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Noise-induced Robust Collective Behaviors in a Multicellular System

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Abstract The effects of an additive noise due to stochastic environmental fluctuations on robust collective behaviors in a population of oscillators with dynamical coupling are investigated. We show that an appropriate noise intensity may induce robust collective behaviors by compensating the coupling inefficiency, reducing the coupling redundance, and eliminating the sensitive dependence on initial conditions. The interplay between the noise and the coupling reduces the large fluctuation on period, thereby enhancing its robustness. The comparison of synchronization probability for two interacting and noninteracting oscillators shows that the noise can play a more active role in synchronizing interacting oscillators than noninteracting oscillators due to the combined influences of the noise and coupling. The constructive roles of the noise are verified with a multicellular system of coupled glycolytic oscillators.

1 Introduction

Cells are continuously subjected to conditions in the form of both intrinsic rhythms generated by intracellular clocks and outside fluctuating environment [4,12]. The rhythm generators are composed of a lot of clock cells which manage to function in a coherently oscillatory manner [2, 24]. Physiological functions derive from the interactions of the cells not only with each other but also with extracellular medium to generate rhythms essential for life [5]. It seems likely that many bodily activities require synchronization of cellular activities such as circadian clocks residing at the suprachiasmatic nuclei [6, 28]. Most previous works are performed to the case of direct coupling, i.e. there is a physical contact between cells. It is probably more realistic to consider an indirect coupling by taking into account substances which may diffuse across the cellular membrane into the extracellular space and may enter the cytoplasm of other cells [1, 18]. Recently, different mathematical models such as coupled repressilators [4, 23, 24], relaxation oscillators [12], and glycolytic oscillators [26, 27] have been proposed to analyze collective behaviors in a population of oscillators with indirect coupling.

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Oscillators are rarely strictly periodic but rather fluctuate irregularly over time. The fluctuations arise from the combined influences of the fluctuating environment, i.e. external noise due to the environmental perturbations or stochastic variations of externally set parameters, intrinsically random nature of chemical reactions, i.e. internal noise due to random transitions among discrete chemical states, and biological variance, i.e. small differences between cells [3,10,19,22]. The continual interaction between the fluctuating environment and individual internal feedback mechanisms makes the separation of dynamics impossible. In either case, additive, multiplicative stochastic terms or random parameters are used to simulate the stochastic fluctuations [8,4]. Different from the introduction of a common noise in independent oscillators, for a population of oscillators with indirect coupling, the fluctuating environment induces fluctuations in the coupling substances, the dynamics of individual cells is thus inevitably affected [2,30].

It is not usually clear whether the stochastic fluctuations are essential to physiological functions or whether physiological functions are carried out despite the fluctuations. It has been found that the stochastic fluctuations may not only affect dynamics of both individual cells and the entire multicellular system but may also be exploited to actively facilitate certain functions such as synchronization [2, 30]. Some other important roles in single cells such as being a switch or amplifier for gene expression through additive and multiplicative external noise [8, 15] and enhancing sensitivity of intracellular regulation [14] have been also found. For populations of oscillators, some phenomena induced by stochastic fluctuations such as phase synchronization of limit cycle oscillators [21], perfect synchronization of chaotic systems [20], and coherence resonance [11] have been extensively studied. Although these significant advances on elucidating noise-induced synchronization in recent years, active roles of the stochastic fluctuations in collective behaviors and details of the roles are still not precisely known although stochastic fluctuations are indeed ubiquitous throughout biological systems.

The main purpose of this paper is to investigate the active roles of an additive noise due to stochastic environmental fluctuations in collective behaviors of interacting oscillators. Specifically, we show that the noise can induce collective behaviors of the oscillators when the coupling strength is below or above the synchronization threshold by compensating the coupling inefficiency or reducing the coupling redundance. The large fluctuation in the period of the oscillations due to the variation of the coupling strength in the noiseless case can be reduced by the interplay between the noise and the coupling, therefore enhancing robustness of the period. Our analysis focuses on a multicellular system of coupled glycolytic oscillators.

2 Multicellular networks with stochastic noise

In a cell, the processes that generate mass, energy, information transfer and cell-fate speciation are seamlessly integrated through a complex network of cellular

constituents and reactions. The network in a cell can be expressed as

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

where $x(t) = (x_1(t), \cdots, x_m(t))$ is the concentrations of the components, e.g., mRNA, proteins, enzymes, substrates or other chemical complexes, and m is the total number of species in the cell.

Assume that there are N cells and the individual cells interact via the flux of substances which are produced in all cells and may permeate though the cell membrane. Then, the multicellular system can be represented as

$$\frac{dx_j(t)}{dt} = f(x_j(t)) + \kappa(y(t) - x_j(t)), \quad j = 1, \cdots, N, \tag{2}$$

where $y(t) = (y_1(t), ..., y_m(t))$, corresponding to intracellular $x(t)$, is the concentrations of the species in the extracellular environment that are assumed to be spatially well mixed. The matrix $\kappa = \mathrm{diag}(\kappa_1, \cdots, \kappa_m)$ is the coupling strength from the extracellular environment to cell-j due to the flux of substances and defined by

$$\kappa_i = \frac{AP_i}{V}, \quad i = 1, \cdots, m, \tag{3}$$

where V is the volume of the individual cells, P_i is permeability of the membrane to the substance y_i, and A is the cell surface area.

Different from directly coupled networks such as interconnected neural networks [6], any two oscillators in (2) are not directly coupled but interacted indirectly through a diffusive and mixing process with a dynamical extracellular environment $y(t)$. By assuming freely and quickly diffusive coupling between the individual oscillators and the environment so that $y(t)$ becomes quickly homogenous to establish an average level in the extracellular medium, as in [4,12,24,29], the dynamics of $y(t)$ in the extracellular medium is given by

$$\frac{dy(t)}{dt} = \frac{\kappa\varphi}{N}\left(\sum_{j=1}^{N} x_j(t) - Ny(t)\right), \tag{4}$$

where φ is the ratio of cell volume and total extracellular volume. The collective behaviors of Equations (2) and (4) are still a challenging problem although some pioneering works have been achieved [25].

Living systems are inherently noisy and are optimized to function in the presence of stochastic fluctuations. Stochastic effects in biological systems have now been recognized as a major physiological and evolutionarily important factor in the development and function of any living organisms. Basically, three different types of noise can be recognized in real biological systems: external noise, internal noise and biological variance. External noise is the type of stochastic fluctuations introduced by environment perturbations such as climate fluctuations, imperfect culture

mixing or random fluctuations of externally set parameters. Internal noise is inherent because of the intrinsically random nature of chemical reactions. Its magnitude is proportional to inverse of the system size and its origin can be traced to random transitions among discrete chemical states. Biological variation, which is not truly a form of noise, is due to small differences in intrinsic properties between individuals. A way of representing biological variation is to make biological units different from each other. Obviously, multicellular systems are subject to all these types of noise and possibly others, but the effects of these stochastic fluctuations can be studied independently or as a group.

The latter types of noise, i.e. the internal noise and biological variation, and the external noise may play different roles. The intracellular noise and the biological variation play an independent role inside each cell and contribute mainly to the differences of individual cells, therefore, they generally have a tendency to disturb cooperative behaviors between individual cells. On the other hand, the external noise is common to all cells because the fluctuating environment is shared by all cells. By exerting the same stochastic fluctuations on each cell through coupling substances, stochastic fluctuations in the environment may induce collective behaviors and possibly play other active roles. Therefore, by assuming large number of components or large size of the system, we ignore the internal fluctuations and use Equation (1) as an approximation of the concentrations of all components involved and just consider effects of stochastic fluctuations in the environment.

To take the stochastic fluctuating environment into account and study its effect on the collective behaviors, Equation (4) is augmented with an additive stochastic term

$$\frac{dy(t)}{dt} = \frac{\kappa\varphi}{N}\left(\sum_{j=1}^{N} x_j(t) - Ny(t)\right) + \sigma\eta(t), \tag{5}$$

where $\eta(t)$ is a Guassian white noise with mean zero $\langle\eta(t)\rangle = 0$ and delta correlated $\langle\eta(t)\eta(t')\rangle = \delta(t-t')$. σ is the noise intensity.

The multicellular system described by Equations (2) and (5) is stochastic differential equations with combined effects of noise and coupling, which remain seldom studied regardless of their ubiquitous nature. It is believed that the interplay between the nonlinear dynamics of individual cells, noise, and coupling can play an important role in the multicellular system, and often generate some interesting phenomena. For example, an ensemble of independent neuronal oscillators may be synchronized by a fluctuating input applied commonly to all of them, and common environment fluctuations such as climate changes may synchronize different populations separated by a large geographical distance. Some analytical and numerical studies of noise-induced synchronization phenomena such as phase synchronization of limit cycle oscillators [21], perfect synchronization of chaotic systems [20], and coherence resonance [11] were also given. Although these significant advances on elucidating noise-induced synchronization in a population of oscillators in recent years, active roles of the noise in collective behaviors of the oscillators and details of the roles are still not precisely

known although stochastic fluctuations are indeed ubiquitous throughout biological systems.

Next, we show that the additive noise actually play active roles to induce collective behaviors. Our analysis focuses on a multicellular system of coupled glycolytic oscillators.

3 The model

We investigate models for suspensions of interacting cells, in which the individual cells show metabolic oscillations. The dynamics of the metabolites is described by kinetic equations which were proposed for the explanation of glycolytic oscillations [9, 16, 26]. The dynamics of the metabolites inside each cell is governed by equations:

$$\begin{aligned} \frac{dx_1}{dt} &= v - x_1 x_2^2, \\ \frac{dx_2}{dt} &= x_1 x_2^2 - \beta x_2. \end{aligned} \tag{6}$$

The equations describe a system where the compound x_1 is supplied by a constant input v and degraded by an autocatalytic reaction. The latter reaction produces the compound x_2.

We consider suspensions consisting of arbitrary number N interacting cells. Each cell contains an oscillatory reaction system described by Equation (6). It is supposed that the individual cells interact via the flux of metabolite x_2, which is produced in all cells and may permeate through the cell membranes. Moreover, the release of metabolite x_2 is supposed to be fast enough so that it quickly becomes homogeneous to establish an average level or a mean field in the extracellular medium. For the case of slow diffusion or inhomogeneity, diffusion-reaction equations or other techniques are more appropriate to describe the spatially heterogeneous culture. To handle inhomogeneity in a more accurate manner is important on studying cellular dynamics, and we leave this for our future work.

Let y represent the concentration of x_2 in the extracellular medium. The system comprises N oscillators which are coupled by the transmembrane flux of the metabolite x_2. To take stochastic fluctuations in the extracellular medium into account, an additive noise is used to simulate the situation where a population of oscillators are subjected to the environmental fluctuation $\eta(t)$

$$\begin{aligned} \frac{dx_{1i}}{dt} &= v - x_{1i} x_{2i}^2, \\ \frac{dx_{2i}}{dt} &= x_{1i} x_{2i}^2 - \beta x_{2i} - \kappa(x_{2i} - y), \\ \frac{dy}{dt} &= \frac{\kappa\varphi}{N}\left(\sum_{j=1}^{N} x_{2j} - Ny\right) + \varepsilon\eta(t), \end{aligned} \tag{7}$$

where $\eta(t)$ is an independent white noise with intensity ε. In the noise-free case, i.e. $\varepsilon = 0$, synchronous or asynchronous oscillations may occur for different parameter regions [26].

The transmembrane flux of the metabolite provides a mechanism of intercellular coupling. All cells interact with each other through a common fluctuating extracellular environment and stochastic fluctuations are indeed ubiquitous through biological systems. Next, we will investigate the active roles of the common additive noise in collective behaviors of interacting oscillators. Specifically, we will study the collective behaviors induced by the noise and the relationship between the coupling and the noise, and compare the synchronization probability for two interacting and noninteracting oscillators.

4 Results

4.1 Synchronization of noisy oscillators by stochastic fluctuations

Since individual cells interact with each other among the fluctuating extracellular medium, the change of effective rate of transmembrane diffusion, disruption of the oscillatory processes beyond normal bounds, and emergence of abnormal oscillations are often associated with the loss of collective behaviors. Moreover, diseases can also lead to alternations from normal collective behaviors to abnormal non-collective ones. However, large fluctuations of the extracellular medium have long been considered to be associated with the loss of collective behaviors, i.e. exert a negative influence on the precise temporal relationship between oscillators.

In the absence of the stochastic fluctuations, i.e. $\sigma = 0$, collective behaviors may not occur due to coupling inefficiency or some other reasons. The population of oscillators contain small differences in intrinsic properties between individual cells, giving rise to a relatively broad distribution in the periods and amplitudes of the individual oscillators. We consider a system of 100 cells, where κ follows a Gaussian distribution with a mean of $\kappa = 1.8$ and standard deviation $\Delta\kappa = 0.04$ due to different permeability. The temporal evolution of the component x_{1i} concentrations for 10 randomly chosen oscillators is plotted in Figure 1(a), showing that collective behaviors can not be observed under these conditions.

Different from the generally used method, i.e. increasing the coupling strength to compensate the coupling inefficiency, we try to investigate how to induce collective behaviors by the stochastic fluctuations. Figure 1(b) shows that the stochastic fluctuations can indeed induce collective behaviors although their natural periods and amplitudes are broadly distributed. Thus, a transition from desynchronization to synchronization exists for an appropriate noise intensity. The synchronized oscillators are not strictly periodic due to the stochastic fluctuations. Actually, in natural environment, oscillators are rarely strictly periodic. The approximate period is identical for all oscillators. Because not all of the oscillators have the same individual period, a perfect synchronization cannot be achieved and phase differences between some oscillators still persist, as shown in Figure 1(b). Actually, perfect synchronization

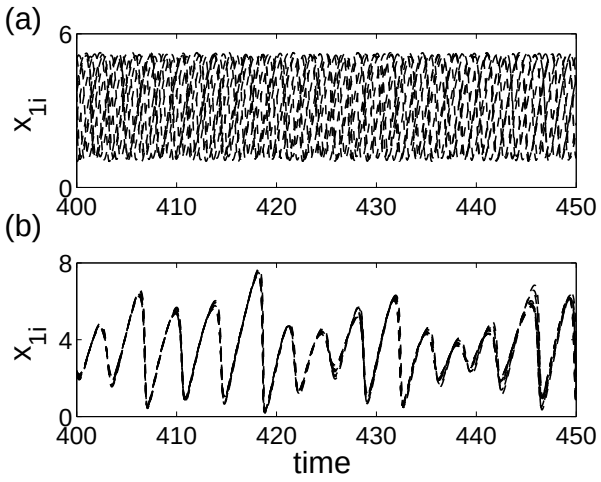

Figure 1: Noise-induced collective behaviors in a population of noisy oscillators at $\beta = 3.3$, $\nu = 3.0$, and $\phi = 0.2$. The coupling strength κ is chosen from a random Gaussian distribution of mean $\kappa = 1.8$ and $\Delta\kappa = 0.04$. (a) Asynchronous oscillations of x_{1i} for 10 randomly chosen oscillators in the absence of the stochastic fluctuations. (b) Synchronous oscillations induced by the stochastic fluctuation at $\sigma = 0.09$.

can be easily induced by the stochastic fluctuations if all individual oscillators are identical.

Notice that although the noise intensity required is large enough so as to induce collective behaviors, the deterministic parts of the system still paly an important role in the collective behaviors. In other words, the basic structure of the periodic oscillations remains present although there are some fluctuations in their amplitudes and periods. Moreover, when collective behaviors occur in the noise-free case, they can be also preserved for moderate levels of noise except some fluctuations in their amplitudes.

4.2 Enlarging synchronization region

Understanding dynamics of the coupled nonlinear oscillators with an additive noise is not straightforward. Therefore, it is useful to study a reduced system comprising only two identical coupled oscillators. The bifurcation diagram of the reduced system comprising two identical coupled oscillators is shown in Fig.2. Three different regions in the $\beta - \kappa$ parameter space, i.e. the regions of stable equilibria, asynchronous oscillations, and synchronous oscillations, are found. In the blank region above the solid line, where Hopf bifurcation occurs, the equilibria are stable and no oscillations occur. The oscillations in the regions indicated by solid and open circles are synchronous and asynchronous, respectively. For $\beta < \tilde{\beta} \approx 2.9$, when the coupling strength κ is below the solid line, asynchronous oscillations occur, while

when the coupling strength κ is above the solid line, the system will converge to a stable equilibrium. Therefore, collective but oscillatory behaviors never occur. In other words, collective behaviors can not be achieved by just increasing the coupling strength κ. While for $\beta > \bar{\beta}$, an appropriate coupling strength can induce collective behaviors. Collective behaviors can be achieved by increasing the coupling strength κ if it is insufficient to induce the collective behaviors. However, different from the results in [6], where better synchrony can be obtained by increasing the coupling strength, lose of the collective behaviors may occur if we further increase the coupling strength, i.e. redundant coupling strength may induce desynchronization. To get insight into the relative importance of the noise, we consider two cases: $\beta > \bar{\beta}$ and $\beta < \bar{\beta}$.

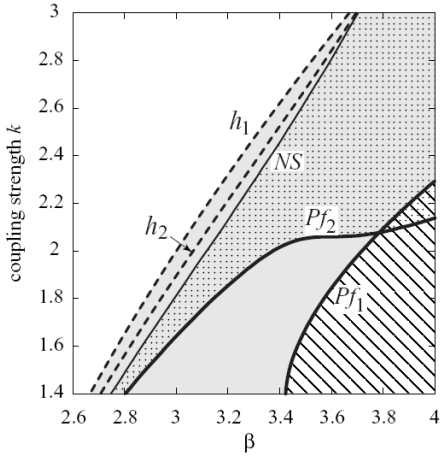

Figure 2: Bifurcation diagram established as a function of β and κ for two coupled oscillators at $v = 3.0$ and $\phi = 0.2$. Shown are the regions of occurrence of stable equilibria, synchronous (solid circles) and asynchronous (open circles) oscillations.

The time evolution of collective behaviors induced by the additive noise for the first case, i.e. $\beta > \bar{\beta}$, is shown in Figure 3, where the coupling strength is chosen from the regions below and above the synchronization region, respectively. The trajectories starting with different initial conditions are asynchronous in the noise-free case. However, they can be synchronized perfectly when moderate levels of the noise are introduced. Therefore, when the coupling strength is below the synchronization threshold and insufficient to induce collective behaviors in the noise-free case, the stochastic fluctuations can be used to compensate the coupling inefficiency, as shown in Figure 3(a). While when the coupling strength lies above the synchronization threshold, the stochastic fluctuations can be also used to reduce the redundant coupling strength so as to induce collective behaviors, as shown in Figure 3(b). Actually, for any parameters chosen in the oscillatory region, an appropriate noise intensity can always be found to induce collective behaviors, therefore enlarging the synchroniza-

tion region in the parameter space.

Collective behaviors can not be achieved by just regulating the coupling strength when $\beta < \bar{\beta}$. The stochastic fluctuations can still induce collective behaviors, as shown in Figure 4(b). Different from the case $\beta > \bar{\beta}$, where collective behaviors can be obtained by regulating the coupling strength or the noise intensity, when $\beta < \bar{\beta}$, only appropriate stochastic fluctuations can induce collective behaviors. Therefore, the noise plays a more crucial role in inducing collective behaviors for such a case. In the noise-free case, asynchronous oscillations emerge with a constant phase shift, as shown in Figure 4(a), which was denoted by *regular asynchronous oscillations* or *anti-synchronous oscillations* [26].

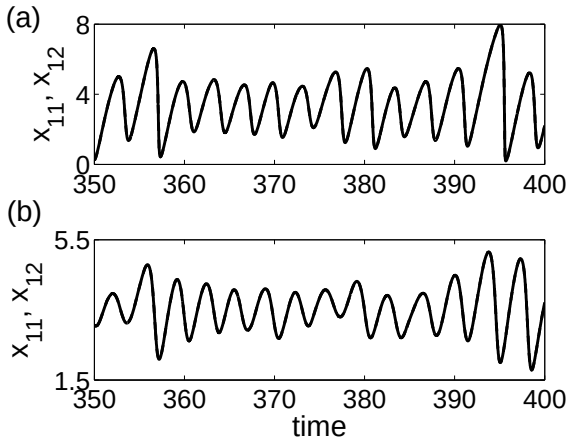

Figure 3: Noise-induced collective behaviors at $\beta = 3.3$, $v = 3.0$, and $\phi = 0.2$. (a) $\kappa = 1.9$ and $\varepsilon = 0.09$. (b) $\kappa = 2.35$ and $\varepsilon = 0.04$.

4.3 Relationship between the coupling and noise

In the noise-free case, there is only a small region in the parameter space where collective behaviors can be induced by the coupling, as shown in Figure 2. The coupling, however, can still play an important role in the noise-induced collective behaviors even when it lies outside the synchronization region. The synchronization probability $P_s = n_s/n$ as a function of the coupling strength for different noise intensity is shown in Figure 5, where n is the number of performances of the trial and n_s is the number of occurrence of synchronization in the course of the n performances. The probability increases with the increasing of the coupling strength. When the coupling strength and noise intensity are large enough, collective behaviors occur with probability 1. Moreover, for the same coupling strength, the larger the noise intensity is, the larger the synchronization probability becomes. The results show that the collective behaviors are induced by both the coupling and the noise, rather than only by the coupling or noise, although noise can also induce synchronization in a population

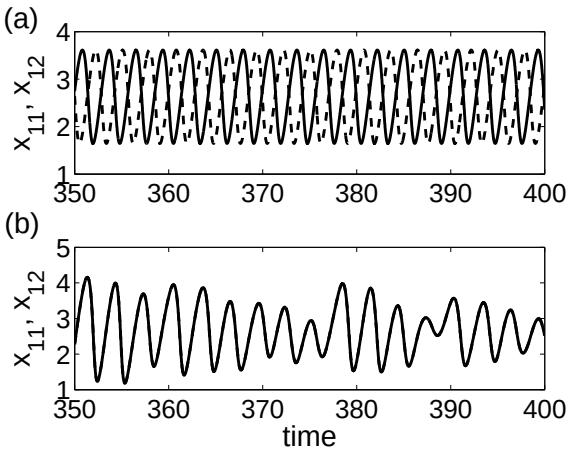

Figure 4: Noise-induced collective behaviors at $\kappa = 1.6$ and $\beta = 2.85$. (a) Asynchronous oscillations in the noise-free case. (b) Synchronous oscillations at $\varepsilon = 0.08$.

of noninteracting oscillators [21, 20].

The minimum noise intensity $\sigma_{\min}$ required to induce collective behaviors with probability 1 as a function of the coupling strength κ is shown in Figure 6. The system can be easily synchronized by the stochastic fluctuations with probability 1 although collective behaviors never occur in the noise-free case at the chosen parameter $\beta = 2.8$. Furthermore, approximately, the smaller the coupling strength is, the larger the noise intensity is required to induce collective behaviors. When spontaneous synchronization cannot occur just by adjusting the coupling strength under the natural fluctuations, artificial noise or external input can be also adopted [2, 24]. The results show that the stochastic fluctuations of the coupling substance in the extracellular medium accelerate the transmembrane diffusion and finally induce collective behaviors. Therefore, the coupled system with stochastic environmental fluctuations can be more easily synchronized and has a less requirement to the system parameters.

4.4 Noise-improved robustness of period

In the noise-free case, a transition from asynchrony to synchrony or from synchrony to asynchrony due to the variation of the coupling strength may also induce fluctuations in the period or amplitude of the oscillations because of the dependence of the system dynamics on the coupling. However, the fluctuations may be reduced due to the combined influences of the coupling and the noise. The period as a function of the coupling strength κ for the cases of with and without noise is shown in Fig.7. In the noise-free case, sudden changes in the period take place at $\kappa_a \approx 1.98$ and $\kappa_b \approx 2.28$, where transitions from asynchrony to synchrony and from synchrony to asynchrony occur, as shown in Figure 2. When $\kappa < \kappa_a$ or $\kappa > \kappa_b$, there is a phase shift between the two oscillators and synchronization does not occur. Moreover, the

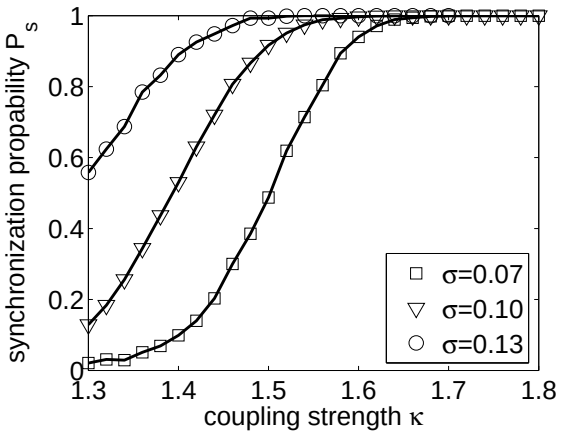

Figure 5: The synchronization probability P_s as a function of the coupling strength κ at $\beta = 2.8$.

external metabolite oscillates with the double frequency compared to the internal substances. While when $\kappa_a < \kappa < \kappa_b$, synchronization occurs and the the external metabolite oscillates with the same frequency as the internal substances. Such a case can still occur for a high number cells [26].

However, when the stochastic fluctuations are taken into account, the sudden change in period disappears. An appropriate noise not only reduces the fluctuations in the period but also induces collective behaviors with an approximately constant period despite the noise and the variation in the coupling strength. Moreover, when collective behaviors occur in the noise-free case, i.e. when $\kappa_a < \kappa < \kappa_b$, the period for the two cases of with and without noise is very close. In other words, the period are very well conserved despite the noise, and only the amplitude undergoes small variations.

The noise reduces the large fluctuations in the period and makes the change of the period very smooth, therefore enhancing the robustness of the period against variations in the coupling strength. Generally, investigation of robustness for oscillators focus on the period sensitivity to evaluate the precise time-keeping ability with respect to noises or other parameters [17]. Our results show that noise may play more constructive roles in robustness properties and makes living organisms harmoniously organize their components and produce collective behaviors more easily. The results may also help us to understand complex physiological rhythms such as circadian oscillators which keep a period of 24 hours despite alternation of light and darkness, variation of climate, or some other environmental perturbations [6].

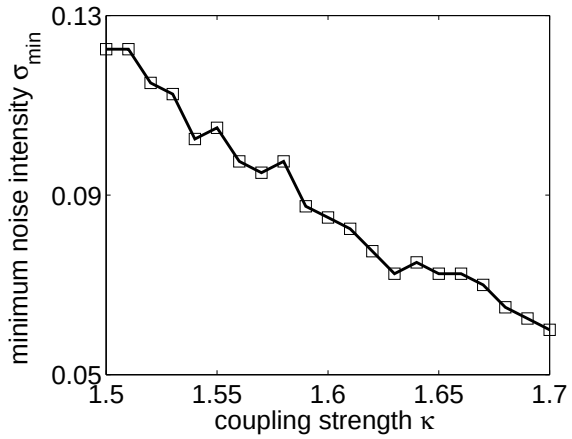

Figure 6: The minimum noise intensity $\sigma_{\min}$ required to induce collective behaviors with probability 1 as a function of the coupling strength κ at $\beta = 2.8$.

5 Conclusion

In this paper we have investigated noise-induced cooperative behaviors in a coupled system for microbial cells. The active roles played by stochastic fluctuations in the extracellular medium have been obtained for a multicellular system of coupled glycolytic oscillators. The relationship between the coupling and the noise was examined. We showed that both the noise and coupling play active roles in inducing cooperative behaviors of the coupled system. The results enable us to predict, by assessing parameter values including noise, whether or not the intercellular coupling and the noise can induce collective behaviors in a population of cells so as to fulfill the intercellular communication or attain concerted biological behaviors. Such dynamical analysis can be also used to design robust collective behaviors with probability 1 despite stochastic fluctuations in the extracellular medium.

The effects of stochastic fluctuations on cooperative behaviors across a population of coupled oscillators have not been extensively studied and roles of noise is not well understood or still unclear. We show that a common noise and coupling can play some active roles, which seems to contradict to our intuitive predictions based on a 'negative' meaning of the word 'noise'. Our results suggest that perhaps just such essential and constructive roles played by the noise and coupling may make living organisms harmoniously organize their various apparatuses and actively accomplish collective behaviors.

References

[1] Bulter, T., Lee, S., Wong, W. W., Fung, E., Connor, M. R. and Liao, J. C. (2004) Design of artificial cell-cell communication using gene and metabolic networks.

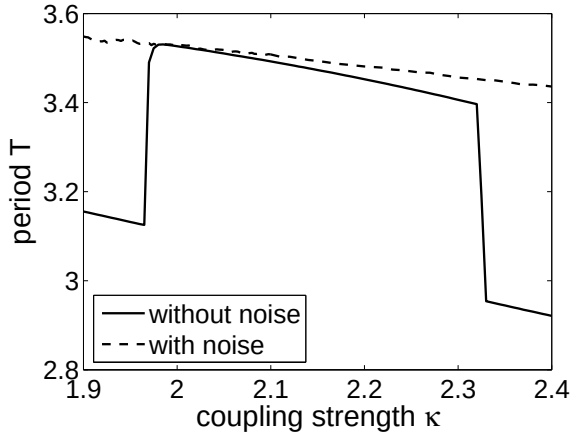

Figure 7: Noise-improved robustness of period at $\beta = 3.3$ and $\varepsilon = 0.08$.

Porc. Natl. Acad. Sci., **101**, 2299-2304.

[2] Chen, L., Wang, R., Zhou, T., and Aihara, K. (2005) Noise-induced cooperative behavior in a multicell system. *Bioinformatics*, **21**, 2722-2729.

[3] Elowitz, M. B., Levine, A. J., Siggia, E. D. and Swain, P. S. (2002) Stochastic gene expression in a single cell. *Science*, **297**, 1129-1131.

[4] Garcia-Ojalvo, J., Elowitz, M., and Strogatz, S. H. (2004) Modeling a synthetic multicellular clock: Repressilators coupled by quorum sensing. *Porc. Natl. Acad. Sci.*, **101**, 10955-10960.

[5] Glass, L. (2001) Synchronization and rhythmic processes in physiology. *Nature*, **410**, 277-284.

[6] Gonze, D., Bernard, S., Waltermann, C., Kramer, A., and Herzel, H. (2005) Spontaneous synchronization of coupled circadian oscillators. *Biophys. J.*, **89**, 120-129.

[7] Goldbeter, A. (1996) *Biochemical oscillations and cellular rhythms: The molecular bases of periodic and chaotic behaviour*. Cambridge University Press, Cambridge.

[8] Hasty, J., Pradines, J., Dolnik, M. and Collins, J. J. (2000) Noise-induced switches and amplifiers for gene expression. *Porc. Natl. Acad. Sci.*, **97**, 2075-2080.

[9] Higgins, J. (1964) A chemical mechanism fro oscillation of glycolytic intermediates in yeast cells. *Porc. Natl. Acad. Sci.*, **51**, 989-994.

[10] Kepler, T. B. and Elston, T. C. (2001) Stochasticity in transcriptional regulation: Origin, consequences, and mathematical representations. *Biophys. J.*, **81**, 3116-3136.

[11] Kiss, I. Z., Zhai, Y., Hudson, J. L., Zhou, C, and Kurths, J. (2003) Noise enhanced phase synchronization and coherence resonance in sets of chaotic oscillators with weak global coupling. *Chaos*, **13**, 267-278.

[12] McMillen, D., Kopell, N., Hasty, J., and Collins, J. J. (2002) Synchronizing genetic relaxation oscillators by intercell signaling. *Porc. Natl. Acad. Sci.*, **99**, 679-684.

[13] Neiman, A., Schimansky-Geier, L., Moss, F. Shulgin, B. and Collins, J. J. (1999) Synchronization of noisy systems by stochastic signals *Physical Review E*, **60**, 284-192.

[14] Paulsson, J., Berg, O. G. and Ehrenberg, M. (2000) Stochasitc focusing: Fluctuation-enhanced sensitivity of intracelular regulation. *Porc. Natl. Acad. Sci.*, **97**, 7148-7153.

[15] Samoilov, M., Plyasunov, S. and Arkin, A. P. (2005) Stochasitc amplification and signaling in enzymatic futile cycles through noise-induced bistability with oscillations. *Porc. Natl. Acad. Sci.*, **102**, 2310-2315.

[16] Sel'kov, E. E. (1968) Self-oscillations in glycolysis. 1. A simple kinetic medol *Eur. J. Biochem.*, **195** 109-113.

[17] Stelling, J., Sauer, U., Szallasi, Z., Doyle III, F. J., and Doyle, J. (2004a). Robustness of cellular functions. *Cell* **118**, 675-685.

[18] Taga, M. E. and Bassler, B. L. (2003) Chemical communication among bacteria. *Porc. Natl. Acad. Sci.*, **100**, 14549-14554.

[19] Tao, Y. (2004) Intrinsic and external noise in auto-regulatory genetic network *J. Theor. Biol.*, **229**, 147-156.

[20] Toral, R., Mirasso, C. R., Hernández-García, E. and Piro, O. (2001) Analytical and numerical studies of noise-induced synchronization of chaotic systems. *Chaos*, **11**, 665-673.

[21] Teramae, J. and Tanaka, D. (2004) Robustness of the noise-induced phase synchronization in a general class of limit cycle oscillators. *Phys. Rev. Lett.*, **93**, 204103.

[22] Thattai, M. and van Oudenaarden, A. (2001) Intrinsic noise in gene regulatory networks. *Porc. Natl. Acad. Sci.*, **98**, 8614-8619.

[23] Wang, R. and Chen, L. (2005) Synchronizing genetic oscillators by signaling molecules. *J. Biol. Rhythms*, **20**, 257-269.

[24] Wang, R., Chen, L. and Aihara, K. (2006) Synchronizing a multicellular system by external input: an artificial control strategy. *Bioinformatics*, doi:10.1093/bioinformatics/btl182.

[25] Winfree, A. T. (1980) *The geometry of biological time*. Springer-Verlag, New York.

[26] Wolf, J. and Heinrich, R. (1997) Dynamics of two-component biochemical systems in interacting cells; Synchronization and desynchronization of socillations and multiple steady stetes. *BioSystems*, **43**, 1-24.

[27] Wolf, J., Passarge, J., Somsen, O. J. G., Snoep, J. L., Heinrich, L., and Westerhoff, H. V. (2000) Transduction of intracellular and intercellular dynamics in yeast glycolytic oscillations. *Biophys. J.*, **78**, 1145-1153.

[28] Yamaguchi, S., Isejima, H., Matsuo, T., Okura, R., Yagita, K., Kobayashi, M. and Okamura, H. (2005) Synchronization of cellular clocks in the suprachiasmatic nucleus. *Science*, **302**, 1408-1412.

[29] You, L., Cox, R. S., Weiss, R., and Arnold, F. H. (2004) Programmed population control by cell-cell communication and regulated killing. *Nature*, **428**, 868-871.

[30] Zhou, T., Chen, L., and Aihara, K. (2005) Molecular communication through stochastic synchronization induced by extracellular fluctuations. *Phys. Rev. Lett.*, **95**, 178103.