Effective mechanisms for the synchronization of stochastic oscillators

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The emergence of synchronization is a phenomenon that is ubiquitous in a wide variety of natural systems. Such behavior is also often robust: systems subject to large stochastic fluctuations and which possess a range of internal time scales are capable of exhibiting sustained correlated dynamics. Here we study model chemical reactions and genetic networks that have stochastic oscillatory dynamics, and discuss microscopic mechanisms through which two or more such distinct stochastic processes can be coupled so as to result in the *phase* synchronization of their dynamical variables. We also consider the effect of time delay in the interaction and show that for suitable choices of the delay parameter, in-phase or antiphase synchronization can occur.

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I. INTRODUCTION

The concerted dynamical behavior of different stochastic processes can be of considerable importance in a variety of situations. The emergence of synchronization even in the presence of large fluctuations is a phenomenon that is both familiar and important in nature. Examples can be drawn from a number of areas of study [1]: coupled weather systems, coupled populations [2], coupled neurons [3], or coupled chemical reactions, particularly at the cellular level [4,5] all offer instances of systems which while being individually stochastic, nevertheless can respond synchronously. In the last cited example, in particular, the synchrony can be crucial: within the cell, individual genetic networks each result in stochastic oscillations, but in spite of the large number of such networks in a typical cell and the very different molecular species involved, the patterns of temporal variation of the various products fall into a relatively small number of groups [4,5]. Such synchronization results in robust internal clocks which are accurate time keepers of biological events although they are all based on processes that are intrinsically random.

The manner in which two or more independent (or unrelated) stochastic phenomena can become temporally synchronized—and indeed the sense in which stochastic systems can be said to be synchronized—forms the subject of this paper. Our present results apply to systems which are dominated by fluctuations and whose evolution is properly described by a master equation. We study the microscopic dynamics of small systems and examine general, minimal, mechanisms for coupling them so that the variables show correlated temporal variation, namely synchrony.

Some comments are necessary in order to set this study in context. The nature of synchronization in deterministic nonlinear dynamical systems can be well defined. This phenomenon has been extensively studied in the past few decades [6], especially chaotic dynamical systems [7]. When two systems synchronize, the simplest situation that can occur when the systems are identical is that the variables coincide. This is the case of complete synchronization. Beyond this, when the systems are not identical, there can be a variety of forms of synchrony—phase, lag, or general synchronization—and these have been described in detail [6]. The coupling mechanisms and topologies that give rise to these various forms of synchronization have also been extensively studied [6]. Early studies that addressed the phenomenon of synchronization in extended systems include those by Kuramoto and co-workers [8,9] who examined ensembles of coupled phase oscillators, and the paradigmatic studies of Mirollo and Strogatz [10] who considered coupled integrate-and-fire or pulse-coupled oscillators models.

Robustness is of particular importance when addressing issues relating to experimental observation of synchronization, and in this respect, the effect of additive external noise has been examined by analyzing the role of additive stochastic terms in the coupled equations [11–14]. The role of multiplicative noise has also been studied earlier by Goldobin and Pikovsky [15] and more recently by Nakao *et al.* [16] among others and the conditions under which systems remain synchronized with additive or multiplicative noise have been explored to some extent. Indeed, it is also known that ensembles of nonlinear systems undergo synchronization when subjected to identical noise, and this is a phenomenon that is reasonably well understood [17]. Systems subject to noise also display stochastic resonance [18] and under some circumstances, this can also serve to synchronize them.

Our approach in contrast, is to consider systems at the microscopic level and study them through simulations of the corresponding master equation [20,21]. The fluctuations that arise are inherent, in the sense that they are a consequence of the manner in which the state of the system evolves [22] and cannot be (externally) switched off. In specific limits or through specific approximations, one can derive corresponding coupled Langevin equations or coupled kinetic equations, but these are often not appropriate when dealing with the dynamics of small systems wherein the fluctuations can be large. In order to study finite systems for finite times therefore, we analyze synchronization by considering the master equation for the coupled system and introduce coupling schemes at the level of the elementary processes. Such mechanisms may be more germane when the systems are intrinsically different, when finite-size effects are significant,

and when the processes that are involved occur at spatially widely separated locations.

In the present paper we have focused on systems with oscillatory stochastic dynamics. This motivation arises in part from observations that suggest synchronizationlike behavior in intracellular dynamics [5]. Microarray gene-expression data from yeast that interrogates a large fraction of the total number of genes suggests that the dynamical behavior of sets of genes can be very similar. Although these observations [5] are over a relatively short time (so that the number of oscillations is small) it is striking that genes that are produced in distinct pathways, with very different characteristics, should have the same time variation. A stochastic description is appropriate, for instance, in considering the dynamics of molecular species within individual cells or in genetic circuits.

The model systems of chemical and biochemical oscillators that we consider here, the Brusselator and a circadian oscillator system, are described in Sec. III. A discussion of how such systems can be coupled is given in Sec. II where we present a general master-equation formalism for the treatment of coupled stochastic systems. The bulk of our results are presented in Sec. III where we describe the settings in which stochastic synchronization results for a variety of coupling scenarios and topologies. The Gillespie method [23] is employed to simulate the evolution of the coupled system. Equivalently, the corresponding chemical Langevin equation (CLE) can be deduced from the composite system and the system can be studied as a stochastic differential equation [24]. Techniques that are useful in detecting phase synchronization in chaotic oscillators [25–27] can also be used to show phase synchronization in stochastic systems. The case of time delay in the coupling between subsystems and its effect on the phase properties of the synchronizing dynamics is also studied here.

In Sec. IV we consider the limit when the evolution is described through corresponding rate equations (typically a set of coupled differential equations). Knowledge of the scenarios in which synchronization is known to occur in deterministic dynamical systems give some guidelines as to what elementary processes are likely to play a similar role in stochastic systems. We conclude the paper in Sec. V with a discussion and a summary of our results.

II. COUPLING MECHANISMS

Consider a system specified by a set of elementary processes, symbolically written as a set of "reaction" channels,

$$X_i + X_j + \cdots \xrightarrow{c_m} X_k + X_\ell + \cdots, \tag{1}$$

where X represents the number of molecules of different chemical species (represented by the subscript), and therefore is a non-negative integer and c_m is the rate for the mth such channel (of which there may be several). A configuration of the system C is a specification of the values of the variables, $(X_1, X_2, \ldots, X_n, \ldots)$. A master equation for the evolution of configurational probabilities [20] can be written as

$$\frac{d}{dt}P(C,t) = -\sum_{C'} P(C,t)W_{C\to C'} + \sum_{C'} P(C',t)W_{C'\to C}, \tag{2}$$

where in standard notation [21], $P(C,t)$ is the probability of configuration C at time t and $\{W\}$ are the transition probabilities. For a given realization, one starts from some initial configuration and examines the history of the system; the configurations that are realized as a function of time give a probabilistic description of the system as it traverses the state space of the problem.

Such a system can be studied by using stochastic (Monte Carlo) simulation techniques [23]. The so-called Gillespie algorithm is consistent with the master-equation formalism and gives a numerical method to study the time evolution of different chemical species. In order to compute observable quantities it is necessary to study an ensemble of histories and also to examine stationary quantities such as probability densities. Each individual realization even if started with the same initial configuration will be distinct. Alternately one can obtain the chemical Langevin equation for the system [24]. The CLE provides an approximate description under certain assumptions [24,28].

The dynamics of the system, Eq. (1), is stochastic. This noise is often termed internal as its origin is in the very mechanism of the evolution of the state of the system [22]. The strength of the noise depends on the volume of the system and the reaction propensities, and is not always small enough to be treated perturbatively.

Our concern can be formulated as follows. Consider two such identical but *independent* stochastic systems with the variables of the two systems being denoted by unprimed and primed quantities, say. Starting with configurations C and C', the subsequent evolution of each of the subsystems will typically be unrelated. How can the subsystems be coupled so as to synchronize? Since complete synchronization is not possible in stochastic systems, we look here for the case of phase synchronization.

When the dynamics of the subsystems is specified by a set of differential equations, for instance, then a number of coupling scenarios are known which will bring about synchronization. Indeed, this is the framework within which the phenomenon is generally understood, namely by introducing coupling terms in the dynamical equations specifying the evolution of the two subsystems [6,9,11–14,18,19]; weak linear perturbations have long been known as a mechanism for effecting synchronization in linear [6] as well as nonlinear systems.

Here, in contrast, we identify mediating processes—the microscopic coupling mechanisms—by which two stochastic subsystems will *phase synchronize*: while the variables of the systems do not coincide, they however vary in unison. Furthermore, such synchronization can persist even when fluctuations are large, although it depends on the nature and strength of the coupling.

In the mechanisms described below, for simplicity we consider that the two subsystems, specified by the variables $\{\mathbf{X}\}$ and $\{\mathbf{X}'\}$, respectively, have similar channels. The corresponding rates need not however be identical.

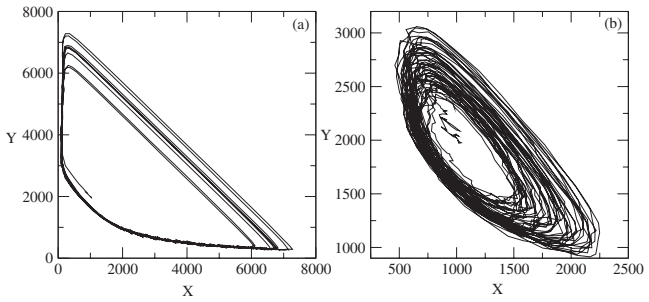

FIG. 1. Phase portrait of single Brusselator model [Eqs. (4)–(7)] obtained using Gillespie algorithm. (a) Phase portrait in the low noise limit. The parameter values are $c_1=5000$, $c_2=50$, $c_3=0.000\,05$, and $c_4=5$. (b) Phase portrait in the high noise limit. The modified parameter values are $c_1=4.5\times5000$ and $c_4=4.5\times5$.

(i) *Exchange coupling*. The simplest means of coupling the two subsystems is to introduce an "exchange" process whereby the variables X_i and X_i', say, interconvert. This introduces additional channels

$$X_i \underset{c'}{\overset{c}{\rightleftharpoons}} X_i' \tag{3}$$

that serve to couple the subsystems, and depending on the rate of interconversion (governed by c and c'), the other variables X_j and X_j' show synchronization. When the rates of exchange are equal, in the limit $c=c'\to\infty$, this reduces to the following case.

(ii) *Direct coupling, where the variables X_i and X_i' are identical*. This is essentially a "master-slave" coupling scenario, very similar to the strategies introduced by Pecora and Carroll [7] for deterministic dynamical systems. Thus, the two subsystems share a common variable (or drive) and consequently the dynamics of the remaining variables rapidly becomes highly correlated.

Both the above forms of coupling are easily realized in practice. In the case of direct coupling, effectively one species X_i is common to two reaction schemes, a not uncommon occurrence in chemical and biochemical systems. Similarly, in the exchange scenario, the species X_i and X_i' can be considered as different forms (say by allosteric modification) of each other. We discuss these in representative examples in the next section.

III. APPLICATIONS

Here we present some simple examples of how the coupling schemes discussed above can be implemented. We consider a model elementary chemical reaction system, the so-called Brusselator [29] as well as a circadian (genetic) oscillator system [30].

A. The Brusselator model

The stochastic dynamics of the Brusselator model, which has been studied extensively [29] derives from consideration of the following "chemical" reactions [23]:

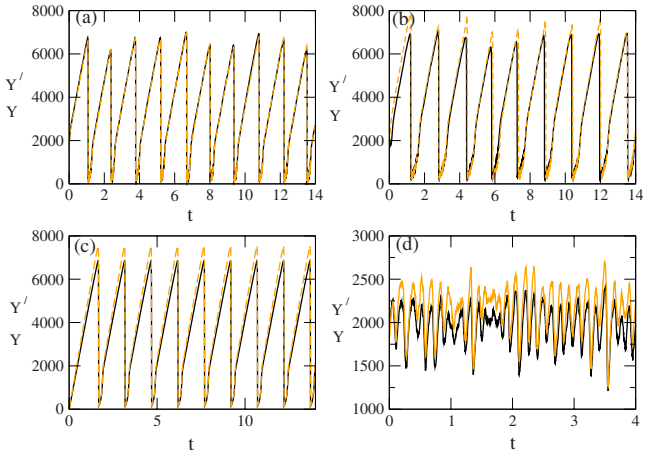

FIG. 2. (Color online) Species Y and Y' as a function of time for the coupled Brusselator system. The parameter $c_2=50$ differs from $c_2'=c_2+5$. The other parameters are $c_1=c_1'=5000$, $c_3=c_3'=0.000\,05$, and $c_4=c_4'=5$. c_1 and c_4 are taken as 2 times the given value in the case of direct coupling. (a) Stochastic simulation results for Y and Y' using direct coupling. (b) As in (a), but for the case of exchange coupling, Eq. (11) with $c=c'=0.6$. (c) Results obtained from the chemical Langevin equation [see Eq. (29)] with noise amplitude 0.01 for direct coupling. Parameter values are the same as in (a). (d) As in (a), but in the high noise limit. The modified parameters are $c_1=c_1'=16\times5000$ and $c_4=c_4'=16\times5$. Note that the in case (d), the deterministic equations asymptotically lead to a fixed point. In all of the cases, the volume is taken to be unity.

$$A_1 \overset{c_1}{\to} X, \tag{4}$$

$$A_2 + X \overset{c_2}{\to} Y + A_3, \tag{5}$$

$$2X + Y \overset{c_3}{\to} 3X, \tag{6}$$

$$X \overset{c_4}{\to} A_4. \tag{7}$$

In the thermodynamic limit, when fluctuations are negligible, one can derive (see Sec. IV) a set of deterministic reaction-rate equations for the average concentrations of species X and Y,

$$\dot{x} = c_1 - c_2 x + \frac{c_3}{2} x^2 y - c_4 x, \tag{8}$$

$$\dot{y} = c_2 x - \frac{c_3}{2} x^2 y. \tag{9}$$

For a suitable choice of parameters, Eqs. (8) and (9) give a limit-cycle solution. Simulations of Eqs. (4)–(7) give orbits that describe a noisy limit cycle [23] as shown in Fig. 1.

Another Brusselator system (denoted by similar equations, but with primed variables and parameters) would also naturally give another, uncorrelated, noisy limit cycle solution, the characteristics of which would depend on the parameters of the problem. Thus, if the parameters $\{c_i\}$ and $\{c_i'\}$

are different the evolution of the two subsystems will be independent and uncorrelated.

Coupling the two systems through X and X' leads to synchronization of species Y and Y'. For example, in the case of direct coupling, the coupled system is represented by the following chemical reactions:

$$A_1 \xrightarrow{c_1} X,$$

$$A_2 + X \xrightarrow{c_2} Y + A_3,$$

$$2X + Y \xrightarrow{c_3} 3X,$$

$$X \xrightarrow{c_4} A_4,$$

$$A_2 + X \xrightarrow{c_2'} Y' + A_3,$$

$$2X + Y' \xrightarrow{c_3'} 3X. \tag{10}$$

With exchange coupling, the system is enlarged to

$$A_1 \xrightarrow{c_1} X, \quad A_1 \xrightarrow{c_1'} X',$$

$$A_2 + X \xrightarrow{c_2} Y + A_3, \quad A_2 + X' \xrightarrow{c_2'} Y' + A_3,$$

$$2X + Y \xrightarrow{c_3} 3X, \quad 2X' + Y' \xrightarrow{c_3'} 3X',$$

$$X \xrightarrow{c_4} A_4, \quad X' \xrightarrow{c_4'} A_4,$$

$$X \underset{c'}{\overset{c}{\rightleftharpoons}} X'. \tag{11}$$

It is easy to see that the master equation corresponding to the case of direct coupling is given by

$$\begin{aligned}\frac{dP(X,Y,Y',t)}{dt} &= c_1[P(X-1,Y,Y',t) - P(X,Y,Y',t)] + c_2[(X+1)P(X+1,Y,Y'+1,t) - XP(X,Y,Y',t)] \\ &+ c_2'[(X+1)P(X+1,Y,Y'+1,t) - XP(X,Y,Y',t)] + \frac{c_3}{2}[(X-1)(X-2)(Y+1)P(X-1,Y+1,Y'+1,t) \\ &- X(X-1)YP(X,Y,Y',t)] + \frac{c_3'}{2}[(X-1)(X-2)(Y'+1)P(X-1,Y+1,Y'+1,t) - X(X-1)Y'P(X,Y,Y',t)] \\ &+ c_4[(X-1)P(X+1,Y,Y',t) - XP(X,Y,Y',t)] \end{aligned} \tag{12}$$

which, in the infinite volume limit, leads to the following kinetic (mass-action) equations:

$$\dot{x} = c_1 - (c_2 + c_2')x + \frac{c_3}{2}x^2y + \frac{c_3'}{2}x^2y' - c_4x, \tag{13}$$

$$\dot{y} = c_2x - \frac{c_3}{2}x^2y, \tag{14}$$

$$\dot{y}' = c_2'x - \frac{c_3'}{2}x^2y', \tag{15}$$

namely, a set of coupled deterministic equations (see Sec. IV).

Similarly, the exchange coupling has the following set of mass-action equations:

$$\dot{x} = c_1 - c_2x + \frac{c_3}{2}x^2y - c_4x + c(x' - x), \tag{16}$$

$$\dot{y} = c_2x - \frac{c_3}{2}x^2y, \tag{17}$$

$$\dot{x}' = c_1' - c_2'x' + \frac{c_3'}{2}x'^2y' - c_4'x' + c'(x - x'), \tag{18}$$

$$\dot{y}' = c_2'x' - \frac{c_3'}{2}x'^2y'. \tag{19}$$

Both direct as well as exchange coupling mechanisms effect stochastic synchronization, although they differ in the details of how they act. Figure 2 shows the variation of species Y and Y' as a function of time, from stochastic simulations as well as the chemical Langevin approach. The numerical procedure employed in simulating the chemical Langevin equation is elaborated in Sec. IV; this effectively adds stochastic noise to the deterministic dynamics [Eqs. (13)–(15) and Eqs. (16)–(19)] [24]. Note that the nature of the dynamics in the deterministic limit can be significantly different from that obtained through master-equation simulations [31].

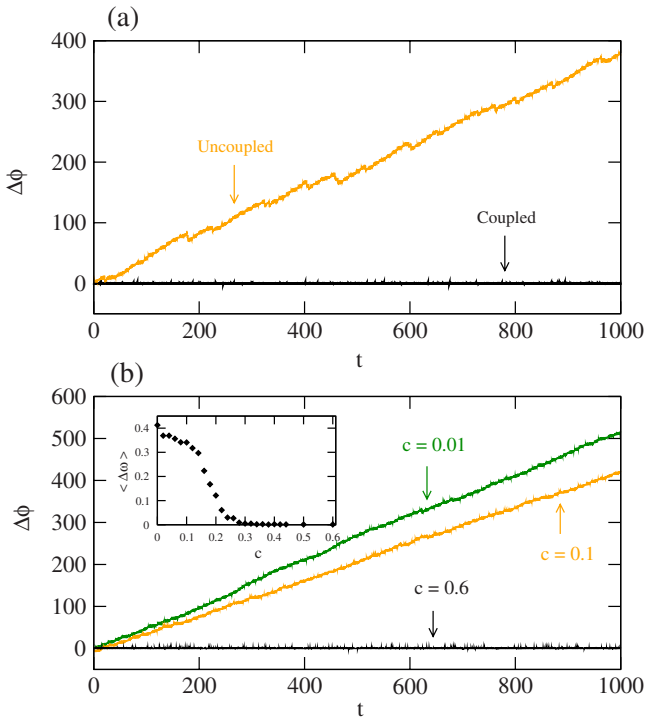

FIG. 3. (Color online) Phase synchronization in coupled Brusselators with parameters as in Figs. 2(a)–2(c). Phase difference as a function of time for (a) direct coupling of species X and X', and (b) exchange coupling, for different strengths. The inset shows the average frequency difference $\langle \Delta\omega \rangle$ which goes to zero with increasing coupling strength.

Clearly the two concentrations vary in unison. However, to judge the phase synchronization of two stochastic oscillators in a more quantitative fashion, it is necessary to first obtain a phaselike variable [9] for a single oscillator. Earlier work on chaotic oscillators [27] suggests that a suitable measure is provided by the Hilbert phase, obtained through the analytical signal approach introduced by [25]. Given a signal $s(t)$, define the Hilbert transform,

$$\bar{s}(t) = \frac{1}{\pi} \mathrm{PV} \int_{-\infty}^{\infty} \frac{s(\tau)}{t-\tau} d\tau. \tag{20}$$

PV denotes principal value. The instantaneous amplitude $A(t)$ and phase $\phi(t)$ are then defined through the identity

$$A(t)e^{i\phi(t)} = s(t) + i\bar{s}(t). \tag{21}$$

The difference in the Hilbert phases ϕ and ϕ' of the two stochastic oscillators is shown in Fig. 3. When the subsystems are uncoupled, the phase difference $\Delta\phi = |\phi - \phi'|$ increases linearly in time with average slope $\langle \Delta\omega \rangle$ since the oscillators evolve independently. With coupling, the two oscillators phase synchronize and the phase difference fluctuates around a constant value. One can use other phase definitions in the presence of noise [12], such as the natural phase, linear interpolating phase, discrete phase, etc., depending on the systems, but the Hilbert phase appears to be the most appropriate when the signal exhibits irregularity.

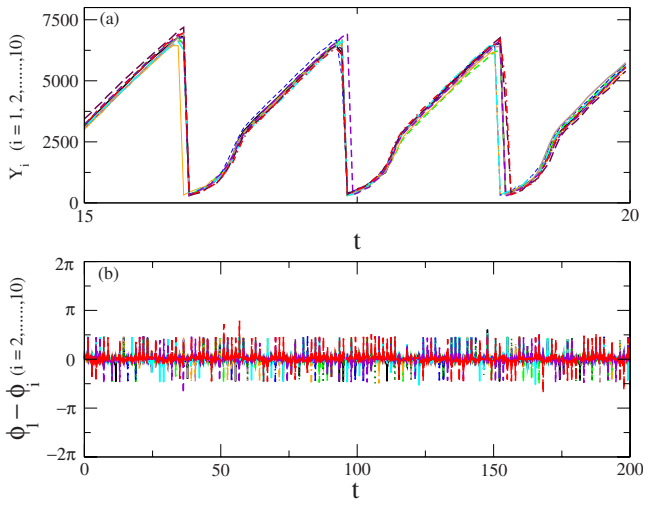

FIG. 4. (Color online) Synchronized behavior of 10 distinct Brusselator systems, namely, where all the parameters differ. We use a mean-field (all-to-all) coupling with $c=0.9$. (a) Temporal behavior after the coupling is switched on. (b) Hilbert phase difference of one of the oscillators with all others.

With exchange coupling, stochastic synchronization occurs only above a threshold. The rate of increase of the phase difference is shown as a function of the exchange rate in the inset to Fig. 3(b) and the behavior is suggestive of a phase transition; similar results have been seen earlier in the dynamics of coupled Langevin equations [32].

The scheme discussed above works for coupling an ensemble of oscillators. Figure 4 shows the synchronized behavior for a large number of Brusselators where each oscillator is coupled to every other oscillator via exchange coupling.

B. The circadian oscillator

A second system we consider is a model genetic oscillator that has been quantitatively studied in detail recently [30] in the context of circadian rhythms. This system also serves to make more concrete the nature of direct and exchange coupling in mechanistic terms. Furthermore, such genetic circuits are experimentally realized in natural and synthetic biological systems [33–35] and therefore provide a natural testing ground for the ideas presented here.

The biochemical network for two such oscillators with direct coupling is shown in Fig. 5 (also see Table I). This is a system of *two* genetic circuits that share a single activator which binds to the two promoter sites for repressor proteins R and S. For the case of exchange coupling, the genetic circuit differs somewhat from Fig. 5: the circuit of Ref. [30] is essentially doubled, and there is an additional activator A'. The activators of the two circuits are allowed to interconvert at a finite rate (in biochemical terms, the two activators could be allosteric variants of each other).

Each individual circuit gives stochastic oscillations in the number of repressor molecules. When the two systems are coupled the stochastic oscillations of the two subsystems rapidly phase synchronize. The temporal behavior of the two

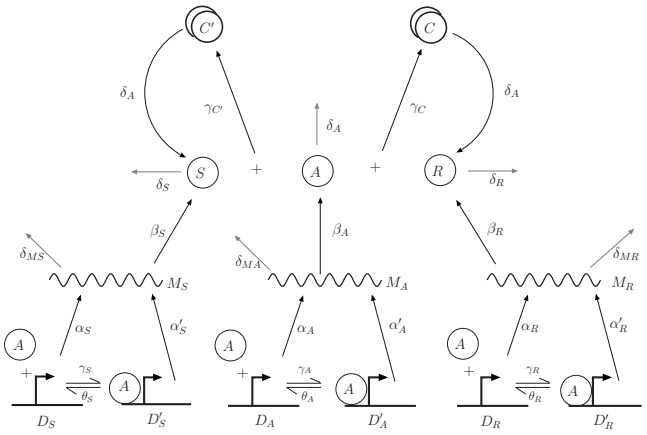

FIG. 5. Biochemical network of the extended circadian oscillator model. D_A and D'_A denote the number of activator genes with and without A bound to its promoter, respectively, and D_R, D'_R and D_S, D'_S refer to the two repressors driven by the common promoter A. M_A, M_R, and M_S denote mRNA corresponding to the activator A, and the repressors R and S. C and C' corresponds to the inactivated complexes formed by A and R, and A and S, respectively. The constants α and α' denote the basal and activated rates of transcription, β denotes the rates of translation, δ denotes the rates of spontaneous degradation, γ denotes the rates of binding of A to other components, and θ denotes the rates of unbinding of A from those components. The values of the parameters are given in Table I. The initial conditions are $D_A=D_R=D_S=1$ mol, $D'_A=D'_R=D'_S=M_A=M_R=M_S=A=R=C=0$, $S=1$, $C'=1$. The cell has a single copy of the activator and repressor genes: $D_A+D'_A=D_R+D'_R=D_S+D'_S=1$ mol, and the volume is assumed to be unity.

repressors and their phase difference for both direct and exchange coupling are shown in Fig. 6. The synchronization is robust to parameter variation: we allow all the corresponding parameters of the two subsystems to differ by as much as 10%; nevertheless, the variables of the two systems oscillate in phase in a stable and sustained manner.

In (a) the two systems are initially uncoupled and therefore evolve independently. The direct coupling is switched on for $t \geq 2000$, leading rapidly to a constant phase difference, indicative of the phase synchronization [Fig. 6(b)]. The exchange coupling results are shown in Figs. 6(c) and 6(d); as in the case of the Brusselator, there is stochastic synchronization above a threshold rate of interconversion.

C. Time-delay and "relay" synchronization

Given the two mechanisms above, it is possible to analyze a number of situations that are likely to arise in natural systems. For instance, when considering synchrony in spatially extended systems, it is necessary to include time delay in the interactions [36]. This could, for instance, arise from diffusion processes: when dealing with the coupling of biochemical networks in different cells, intercellular diffusion must be taken into account [37]. In such situations, as a function of the delay time τ, the nature of synchronization can itself change, from being in phase to being antiphase (or out of phase); the Hilbert phase difference in the latter case takes the value π rather than zero.

TABLE I. Parameter values for the coupled circadian oscillator shown in Fig. 5.

Parameters	Values
α_A, α'_R, β_A, θ_A	50 h^{-1}
α'_A	500 h^{-1}
α_R	0.01 h^{-1}
α_S	α_R+0.001 h^{-1}
α'_S	α'_R+5 h^{-1}
β_R	5 h^{-1}
β_S	β_R+0.5 h^{-1}
δ_{MA}	10 h^{-1}
δ_{MR}	0.5 h^{-1}
δ_{MS}	δ_{MR}+0.05 h^{-1}
δ_A,	1 h^{-1}
γ_A,γ_R,γ_S	1 mol^{-1} h^{-1}
δ_R	0.2 h^{-1}
δ_S	δ_R+0.2 h^{-1}
γ_C, γ'_C	2 mol^{-1} h^{-1}
θ_R, θ_S	100 h^{-1}

The time evolution of such systems can be studied through appropriately adapted stochastic simulation techniques [37,38]. (In the infinite volume limit, this will reduce to a system of delay-differential equations.) Here we extend the exchange process to include time delay, namely,

$$X_i \overset{c}{\longrightarrow} X'_i \quad \text{with delay} \quad \tau, \tag{22}$$

$$X'_i \overset{c'}{\longrightarrow} X_i \quad \text{with delay} \quad \tau. \tag{23}$$

In our simulations we use a modification of the standard Gillespie algorithm which takes into account the non-Markovian nature of the dynamics when time delay is present [38]. We find that both the Brusselator as well as the circadian oscillator systems synchronize for appropriate combinations of delay time and exchange rate. Apart from in-phase synchronization, the coupled oscillators also exhibit antiphase synchronization for specific combinations of (c, τ); an example of this latter case is shown in Fig. 7.

A coupling topology that is of particular interest in presence of time delays is the case of one oscillator coupled to two others as schematically shown in Fig. 8. Recent experiments on laser systems [39] and electronic circuits [40] have uncovered the phenomenon of zero-lag phase synchronization: the two oscillators (denoted 1 and 3) which are time-delay diffusively coupled to a third oscillator (marked 2), are in phase synchrony even though they are not directly coupled. Shown in Fig. 9 are results of such "relay" synchronization in a system of three circadian oscillators coupled as in Fig. 8. The repressors from the three subsystems are labeled R, S, and T, respectively (the circuitry expands Fig. 5 appropriately). Although each of the oscillators is distinct—all the parameters of the systems differ—there is phase synchrony between the repressor output from oscillators 1 and 3,

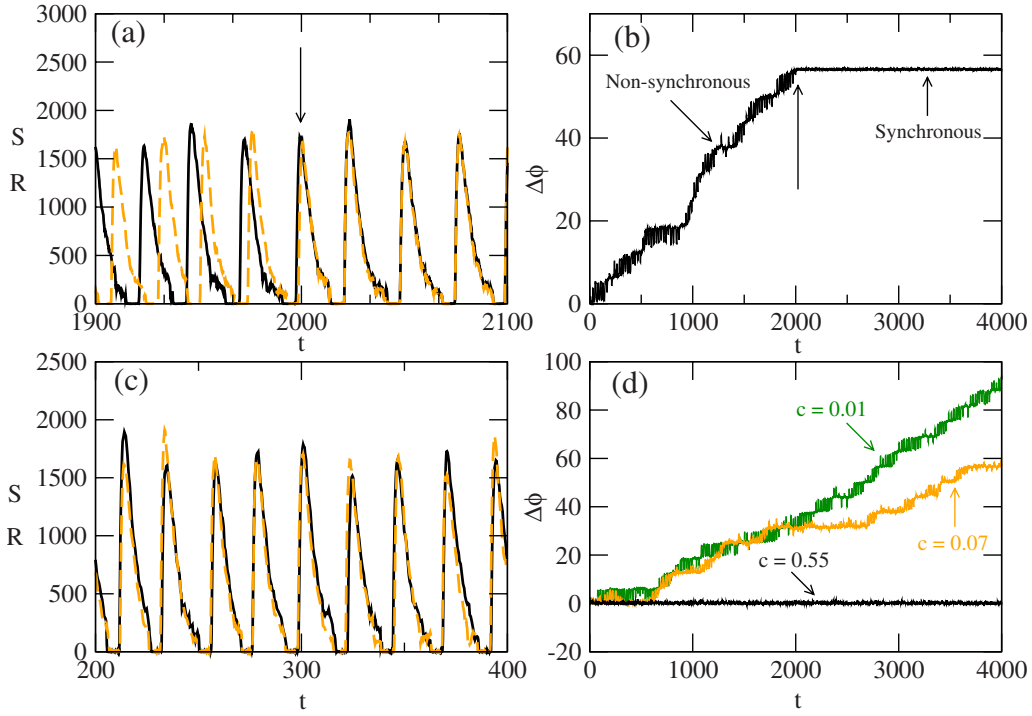

FIG. 6. (Color online) Temporal behavior and the phase difference of the repressors in the circadian oscillator model. (a) The two repressors are initially uncoupled and the coupling is switched on at time $t=2000$. (b) The corresponding Hilbert phase difference shows a linear increase which becomes constant for $t \geq 2000$. (c) Time series of the repressors oscillating in unison for diffusive coupling with $c=c'=0.55$. (d) Phase difference for different values of c.

namely R and T. For different combinations of delay time and coupling, we find regimes where (i) oscillator 2 is out of phase with the outputs of oscillators 1 and 3 which are in phase as well as (ii) regimes where oscillator 2 is antiphase to oscillators 1 and 3 which are in phase with each other, as shown in Fig. 9. This strategy appears to be very powerful: it is possible to make arbitrary numbers of oscillators synchronize (in phase or out of phase) by suitably altering the coupling topology and the delays.

IV. KINETIC ANALYSIS

Examination of the macroscopic dynamics offers some clues as to how the stochastic oscillators synchronize. While the master equation description is formally exact at the microscopic level, the kinetic equations that describe the system at a macroscopic level can be derived as a limiting case, from the master equation by using the generating function technique, followed by a cumulant expansion [41] to give a set of ordinary differential equations. Defining $x_i=\langle X_i\rangle/\Omega$, Ω being the system size, the kinetic equation has the form

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x},t) + O\left(\frac{1}{\Omega}\right) + O\left(\frac{1}{\Omega^2}\right) + \cdots . \tag{24}$$

In the large volume limit, then, these reduce to the mass-action kinetic equations; the stochastic fluctuations appear as corrections that depend inversely on the system volume Ω.

When two such systems are coupled at the level of the microscopic processes, the above procedure yields a set of coupled differential equations. The circumstances under which these will phase synchronize have been studied to some extent [6,13]. For example, taking the coupled Brusselator system, Eqs. (13)–(15), the master equation for the coupled Brusselator system is given by Eq. (12). Setting $c_i=c_i'$ in Eq. (12), the above analysis gives

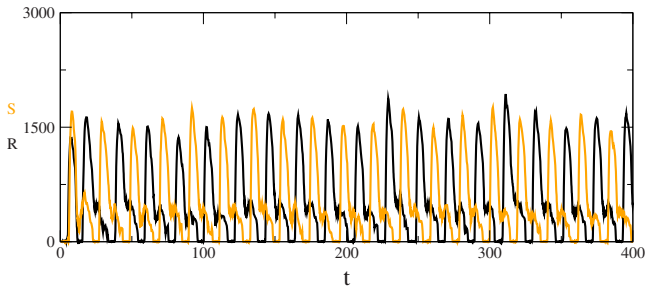

FIG. 7. (Color online) When the two circadian oscillators are coupled bidirectionally with time delay, the repressors R and S can vary out of phase. The antiphase synchrony for time delay $\tau=10$ and coupling strength $c=c'=0.7$ is shown. Results were obtained by using the modified Gillespie method [38].

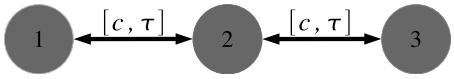

FIG. 8. Schematic representation of the relay mechanism. Oscillators 1 and 3 are coupled bidirectionally to oscillator 2 with time delay τ and coupling c. There is no direct coupling between 1 and 3.

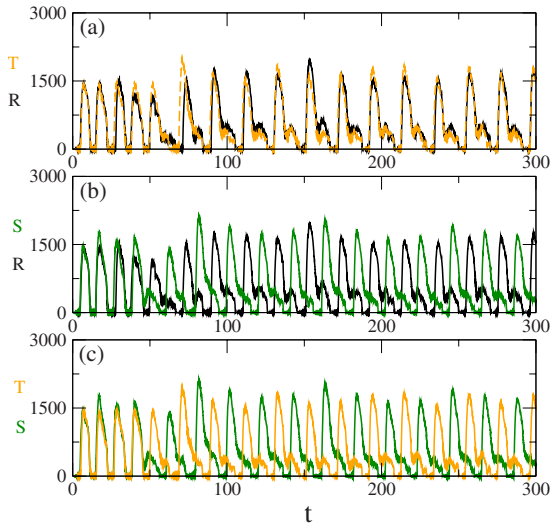

FIG. 9. (Color online) Temporal behavior of the repressors for relay synchronization in three coupled circadian oscillators for time delay $\tau=10$ and coupling strength $c=0.8$. (a) Phase synchronization between repressors R and T of circadian oscillators 1 and 3 coupled to a third oscillator (with repressor S). (b) and (c) show "lag synchronization" between the repressors R and S and repressors S and T, respectively. Results were obtained by using the modified Gillespie method [38].

$$\dot{x} = k_1 - 2k_2x + \frac{k_3}{2}x^2(y + y') - k_4x + O(1/\Omega) + O(1/\Omega^2) + \cdots, \tag{25}$$

$$\dot{y} = k_2x - \frac{k_3}{2}x^2y + O(1/\Omega) + O(1/\Omega^2) + \cdots, \tag{26}$$

$$\dot{y}' = k_2x - \frac{k_3}{2}x^2y' + O(1/\Omega) + O(1/\Omega^2) + \cdots, \tag{27}$$

with appropriately defined rate constants, k_i [42]. In the macroscopic limit $\Omega \to \infty$, the difference variable $z=y-y'$ obeys the dynamics

$$\frac{d}{dt}z = -\frac{k_3}{2}x^2z. \tag{28}$$

Direct coupling in the deterministic limit leads to dynamical equations which are similar to (but not always identical with) those that derive from the coupling scheme proposed by Pecora and Carroll [7] for the synchronization of chaotic oscillators. Although it is not possible to define Lyapunov exponents for stochastic systems, analysis of the deterministic limit gives indications of which coupling schemes could be effective. In the present example making species Y the common drive between the two Brusselator subsystems does not serve to synchronize them but instead leads to the stochastic analog of oscillator death.

Similarly, the exchange process, Eq. (11), results in diffusive coupling [43] in the kinetic equations for the species X and X', namely, terms of the form $c(x'-x)$. The conditions under which this form of the coupling leads to synchronization have also been studied [43]. By coupling many oscillators through this mechanism, one can obtain the mean-field limit [44].

One can also consider the appropriate CLE's [24]. In general, these will have the form

$$\frac{dX_i(t)}{dt} = \sum_{j=1}^{M} \nu_{ji}a_i[\mathbf{X}(t)] + \sum_{j=1}^{M} \nu_{ji}a_i^{1/2}[\mathbf{X}(t)]\Gamma_j(t), \tag{29}$$

where ν_{ji} is the change in X_i produced by the R_jth reaction, $a_i[\mathbf{X}(t)]$ is the propensity of reaction R_i, and $\Gamma_j(t)$ is temporally uncorrelated, statistically independent Gaussian white noise. Note that the X_i's are treated as continuous rather than discrete variables. This equation is solved numerically by evolving the variables through the equation

$$X_i(t + dt) = X_i(t) + dt\sum_{j=1}^{M} \nu_{ji}a_i[\mathbf{X}(t)] + \sum_{j=1}^{M} \nu_{ji}a_i^{1/2}[\mathbf{X}(t)]N_j(t)(dt)^{1/2}, \tag{30}$$

where $N_j(t)$ are normally distributed variables with zero mean and unit variance [24].

When the system volume is large or the reaction propensities are small, noise effects will be small. Goldobin and Pikovsky [15] have studied coupled Langevin equations with multiplicative noise terms and show that, if the deterministic part of the Langevin equation has a stable limit cycle solution, and the deviation of the stochastic evolution from this limit cycle is small, application of phase reduction method leads to phase synchronization.

V. DISCUSSION AND SUMMARY

In the present work we have explored the nature of synchronization in stochastic systems, and have identified some of the simplest mechanisms through which such synchrony can be effected. The emergence of synchrony in natural systems appears to be widespread and examples can be drawn from a number of areas [45].

We have focused on the manner in which independent stochastic systems can synchronize (or vary in concert) when they are coupled through mediating processes. Such synchronization is largely independent of the size of fluctuations and has some similarity to the phenomenon of synchronization in chaotic systems [7] or more generally, in dynamical systems with and without added noise. There are also important differences in that the mechanisms that we have described here pertain to systems with intrinsic stochasticity, and are, in some sense, in a nonperturbative limit.

The coupling schemes that we have proposed here can find application in the design and control of synthetic biological networks where synchronous oscillation may be a desirable feature. McMillen *et al.* [46] have shown that intercell signaling via a diffusing molecule can couple genetic oscillators and effect synchrony. The present results indicate that such phase synchrony can emerge under very general

conditions with high levels of ambient noise. In a related vein, one can speculate that similar mechanisms underlie the synchrony that is so dramatically evident in cellular processes. As recent time-resolved microarray experiments of yeast have revealed, the multitude of variable gene expression patterns classify into a small number of groups, all genes of a given group having very similar temporal variation profiles [5]. We have observed that the above coupling schemes are effective in synchronizing ensembles of stochastic oscillators [44,47]. Other physical situations where such mechanisms may be relevant are in the study of coupled financial systems (markets), weather systems, or coupled ecosystems: the individual subsystems show stochastic dynamics, which however have phase synchrony [2].

Although we have discussed the explicit case of stochastic oscillators, there is reason to believe that similar microscopic intersystem couplings can bring about temporal correlations in more general stochastic systems. Investigations of such phenomena are currently under way [47].

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