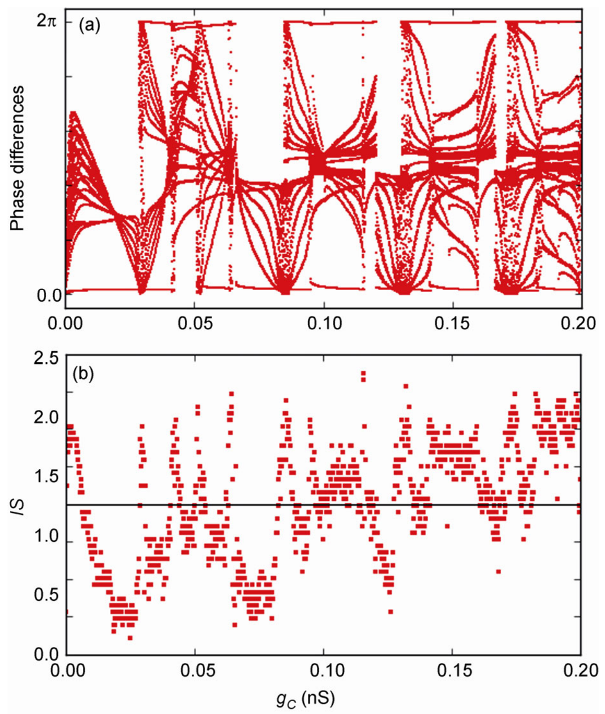

Figure 6 Variation of phase differences (a) and *IS* (b) with increment of coupling strength when C_m = 22.42 μF.

When C_m = 17.0 μF, the phase differences varied relatively simply. Weak coupling made coupled neurons completely synchronize for phase differences equal to 0 or 2π. In this in-phase synchronization state, we could observe that the corresponding *IS* is less than 1.0 (Figure 3). As g_C exceeds 0.005 nS, phase differences become chaotic, and their values are between 0 and 2π. In these states, two neurons fire asynchronously and *IS* is greater than 1.0. In the parameter range 0.023 nS < g_C < 0.0306 nS, neurons turn into the out-of-phase synchronization state as *IS* falls below 1.0 and phase differences are between 0 and 2π. Similarly, according to *IS* and phase differences, we could judge that the ranges 0.0306 nS < g_C < 0.0500 nS and 0.0692 nS < g_C < 0.0758 nS are asynchronization areas while in the range of 0.0500 to 0.0692 nS neurons turn into the out-of-phase synchronization.

After varying the C_m, we find that the diagram of phase differences change correspondingly, indicating that C_m is one of the factors that affect the synchronization state of neurons. Although the increment of C_m makes the variation of phase differences become much more complicated, the same judgment method could be applied to these diagrams. When C_m = 17.60 μF, neurons enter an in-phase synchronization state as g_C > 0.142 nS. In the other range of g_C, it is asynchronous region as its corresponding *IS* >1.0. Otherwise, it would be the out-of-phase synchronization region (Figure 4). The diagrams in Figure 5 have analogical rhythm. Neurons return to the in-phase synchronization state when g_C > 0.0758 nS.

Figure 6 shows the diagrams of phase differences and *IS* when C_m = 22.42 μF. Neurons do not exhibit in-phase synchroization state. Thus, we just need to judge if *IS* > 1.0 can distinguish out-of-phase synchronization or asynchronization.

3.3 Different synchronization states in coupled model

After studying the effects of coupled strength on synchronization, we focus attention on the relationship between the variation of firing patterns and the synchronization states of the coupled neurons. The phase portraits of *V*1 versus *V*2 and the firing patterns of each neuron are shown in Figure 7.

While g_C = 0.0024 nS, two neurons produce tonic spiking firing patterns with almost the same phase, which indicates that they are in almost in-phase synchronization state (Figure 7(a)). It seems like that weak coupling makes the firing modes of two neurons have little influence on each other. Asynchronization state appears when g_C = 0.0169 nS (Figure 7(b)). In this state, neurons generate irregular bursting patterns, and the corresponding phase portraits are rather chaotic. As g_C increases to 0.0720 nS, neurons reveal out-of-phase synchrony state. Although the firing modes of two neurons in shape are the same, the phase differences between them do not equal to 0 or 2π and maintain constant (Figure 7(c)). Further increment of g_C leads the bursting firing pattern to be replaced by single spike pattern. The synchronization state also returns to almost in-phase state (Figure 7(d)). The 45° line that presents in the phase plane of Figure 7(e) implies that two neurons completely

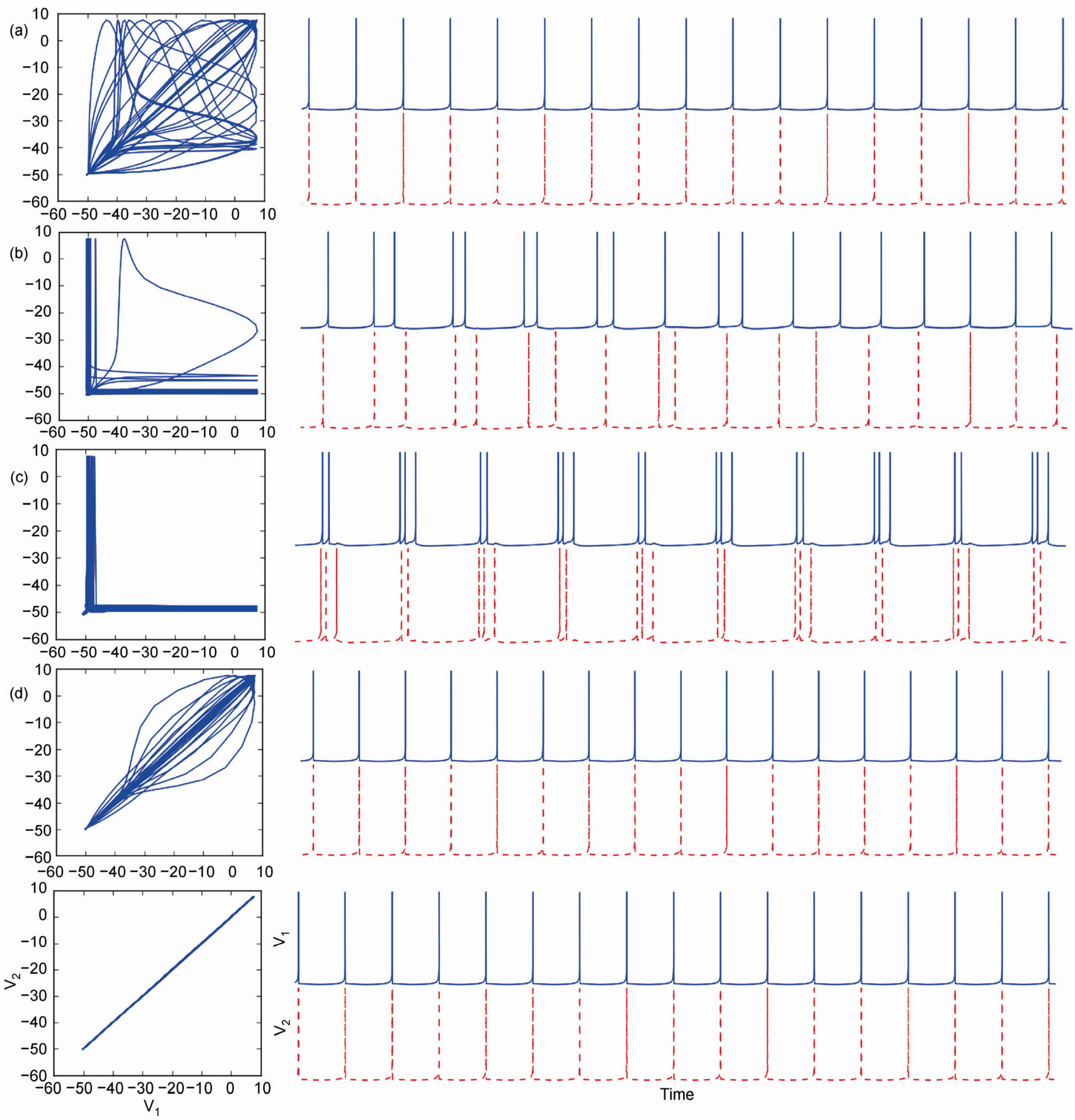

Figure 7 Phase portraits (left column) and dynamic response (right column) of two coupled neurons. (a) Almost in-phase synchronization state (g_C = 0.0024 nS); (b) asynchronization state (g_C = 0.0169 nS); (c) out-of-phase synchronization state (g_C = 0.0720 nS); (d) almost in-phase synchronization state (g_C = 0.0769 nS); (e) in-phase synchronization state (g_C = 0.0890 nS).

synchronized. In this state, phase differences are constant in 0 or 2π.

3.4 Synchronization state area

As we have found in the above results, the variation of both coupling strength g_C and membrane capacitance C_m could induce the synchronization state to change correspondingly. In order to understand how the synchronization state varies under the influence of these two factors, we explored the synchronization state area in different combinations of C_m and g_C.

In Figure 8, different colors represent different synchronization state areas. The regions of the least area are in-phase synchronization regions induced by weak coupling or strong coupling with relatively low C_m. The most interesting thing is that the out-of-phase synchronization region and asynchronization region appeared alternately along the

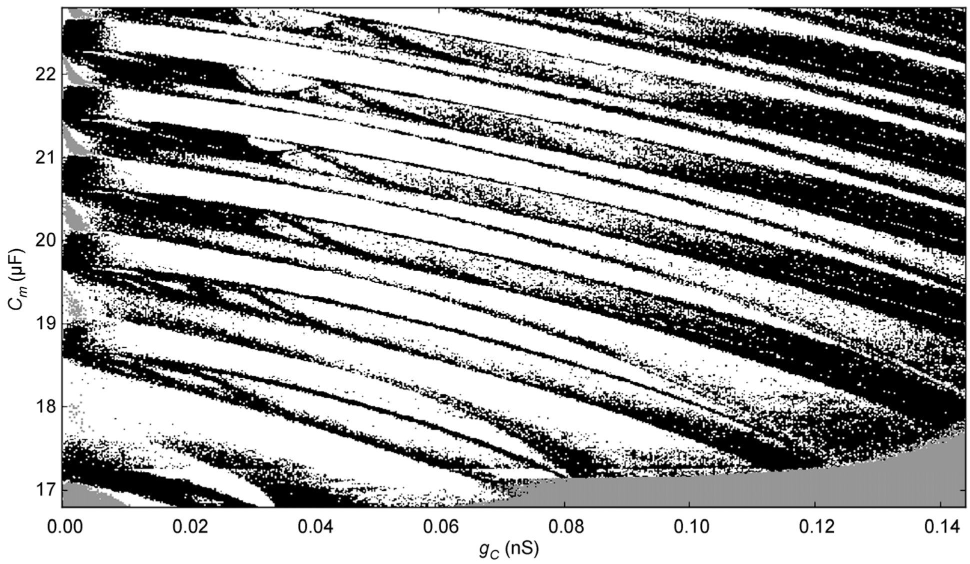

Figure 8 Synchronization state area in different membrane capacitance (C_m) and coupling strength (g_C). The black area represents the region of asynchronization. The white area is the region of out-of-phase synchronizaiton. The gray area is the region of in-phase synchronization.

45° line of the diagram, forming some zonal areas. It seems that the emergence of asynchronization state and out-of-phase synchronization state have a kind of periodicity.

4 Conclusions

In this research, we have studied how electrical coupling affected the synchronization state and firing patterns by computational method. From the results, we draw some conclusions below.

1) Comparing with single neuron, coupled neurons have a more complicated bifurcation mode, which indicates that electrical coupling could influence the transitions between firing patterns. Their differences may be related to respiratory rhythm. Although the mechanism behind how firing patterns control respiratory rhythm is unknown, we think that a much more complicated transition mode of firing patterns could control some more accurate movements.

2) On one hand, the variation of coupling strength could alter the synchronization state. On the other hand, the change of parameters in neurons, such as membrane capacitance, is another factor that has an effect on the synchronization state. Combination of phase differences and *IS* that we developed could completely distinguish different synchronization states. Maybe this method could extend to other neurons or some fields involving synchronization.

3) We have explored the synchronization state area that is affected by two variables: *Cm* and g_C. However, according to our other results of simulations, some parameters such as the conductance of persistent sodium channels g_{NaP} and external stimulus I_{ext} could also affect the synchronization state of the coupled neurons. Further researches may focus on how synchronization state varies with influence of three or more factors.

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