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Synchronizing Independent Gene Oscillators by Common Noisy Signaling Molecule

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Abstract The ability to detect and respond to changes in the extracellular environment is a basic necessity for survival of all organisms. Consequently, diverse bio-rhythms are generated by hundreds of cellular oscillators that somehow manage to operate synchronously under various fluctuated environments. It remains, however, to be exploited how behaviors of a noisy microscopic molecule affect the macroscopic behaviors in the weak coupling or even without coupling between cells. Using a multi-cell system, we show that a common noisy signaling molecule can induce in-phase synchronization across an ensemble of independent gene oscillators in *Escherichia coli*, leading to a collective response or rhythm. Such a mechanism of achieving biological rhythms would be exploited by realistic living cells to sense the extracellular signal. In addition, the model system considered here provides a quantitative example of phase transition from non-synchronization to synchronization across a population of biological oscillators.

1 Introduction

All organisms have the ability to detect and respond to changes in the environment for their survival, and as a result, a variety of mechanisms have evolved by which organisms sense their environment and respond to signals that they detect, e.g., bacterial "quorum sensing"[1,2]. The response involving movement may be *kinesis* or *taxis*, or their combination. Both tactic and kinetic responses involve two major steps: (1) detection of the signal and (2) transduction of the external signal into an internal signal that triggers the response. In the absence of external cues, a random walk strategy is usually adopted to determine their pattern of movement. In several systems [3], including the flagellated bacterium *E. coli* and the amoeboid cell *Dictypostelium discoideum*, a detailed understanding of how extracellular signals are transduced into behavioral changes is emerging from experimental works, while at the macroscopic level solutions of the classical chemotaxis equations have been

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well investigated. However, the chemotaxis equations to date have been based on phenomenological descriptions of how cells respond to signals, and at present there is little understanding of how behaviors of a microscopic molecule affect the macroscopic behaviors or induce the collective rhythms. In particular, how a common noisy signaling molecule induces collective behaviors of independent oscillatory cells has not been well explored yet.

Previous works have indicated that some mechanisms of intercell coupling (e.g., quorum-sensing mechanism) would globally enhance the collective response of a population of genetic oscillators. However, coupling among oscillators is not, in general, sufficient to achieve synchronization, and many ensembles of coupled oscillators exhibit phase dispersion rather than a synchronized state either because the oscillators actively resist synchronizing [4] or because coupling is too weak or even nonexistent [17,5]. Here, by mathematical and computational modelling, we show that a common noisy signaling molecule can drive an ensemble of uncoupled genetic oscillators in *Escherichia coli* to be in-phase synchronized, leading to a robust collective response in the system. The essential factor of achieving such an effect is the extracellular noise.

In general, physiological oscillators can be synchronized through appropriate external stimuli. These stimuli would be some noisy signals which are in this paper assumed to stand for uncertain factors in the extracellular environment. It is important to analyze the effect of the stimuli on intrinsic physiological rhythms since the better understanding of the interactions between the stimuli and physiological rhythms may lead to the development of artificial control strategy and medical therapy. However, the wiring of naturally occurring gene regulatory networks would be too complex for qualitative description devoid of mathematics. This complexity has hindered a complete understanding of natural gene oscillators. Synthetic gene networks, on the other hand, offer an alternative approach aiming at providing a relatively well controlled test bed in which the functions of natural gene networks can be isolated and characterized in detail [6]. In this direction, several synthetic biological systems, e.g., the toggle switch [7], the repressilator [8] and the relaxation oscillator [9], were developed recently in *Escherichia coli*. Such simple networks represent a first step towards logical cellular control, whereby biological processes can be manipulated or monitored at the DNA level [10]. Clearly this control could have a significant impact on post-genomic research [6].

In this paper, based on an artificial gene regulatory network [9], we introduce a multicellular system where there is no coupling between cells but a common noisy signaling molecule freely diffuses into each cell through the cellular membrane to regulate the expression of a target gene. The resulting diffusion results in a collective rhythm across a population of such gene oscillators, where phases of the oscillators are recoordinated mainly by the noise.

Recently, J.Garcia-Ojalvo *et al* [12] modelled a synthetic multicellular clock by using repressilators coupled by quorum sensing. In that model, since there is an information exchange between cells through an intercell signaling, it is not difficult to

understand that a population of the cells finally achieve a cooperative behavior. The similar types of models including those in refs.[13-15] were also investigated. However, if there is no coupling between cells, achieving a collective behavior across a population of the cells is not easy and must be carefully investigated. This is because the different transmission way of signaling molecules between cells would result in a different synchronization mechanism.

Our results indicate that the noise signaling molecule not only drives the multicellular system to realize transition from non-synchronization to synchronization, but also amplifies the amplitude of oscillation of the individual cells. The latter effect that is not intuitive but still can be identified in the repressilators coupled by quorum sensing [12], implies that the external signaling molecule can be taken as an amplifier, which actually makes biological quantities (e.g., the expression levels of genes and the concentrations of proteins) more observable in the biological experiments.

2 Results

2.1 Model

The designed synthetic gene networks are shown in Fig.1, where we utilize genetic components from the virus bacteriophage λ. We assume that there are two DNA plasmids consisting of the promoter and gene regions. On one plasmid, we adopt the promoter P_{RM}, which contains three operator sites known as OR_1, OR_2 and OR_3. The gene *cI* under control of the promoter P_{RM} produces the protein *CI*, which stimulates its own production at a low concentration and shuts off the promoter at a high concentration. On a second plasmid, we again utilize the promoter P_{RM}, but here we insert the gene encoding the protein *RcsA*. The crucial interaction is between the proteins *RcsA* and *CI*. To introduce an external perturbation to each cell, a promoter $P_{lacLux0}$ that is enhanced by a small molecule *AI*, is also inserted on the first plasmid to control another gene *cI*.

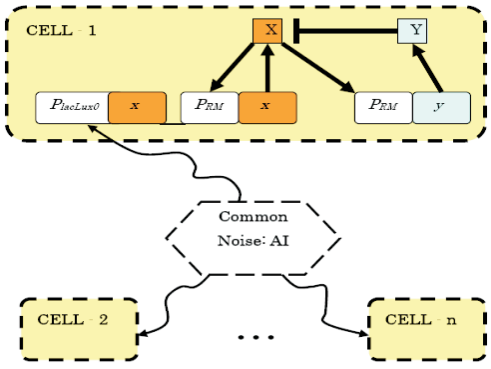

Figure 1: The schematic diagram of a gene regulatory network

Define the concentrations of proteins as dynamical variables: $x = [CI]$, $y = [RcsA]$ and $z = [AI]$ (here we use the same symbol to represent the concentration of the signal molecule inside the cells and in the extracellular environment). Then, the rate equations describing the evolution of the concentrations of the proteins *CI* and *RcsA* are given by (3) (see Methods for details). The dynamical evolution of the signaling molecule *AI* in the extracellular medium is assumed to be affected by degradation and synthesis, and also to be fluctuated by a noise. The dynamics of the protein *AI* are given in (4) (see Methods for details).

In the hypothetical case of infinite cell dilution ($\gamma \to 0$), the system consists of independent relaxational-type oscillators. γ represents the degradation of the *AI* in the extracellular medium, and σ is the intensity of the common noise, as described in Methods. In the presence of the noisy signaling molecules, a new degree of freedom is added to the original two-dimensional phase space to represent dynamics of the molecules governed by Eq. (4). The resulting system can exhibit synchronous periodic oscillations in a wide region of parameter space (see Fig. 2 (b)). In particular, the amplitude of the oscillation can be amplified (see an example in Fig. 2(a)) with the increasing of the intensity of the noise or the value of the parameter β or with the decreasing of the degradation rate γ of the signalling molecules (but the shape of the waveform does not change significantly). In other words, the characteristic oscillation of the original relaxation oscillator does not change qualitatively. Such a case is somewhat similar to that observed in the repressilators coupled by quorum sensing (but the oscillation amplitude for the latter is only slightly changed). Since the parameters γ and σ play a similar role within the synchronization region in our model, in the following we will mainly investigate the effect of the parameter σ on the dynamics of the entire system. In fact, we are more interested in the effect of noise.

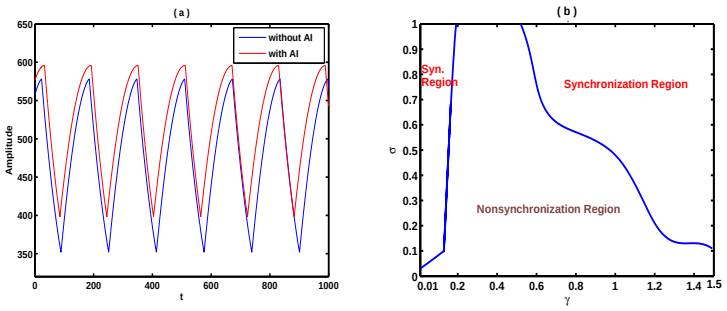

Figure 2: (a) An extracellular noisy signalling can amplify the oscillation amplitude, where $\gamma = 0.2$ and $\sigma = 0.5$; (b) The phase diagram for the parameters γ and σ. In both of cases, $m_x = 10$, $m_y = 1$, $\gamma_x = 0.1$, $\gamma = 0.01$, $\gamma_{xy} = 0.1$, $\varepsilon_1 = 2.0$, $\varepsilon_2 = 0.08$, $\alpha = 11$, $\beta = 2.0$ and $z_0 = 3.0$;

2.2 Phase Transition

Observing the change of phases is a precision way for identifying synchronization of a population of oscillators. To quantify the degree of synchronization of states of the N genetic oscillators, we introduce a "synchronization quantity" $\rho(t)$ for the entire system, which is defined as [16]

$$\rho(t) = \left| \frac{1}{N} \sum_{k=1}^{N} \exp\left(2\pi i \theta_k(t)\right) \right|, \tag{1}$$

using phase θ_k of each oscillator, where $i = \sqrt{-1}$. Then, $\rho(t) \to 1$ or 0 with $t \to \infty$ indicate that the N oscillators achieve or do not achieve synchronization, respectively, whereas $\rho(t) \to \rho_0$ with $0 < \rho_0 < 1$ displays that they merely reach partial synchronization.

We initially set the phase θ_k of each oscillator uniformly and randomly on $[0, 2\pi/T]$ (T denotes the period of oscillation), where the zero-crossing point of $\bar{x}_k(t) = x_k(t) - X_0$ (X_0 is chosen to be between the minimal and the maximal amplitudes of oscillation) from $\bar{x}_k < 0$ to $\bar{x}_k > 0$ is chosen as the origin of phase, $\theta_k = 0$. Fig. 3 displays the temporal evolution of the synchronization quantity $\langle \rho(t) \rangle$ averaged over 1000 realizations from different initial conditions. It gradually increases from a small value to 1 for the intensity of noise $\sigma = 0.8$, implying that a transition from initial unsynchronous phases to the final synchronous phase takes place in the population of the cells. In this case, the noise plays a role of "ordering" by recoordinating phases of the individual oscillators.

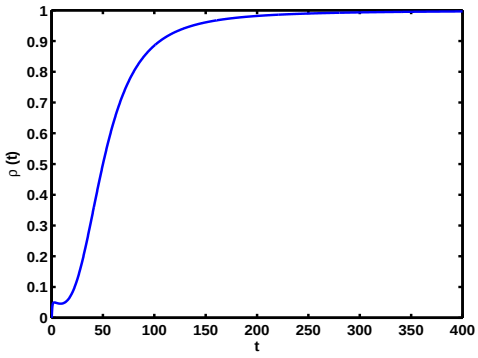

Figure 3: The synchronization quantity introduced here shows phase transition, where $\gamma = 0.1$ and $\sigma = 0.8$. The other parameters are the same as those in Fig. 2

2.3 Transition to Synchronization

The synchronization transition was predicted theoretically in the mid-1960s [4,17], but only recently, a quantitative experimental realization of this phenomenon

was reported in the repressilators coupled by quorum sensing [11,12]. Here, we provide another example for such an interesting phenomenon, where a population of independent gene oscillators are unidirectionally linked only by a common noisy signaling (see Fig. 1 or Eqs. (3) and (4). The corresponding frequency distribution of 1000 independent cells is shown in Fig.4 (a) and (c) for two different $\sigma = 0.6$ and $\sigma = 0.8$. The temporal evolution of concentration of the protein *CI* in 10 of those cells is plotted in Fig.4. (b) and (d), showing how the multicellular system undergoes a transition from the completely disorganized to the synchronized state.

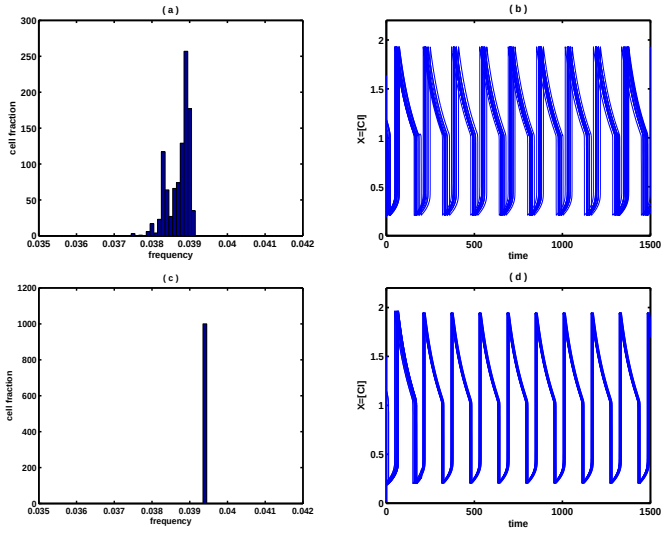

Figure 4: Frequency histogram and time evolution of *CI* for 10 cells. (a) and (b) correspond to $\gamma = 0.3$ and $\sigma = 0.6$, and (c) and (d) to $\gamma = 0.1$ and $\sigma = 0.8$. The other parameters are the same as those in Fig. 2.

Fig. 4 indicates that a transition to synchronization takes place when the intensity σ of the noise changes. To describe quantitatively the dependence of the global behaviors of the N genetic oscillators on the the parameter σ, we introduce an "order parameter". For this, we first compute the average signal $S(t) = (1/N)\sum_{k=1}^{N} x_k(t)$. Note that its temporal behavior in the synchronized case (Fig. 4(c)) will be similar to each one of the local signals $x_k(t)$. On the other hand, in the unsynchronized situation Fig. 4(b), the individual signals $x_k(t)$ are completely out of step with respect to each other, and their sum will be averaged out to an approximately constant value at all times. Accordingly, we define the "order parameter" R as the ratio of the standard deviation of the time series of S to the standard deviation of $x_i(t)$ averaged over i,

$$R = \frac{\langle S^2(t)\rangle - \langle R(t)\rangle^2}{\langle x_i^2(t)\rangle - \langle x_i(t)\rangle^2}, \tag{2}$$

where $\langle\cdot\rangle$ denotes time average, and $\overline{\cdots}$ indicates average over all cells. In this way, $R = 1$ corresponds to complete synchronization, $R = 0$ to non-synchronization, and $0 < R < 1$ to partial synchronization. A slow (but not sudden as in ref.[12]) change between these two limiting values indicates that the system undergoes a transition from unsynchronization to complete synchronization. Such a change is shown in Fig. 5, which plots the dependence of R on the intensity of noise. Such a noise-induced transition to synchronization also occurs in the case that k is changed (the corresponding numerical results are not shown here).

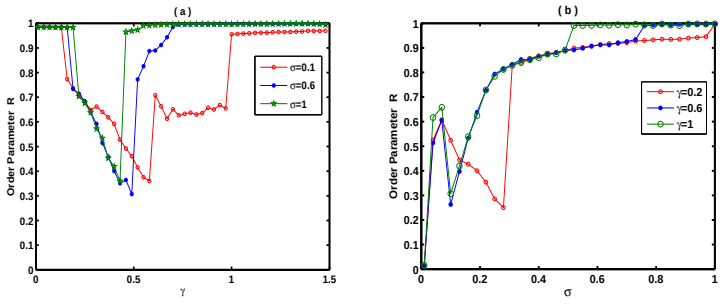

Figure 5: Synchronization transition induced by σ and γ. The other parameters are the same as those in Fig. 2.

2.4 The Characteristic of the Lyapunov Exponent

It is well known, the Lyapunov exponents are important quantities, which can characterize the dynamical behaviors of a nonlinear system qualitatively, e.g., the negative Lyapunov exponents indicate that the system is contracting. To describe further the transition to synchronization appearing in the above section, we plot Fig. 6, which displays the dependence relationship of the Lyapunov exponent *LE* for the phase difference equation (see Supporting Materials of the paper) on the intensity σ of the noise.

3 Discussion

A recent experimental study [18] has shown that the interplay of gene regulatory networks with population dynamics can lead to the diversity of cell activity that in turn affects (possibly enhances) global behaviors of the entire system due to the effect of noise. Another related study [8] has indicated that extracellular noises arising from changes in cellular environment possibly prevent the observation of macroscopic rhythms in an ensemble of synthetic gene oscillators. On the other hand, it has been verified that the noise has the “ordering" effect [19-21]. Our result has provided another evidence in verifying such an effect of the noise.

Previous works have demonstrated that quorum sensing can lead to synchronization in an ensemble of identical gene oscillators [12-14]. Even in the case that

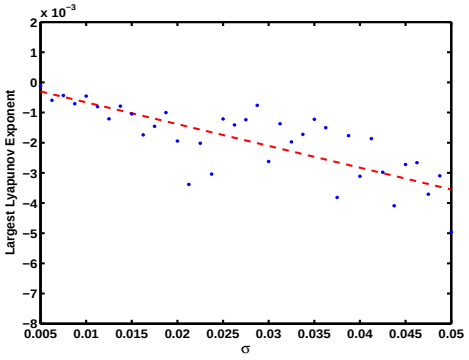

Figure 6: The dependence of the Lyapunov exponent on σ, where $\gamma = 0.05$, and the other parameters are the same as those in Fig. 2.

individual oscillators oscillate in a noisy fashion, Jordi *et al*'s work has indicated that coupling can transform effectively an ensemble of "sloppy" biological clocks into a very reliable collective oscillator [12,22-24]. In both cases, there is an information exchange between cells through intercellular signaling. Our results has displayed that an ensemble of independent gene oscillators can be also synchronized by noisy signaling molecules that enter each cell through the cell membrane to regulate the expression of a target gene.

In McMillen *et al*'s theoretical study [13], the individual relaxation oscillators are based on both positive and negative feedback, and their dynamics are governed by two widely different time scales. Oscillations are characterized by abrupt changes in the chemical concentrations. The dominant mechanism leading to synchronization of an ensemble of the oscillators is fast threshold modulation; In Jordi *et al*'s work [12], only negative feedback is made use of and all biochemical species are assumed to have similar decay rates. Oscillations are approximately sinusoidal, with no abrupt jumps or decays of the dynamical variables. The synchronous behavior of a population of the oscillators can be robustly achieved. In both of cases, the quorum-sensing apparatus is incorporated into the repressilator, implying also that there is an information exchange between cells through signaling molecules. In contrast to these two models, our model only makes use of a negative feedback and an extracellular noisy signal is added to relaxational-type genetic oscillators to mediate the collective rhythm of a multicellular system. Except that a collective behavior across the population of the cells is robustly achieved, the oscillations are approximately sinusoidal, without jumps, similar to what happens in the phase oscillators that have long been used to model biological rhythms [4,25].

In synchronization efficiency, McMillen *et al* found that a perfect synchrony was achieved within two oscillation periods, starting from an ensemble of oscillators with randomly distributed phases, whereas Jordi *et al* found that synchronization can be

achieved in a few cycles, i.e., in time windows of the same order of magnitude as those required by fast threshold modulation in relaxation oscillators. We also examined whether synchronization of repressilators requires much longer time windows, and found that the result is basically similar to that obtained by Jordi *et al*. In addition, for our model the synchronization efficiency depends on the intensity of the noise: for some moderate strengths of the noise, the efficiency is optimal (see Fig.).

In mathematical analysis, we have provided a rigorous treatment in Appendix of the paper in the case of weak noisy signals. We have shown, by applying phase reduction methods in the limit where the individual oscillators are indirectly driven by common weak noisy signal molecules, that the collective phase synchronization is achieved in the sense of negative Lyapunov exponent. Our theoretical and numerical results (see Fig.) have also demonstrated that the system undergoes a phase transition to mutual synchronization of the same type seen in the Kuramoto model [17].

Finally, we point out that extracellular weak noisy signals can enhance collective phenomena among non-coupled cells in a constructive way where the noise first affects a signaling molecule which is then diffused into each cell through the cell membrane to regulate the expression of a target gene. The signaling molecule plays a role similar to a common “baiter" for a population of cells in $E.\ coli$, which leads to chemotaxis, or other cooperative behaviors in the living organisms. It has been observed in many biological and physical systems that weak noisy signal can enhance ordering, such as stochastic resonance in Ion Channels and noise-mediated signal-sensing. Our result further confirms that the common additive noise is one of the important forces for mediating the cooperative dynamics.

4 Methods

We define the concentrations of proteins as dynamical variables: $x = [CI]$, $y = [RcsA]$ and $z = [AI]$ (here we use the same symbol to represent the concentration of the signal molecule inside the cells and in the extracellular environment). Then, the rate equations describing the evolution of the concentrations of the proteins *CI* and *RcsA* are given by (see [9] for details):

$$\begin{array}{l} \frac{dx_k}{dt} = m_x f(x_k) - \gamma_{xy} x_k y_k - \gamma_x x_k + \frac{\beta z}{1+z}, \\ \frac{dy_k}{dt} = m_y f(x_k) - \gamma_y y_k, \end{array} \tag{3}$$

where $f(x) = (1 + x^2 + \alpha\varepsilon_1 x^4)/(1 + x^2 + \varepsilon_1 x^4 + \varepsilon_1\varepsilon_2 x^6)$. Here m_x and m_y are the numbers of plasmids per cell, respectively; $\alpha > 1$ is the degree to which transcription is enhanced by dimer occupation of OR_2; ε_i ($i = 1,\ 2$) represent binding strengths relative to the dimer-OR_1 strength; β is the maximal contribution to *CI* transcription of saturating amounts of *AI*. The *AI* activation is chosen to follow a standard Michaelis-Menten kinetics. In deriving the equations, we assume that the concentration of *RNA* polymerase remains constant during time. Note that the two *cI* transcripts are assumed to be identical. The model is rendered dimensionless, and the *AI* concentration is scaled by its Michaelis constant.

Finally, the dynamical evolution of the signaling molecule *AI* in the extracellular medium is assumed to be affected by degradation and synthesis, and also to be fluctuated by a noise. Consequently, the dynamics of the protein *AI* are governed by

$$dz/dt = z_0 - \gamma z + \xi(t), \tag{4}$$

where z_0 and γ are the initial synthesis quotiety and degradation of the *AI*, respectively. Here $\xi(t)$ is assumed as the Gaussian white noise, which is normalized as $\langle \xi(t) \rangle = 0$ and $\langle \xi(t)\xi(t') \rangle = 2\sigma\delta(t-t')$.

The model system (3) and (4) is different from the ones for cellular communication [12-14], and the important difference between them is that for the former there are no information exchanges between cells (the signaling molecule unidirectionally regulates the expression of a target gene), whereas for the latter there are information exchanges between cells (a signaling molecule freely diffuses into the extracellular environment through the cell membrane, and in turn enters each cell to regulate the expression of a target gene after a mixing process).

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Supplementary Information

Theoretical analysis for synchronization of gene oscillators

In this appendix, we prove that the system with small common noise can be ensured to be synchronized even without coupling, and also provide the condition for partial synchronization.

To describe qualitatively the synchronization phenomenon of N nonlinear oscillators (including identical and slightly different limit cycle oscillators) induced by the common noise, we first analyze the variable z in Eqs. (3)–(4) by introducing the probability distribution $P(z,t)$ in a state z at time t. Note that z independently changes in contrast to other variables, and is a stochastic variable. Since a translational transformation of z does not affect the dynamics of system (3)–(4), we may assume $z_0 = 0$. In this case, we can give the expression of the steady-state mean of z by

$$\langle z\rangle_{ss} = \Gamma_0 \int_0^\infty z e^{-(1/\sigma)\phi(z)} dz = \frac{\Gamma_0 \sigma}{\gamma_z},$$

where the potential $\phi(z)$ is introduced: $\phi(z) = -\int(-\gamma_z z)dz = (\gamma_z/2)z^2$, and Γ_0 is a normalization constant determined by requiring that the integral of $P_s(z)$ (here we denote by $P_s(z)$ the steady-state solution to the Fokker-Plank equation for $P(z,t)$) over all z is unity. Therefore, the variable z and further the term $\beta z/(1+z)$ can be viewed as Markov processes for sufficiently small σ and β, respectively. After a translational transformation of z (see the above context for reasons), we may consider a more general model instead of Eqs. (3)–(4):

$$\frac{dX_i}{dt} = F_i(X_i) + \eta(t),\ 1 \le i \le N. \tag{5}$$

Here, $F_i(X_i) = F(X_i) + \Delta F_i$ in which ΔF_i is a small deviation and derived from different β or γ_k for the different cell, and $\eta(t)$ is a vector of Gaussian white noises, whose elements are normalized as $\langle \eta_k(t)\rangle = 0$, $\langle \eta_k(t)\eta_l(t')\rangle = 2D_{kl}\delta(t-t')$ with $\mathbf{D} = (D_{kl})$ being a variance matrix of the noise components. For generality, here some $\eta_j(t) \equiv 0$ are included in the case of consideration. We suppose that the common additive noise is weak (i.e., $D_{kl} << 1$) to the deterministic perturbed oscillators.

Note that a self-sustained oscillator with a small external force can be adequately described within the phase approximation [19], where only variations of the phase are concerned. With a stochastic force, the equation for the phase of the oscillator $dX/dt = F(X)$ reads

$$\dot{\varphi} = \frac{d\varphi}{dt} = \omega + \varepsilon \sum_{i=1}^{n} f_i(\varphi)\eta_i(t), \tag{6}$$

where ε is a small noise amplitude and each component of $(f_1(\varphi), f_2(\varphi), \cdots, f_n(\varphi)) = Z(\varphi) = grad_X \varphi|_{X=X_0(\varphi)}$(where $X_0(\varphi)$ is the unperturbed limit-cycle solution) is normalized: $\overline{f_i^2} \equiv (2\pi)^{-1}\int_0^{2\pi} f_i^2(\varphi)d\varphi = 1$. The Lyapunov exponent (LE) for the noisy

dynamics is defined as $\lambda =< d\dot{\varphi}/d\varphi >=< \varepsilon \sum_{i=1}^{n} f_i(\varphi)\eta_i(t) >$. In the case of white Gaussian noise $< \eta_i(t) >= 0$ and $< \eta_i(t)\eta_j(t+t') >= 2\delta_{ij}\delta(t')$, the LE $\lambda = -\varepsilon^2 \sum_{i=1}^{n} \overline{(f_i')^2}$ (see Refs.[18,26]) is negative. This implies that two or more oscillators driven by the same noise will be synchronized and attain the same random variation in time phases.

On the other hand, the evolution of N slightly different limit cycle oscillators can be described by the following generalization of Eq.(6):

$$\frac{d\varphi_k}{dt} = \omega + \sigma_k + \varepsilon \sum_{i=1}^{n} f_i(\varphi_k)\eta_i(t), \tag{7}$$

where σ_k are deviations of frequencies from the mean frequency $\varphi = N^{-1}\sum_{k=1}^{N}\varphi_k$, and assumed to be satisfied $\sum_{k=1}^{N}\sigma_k = 0$. Note that the differences in functions $f_i(\varphi_k)$ can be neglected due to smallness of ε. It is expected that the states of the oscillators are close if the mismatch is small compared to the LE, i.e., if $|\sigma_k| << |\lambda| << 1$. Now, we introduce new variables: $\vartheta_j = \varphi_j - \varphi$ $(1 \le j \le N-1)$. Then,

$$\begin{array}{l} \frac{d\varphi}{dt} = \omega + \varepsilon f(\varphi)\eta(t), \\ \frac{d\vartheta_j}{dt} = \sigma_j + \varepsilon \sum_{i=1}^{n} f_i'(\varphi)\vartheta_j\eta_i(t). \end{array} \tag{8}$$

Since the deviations ϑ_j with the different j are independent, we can study the evolution of each deviation ϑ_j separately and drop index j. For simplicity, we consider only the case that the noisy is one component (scalar noise in terms of Ref. [26]) in the following.

From Eqs.(8), the Fokker-Planck equation for the probability density distribution $W(\varphi,\vartheta,t)$ reads

$$\frac{\partial W}{\partial t} + \omega\frac{\partial W}{\partial \varphi} + \sigma\frac{\partial W}{\partial \vartheta} - \varepsilon^2 L^2 W = 0, \tag{9}$$

where the operator L is defined as $Lg = (\partial/\partial\varphi)(f(\varphi)g) + (\partial/\partial\vartheta)[f'(\varphi)\vartheta g]$. Without loss of generality, we assume that σ is of the same order as ε^2. Then, for the stationary solution of Eq.(9) we can expand W in ε as the following form:

$$W = W_0 + \varepsilon^2 W_1 + \cdots, \tag{10}$$

where $W_0 = w(\vartheta)$ is a certain function only in ϑ and W_1 is a function in both φ and ϑ. By utilizing periodicity of W_1 in φ, we can obtain

$$\sigma\frac{du}{d\vartheta} = \varepsilon^2\overline{f'^2}\left(\vartheta^2\frac{d^2u}{d\vartheta^2} + 4\vartheta\frac{du}{d\vartheta} + 2u\right), \tag{11}$$

where $u = w + (2\pi)^{-1}(ff')|_0^{2\pi}$. Finally, we obtain by solving the two-order differential equation,

$$w(\vartheta) = \begin{cases} \frac{|\sigma|}{2\pi|\lambda_0|\vartheta^2}\exp\left(-\frac{\sigma}{|\lambda_0|\vartheta}\right) - \frac{1}{2\pi}(ff')|_0^{2\pi}, & \sigma\vartheta > 0 \\ 0, & \sigma\vartheta \le 0 \end{cases} \tag{12}$$

where $\lambda_0 = -\varepsilon^2\overline{(f')^2}$. Furthermore, we can evaluate the moments

$$\left\langle |\vartheta|^k \right\rangle = \left(\frac{|\sigma|}{|\lambda_0|}\right)^k \Gamma(1-k) - \frac{1}{2\pi}(ff')|_0^{2\pi}\Gamma(1). \tag{13}$$

The formula gives finite moments for $k < 1$ only. Higher moments diverge due to the power-law distribution of ϑ. In the case, to obtain finite moments one has to go beyond the linear approximation in ϑ even for small mismatches σ. Under some circumstances, some leading LEs of Eqs.(7) are positive whereas other LEs are negative, implying that the partial synchronization is achieved. Also refer the previous Fig. 6.