

## Synchronization of coupled stochastic oscillators: The effect of topology

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**Abstract.** We study sets of genetic networks having stochastic oscillatory dynamics. Depending on the coupling topology we find regimes of *phase* synchronization of the dynamical variables. We consider the effect of time-delay in the interaction and show that for suitable choices of delay parameter, either in-phase or anti-phase synchronization can occur.

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### 1. Introduction

The phenomenon of synchronization of oscillatory dynamics is observed in a wide variety of natural systems [1–3]. This behaviour is also robust: systems subject to large stochastic fluctuations and which possess a range of internal time-scales are capable of exhibiting sustained correlated dynamics. Although the synchronization of weakly coupled nonlinear systems is well-studied and largely understood [4], similar behaviour in oscillatory stochastic systems has not been explored in great detail. Studies have mainly been confined to examining the nature or extent of synchronization in deterministic dynamical systems when external noise is added [5–7].

We have recently studied the synchronization of stochastic oscillators by examining the actual microscopic processes that give rise to correlated stochastic behaviour [8]. These mechanisms have analogues in the various coupling schemes that have been shown to be very effective in driving coupled nonlinear dynamical systems into synchrony [4]. The existence of synchronization and the stability of the synchronized state is independent of the nature of the dynamics which can be periodic, quasiperiodic, or even chaotic [9]. Furthermore, for small systems, where intrinsic fluctuations are large, the connection between the macroscopic description of dissipative processes, and the corresponding microscopic description is not straightforward. As a result study of the macroscopic equations as a limiting case can give unreliable results.

In the present work, we extend this study to examine the nature of synchrony in ensembles of coupled stochastic oscillators. One major area where we believe that stochasticity is intrinsic is in subcellular dynamics, where different genes are known to interact via complicated regulatory networks [10]. We therefore study model genetic networks and couple them via elementary mechanisms, and with different topologies: each genetic network is therefore treated as a node within the larger regulatory network, and the temporal behaviour that emerges as a consequence of coupling network motifs is studied through Monte Carlo simulations of the relevant master equation [11].

We also consider the effect of time-delay in the coupling mechanisms, in part as an approximate means of accounting for a separation of time-scales between different reactions. This can also be incorporated in the simulation method [12], and our results suggest that by adjusting time-delay, it is possible to achieve precise phase relationships between coupled oscillator systems as well as to effect a variety of temporal patterns in extended coupled stochastic dynamical systems.

## 2. Coupling mechanisms

A stochastic system can be specified by a set of elementary processes which are symbolically written as a set of ‘reaction’ channels [8]



where the  $X$ ’s represent the number of molecules of different chemical species (represented by the subscript) and  $c_m$  is the rate for the  $m$ th such channel. The fluctuations are often termed as internal noise since their origin is in the very mechanism of the evolution of the state of the system [13]. 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.

As is well known, such a system is formally described by a master equation [14] for the evolution of configurational probabilities [14], which is written as

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

where in standard notation [14],  $P(C, t)$  is the probability of configuration  $C$  at time  $t$  and  $\{W\}$  are the transition probabilities.

We have earlier [8] addressed the question of how two identical but *independent* stochastic systems (denoted by unprimed and primed quantities, say) can be coupled by additional processes (at the level of the chemical equations) such that they exhibit phase synchronization. We identified the mediating processes – the microscopic coupling mechanisms [8], which lead to such synchronous behaviour. We briefly recall them below.

- *Exchange coupling:* We consider an ‘exchange’ process whereby the variables  $X_i$  and  $X'_i$  of the two subsystems, interconvert. This introduces additional channels

$$X_i \rightleftharpoons X'_i \tag{3}$$

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  $c = c' \rightarrow \infty$ , this reduces to the case of direct coupling.

- *Direct coupling:* Here the variables  $X_i$  and  $X'_i$  are identical. This is essentially a ‘master–slave’ coupling scenario, where the two subsystems share a common drive and consequently the dynamics of the remaining variables becomes correlated.

Both the above forms of couplings 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 of each other, or the same species in different locations (in different cells, say). We discuss these schemes in a representative example in the next section.

### 3. The circadian oscillator

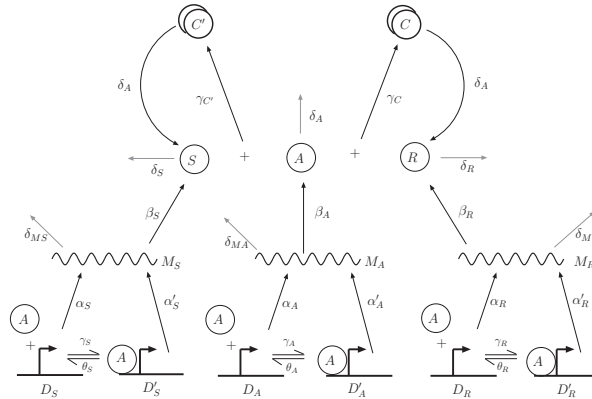
Consider a model genetic oscillator that has been quantitatively studied in detail [15] in the context of circadian rhythms.

The biochemical network for two such oscillators with direct coupling is shown in figure 1. 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 figure 1: the circuit of ref. [15] 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).

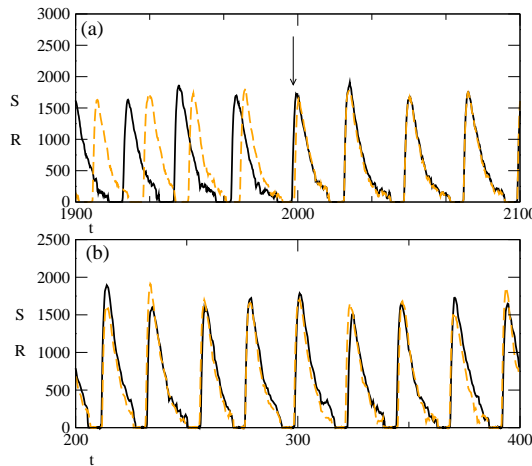
When the two systems are coupled, the stochastic oscillations of the number of repressor molecules of the two subsystems rapidly phase-synchronize. Figure 2 shows the variation of the repressors  $R$  and  $S$  as a function of time, for both direct and exchange couplings. In (a) the two systems are initially uncoupled and therefore evolve independently. The direct coupling is switched on for  $t \geq 2000$  and clearly the repressors start varying in unison. With exchange coupling, stochastic synchronization occurs only above a threshold which is achieved by tuning the coupling strength. 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.

### 4. Time-delay and relay synchronization

When considering spatially extended systems, it is necessary to incorporate time-delay in the interactions [16]. This could, for instance, arise from diffusional processes: when dealing with the coupling of biochemical networks in different

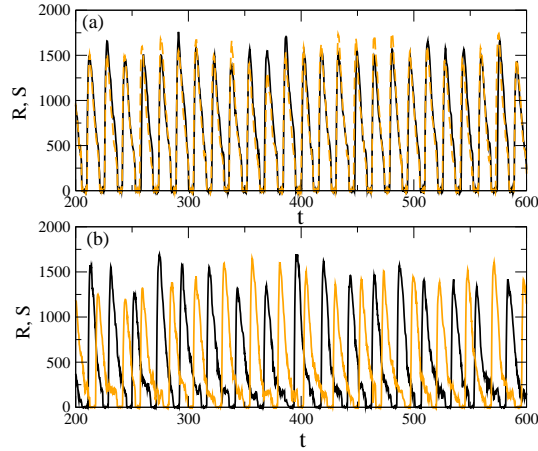


**Figure 1.** Biochemical network of the extended circadian oscillator model.  $D_A$  and  $D'_A$  denote the number of activator genes with and without  $A$  bound to its promoter respectively, and  $D_R$ ,  $D'_R$  and  $D_S$ ,  $D'_S$ , refer to the two repressors driven by the common promoter  $A$ .  $M_A$ ,  $M_R$  and  $M_S$  denote mRNA corresponding to the activator  $A$ , and the repressors  $R$  and  $S$ .  $C$  and  $C'$  correspond to the inactivated complexes formed by  $A$  and  $R$ , and  $A$  and  $S$  respectively. The constants  $\alpha$  and  $\alpha'$  denote the basal and activated rates of transcription,  $\beta$  the rates of translation,  $\delta$  the rates of spontaneous degradation,  $\gamma$  the rates of binding of  $A$  to other components, and  $\theta$  denotes the rates of unbinding of  $A$  from those components. The parameter values and the initial conditions are as taken in [8] and the volume is assumed to be unity.



**Figure 2.** Temporal behaviour of the repressors in the circadian oscillator model for (a) the direct coupling case and (b) the exchange coupling. In (a), the two repressors are initially uncoupled and the coupling is switched on at time  $t \leq 2000$  and (b) shows the repressors oscillating in unison for diffusive coupling with  $c = c' = 0.55$ .

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**Figure 3.** Circadian oscillators coupled bi-directionally with coupling strength  $c = c' = 0.7$  and time-delay  $\tau + \Delta\tau$ , where  $\tau = 15$  and  $\Delta\tau = a_0\eta(t)$ . (a) With noise amplitude  $a_0 = 1$ , the repressors  $R$  and  $S$  are phase-synchronized. (b) for  $a_0 = 10$  there is anti-phase synchronization.

cells, intercellular diffusion must be taken into account [17]. In such situations, as a function of the delay time  $\tau$ , the nature of synchronization can itself change, from being in-phase to being anti (or out-of-) phase; the Hilbert phase difference in the latter case takes the value  $\pi$  rather than zero.

The time evolution of such systems can be studied through appropriately adapted stochastic simulation techniques [12]. (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,

$$X_i \rightarrow X'_i \quad \text{with delay } \tau, \tag{4}$$

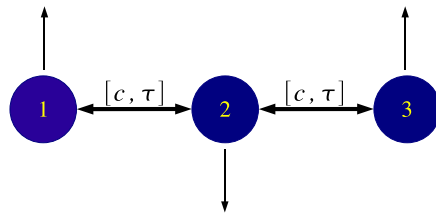
$$X'_i \rightarrow X_i \quad \text{with delay } \tau. \tag{5}$$

We find that for appropriate combinations of delay time and exchange rate, the two systems synchronize. Apart from in-phase synchronization, the coupled oscillators also exhibit anti-phase synchronization for specific combinations of  $(c, \tau)$  [8].

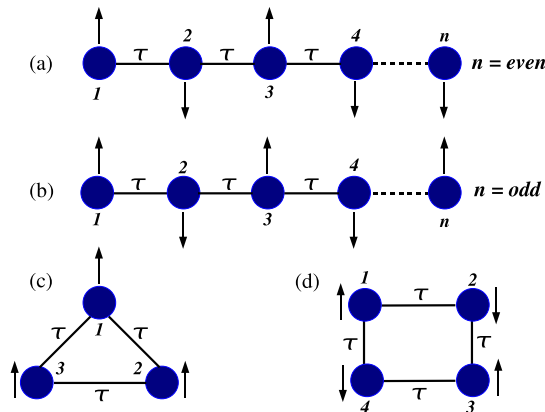
The stochastic variations of the delay time can itself be an additional source of noise. Such systems can be modeled by choosing delay time from the interval  $\tau$  to  $\tau + \Delta\tau$ , where  $\Delta\tau$  is the noise width.

In figure 3 we show results for  $\Delta\tau = a_0\eta(t)$ :  $a_0$  is the amplitude and  $\eta(t)$  is the uniformly distributed noise in the range  $[-0.5 : 0.5]$ . For small  $a_0$ , the dynamics remains unchanged from the case of fixed time-delay, but for higher  $a_0$  there can be changes in the dynamical behaviour. As shown in figure 3 the two oscillators were phase-synchronized for fixed delay, but for  $a_0 = 10$  they become anti-phase-synchronized. On further increasing the noise amplitude the synchronization can be destroyed.

A coupling topology that is of particular interest in the presence of time-delays is the case of one oscillator coupled to two others as schematically shown in figure 4. Recent experimental studies [18] have revealed the phenomenon of zero-lag phase



**Figure 4.** Schematic representation of the relay mechanism. Oscillators 1 and 3 are coupled to oscillator 2 bi-directionally with time-delay  $\tau$  and coupling  $c$ . There is no direct coupling between 1 and 3. Such coupling leads to phase synchronization between 1 and 3 and lag synchronization between 1, 2 and 2, 3 as shown by the arrow.



**Figure 5.** Different network motifs for oscillators coupled bi-directionally via delayed channels. (a) and (b) show one-dimensional open chains with even and odd number of nodes. (c) shows a triangle motif with identical delay times  $\tau$ , and (d) shows a square motif. The arrows indicate the relative phases of the oscillators at the nodes.

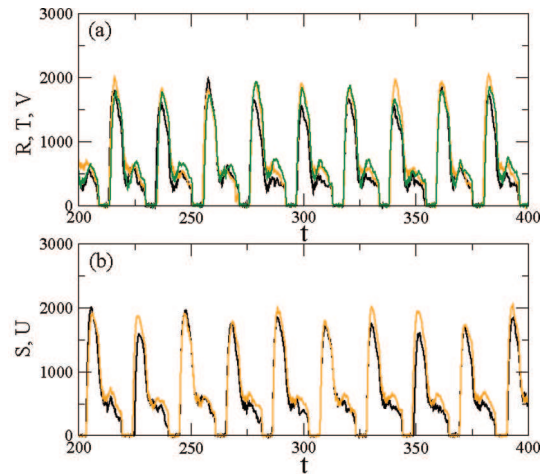
synchronization: the two oscillators (denoted as 1 and 3) which are time-delay diffusively coupled to a third oscillator (marked 2), are in phase-synchrony even though they are not directly coupled.

Our studies with circadian oscillators coupled as in figure 4 in the microscopic limit showed similar behaviour [8]. This strategy appears to be very powerful in the sense that 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. We consider such situations in the next section.

### 5. Variation in coupling topology

Having discussed the manner in which two units can be coupled so as to synchronize, we now consider the dynamics of extended systems composed of stochastic

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**Figure 6.** Phase synchronization of the circadian oscillators in an odd chain with  $n = 5$ ,  $\tau = 10$  and  $c = 0.8$ . In (a), the repressors  $R$ ,  $T$  and  $V$  of the oscillators 1, 3 and 5 are phase-synchronized, whereas in (b) the repressors  $S$  and  $U$  of the oscillators 2 and 4 are in phase. The alternate oscillators are anti-phase-synchronized.

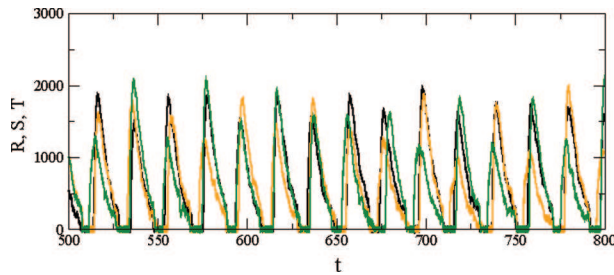
oscillators. Such coupled systems are of great current interest, in particular on networks; the study of complex networks has assumed considerable importance in the past few years in numerous fields of study, including biochemistry [19], neurobiology [20] and ecology [21].

Spatiotemporal patterns that emerge as a consequence of the complex network topology play a crucial role in determining cellular function. It is useful to identify the simplest units of commonly used network architectures [22] in order to understand the manner in which complex networks function. It is believed that these simple units – network motifs – provide the basic regulatory capacities and hence contribute in building complex temporal behaviour.

We study a set of stochastic oscillators coupled in a motif. The coupling incorporates delay and thus there is a possibility of relay synchronization. In the examples that follow, we use the circadian oscillator system at each node; the nodes are coupled via the mechanisms discussed in §4, and we consider the resulting *temporal* patterns.

#### 5.1 Open chains

The simplest motif is a one-dimensional chain where oscillators are coupled sequentially, with time-delay (figures 5a,b). Depending upon the choice of  $(\tau, \epsilon)$ , there could be several possibilities. If the time-delay is small in comparison with the intrinsic time-scale of oscillation, say, then with increasing coupling strength all the oscillators get phase-synchronized. When the time-delay is of the order of the characteristic time-scale of the system, alternate oscillators can become phase-



**Figure 7.** Circadian oscillators put in a triangular motif as in figure 5c. Phase synchronization of the repressors is achieved when equal coupling strength and time-delay are used. Here  $c = 0.9$  and  $\tau = 20$ .

synchronized while neighbouring oscillators are lag-synchronized. This is a consequence of the relay synchronization mechanism discussed in the previous section. With an even number of oscillators, oscillators at the end of the chains will necessarily be in lag synchrony, while if there is an odd number of oscillators they will be in phase. Figure 6 shows one such situation with  $n = 5$  where the oscillators 1, 3 and 5 are phase-synchronized.

This phenomenon is quite robust and is observed in the weak coupling limit. The phase difference between the consecutive oscillators is a function of the coupling, and decreases with increased coupling. For sufficiently strong coupling, this eventually leads to the phase synchronization of all the oscillators.

## 5.2 Closed chains

We can also consider closed chains, three oscillators each coupled to the others, resulting in a triangular motif (figure 5c), or four oscillators coupled in a quadrilateral geometry (figure 5d). For simplicity, we consider the case of equal time-delays (hence the triangle is equilateral and the quadrilateral is a square). In the case of the equilateral triangle, node 2 acts as a relay between nodes 1 and 3. As a consequence, all of them can be phase-synchronized. But node 3 can act as a relay between nodes 1 and 2 to get them in-phase. Thus there are two possibilities. Due to these competing effects, the synchronization can either be destroyed or all three become synchronized depending on the coupling strength and time-delay. Figure 7 shows one such state for  $\epsilon = 0.9$  and  $\tau = 20$ , where all the repressors are phase-synchronized.

For the square motif, no such competition arises and as before the alternate oscillators are phase-synchronized. Moreover, the phase synchronization is very robust because two oscillators act as relay between a pair of oscillators. This suggests that for systems coupled in a ring with an odd number of nodes, all oscillators can be phase-synchronized, but with an even number of nodes, a closed chain behaves like an open chain.

The synchronization phenomena discussed above are robust, in the sense that they are insensitive to initial conditions. However, it will be interesting to see whether such behaviour is maintained while going to the high noise limit. In the



high volume (macroscopic) limit, similar cooperative behaviour results, and a detailed study is currently in progress [23].

## 6. Discussion and summary

The main objective of the present work has been to study the nature of synchronization in ensembles of stochastic systems. Such synchronization is robust and largely independent of the size of fluctuations or small parameter variations.

We believe that the coupling schemes discussed here could find application in the design and control of synthetic biological networks where synchronous oscillation may be a desirable feature. Our studies have shown that depending on the delay time, either in-phase or anti-phase synchronization can occur. Further, using the idea of relay synchronization we have constructed various network motifs showing the possibility of achieving isochronous synchronization as well as complex temporal variations over large distances.

It should be noted that the coupling strategies suggested here are not the only ones that may result in long-range synchrony. Indeed, Gonze and Goldbeter [24] and most recently Li *et al* [25] have employed a ‘mean-field’ coupling scheme where all nodes are coupled to all other nodes, and find that the such coupling leads to synchronization of all the oscillators. Taken together, the present studies, and other investigations of synchrony in extended systems may provide a framework within which variety of oscillatory processes within cells can be understood, and may also prove to be useful in analyzing intercellular communication.

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