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Spatial phase pattern in one-dimensional arrays of limit cycle oscillators with discrete coupling

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Abstract

We present a model of limit cycle oscillators for collective oscillations in intracellular calcium concentration in cell communities. A phase-dependent discrete coupling between nearest neighbors is introduced into the model on the basis of the experimental observation that intercellular transmission of calcium or calcium mobilizing messenger is effected by gap junction and gap junctional permeability is affected by intracellular calcium concentration. The spatial phase pattern of several clusters in which oscillations are in phase is found with the phase-dependent discrete coupling.

Keywords: Limit cycle oscillator; Gap junctionally coupling; Clustering

1. Introduction

Coupled chemical oscillator systems have been thought to be useful as models for living cell communities, in which each cell exhibits oscillatory behaviors. Dynamical features of two or three chemical oscillators coupled together have been extensively studied experimentally [1–6]. Much more theoretical and computational studies have been performed on the systems of not only two or three coupled oscillators but also large populations of coupled oscillators [7–15]. There are some biological systems where the coupling of oscillators and the resulting collective oscillation play important roles. For example, the heart contraction occurs due to the electrical coupling of oscillatory myocardial cells and the resulting synchronous oscillation. Striking in this regard is a study by Jagadeesh et al. using the cells of the cat visual cortex [16]. Visually evoked collective oscillations of membrane potential have been suggested to contribute to the information integration.

Oscillations in concentration of intracellular calcium ion have been experimentally observed in some cell communities and a number of models proposed [17–19]. Synchronous and asynchronous collective oscillations of calcium ion, clusters with phase difference in which the concentration of calcium ion in each cell oscillate synchronously, and calcium traveling wave have been observed in the cell populations [20,21]. There has been a hypothesis that spatially organized calcium transients play important roles in cell-to-cell communication and synchronous responses [20]. The intercellular coupling of calcium oscillations has

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been thought to be caused by transmission of calcium or calcium mobilizing messenger, inositol 1,4,5-triphosphate, through gap junction [22,23]. Gap junction is comprised of cell-to-cell channel protein termed connexin. Gap junctional permeability is known to be affected by intracellular concentrations of cAMP, proton and so on [24]. In some cases, an increase in intracellular calcium concentration is known to depress intercellular communication by gap junction [24], although it is unclear whether physiological increase in intracellular calcium concentration evokes the closure of gap junction [23]. In rat hepatocytes, gap junctional protein (connexin 32) is reported to be phosphorylated by calcium-dependent protein kinases, resulting in the closure of gap junction [25].

In this study, we examine the behaviour of limit cycle oscillators in one spatial dimension. Phase-dependent discrete coupling is introduced on the basis of the hypothesis that the open-close cycle of gap junction is coupled with intracellular calcium oscillation. It is suggested that the discrete coupling is important for the explanation of the spatio-temporal patterns of calcium ion observed experimentally, in particular, clustering. Many studies on mathematical models for coupled oscillator systems have been performed. However, as far as we know, the influence of discrete coupling on the dynamical behavior has not been examined in the coupled oscillator systems. On the other hand, the effect of discrete gap junction coupling has been extensively studied for the explanation of action potential propagation failure in excitable myocardial cells [26,27].

2. Model

The present model is based on the circule map using the phase transition curve, which was introduced by Glass et al. in the study of single oscillator forced periodically [28]. In the present study, this circle maps are discretely coupled in one dimension. Our model consists of 100 limit cycle oscillators coupled to their nearest neighbors in one spatial dimension and time is discretized. One point on the limit cycle trajectory is represented by phase $\phi(0 \leqslant \phi < 1)$. When the nth oscillator is coupled between the nearest neighbors, it is perturbed by a mass transfer proportional to the concentration difference between the nearest neighbors. The relaxation to a native limit cycle after a stimulus results in the change of the oscillator phase. New phase is given by $\phi + g(\phi)$, in which ϕ is the phase just before the stimulus occurs and $g(\phi)$ is the phase transition curve. According to Glass et al. [28], we assume that the oscillator state rapidly returns to the limit cycle following the stimulus. Thus, the time evolution of the phase of the nth oscillator is as follows;

$$\phi(n, t+1) = \phi(n, t) + g(\phi(n, t)) + a(n), \tag{1}$$

where $a(n)$ is the native frequency of the nth oscillator. The phase transition curve used in this model is

$$g(\phi(n, t)) = -b(n, t)\sin[2\pi\phi(n, t)]. \tag{2}$$

$b(n, t)$ is the stimulus strength. The stimulus strength is usually a constant [28,29]. In the present model, the stimulus at the time t corresponds to the change in the nth oscillator's concentration due to a diffusion-type spatial coupling between the nearest neighbors. The present coupling fashion is served as a model for intercellular mass exchange through gap junctions. A bore of the gap junction is known to be hydrophilic enough and wide enough to pass small cytoplasmic molecules (e.g., inorganic ions, metabolites, messengers) [24]. Thus, the intercellular exchange of the cytoplasmic molecules through the gap junctions has been thought to be due to their diffusions. So, in our model, $b(n, t)$ is assumed to be as follows;

$$b(n, t) = M\{\tfrac{1}{2}[C(n+1, t) + C(n-1, t)] - C(n, t)\}, \tag{3}$$

where M is the coupling constant and $C(n, t)$ is the mass concentration. $C(n, t)$ is assumed to be given by $\exp[-10\phi(n, t)]$. By iterating Eq. (1), we obtain the time evolution of the phases of 100 oscillators.

The purpose of this study is to examine how the time evolution of the oscillator phases is affected by a phase-dependent discrete coupling. The discrete coupling in the present study is served as a model of the intercellular communication by the gap junctions in hepatocytes. It has been known that some agonists induce oscillations in intracellular calcium concentration of hepatocytes [30]. In addition, there has been evidence that calcium can transmit through the gap

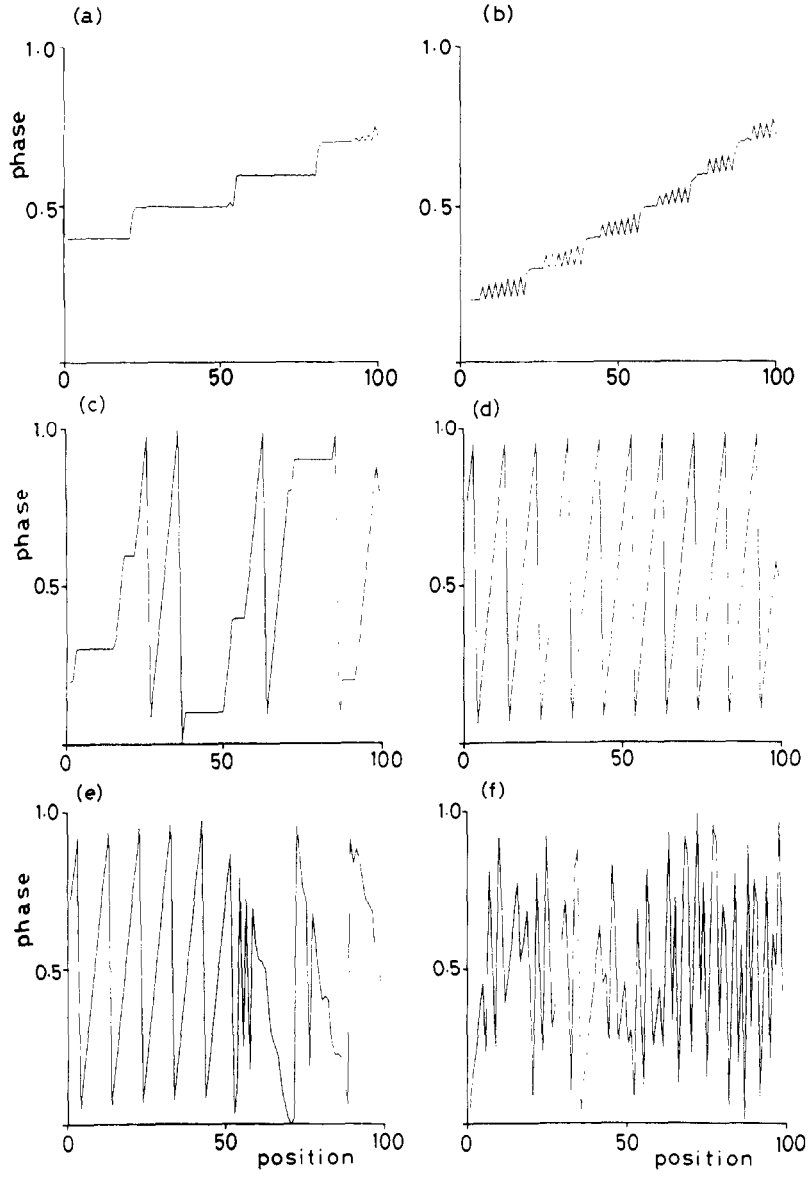

Fig. 1. Spatial phase patterns in the case of the phase-dependent discrete coupling after the 100000 iterations of transients with a random set of initial phases of the 100 oscillators. (a) Cluster pattern, $M = 0.1$, $\phi' = 0.51$; (b) cluster pattern, $M = 0.1$, $\phi' = 0.54$; (c) coexistence of cluster pattern and ordered oscillatory pattern, $M = 0.2$, $\phi' = 0.74$; (d) ordered oscillatory pattern, $M = 0.1$, $\phi' = 0.70$; (e) coexistence of ordered oscillatory pattern and unlocked pattern, $M = 0.15$, $\phi' = 0.80$; (f) unlocked pattern, $M = 0.2$, $\phi' = 0.86$.

junctions in a chain of hepatocytes [22]. On the other hand, it has been reported that elevation of intracellular calcium concentration results in the closure of the gap junctions in hepatocytes [25]. It is borne in mind with those experimental results that the gap junction is close with high calcium concentration and open with low calcium concentration in the cycles of the intracellular calcium oscillations. Thus, the following rules are introduced into our model. If $\phi(n, t) \geqslant \phi'$ (a threshold value), that is, if $C(n, t) \leqslant \exp(-10\phi')$, then the nth oscillator is coupled between its nearest neighbors. Otherwise, the coupling is impossible ($b(n, t) = 0$), except for the case of $\phi(n-1, t) \geqslant \phi'$ or $\phi(n+1, t) \geqslant \phi'$.

There have been only a few studies of similar coupled oscillators using phase-resetting formulations [29,31]. The stimulus strengths in those models are constant and there have been no models with the stimulus strength defined as the change in concentration due to mass diffusion, as far as we know. Bruin et al. [31] have studied synchronization in chains of cardiac pacemaker cells. In their model, interactions between nearest neighbors are defined by a latency-phase curve which can be easily converted to a phase resetting curve. A cell in the chain fires an action potential at the phase $\phi = 0$ (is equal to $\phi = 1$). Only the cells at $\phi = 0$ can influence the cycle lengths of their neighbor cells according to the latency-phase curve. That is, the interaction between the neighbor cells is regarded as a special case of the phase-dependent discrete coupling and similar to that in the present model. Ermentrout and Edelstein-Keshet [29] have studied two-dimensional coupled oscillators by use of the same formulations as shown in (1) and (2), except that the phase is also discretized. The effect of the phase-dependent discrete coupling has not been examined.

3. Results and discussion

Computations were carried out for an initial condition of a set of randomly chosen phases and without natural frequency distribution ($a(n) = 0.1$, $1 \leqslant n \leqslant 100$). We calculated the phases of one-dimensional oscillators with four small values of the coupling constant($M = 0.05, 0.10, 0.15, 0.20$). Calculated phase patterns were classified as follows. (1) Plateau pattern: In-phase locking occurs over all the space. This pattern is found in the regime of the threshold phase $\phi' \leqslant 0.50$ for four values of the coupling constant. (2) Cluster pattern (Fig. 1a): several clusters including in-phase locked oscillators are found. Coexistence of in-phase locked and zigzag regions is also found as shown in Fig. 1b. (3) Ordered oscillatory pattern (Fig. 1d): the frequency of spatial oscillation is almost constant. The phase peaks propagate along the oscillator chain with time. This may capture the phenomena of calcium traveling wave in vivo. (4) Unlocked pattern (Fig. 1f): the phases of the oscillators are unlocked and the spatial pattern of random phases continues with time. In addition to the above four patterns, coexistence of the cluster pattern and the ordered oscillatory pattern, or of the ordered oscillatory pattern and the unlocked pattern is found as shown in Fig. 1c and Fig. 1e, respectively. Phase diagram for the ϕ'–M parameter space is shown in Fig. 2. While the regime ($0.51 \leqslant \phi' \leqslant 0.58$) of the cluster pattern is almost invariant for four values of the coupling constant M, the regime of coexistence of the cluster pattern and the ordered oscillatory pattern (Fig. 1c) increases by increasing M.

For the sake of comparison, phase patterns for the continuous coupling ($\phi' = 0$) were also exam-

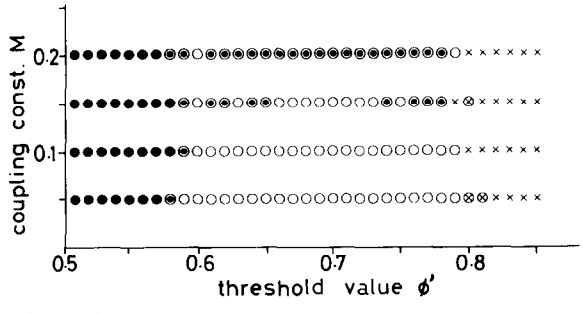

Fig. 2. Phase diagram for the threshold phase value ϕ' – the coupling constant M parameter space. Symbols denote the phase patterns as follows: (●) cluster pattern; (⊙) coexistence of cluster pattern and ordered oscillatory pattern; (○) ordered oscillatory pattern; (⊗) coexistence of ordered oscillatory pattern and unlocked pattern; (×) unlocked pattern.

ined. As the coupling constant M is decreased, the phase pattern changes gradually to be from plateau pattern to unlocked pattern. However, no cluster and ordered oscillatory patterns as shown in Fig. 1a–1e are found with the continuous coupling.

Recently, clustering behavior has been found in a few theoretical studies with globally coupled chaotic oscillator models and discussed from the viewpoint of biological information processing and engineering applications [15]. However, as far as we know, only a few oscillator systems with nearest coupling exhibit the formation of clusters in which oscillations are in phase. Bruin et al. [31] have studied an oscillator model with coupling using a phase-resetting formulation and reported partial in-phase synchronization in one dimension. However, the phase patterns with three or more in-phase clusters found in the present study have not been reported. Kopell and Ermentrout [32] have found clusters in which oscillations are out of phase (not in-phase) in one-dimensional oscillators with nearest weakly coupling.

In the nervous system, intercellular calcium signaling has been thought to be effected by gap junctions but not by synaptic coupling, although the regulation of their permeability has not been clarified. Recently, in reconstituted neural network systems by use of cultured neurous, in-phase synchronization of intracellular calcium oscillations has been experimentally observed with multi-site optical recording technique [21]. In addition, coexistence of two clusters with phase difference has also been observed, although physiological implication of such clustering has not been clarified [21]. The clustering found in our gap-junctionally coupled oscillator model may be useful for the explanation of such experimental results.

References

[1] M. Marek and I. Stuchl, Biophys. Chem. 3 (1975) 241.

[2] K. Nakajima and Y. Sawada, J. Chem. Phys. 72 (1980) 2231.

[3] M.F. Crowley and I.R. Epstein, J. Phys. Chem. 93 (1989) 2496.

[4] M.F. Crowley and R.J. Field, J. Phys. Chem. 90 (1986) 1907.

[5] K. Bar-Eli and S. Reuveni, J. Phys. Chem. 89 (1985) 1329.

[6] K. Yoshikawa and K. Fukunaga, Chem. Phys. Letters 174 (1990) 203.

[7] J.J. Tyson and S. Kauffman, J. Math. Biol. 1 (1975) 289.

[8] I. Schreiber and M. Marek, Physica D 5 (1982) 258.

[9] K. Bar-Eli, Physica D 14 (1985) 242.

[10] C. Baesens, J. Guckenheimer, S. Kim and R.S. MacKay, Physica D 49 (1991) 387.

[11] I. Waller and R. Kapral, Phys. Rev. A 30 (1984) 2047.

[12] A.T. Winfree, The geometry of biological time (Springer, Berlin, 1980).

[13] Y. Kuramoto, Progr. Theoret. Phys. 79 (1984) 223.

[14] D.G. Aronson, G.B. Ermentrout and N. Kopell, Physica D 41 (1990) 403.

[15] K. Kaneko, Physica D 41 (1990) 137.

[16] B. Jagadeesh, C.M. Gray and D. Ferster, Science 257 (1992) 552.

[17] T. Meyer and L. Stryer, Proc. Natl. Acad. Sci. USA 85 (1988) 5051.

[18] A. Goldbeter, G. Dupont and M.J. Berridge, Proc. Natl. Acad. Sci. USA 87 (1990) 1461.

[19] J. Sneyd, S. Girard and D. Clapham, Bull. Math. Biol. 55 (1993) 315.

[20] M.J. Berridge and R.F. Irvine, Nature 341 (1989) 197.

[21] Y. Kuroda, Biophysics 31 (1991) 239.

[22] J.C. Sàez, J.A. Connor, D.C. Spray and M.V. Bennett, Proc. Natl. Acad. Sci. USA 86 (1989) 2708.

[23] A.C. Chales, C.C.G. Naus, D. Zhu, G.M. Kidder, E.R. Dirksen and M.J. Sanderson, J. Cell Biol. 118 (1992) 195.

[24] W.R. Loewenstein, Cell 48 (1987) 725.

[25] J.C. Sàez, A.C. Nairn, A.J. Czernik, D.C. Spray, E.L. Hertzberg, P. Greengard and M.V.L. Bennett, Eur. J. Biochem. 192 (1990) 263.

[26] M.S. Spach, W.T. Miller, D.B. Geselowitz, R.C. Barr, J.M. Kootsey and E.A. Johnson, Circ. Res. 48 (1981) 39.

[27] J.P. Keener, J. Theoret. Biol. 148 (1991) 49.

[28] L. Glass, M.R. Guevara, J. Belair and A. Shrier, Phys. Rev. A 29 (1984) 1348.

[29] G.B. Ermentrout and L. Edelstein-Keshet, J. Theoret. Biol. 160 (1993) 97.

[30] N.M. Woods, K.S.R. Cuthbertson and P.H. Cobbold, Nature 319 (1986) 600.

[31] G. Bruin, D.L. Ypey and W.P.M. Van Meerwijk, Biol. Cybern. 48 (1983) 175.

[32] N. Kopell and G.B. Ermentrout, Commun. Pure. Appl. Math. 39 (1986) 623.