The Mechanism of Synchronization of Chemical Coupled Neurons

Yingyuan Chen, Jiang Wang*, Yanqiu Che, Xile Wei and Feng Dong, Senior *Member, IEEE*

Abstract—The synchronous effects of a pair of Morris-Lecar neurons, which was connected by excitable and inhibitory coupling, is studied in this paper. The theory of phase response is applied to examine how synchronization patterns are influenced by coupling strength. Based on the numerical simulation, we derive the region of synchrony and asynchrony as a function of coupling strength and the external stimulation. These analysis may provide us better insight into neuronal encoding and information transmission.

I.   INTRODUCTION

Synchronization phenomena are important for neural encoding in neuronal system and attract many people to explain the very existence of coherent oscillatory activity. It has been suggested that the neuronal system process information through the discrete action potential array. This activity may be important for neuronal coherent activity[1], cognition, memory and study[2] and functionality handicaps[3]. But the mechanisms of synchrony remain an subject of debate and spurred us to study the synchronization and desynchronization of the neuronal system.

Recently investigations focusing on the synchronization of coupled neurons provide me some inspiration to study this problem. Chow and Kopell[4] study the dynamics of two coupled neurons with gap junction. They found that weak electrical coupling can promote synchrony and sometimes foster antisynchronous activity as well. Whereas Lewis and Rinzel[5] pay their attention to the combination of electrical and chemical coupling. They use an integrate-and-fire model to examine the synchronization patterns and find that increasing the electrical coupled strength can promote synchrony and antisynchrony which is dependent on the speed of inhibitory synapses. Park et al. [6] focus on the effects of applied electric fields on synchronization. They don't care the type of coupling and introduce a simple phase oscillator reduction to evaluate the synchronization of neuron cells.

Here, we study pairs of intrinsically oscillating Morris-Lecar neurons connected by chemical coupling. Phase-locking patterns in the neural cells are systematically examined over a wide range of intrinsic frequencies and coupling parameters. The ultimate goal of our work is to build a

Y.Y.Chen is with the School of Electrical Engineering and Automation, Tianjin University, Tianjin, P. R. China. E-mail: gerard@tju.edu.cn.

J.Wang is the Corresponding author with the School of Electrical Engineering and Automation, Tianjin University, Tianjin, P. R. China. E-mail: jiangwang@tju.edu.cn, Tel: 86-22-27402293.

Y. Q. Che, **X. L. Wei** and **F. Dong** (IEEE senior member) are with faculty of the School of Electrical Engineering and Automation, Tianjin University, Tianjin, P. R. China.

qualitative framework for understanding how excitable and inhibitory coupling affect dynamics in neuronal networks.

II.   MODELS AND METHODS

A.   Morris-Lecar Model

In this paper, the Morris-Lecar model was put forward to study because it is appreciate variable range of class I excitation and can simulate quite a few of phenomenon in different systems of excitability. The equation of the model can be described as

$$\dot{V}_1 = \frac{1}{C_m}\left(I_{ext}^1 - I_{ion}^1 - 2\rho g_{syn}s_2(V_1 - V_{syn}^{post})\right)$$

$$\dot{N}_1 = \phi\frac{N_\infty(V_1) - V_1}{\tau_N(V_1)}$$

$$\dot{s}_1 = \alpha s_\infty(V_1)(1 - s_1) - \beta s_1$$

$$\dot{V}_2 = \frac{1}{C_m}\left(I_{ext}^2 - I_{ion}^2 - 2(1-\rho)g_{syn}s_1(V_2 - V_{syn}^{post})\right) \quad (1)$$

$$\dot{N}_2 = \phi\frac{N_\infty(V_2) - V_2}{\tau_N(V_2)}$$

$$\dot{s}_2 = \alpha s_\infty(V_2)(1 - s_2) - \beta s_2$$

Where $I_{ion}^i = \bar{g}_{Ca}M_\infty(V_i)(V_i - V_{Ca}) + \bar{g}_K N_i(V_i - V_K) + \bar{g}_L(V_i - V_L)$,
$i = 1, 2$. $\rho \in [0, 0.5]$ is the symmetric factor. g_{syn} is channel conductor of synapse, s is the ratio of connective acceptor. V_{syn}^{post} is the threshold potential of post-synapse which value determines the style of the synapse connection, excitable or inhibitory. The monotone increasing function, $s_\infty(V)$, can be described as $s_\infty(V) = \frac{1}{1+\exp\left[-(V - V_{syn}^{pre})/\sigma\right]}$, $\sigma > 0$. The open-state probability functions, M_∞ , N_∞ , and the time constant τ_N , are given as

$$M_\infty(V_i) = 0.5\left(1 + \tanh\left(\frac{V_i - V_{1m}}{V_{2m}}\right)\right)$$

$$N_\infty(V_i) = 0.5\left(1 + \tanh\left(\frac{V_i - V_{3m}}{V_{4m}}\right)\right) \quad (2)$$

$$\tau_N(V_i) = \frac{1}{\cosh\left(\frac{V_i - V_{3m}}{2V_{4m}}\right)}$$

Throughout this paper, the parameters are chosen to be C_m=20 , g_K=8 , g_L=2 , g_{Ca}=4 , V_K=-80 , V_L=-60 , V_{Ca}=120 , V_{1m}=-1.2 , V_{2m}=18 , V_{3m}=12 , V_{4m}=17.4 , ϕ_m=1/15 .In this paper, we treat I_{ext} as the main control parameter, and analyze synchronizations in the parameter plane of I_{ext} and g_{syn} . The standard parameter of the

excitable and inhibitory synapse is given by Destexhe et al. [7]. For excitable synapse, the parameters are shown as $V_{syn}^{post} = 0$, $V_{syn}^{pre} = 2$, $\alpha = 2.2$, $\beta = 0.19$, $\sigma = 4.5$. But for inhibitory synapse, the parameters can be described as $V_{syn}^{post} = -70$, $V_{syn}^{pre} = 2$, $\alpha = 10$, $\beta = 0.18$, $\sigma = 4.5$.

B. The Measurement of Phase-Lock Synchronization

Consider a periodically spiking neuron receiving an external stimulation that increases the membrane potential, and put the arbitrary initial point corresponding to the zero phase anywhere else on the limit cycle. We define the spike times t_k, where $k = 1, 2, 3...$ are the k th peak of the spike, as the times when the spike reach the peak. Then the phase of an active spiking neuron at an arbitrary time t between the two peaks ($t_k \leq t \leq t_{k+1}$) can be defined as: $\phi(t) = 2\pi(\frac{t - t_k}{t_{k+1} - t_k}) + 2\pi k$ [6, 8]. The phase-locked state of two coupled oscillators can be defined as $\Psi(t) = n\phi_2 - m\phi_1$ where n and m are integers ($n, m = 1, 2, 3…$), ϕ_1 and ϕ_2 are the phase of the two oscillators. the condition of an $n : m$ phase-lock state can be written as $|n\phi_2 - m\phi_1 - \Psi_0| < \varepsilon$, $0 \leq \Psi_0 < 2\pi$ and $\varepsilon \to 0$ when $t \to \infty$ When $1 : 1$ phase locked the relative phase of two coupled neurons can be expressed as:

$$\psi\left(t_k^1\right) = 2\pi \left(\frac{t_k^1 - t_m^2}{t_{m+1}^2 - t_m^2} \right), (t_m^2 \leq t_k^1 < t_{m+1}^2, m, k = 0, 1, 2, 3...) \quad (3)$$

where the superscript of t_k is the sequence number of the neuron. The degree of phase-locking can be quantified by the synchronization index γ, incomplete in the form

$$\gamma = \left\langle \sin(\psi(t_i)) \right\rangle^2 + \left\langle \cos(\psi(t_i)) \right\rangle^2 \quad (4)$$

where $\langle\ \rangle$ is an average of all the spiking events. When the two neurons are incoherent, γ will approach to zero for the large N. On the other hand, if the neurons are phase-locked, γ will approach its maximal value of one [6].

C. Phase Response

In this paper, we consider two heterogeneous neurons to be synchronized if they simply phase lock to each other. We just study the out-of-phase synchronization and the relationship between the phase lock state, the coupled intensity and the degree of the neurons' heterogeneity. Any dynamic system with stable limit cycle, if which the perturbation aplied to is sufficiently weak, can typically be reduced to one-dimensional phase equation [9]. For the following discussion, we assume a differential dynamical system of the ith uncoupled neuron which can be written as

$$\dot{x}_i = f(x_i) , x_i \in \mathbb{R}^m , i = 1, 2,... \quad (5)$$

where x_i is a multi-dimensional vector describing the state of the ith neuron. Supposed there is a period-T limit circle in this system, one can get the reduced phase system through introducing the scalar phase variable $\theta(x) \in [0, T]$. Now we add the time-varying item $\varepsilon p(x_i, t)$ to (5), the dynamical system can be expressed as

$$\dot{x}_i = f(x_i) + \varepsilon p(x_i, t) , x_i \in \mathbb{R}^m , i = 1, 2,... \quad (6)$$

where $\varepsilon \ll 1$ is the strength of disturbance which is positive. When $\varepsilon = 0$, (5) can be translated to $\dot{\theta}(x_i) = 1$; but when $\varepsilon \neq 0$, $\dot{\theta} = \frac{\partial\theta}{\partial x} \cdot \dot{x} = 1 + \varepsilon\frac{\partial\theta}{\partial x} \cdot p(x, t)$. The PRC can be defined as $Q(\theta) = \frac{\partial\theta}{\partial x_i}\Big|_{\Gamma_0(\theta)}$, so (6) can be translated to the phase equation:

$$\dot{\theta} = 1 + \varepsilon Q(\theta) p(x_i(\theta), t) \quad (7)$$

To get a conceptual picture of the whole network character such as synchronization, the equation $\theta = t + \varphi$ is given where t is isolated oscillator without couple, φ is the phase deviation to the isolated oscillator generated by the network input. Combining (9), the relative phase equation can be expressed as $\dot{\varphi} = \varepsilon Q(t + \varphi) p(x_i(t + \varphi), t)$. For N neurons coupled each other, the phase variable $x_i = x_i(\theta_i)$, $\varphi_i = \theta_i - t$, then

$$\dot{\varphi}_i = Q_i(t + \varphi_i) \cdot \sum_{j=1}^{N} \varepsilon_{ij} p_{ij}(x_i(t + \varphi_i), x_j(t + \varphi_j)) \quad (8)$$

Because the couple strength is very weak ($|\varepsilon| \ll 1$), the change of θ_i is more quickly than φ_i, so we can integrate (11) in the period of nondisturbant system by mean value theory, get $\dot{\varphi}_i = \sum_{j=1}^{N} \varepsilon_{ij} H_{ij}(\varphi_j - \varphi_i)$, where

$$H_{ij}(\varphi_j - \varphi_i) = \frac{1}{T} \int_0^T Q(t) \cdot p_{ij}(\Gamma_0(t), \Gamma_0(t + \varphi_j - \varphi_i)) dt \quad (9)$$

is the effective couple function. In this paper, Malkin method is introduced to calculate the PRC [9]. $Q(\theta)$ (period-T), called the adjoint solution, is determined by the linearized dynamical equation $\dot{Q} = -[Df(x(t))]^T Q$, where $[Df(x(t))]^T$ is the transpose of the Jacobian matrix of $f(x)$ with respect to the state variable x. $Q(\theta)$ is then further normalized according to the condition $Q(t) \cdot f(x(t)) = 1$, where the prime denotes the rate of change of the vector field along the periodic orbit $f(x(t))$.

III. RESULTS AND ANALYSIS

A. Inhibitary Coupling

In this section, we show numerical results obtained by the analysis of synchronization characteristics of two coupled M–L neurons as the current stimulation and the heterogeneity parameter is varied. We only set different current stimulate of different coupling style. Supposed the natural frequency of the two neurons is $1 + \omega_i$, $i = 1, 2$, the coupled function can be described as $p_{ij}(x_i, x_j) = (-(V_j - V_i)/C_m, 0)$. Therefore the reduced phase equation from (1) is shown as follows:

$$\begin{aligned} \dot{\varphi}_1 &= \omega_1 + 2\rho g_{syn} H_{12}(\varphi_2 - \varphi_1) \\ \dot{\varphi}_2 &= \omega_2 + 2(1 - \rho) g_{syn} H_{21}(\varphi_1 - \varphi_2) \end{aligned} \quad (10)$$

We can study the dynamics of phase synchronization of two oscillators by phase relation between them. The equation $\eta = \varphi_2 - \varphi_1$ denotes the relative phase between two neural oscillators, so that (10) can be transformed to:

$$\dot{\eta} = \omega + 2g_{syn}((1-\rho)H_{21}(-\eta) - \rho H_{12}(\eta)) \qquad (11)$$

where $\omega = \omega_2 - \omega_1$ is the natural frequent mismatch of two neurons in isolation. H_{12} and H_{21} is the effective coupling function. For general identical neurons, the effective phase sensitivity function can be defined as follows:

$$G(\eta) = 2(1-\rho)H_{21}(-\eta) - 2\rho H_{12}(\eta) \qquad (12)$$

The two-dimension system is reduced to one-dimension:

$$\dot{\eta} = \omega + g_{syn}G(\eta) \qquad (13)$$

For the asymmetric part of coupled connection, the effective coupling function is equal to each other ($H = H_{12} = H_{21}$), which can be described as:

$$H(\eta) = \frac{1}{C_m T}\int_0^T Q_1(t)s_0(t+\eta)(V_{syn}^{post} - V_0(t))dt \qquad (14)$$

where $s_0(t)$ is the s of membrane potential $V_0(t)$ on the limit cycle corresponding to the isolated neuron. Fig.3(a) illustrate the effective coupling function of the spiking neuron $H(\eta)$ and $H(-\eta)$. As one can see from this graph, the effective coupling function $H(\eta)$ (solid line) and (dashed line) $H(-\eta)$ are symmetrical by $\eta = T/2$.
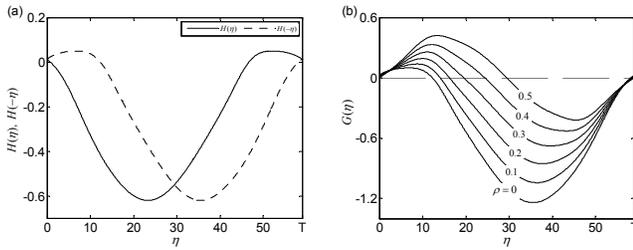
Figure 1. (a) the effective coupling function with inhibitory coupling; (b) the curves of the function $G_\rho(\eta)$ with different symmetric factors ρ; (c) an illustration of the synchronous solution of inhibitory coupling

For a pair of neurons to phase lock to each other, the necessary condition is $\dot{\eta} = 0$. For a particular choice of the parameter I, the natural frequency mismatch of the neurons, ω, is constant and G is a function of the phase difference η only. The condition for phase-locking becomes：

$$\omega = -g_{syn}G(\eta^*) \qquad (15)$$

where η^* is the locked phase lag between the two neurons. A schematic illustration of this phase-locked criterion is given in Fig. 4. As seen from Fig. 4, the crossing points of the constant value of $-\omega/g_{syn}$ and the function $G(\eta)$ are the possible phase-locked equilibrium states predicted by this reduced phase model for a particular choice of the parameter I. The stability of these phase-locked states is given by the sign of the local slope of $G(\eta)$ at these locations. In Fig.4, the left circle (open) is the unstable equilibrium and the right (filled) one is stable. Fig.3 also illustrate this relation of ω, g_{syn} and synchronous solutions. The critical values define the necessary and sufficient condition that the synchronous solution exist, described as follows:

$$\min G(\eta) \leq -\omega/g_{syn} \leq \max G(\eta) \qquad (16)$$

When $-\omega/g_{syn}$ approaches to the thresholds of $G(\eta)$, two equilibria get close to each other and disappear on the extreme points. The more closed to the antiphase synchronous solution, the stronger g_{syn} is acquired. Because of the limit of g_{syn}, the antiphase synchronization can only be achieved if two coupling neurons are completely identical.

Fig.3(b) illustrate how the dynamic characteristics of coupling system was influenced by the coupling symmetric constant ρ. The curve $G(\eta)$ increases with the increasing of ρ, and the stable equilibrium get close to $\eta = T/2$ from left, that is, the out-of-phase state to anti-phase state. In this procession, the in-phase state is always existing and unstable. For strong coupling, the synchronous character may be more complex or even the synchronization is inhibited. One should note that, for non-identical neurons, an exact phase-locked state with $\eta = 0$ is not expected to be stable in this simplified model. Biologically, this is a reasonable conclusion since synaptic coupling cannot be instantaneous, and no two neurons are exactly identical.

B. Excitable Synapsis

Fig.5 illustrate the effective phase sensitivity function of excitable synaptic fire neuron. For identical neurons, the phase sensitivity function with different coupling factor ($\rho = 0, 0.1 \ldots 0.5$) was given (Fig.7). One can note that the phase lock state was determined by the natural frequency mismatch ω and the coupling factor ρ. The $G(\eta)$ increase evidently with decreasing of ρ. When $\rho < 0.4$, $G(\eta)$ is above 0 for any η, which is mean that there is no crossed point between $G(\eta)$ and $\omega = 0$. The two neurons do not phase lock to each other.

The next case is for the bistable states. As we have seen in $G(\eta)$ curves, we study the case for $\rho > 0.4$. For symmetric coupling ($\rho = 0.5$), the $G(\eta)$ curve was shown in Fig.7. Upon magnification, one can note that this curve cross $-\omega/g_{syn}$ four times when $-\omega/g_{syn}$ is between the lines l_1 and l_2. In this region, two of these synchronous solutions are stable (filled circles) and the other two are unstable (open circles). If reducing the coupling factor, one can note that the region of bistable state is increase and vanished when $\rho \leq 0.3$.

C. Simulating Results.

Based the analysis given above, we present the results of our simulation on synchronous characters of ML coupling neurons as the strength of external current stimulate and coupling. Firstly, the estimation of the synchronous region based on the assumption of weakly symmetric coupling is given (Fig.8(a)(b)). But this assumption can not be applied to strong couple because the characters of isolated neuron have been changed and the group properties are represented. A more realized illustration of our network's synchronous behavior is presented in Fig.8(c), (d). In these figures, we show the synchronous region derived from simulation. After the two spiking neurons are stable, we calculate the γ index. If it approaches to one, the system can be synchronized. An interesting feature of this phase diagram is the boundary between the phase-locked and asynchronous (phase-drifting) states. The boundary can be estimated out of which the index

γ decrease dramatically. Comparing Fig.8(c) and Fig.8(d), one can find that the synchronous region is smaller than estimating for the coupling strength has confined the space of synchronous activity and make neurons suppress collective network activity. Lastly, for the same parameters, the excitatory coupling strength needed for synchronization is larger than the inhibitory one. Therefore the inhibitory neurons enjoy larger synchronous region than the excitatory ones for weak coupling. By the way, for any neural coupling, there exist a couple of critical values beyond which the synchronization can not be achieved for any coupling strength.
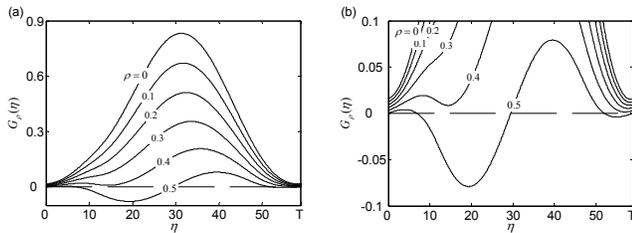
Figure 2. (a) the curves of the function $G_\rho(\eta)$ with different symmetric factors ρ (0, 0.1, 0.2, 0.3, 0.4, 0.5) and (b) the magnification of (a). The current stimulate $I_{ext} = 60$
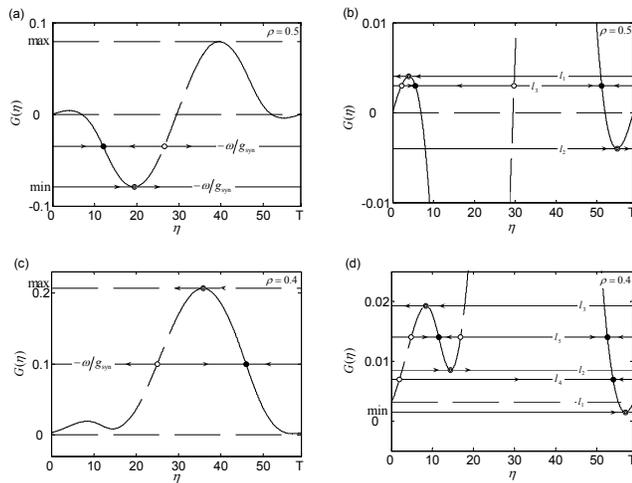
Figure 3. the condition that the phase-locked states of excitable coupling neurons exist when $\rho = 0.5$ (a, b)and $\rho = 0.4$ (c, d)

IV. CONCLUSIONS AND DISCUSSION

In this paper, we employed phase oscillator formalism to attempt to simplify the neuronal interactions using phase sensitivity curves for each individual neuron. Furthermore, we introduced a synchronous index to clarify the degree of synchronization. It has been demonstrated that this method can be used to in-phase, anti-phase, and out-of-phase synchronization. Whether this can be implied to the phase-locking (not 1:1) neurons require more support of simulation and experiment.

We have shown that the synchronous region of ML neurons with excitatory and inhibitory coupling, which help us understand more properties of neuron network. For identical neurons we use in this paper, the same external stimulation can induce synchronization with a very weak couple. With the disparity of stimulation expanding, the coupling strength need to phase-locking increase. It would be specially mentioned that strong coupling may block the spike of single neuron and even wipe the characters of the whole network. Since the computational complexity of such networks increases rapidly with size, further investigation on synchronization dynamics of more types of coupled neurons may help us understand the essence of encoding and decoding of information.
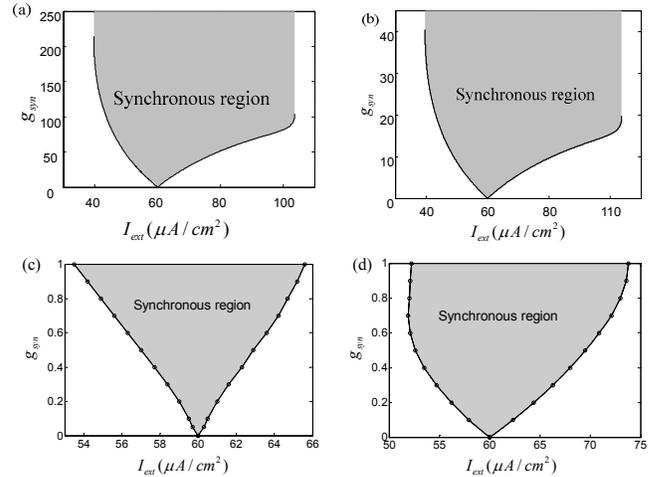
Figure 4. (a, b) the estimate of the synchronous regions based on the weakly coupling. (c, d) the synchronous regions based on the numerical simulation. The left hand side of the figure is excitable coupling whereas the right hand side is the inhibitory one.

REFERENCES

[1] R. Eckhorn, R. Bauer, W. Jordan, M. Brosch, W. Kruse, M. Munk, H.J. Reitboeck (1988) Coherent oscillations: A mechanism of feature linking in the visual cortex? multiple electrode and correlation analyzes in the cat, Biological Cybernetics 60: 121-130.

[2] D. Fricker, R. Miles (2001) Interneurons, spike timing, and perception, Neuroscience 32: 771-774.

[3] F. Mormann, T. Kreuz, R.G. Andrzejak, P. David, K. Lehnertz, C.E. Elger (2003) Epileptic seizures are preceded by a decrease in synchronization, Epilepsy Research 53: 173-185.

[4] C.C. Chow, N. Kopell (2000) Dynamics of spiking neurons with electrical coupling, Neural Computation 12: 1643-1678.

[5] T.J. Lewis, J. Rinzel (2003) Dynamics of spiking neurons connected by both inhibitory and electrical coupling., Journal of Computational Neuroscience. 14: 283-309.

[6] E.-H. Park, E. Barreto, B.J. Gluckman, S.J. Schiff, P. So (2005) A Model of Effects of Applied Electric Fields on Neuronal Synchronization, The Journal of Computational Neuroscience 19: 53-70.

[7] A. Destexhe, Z.F. Mainen, T.J. Sejnowski (1999) Kinetic models of synaptic transmission, in: C. Koch, I. Segev (Eds.), Methods in neuronal modeling: From ions to networks, MIT Press, Cambridge, MA, pp. 1-25

[8] F.C. Hoppensteadt, E.M. Izhikevich (1997) Weakly Connected Neural Networks, Springer-Verlag, New York, NY.

[9] Kuramoto Y (1984) Chemical Oscillations, Waves, and Turbulence.Springer, Berlin.