

# Intercellular Communications Induced by Random Fluctuations

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## Abstract

This paper investigates a general coupled noisy system for a cell-cell communication in a multi-cell system. The main conclusion is that appropriate noise intensity and coupling strength are capable of driving the coupled system to synchrony, which may be exploited by biological organisms to actively facilitate mutual communication. A multi-cell system with a synthetic gene network with both noises and delays is adopted to demonstrate the effect of noises on cellular communication.

**Keywords:** synthetic gene network, cell communication, synchronization, master equation

## 1 Introduction

Cell communication has been shown to be essential for coordinated responses resulting from an integrated exchange of information in both prokaryotes and eukaryotes [12, 15, 19]. Generally, intercellular communication is accomplished, by transmitting individual cell reactions via intercellular signals to neighboring cells and further integrating to generate a global cellular response at the level of molecules, tissues, organ and body. In particular, gene regulation is an inherently noisy process, from transcriptional control, alternative splicing, translation, diffusion to chemical modification reactions of transcriptional factors, which all involve stochastic fluctuations owing to low copy numbers of many species per cell. Such stochastic noises may not only affect the dynamics of the entire system but also be exploited by living organisms to actively facilitate certain functions, such as synchronization or communication.

To understand the basic mechanism of cell-cell cooperative dynamics, a few theoretical models have been successfully developed so far for both natural and synthetic gene networks [3, 10, 15, 19]. In particular, when ignoring effects of noise and diffusion, McMillen et al. proposed a synchronization scheme based on mechanism of relaxation oscillation or “fast threshold modulation” in a synthetic system [10], which fulfills the communication by producing and responding to a small intercell signaling molecules known as autoinducers in the quorum sensing apparatus of the marine bacterium *Vibrio fischeri*. In this paper, we aim to develop a general synchronization model by further considering the effects of stochastic fluctuations and signal diffusion processes or time delays. Specifically, we first present a theoretical framework to equivalently transform a stochastic multi-cell system into a multiple coupled deterministic system by the first and second cumulants when the Gaussian distributions are assumed, and provide sufficient conditions for stochastic synchronization even with time delays based on “global Hopf bifurcation”. Then we design and construct a synthetic gene regulatory network by

using an operon with genes *LuxR* and *LuxI* and promoter  $P_{lacLux0}$ . Intercellular communication is facilitated between cells by diffusing a small protein, autoinducer (AI) produced by a protein LuxI, which results in a synchronization behavior of all cells even with time delays and stochastic perturbations. From the viewpoint of stochastic dynamics, such synchronization is a phase-locking behavior of the probability distributions for all species. As shown both analytically and numerically in this paper, the cells with the constructed gene network can be synchronized with random fluctuations, which actually enhance synchronization by introducing extra dynamics or energy originated from noises. In contrast to couplings that play a dominant role to coordinate the synchronization, noise acts rather as a compensated force to induce the synchronous oscillation but also constantly perturbs the system in an unpredicted manner. The results of this paper establish a theoretical foundation that can be directly applied to model, analyze or even predict synchronous behaviors of a coupled bio-system at the level of molecules. The numerical example also confirms that interplay between noises and couplings induces regular or collective dynamics and actively mediates synchrony of the multi-cell system.

## 2 Gene Regulatory Network with Stochastic Noises

Due to low copy numbers for many species in living cells, the origin of stochasticity can be traced to the random transitions among the discrete chemical states. Generally, the master equation is adopted to present such a random and discrete nature of biochemical reactions [16], which inherently exist in all life processes. The gene regulatory network in a cell is generally expressed by a master equation, which can be approximated by a set of Langevin equations or stochastic differential equations:

$$\frac{dx(t)}{dt} = f(x(t), \eta(t)), \quad (1)$$

where  $x = (x_1, \dots, x_m)$  is the concentrations of the species, e.g. proteins and mRNAs or other chemical complexes, and  $m$  is the total number of species in the cell.  $\eta = (\eta_1, \dots, \eta_m)$  is Gaussian noises with zero means and covariances  $K_{ij}$ , i.e.  $\langle \eta_i(t) \rangle = 0$  and  $\langle \eta_i(t) \eta_j(t') \rangle = K_{ij}(x(t)) \delta(t - t')$ .  $f = (f_1, \dots, f_m)$  is the synthetic rates of each species. Gaussian noises  $\eta$  called intracellular noises are interior noises inside the cell and derived from the random and discrete chemical reactions.

Assume that there are  $n$  identical cells, which are coupled with the common environment. Then, the corresponding Langevin equations of the entire system are for  $k = 1, \dots, n$

$$\frac{dx^k(t)}{dt} = f(x^k(t), \eta^k(t)) + D_k(y - x^k(t)) + \xi^k(t) \quad (2)$$

where the matrix  $D_k = \text{diag}(d_{k1}, \dots, d_{km})$  is coupling coefficients from the environment  $y$  to cell- $k$ , and the variable  $y$  is the concentration of  $x$  in the environment.

The vector  $\xi^k = (\xi_1^k, \dots, \xi_m^k)$  called extracellular noises represents external noises originated outside the cells due to environment perturbations, and are assumed as independent Gaussian white noises with zero means and covariances  $V$ , i.e.,  $\langle \xi_i^k(t) \rangle = 0$  and  $\langle \xi_i^k(t), \xi_j^l(t') \rangle = V \delta_{kl} \delta(t - t')$ .  $V = \text{diag}(\sigma_1^2, \dots, \sigma_m^2)$  is an extracellular noise covariance matrix, where  $\sigma_i^2 = 0$  if  $x_i^j$  is not a coupling variable. Obviously, there are two different type of noises in our model, i.e. intracellular noises derived from the master equation due to the low copy numbers of species inside a cell, and extracellular noises originated from the environment perturbations, such as temperature fluctuations or imperfect culture mixing. Different from the intracellular noises  $\eta$  that are generally correlated each other, it is reasonably to assume that  $\xi_i^k(t)$  are independent each other and are uncorrelated with  $\eta_j^l(t)$  ( $1 \leq j, k \leq n$ ) since the intracellular noises in a cell are generally irrelative to the extracellular noises and vice versa. Assume that the concentration of signal molecules in the environment is approximately expressed by  $y = \sum_{i=1}^n x_i^i/n$ , where  $x_i^i = (x_1^i(t - \tau_1), \dots, x_m^i(t - \tau_m))$ , and  $\tau_j$  represents the extracellular time delay of  $x_j$  due to diffusion or transport processes of the molecule among cells. Intracellular time delays

are omitted for the sake of simplicity, although all theoretical results in this paper hold even with the intracellular time delays in eqn.(2).

When the system is sufficiently large, we assume that the stochastic variables obey Gaussian distribution. Then, it can be proven that eqn.(2) is equivalently expressed by the first and second cumulant evolution equations, which means that we can actually examine the dynamics by deterministic cumulants instead of the complicated stochastic variables. Actually, the numerical simulation also verified that such an assumption is reasonable by a synthetic gene network. Let the first cumulants or means of  $x$  be  $X$ , and the second cumulants or covariances of  $x$  be  $M$ . Then, by integrating over all  $x$ , the cumulant evolution equations of eqn.(2) are

$$\begin{cases} \frac{dX^k(t)}{dt} = F(X^k(t), M^k(t)) + D_k(\frac{1}{n} \sum_{i=1}^n X_t^i - X^k) \\ \frac{dM^k(t)}{dt} = G(X^k(t), M^k(t)). \end{cases} \quad (3)$$

The vector  $X^k$  clearly has  $m$  elements. Let the number of elements for the covariance vector  $M^k$  be  $s$ . Then  $s$  is at most  $m(m+1)/2$  but more than  $m$  because any two species in a cell are not generally independent of each other. Since species among cells are not necessarily all coupled, most of diagonal elements of  $D_i$  are generally zero.

By examining deterministic eqn.(3), we can figure out the qualitative dynamics of the original stochastic eqn.(2), including the stochastic synchronization from the viewpoint of probability distribution. In particular, the synchrony of eqn.(3) corresponds to that of eqn.(2), because the original stochastic dynamics  $x$  can be fully reconstructed from deterministic mean  $X$  and covariance  $M$  due to assumption of Gaussian distributions.

To study synchronization solutions or phase-locked solutions of eqn.(3) is a challenging problem. In Appendix A, we extend the previous works and further derive the sufficient conditions of synchronization. Clearly, if couplings between cells are sufficiently strong, dynamics of all cells are synchronized in an identical phase, or called in-phase synchronization. However, for a general coupled system, a phase-locked solution is usually expected to exist, and is of greater interest in biology. Without loss of generality, let the phase of the first cell be zero, i.e.  $\alpha_1 = 0$ , and the phase of the  $k$ th cell be  $\alpha_k T$  where  $T$  is the least period of the oscillation. From the analysis of Appendix A based on global Hopf bifurcation theory, we can prove that there is a phase-locked solution bifurcated from the steady state for system (3) under the conditions of Theorem A.1, and that the corresponding phase of the  $k$ -th cell is determined by

$$\alpha_k = \frac{k-1}{n}, \quad 1 \leq k \leq n, \quad (4)$$

where time delays are ignored for the sake of simplicity. Eqn.(4) indicates that the phase-locked solution has the uniform phase difference between cells. Notice that all species in the same cell, however, move at the same phase. Due to the symmetry of eqn.(2) or eqn.(3) for identical cells, there are formally  $n$  solutions with the phase in the same form of eqn.(4). When there are time delays, we can still prove existence of a phase-locked solution in which the phases have similar expression as eqn.(4) but in an implicit function form of time delays. Since the synchronization mechanism is based on global Hopf bifurcation that is also a restricted Hopf bifurcation depending on the symmetry of the system, it is also easy to use for designing the bio-circuits or predicting synchronous dynamics by perturbing a set of parameters according to the conditions of Theorem A.1 of Appendix A. From eqns.(1) and (3), apparently noises exert their effects by the second cumulants or covariances. In other words, without the second cumulants, the cumulant evolution equations (3) simply degenerate to a deterministic system or an averaging dynamics. It can also be proven that there is a in-phase synchronization solution when the couplings are sufficient strong or the cell number is large enough.

Instead of random variables, eqn.(4) indicates a synchronized solution in the phase space for the probability distribution (means and covariances) of each cell. This means that the probability distributions of all variables in each cell moves at the same phase, whereas those between arbitrary

two cells have a fixed phase difference. However, provided that random variables follow the Gaussian distributions, the stochastic dynamics of the original cellular system eqn.(2) can be exactly recovered from such probability distributions, which implies that eqn.(4) also corresponds to the solution of the stochastic synchronization for eqn.(2). Next, we will show that noises actually play an active role to induce such cellular synchronization.

### 3 Implementation by a Synthetic System

Recent progress in genetic engineering has made the design and implementation of *de novo* synthetic gene networks realistic from both theoretical and experimental viewpoints [3, 5, 4, 9, 18, 6, 17], in particular for simple organisms, such as *E.coli* and *yeast*. Designing and implementing synthetic gene networks provide a natural framework for reducing the complexity of gene regulation. Actually, from the theoretical prediction, several simple gene networks have been experimentally constructed, e.g., genetic toggle switch [8], repressilator [7] and other bio-circuits [3, 1, 11]. Next, we adopt an artificial gene network as an implementation example to demonstrate noise-mediated communication.

#### 3.1 Model

In this work, we design a synthetic gene regulatory network by using a simple two-gene model, i.e. *LuxI* and *LuxR* with a promoter  $P_{lacLux0}$ , as shown in Figure 1. Genes *LuxI* and *LuxR* coordinating the behavior of bacteria, such as quorum sensing, were initially discovered from the marine bacterium, *Vibrio fischeri*. In Figure 1, genes *LuxI* and *LuxR* are constructed as an operon and are both under the control of the promoter  $P_{lacLux0}$ . Cell to cell coupling is accomplished by diffusing a small signal molecule into the extracellular environment, i.e. autoinducer (AI), which plays a major role in the cell to cell communication or quorum-sensing in *Vibrio fischeri*. Such a circuit can be engineered on plasmids [19], and then be cloned to multiple copies, e.g. by PCR. The engineered plasmids are further assumed to grow in *E. coli*.

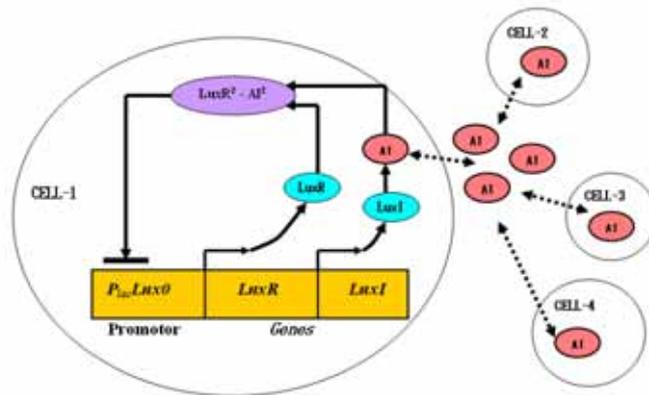


Figure 1: A two-gene model of a gene regulatory network. Gene *LuxR* produces the protein LuxR, which is dimerized. Protein LuxI synthesizes AI, which forms a dimer and further a hetero-tetramer by binding to a LuxR dimer. The AI-LuxR tetramer binds to the promoter  $P_{lacLux0}$  to inhibit the transcription of the genes *LuxR* and *LuxI*. Cell communication or synchronization is accomplished by diffusing AIs to the extracellular environment, which further enter cells as signal molecules to regulate gene expression.

Let  $AI_2$  and  $LuxR_2$  indicate AI and LuxR dimers, and  $AL$  and  $ALD$  represent  $AI_2-LuxR_2$  and  $AI_2-LuxR_2-DNA$  complexes, respectively. Then, in a cell, the multimerization reactions of proteins

and binding reaction on the operator or regulatory region of DNA are described as



Let the copy number of plasmids with the operon  $LuxI$  and  $LuxR$  be  $n_D$ .

On the other hand, the reactions involving transcription and translation, autoinducer synthesis, and degradation in a cell are expressed as



where the last five reactions are degradation reactions, and  $\alpha$  ( $0 < \alpha < 1$ ) is a repression coefficient. As shown in eqns.(10)-(11),  $mRNA_{LuxI}$  and  $mRNA_{LuxR}$  are produced by the same reactions due to the operon.

Among cells, AI freely diffuses between cell membranes, and such diffusion process is modelled by linear coupling with time delays that are mainly due to diffusion process. We assume that all intracellular transportation and diffusion processes of chemical complexes are expressed by the corresponding time delays. Then from eqns.(5)-(16), we first derive the master equation, and then transform into the Langevin equations. By considering cell coupling or the diffusion of AI, the system is finally expressed by the first and second cumulant evolution equations with time delays. When the system is sufficiently large, the fluctuations of variables for the system are assumed to approach to the Gaussian distribution, which can be exactly described by the first and second cumulants (means and covariances). Parameter values are set as follows:  $k_a = 3.0 \text{ min}^{-1}$ ;  $e_i = e_r = \frac{1}{6} \times 10^{-1} \text{ min}^{-1}$ ,  $e_a = \frac{1}{6} \times 10^{-2} \text{ min}^{-1}$  and  $e_{mi} = e_{mr} = 1.0 \text{ min}^{-1}$ ;  $k_1 = k_2 = k_4 = 0.6 / (nM \cdot \text{min})$ ,  $k_3 = 6.0 \times 10^{-5} / (nM \cdot \text{min})$ ,  $k_{-1} = k_{-2} = k_{-4} = 6.0 / (nM \cdot \text{min})$ ,  $k_{-3} = 0.6 / (nM \cdot \text{min})$ ;  $k_m = 3.4 \text{ min}^{-1}$ ;  $k_{pi} = k_{pr} = 4.2 \text{ min}^{-1}$ ;  $\alpha = 0.36$ ; time delay for AI  $\tau = 9.3 \text{ min}$ ; and  $n_D = 10$ , which are mainly from [2] with slight modification.

### 3.2 Implementation Results

We use three identical cells with the gene network of Figure 1 for simulation although our theoretical model has no limitation for the number of cells. Figure 2 shows mean values or the first cumulants of intracellular AI concentrations in three cells, whereas Figure 2 indicates the variances or the second cumulants of intracellular AI concentrations. Therefore, Figure 2 actually represent time evolution of the probability distributions of AIs. When coupling strengths are  $d_{ii} = -152.5 \text{ min}^{-1}$ ,  $d_{ij} = 76.25 \text{ min}^{-1}$  for  $i, j = 1, 2, 3$  and  $i \neq j$ , and the extracellular noise deviation is  $\sigma = 24.6 \text{ nM}$ ,

it is easy to check from Theorem A.1 of Appendix A that the sufficient conditions for the phase-locking synchronization are satisfied for the system (3), which is numerically confirmed from the probability distributions of figure 2 (left and middle). Since intracellular noises are determined by the chemical reactions as indicated from master and Langevin equations, we only take the extracellular noise deviation  $\sigma$  as a parameter to examine the effect of stochastic fluctuations on synchronous oscillation.

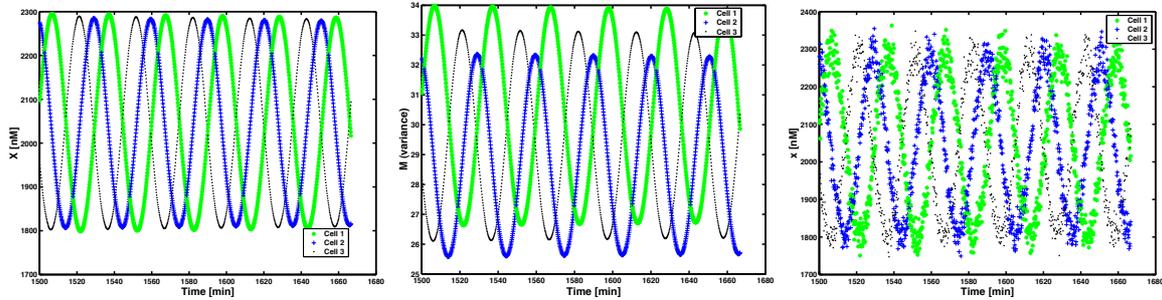


Figure 2: Synchronization for means and variances of intracellular AI concentrations in three noisy cells with the time-delay couplings. Coupling coefficients are  $d_{ii} = -152.5$ ,  $d_{ij} = 76.25$  for  $i, j = 1, 2, 3$  and  $i \neq j$ . (Left): means of AI, (middle): variances of AI, (right): time evolution of AI. The extracellular noise deviation is  $\sigma = 24.6$ , which is imposed on extracellular AIs.

From Figure 2 (left and middle), obviously the phases of dynamics in three cells differ almost with an one-third period, which verifies our theoretical prediction of eqn.(4). The slight large gap between each period is due to time delay  $\tau$ . Figure 2 (right) is a time evolution for intracellular AI concentrations  $x(t)$  of (2) corresponding to the means  $X(t)$  of Figure 2 (left), which clearly shows that dynamics are affected by the stochastic fluctuations around the means  $X$  but still kept in synchrony with the same phase as Figure 2 due to small noise ratio. Comparing with Figure 2 (left and middle), Figure 2 (right) also indicates that the synchronized probability distributions or cumulants correspond to stochastic synchronization of the system.

Next, we examine the effects of extracellular noise intensity and coupling strength on the synchronous oscillation. Without extracellular noise  $\sigma = 0$  or small noise  $\sigma = 11.8$ , the system converges to a stable equilibrium or a stationary probability distribution that has constant means and covariances. However, with a stronger noise  $\sigma = 29.2$ , the multi-cell system is synchronously oscillated, which implies that noise actually enhances the synchronized oscillation. From such numerical simulation, deterministic dynamics of each single cell are not sufficiently active for inducing oscillation even with couplings. However, for such a system, noise provides extra dynamics, e.g. dynamics of the second cumulants that are originated from intrinsic fluctuations or other unknown energy sources beyond the coupled system, so that a cooperative but fluctuating behavior is stimulated among cells.

On the other hand, the coupling strengths also induce or promote the synchronous oscillation in a much similar but strong way to noises. To an extreme case, when the couplings are sufficiently strong, as shown in Figure 3, three cells reach complete synchronization or in-phase synchronization even with noises, i.e., the phase difference between cells is zero [20].

Figure 3 (right) is a bifurcation diagram on the noise deviation, which shows that the noise actually induces the synchronized oscillation by the Hopf bifurcation. Due to global Hopf bifurcation, a stable equilibrium corresponds to a stationary probability distribution, whereas a bifurcated periodic solution is a synchronous oscillation of the coupled system. Notice that different from the local Hopf bifurcation that simply generates a periodic oscillation, the global Hopf bifurcation creates a phase-locked solution among cells, as proven in Theorem A.1. In other words, the oscillation amplitudes and period  $T$  change with the noise deviation, but the phase difference between any two cells is kept to be constant.

In this model, we examine the effects of noise-induced synchronization by using one signal molecule AI in identical cells. Recent research shows that chemical communication among living organisms is widespread, and many bacteria have two or more sensing systems to monitor their environment and

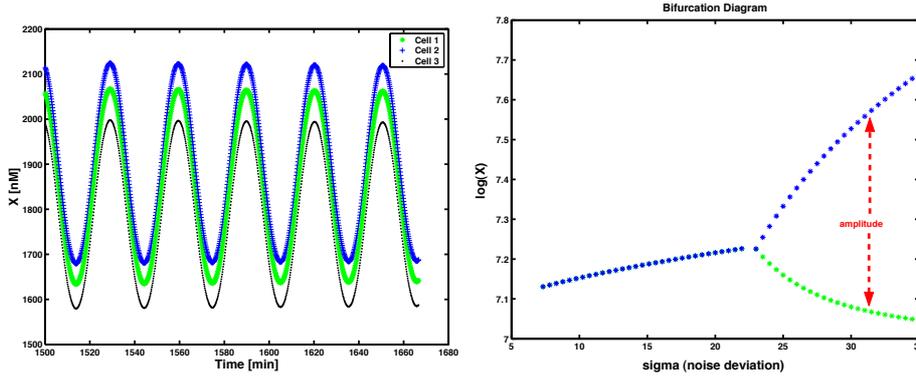


Figure 3: In-phase synchronization with strong couplings and a bifurcation diagram on noise deviation. (Left): In-phase synchronization with strong couplings for means of intracellular AI concentrations where the noise deviation is  $\sigma = 41.7$ , and the coupling strengths are  $d_{ii} = -460.$ ,  $d_{ij} = 230.$  for  $i, j = 1, 2, 3$  and  $i \neq j$ . (right): a bifurcation diagram on noise deviation where the coupling  $d_{ii} = -131.7,$   $d_{ij} = 65.85$  for  $i, j = 1, 2, 3$  and  $i \neq j$ .

respond to fluctuations for the presence of other bacteria or even other species [15]. Therefore, by adding multiple species-specific AIs in the model, we may also expect diverse and complex cooperative behaviors among different species in the similar manner as shown in this work.

## 4 Discussion

We both analytically and numerically examined effects of both noise and coupling on synchronization with the consideration of diffusion processes or time delays, and provide the sufficient conditions of phase-locked solution. We show that both noises and couplings enhance the synchronous oscillation, and play a major role in dynamical behaviors of the coupled system. Our analytical results enable us to predict, by assessing a set of parameter values including noise, whether or not the intercellular couplings and the noises synchronize the cells so as to fulfill the intercellular communication or attain concerted biological behavior in a population. Such dynamical analysis can also be used to design a robust experimental implementation with potential implications for biotechnological applications.

Although we aim to treat cellular dynamics in a more exact manner, e.g. from master equation to Langevin equations to cumulant evolution equations including the derivation of intracellular noises from the chemical reactions, there are still several approximations in our model, such as Langevin equations that approximate discrete numbers of molecules by continuous concentrations, cumulant equations that requires the assumption of Gaussian distributions for random variables, and time delays for diffusion processes.

Generally, noise promotes oscillation by introducing extra dynamics, which are originated from random fluctuations or the second cumulants. Such extra dynamics under certain conditions may play a crucial role as an energy source to excite cooperative behavior or lead to more order among cells, as indicated in this paper. Actually, it is well known that noise plays a significant role in stochastic resonance of a non-autonomous system (with a periodic driving force) and coherence resonance of an autonomous system. In particular, coherence resonance phenomenon shows that noise enhances the temporal regularity of a dynamical system, which was first noticed by Sigeti and Horsthemke [14] and then theoretically analyzed by Pikovsky and Kurths [13] with the activation and the excursion times. Since then, a plethora of theoretical and experimental works including coupled coherence resonance oscillators and coupled chaotic systems has appeared mainly based on analysis of resonance behaviors.

When considering a well mixed homogenous culture, instead of eqn.(3), a mixing dynamics should be adopted, such as mean field or linear diffusion-mixing dynamics for  $y$ . Furthermore, the stochastic simulation for the master equation is also necessary to evaluate the numerical results of the proposed model in an accurate manner.

Although effects of coupling on synchronization across a population of oscillators have been extensively studied, it is not well understood or still unclear for the role of noises. We show that noises can induce nontrivial synchronous oscillatory behavior or ‘order’, which seems to contradict to our intuitive predictions based on a ‘negative’ meaning of the word ‘noise’ or random. Our theoretical and numerical results suggest that perhaps just such an essential and constructive role played by noise and coupling may make living organisms harmoniously organize their various apparatuses and actively accomplish mutual communications.

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## A Sufficient Conditions of Synchronization

Eqn.(3) can be regarded as a system of  $n$  identical cells coupled in a linear way with the time delays. Each cell will be considered as a system with  $m + s$  distinct deterministic variables. Suppose that its steady state satisfies:  $F(\bar{X}, \bar{M}) = 0$ ,  $G(\bar{X}, \bar{M}) = 0$ .

Let a steady state of the coupled system (3) for the  $n$  cells be

$$\bar{U} = (\bar{X}, \bar{M}; \bar{X}, \bar{M}; \dots; \bar{X}, \bar{M}). \quad (17)$$

We now study synchronization solutions of Eqn.(3), i.e., phase-locked solutions with the nonzero phase difference. Suppose that the system Eqn.(3) has a periodic solution of the form

$$X^j(t) = P(t - \alpha_j T), \quad M^j(t) = Q(t - \alpha_j T), \quad 1 \leq j \leq n, \quad (18)$$

where  $P(t)$  and  $Q(t)$  are nontrivial, vector-valued functions with the least period  $T > 0$ , and  $\alpha_1 = 0$ . Such a solution is called a phase-locked solution of Eqn.(3). Essentially, the oscillation in each cell is described by functions  $P(t)$  and  $Q(t)$ . Other cells, however, may be out of phase with the phase difference,  $T\beta_j = T(\alpha_{j+1} - \alpha_j)$ . Here and henceforth we shall index the cells by  $j \bmod n$ .

When (18) is a solution of Eqn.(3), certain compatibility conditions must hold. To derive those conditions, consider the behavior of the  $j^{\text{th}}$  and  $(j+1)^{\text{th}}$  variables at times  $t$  and  $t + \beta_j T$ , respectively. From (18) and (3) one sees that

$$\frac{dP(t - \alpha_j T)}{dt} = \sum_{l=1, l \neq 1}^n D_{1l} P(t - (\alpha_l + \alpha_j) T) + D_{11} P(t - \alpha_j T) + F(P(t - \alpha_j T), Q(t - \alpha_j T))$$

and

$$\frac{dP(t - \alpha_j T)}{dt} = \sum_{l=1, l \neq j}^n D_{jl} P(t - \alpha_l T) + D_{jj} P(t - \alpha_j T) + F(P(t - \alpha_j T), Q(t - \alpha_j T))$$

due to coupling only on  $X$ . Subtracting the two equations, we have

$$\sum_{l=1}^n [D_{1l} P(t - (\alpha_l + \alpha_j) T) - D_{jl} P(t - \alpha_l T)] + (D_{11} - D_{jj}) P(t - \alpha_j T) - D_{11} P(t - (\alpha_1 + \alpha_j) T) + D_{jj} P(t - \alpha_j T) = 0. \quad (19)$$

Let

$$P(t) = \sum_{k=-\infty}^{\infty} \xi_k e^{2\pi i k t / T} \quad (20)$$

be the Fourier expansion of  $P(t)$ , where  $i = \sqrt{-1}$ . Then  $\xi_k = \bar{\xi}_k$ , and  $\xi_k = \frac{1}{T} \int_0^T P(t) e^{-2\pi i k t / T} dt$ . Substituting eqn.(20) into (19), using orthogonality and multiplying through  $e^{-2\pi i k \alpha_j}$ , we find that basic compatibility conditions are

$$\det \left\{ \left[ \sum_{l=1}^n e^{2\pi i k \alpha_l} (D_{1l} - D_{jl} e^{2\pi i k \alpha_j}) - D_{11} e^{-2\pi i k \alpha_1} + D_{jj} \right] + D_{11} - D_{jj} \right\} = 0 \quad (21)$$

for all  $k$  for which  $\xi_k \neq 0$  and for  $2 \leq j \leq n$ , where  $\det\{\cdot\}$  means the determinant.

For convenience, we consider a special coupling, called as **the circulation coupling**, that is,  $D_{ll} \equiv D_1$  ( $1 \leq l \leq n$ ),  $D_{1j} = D_j$  ( $2 \leq j \leq n$ ),  $D_{j1} = D_{n-(j-2)}$ ,  $D_{j2} = D_{n-(j-3)}$ ,  $\dots$ ,  $D_{j(j-1)} = D_n$ ,  $D_{j(j+1)} = D_2$ ,  $\dots$ ,  $D_{jn} = D_{n-(j-1)}$ , as illustrated in Figure 4. Note that the identical coupling of eqn.(2) is a special case of the circulation coupling.

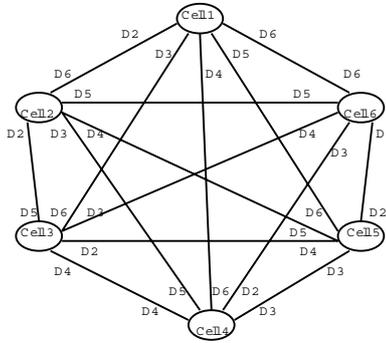


Figure 4: A circulation coupling network for  $n = 6$ , where  $D_j$  nearing a cell represent couplings of the cell with other cells.

For the circulation coupling, (21) becomes:

$$\det [D_2 (e^{-2\pi i k \alpha_2} - e^{2\pi i k (\alpha_j - \alpha_{j+1})}) + D_3 (e^{-2\pi i k \alpha_3} - e^{2\pi i k (\alpha_j - \alpha_{j+2})}) + \dots + D_{n-1} (e^{-2\pi i k \alpha_{n-1}} - e^{2\pi i k (\alpha_j - \alpha_{j-2})}) + D_n (e^{-2\pi i k \alpha_n} - e^{2\pi i k (\alpha_j - \alpha_{j-1})})] = 0. \quad (22)$$

Observe that for any  $D_j$  ( $1 \leq j \leq n$ ), one solution of (22) is (4). Clearly the solution corresponding to such a phase has the uniform phase difference. When considering time delays, we can still derive the form of phase-locked solutions, the phases of which have similar expression as eqn.(4) but in an implicit function form of time delays.

An interesting phenomenon is in the case that  $n$  identical cells are coupled in a ring in which each cell is connected to its nearest neighbors. In such a case, we have  $n \equiv 0 \pmod{4}$ . Next, we give existence conditions of such a periodic solution with period  $T$  for Eqn.(3), which are used to describe synchronization mechanism through cell-cell communication. We show that the conditions required are quite straightforward and is easy to verify for any particular example. These conditions strongly depend on the couplings, the time delay, the variances of the noises and the kinetics.

For system (3) with the circulation coupling, consider a question: finding a phase-locked solution of the form (18). By (18) and (3), we see that

$$\begin{cases} \frac{dP(t)}{dt} = \sum_{l=2}^n D_l P(t - \alpha_l T) + D_1 P(t) + F(P(t), Q(t)) \\ \frac{dQ(t)}{dt} = G(P(t), Q(t)) \end{cases} \quad (23)$$

and the oscillation in the  $j^{th}$  ( $2 \leq j \leq n$ ) cell is given by

$$\begin{cases} X^j(t) = P(t - \alpha_j T) \\ M^j(t) = Q(t - \alpha_j T). \end{cases} \tag{24}$$

Thus, the existence of synchronous solution of Eqn.(3) is converted to finding a periodic solution of system (23). By **Global Hopf Bifurcation Theorem**, we only need to examine some algebraic conditions. To be specific, let  $t' = \omega_0 t$  (where  $\omega_0 = 2\pi/T$ ). Then, (23) may be rewritten as

$$\begin{cases} \omega_0 \frac{dP(t')}{dt'} = \sum_{l=2}^n D_l P(t' - 2\pi\alpha_l) + D_1 P(t') + F(P(t'), Q(t')) \\ \omega_0 \frac{dQ(t')}{dt'} = G(P(t'), Q(t')). \end{cases} \tag{25}$$

Considering the linearization equation of (25) evaluated at  $(\bar{X}, \bar{M})$ , we then have

$$\omega_0 \begin{pmatrix} \frac{dP(t)}{dt} \\ \frac{dQ(t)}{dt} \end{pmatrix} = \begin{pmatrix} \sum_{l=2}^n D_l P(t - 2\pi\alpha_l) + D_1 P(t) \\ 0 \end{pmatrix} + \mathcal{A} \begin{pmatrix} P(t) \\ Q(t) \end{pmatrix}, \tag{26}$$

where  $\mathcal{A} = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix} \equiv \begin{pmatrix} \frac{\partial F(\bar{X}, \bar{M})}{\partial X} & \frac{\partial F(\bar{X}, \bar{M})}{\partial M} \\ \frac{\partial G(\bar{X}, \bar{M})}{\partial X} & \frac{\partial G(\bar{X}, \bar{M})}{\partial M} \end{pmatrix}$ . Let

$$\mathcal{B}_k(\mu) = \begin{pmatrix} \sum_{l=2}^n D_l e^{-2\pi i k \pi \alpha_l} + D_1 + a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix} \tag{27}$$

for  $k = 0, \pm 1, \pm 2, \dots$ . In addition, because our main interest is in effects of noises on synchronization oscillation, we take a parameter  $\mu = \sigma$ . Finally we reach the following theorem to conclude the existence conditions of phase-locked solutions.

**Theorem A.1** *Suppose  $F$  and  $G$  are differentiable with respect to arguments, and the system is in the form of the circulation coupling. If for some  $\mu = \mu_0$  and  $\alpha_j = (j - 1)/n \pmod{1}$ , the following conditions are satisfied:*

1.  $\mathcal{B}_0(\mu_0)$  of eqn.(27) is non-singular;
2.  $\mathcal{B}_1(\mu_0)$  of eqn.(27) has a simple purely complex eigenvalue  $i\omega_0$  with the corresponding left and right eigenvectors  $V_L$  and  $V_R$  respectively;
3.  $i k \omega_0$  is not an eigenvalue of  $\mathcal{B}_k(\mu_0)$  for  $k \geq 2$ ;
4.  $\Re \left( V_L \frac{d\mathcal{A}(\mu_0)}{d\mu} V_R \right) \neq 0$  where  $\Re$  is an operator taking the real part of a complex number,

then there is a global branch of  $2\pi$ -periodic solutions of (25) bifurcating from  $(\bar{U}, \mu_0, \omega_0)$ , or equivalently, the original coupled system (3) has a phase-locked solution with uniform phase difference.

If these conditions in Theorem A.1 are satisfied, then the system (3) definitely has a synchronous solution, and the corresponding synchronization mechanism is based on ‘‘global Hopf bifurcation’’.