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STOCHASTIC SYNCHRONIZATION OF CIRCADIAN RHYTHMS*

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Abstract Models of circadian genetic oscillators involving interlinked feedback processes in molecular level genetic networks in Drosophila melanogaster and Neurospora crassa are studied, and mechanisms whereby synchronization can arise in an assembly of cells are examined. The individual subcellular circadian oscillatory processes are stochastic in nature due to the small numbers of molecules that are involved, and are subject to large fluctuations. The authors investigate and present the simulations of the stochastic dynamics of ensembles of clock–regulating proteins in different nuclei that communicate via ancillary small molecules, environmental parameters, additive cellular noise, or through diffusive processes. The results show that the emergence of collective oscillations is a macroscopic observable which has its origins in the microscopic coupling between distinct cellular oscillators.

Key words Coupling, stochastic dynamics, synchrony.

1 Introduction

Biological internal autonomous time keeping mechanisms allow all living organisms to adapt to external diurnal periodicity[1]. Circadian rhythms are based on specific genetic processes, and are known to originate in negative feedback circuits[1−4] that generate a periodic expression of specific genes[1,5] within a cell. Individual cells in the organism can be viewed as autonomous oscillators that contain a genetic circuit which can be coupled among themselves through various environmental parameters[6−7]. Genetic oscillators based on models involving various molecular mechanisms have been studied in organisms such as D. melanogaster, or N. crassa [7−9], but the larger question of how groups of cells exhibit synchronous rhythms is one that remains incompletely understood. Since synchrony is essential for information processing in such systems[10], the phenomenon of synchronization can be seen in general as the consequence of cell–to–cell communication via specific coupling mechanisms[11]. Cellular synchrony can be achieved via

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various signaling molecules[11] or a number of internal or external stimuli[1,4] and is known to be a robust phenomenon.

In this paper, we examine different mechanisms that can bring about synchrony in an ensemble of circadian oscillators[9]. For instance, in the fruitfly D. melanogaster the clock mechanism depends on the proteins CLOCK and CYC which induce rhythmic transcription of PER and TIM, the latter two being negative feedback regulators[12−13]. Experiments using per mutants have shown that changes in the structure or abundance of this gene product can lengthen, shorten or even completely remove the periodicity of circadian rhythms[14−16]. While PER and TIM are too large to diffuse out of a given cell, there is some evidence that they play the role of "couplers" when positioned near the cell membrane: They can then synchronize (or otherwise organize) clock components[17−18]. The humoral peptide hormone, PDF, which is a pdf gene product secreted from individual cells of D. melanogaster is also believed to act as a synchronizing factor, inducing phase shifts in the same manner as a periodic light pulse[19]. N. crassa on the other hand, has a syncitial morphology[1,7]: Several nuclei are present in a single cell, thus sharing a common cytoplasm. As a consequence the clock gene mRNA and clock proteins are common to a set of clock oscillators and can transport directly from one oscillator to the other by diffusion or convection. The coupling between different oscillators is effected via these molecular mechanisms[7,20].

Cellular and subcellular processes are dynamically diverse since there are a number of distinctly different oscillator types based on a variety of coupling topologies and architectures. At the same time, it is also recognised that the temporal organisation of the different dynamical processes is crucial to the functioning of cells, and thus the manner in which these different oscillators interact with each other as well as with nonoscillatory processes is central to understanding temporal organization at the subcellular level. It is necessary to understand the manner in which synchronization takes place, and indeed the synchronizability of this diverse set of processes. Studies of the general mechanisms that may underlie synchrony in such systems are thus of considerable interest[21].

We focus on a stochastic model for circadian rhythms that has been extensively studied over the past few years[6] and examine how synchrony emerges in an ensemble of such systems. We have considered the oscillators to be similar in type, although we allow for variations in the fundamental parameters of the individual oscillators; this is described in the next section of this paper where we also discuss the simulation methods used. In Section 3, we examine several coupling strategies and topologies, and discuss the manner in which the phase synchronization of distinct oscillators can be judged using quantitative criteria. The main results of this study are presented in Section 4 followed by a discussion.

2 Models of Circadian Oscillator and Simulation Techniques

There are different theoretical models to explain molecular mechanisms in circadian oscillators[8]. One that is specific to D. melanogaster and N. crassa is a single feedback loop model developed by Goldbeter and coworkers[6,22]. The model is based on negative feedback autoregulation of gene expression; the molecular mechanisms associated with the feedback loop in both the species are quite similar even though the specific proteins involved are quite different[9,23] as shown in Figure 1.

The essential steps leading to oscillation of a given protein are as follows. In D. melanogaster, the clock gene is per . Following its transcription, the corresponding mRNA (M_P) is transported into the cytosol where it is translated into protein P_0 and degraded. Reverse phosporylation can also take place from P_0 to P_1 and then P_2: This can be degraded or transported into the

nucleus as the nuclear protein P_N which then represses the transcription of its parent gene per, forming a negative feedback loop.

In N. crassa, the operative protein is frq, and to understand its oscillations the same mechanism can be invoked. In this case the frq gene transcript is transported outside the nucleus as mRNA(M_F). The corresponding cytosol and nuclear proteins are F_0, F_1, F_2, and F_N respectively. The rates of transcription, translation and degradation of mRNA (M_P and M_F) and cytosol proteins (P_C and F_C) from the two organisms (shown in Figure 1) are different, primed constants correspond to the N. crassa case.

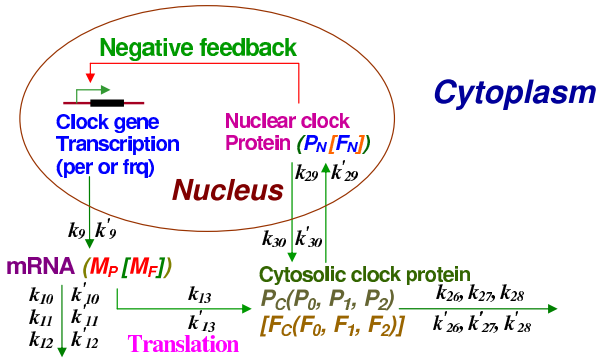

Figure 1 The circadian model studied in this work (see text for details)

Dynamical processes at the subcellular level typically involve a small number of participating entities, and can be seen essentially as noise-driven stochastic processes[6,24–25]. We use stochastic simulation techniques[26–28] in the present study, considering the cell as containing N distinct molecular species $(X_1, X_2, \cdots, X_N)$ that react via M reaction channels R_μ with reaction constants $k_\mu, \mu = 1, 2, \cdots M$, such as

$$X_i + X_j + X_k + \cdots \stackrel{k_\mu}{\rightarrow} X_\alpha + X_\beta + X_\gamma + \cdots \tag{1}$$

where the X's are molecule populations. A configuration $\mathcal{C}$ is the population vector $(X_1, X_2, \cdots, X_N)$, and the configurational probability $P(\mathcal{C}, t)$ obeys the master equation[26]:

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

where the W's are the appropriate transition probabilities. We simulate the above master equation for the models discussed using the Gillespie algorithm[26] and have also considered some of the elementary processes to include timedelay[29]. For all computations reported here, we have taken the cellular volume fixed at $V = 100/N_A$, where N_A is Avogadro's number[7].

3 Synchronization of Stochastic Oscillators

The variables in stochastic systems are in general subject to both intrinsic and extrinsic fluctuations and the stochastic simulation algorithm that we use explicitly accounts for internal noise effects[26]. The synchronization of such two stochastic systems cannot be detected in a simple manner and the situation can be more complex if one deals with an ensemble of such systems[30]. Extensive studies of coupled deterministic dynamical systems has revealed that there can be many forms of synchronization, ranging from complete synchrony, when all

variables of the coupled systems are identical to generalized synchronization, when the variables of the two systems are unique functions of each other.

Phase synchronization is relevant when dealing with stochastic systems and the corresponding variables oscillate together without having identical amplitudes[31]. We therefore discuss, the detection of phase synchronization between two signals[32], and general coupling schemes whereby such phase synchronization occurs.

The time evolution of two independent and identical stochastic systems starting with different initial configurations will be uncorrelated. Upon coupling, the subsystems can synchronize although one should not expect complete synchronization; due to the inherent stochasticity the subsystems show phase synchrony[31−33]: The variables do not coincide but vary in unison even when fluctuations are large[31−32].

It has been pointed out[34] that it is possible to define an instantaneous phase for an arbitrary signal $\eta(t)$ via the Hilbert transform[32]:

$$\widetilde{\eta}(t) = \frac{1}{\pi} P.V. \int_{-\infty}^{+\infty} \frac{\eta(t)}{t-\tau} d\tau, \tag{3}$$

where *P.V.* denotes the Cauchy principal value. Then, through the relation

$$A(t)\mathrm{e}^{i\phi(t)} = \eta(t) + i\widetilde{\eta}(t), \tag{4}$$

one can associate an instantaneous phase $\phi(t)$ and an instantaneous "amplitude" $A(t)$ with a given signal. Given two signals, one can therefore obtain the instantaneous phases ϕ_1 and ϕ_2; phase synchronization is then the condition that $\Delta\phi = m\phi_1 - n\phi_2$ is constant. Of most interest are the cases $\Delta\phi = 0$ or π, namely the cases of in–phase or anti–phase oscillations, but other temporal arrangements may also occur.

We now consider the coupling schemes that lead to the synchronization of two systems. In what follows we will denote the configurations of the the two essentially identical systems by $\mathcal{C} \equiv (X_1, X_2, \cdots, X_N)$ and $\mathcal{C}' \equiv (X_1', X_2', \cdots, X_N')$, respectively. The following forms of coupling have been discussed[31].

Direct coupling The two subsystems share one species in common, say X_i and X_i' are identical. Then the dynamics of the remaining variables (X_j and X_j') become highly correlated. In the deterministic limit, this reduces to an analogue of the master–slave coupling[35].

Exchange or Diffusive coupling In this scenario, the species X_i and X_i' can interconvert via additional reaction channels, $X_i \xrightarrow{c} X_i'$ and $X_i' \xrightarrow{c'} X_i$, where c and c' are interconversion reaction rates. Then the synchronization in other variables X_j and X_j' occurs when the rates c and c' are sufficiently large. In the deterministic limit this corresponds to bidirectional diffusive coupling[35].

Global or mean–field coupling When a given molecular species, say X_1 is common to a group of systems then this species can be an effective means of global coupling, coupling each system to every other. The common species provides a "mean–field" whereby the systems communicate and the remaining variables synchronize[36−37].

Noise coupling When oscillators are subject to common external noise, the dynamics of the similarly affected species, say X_i and X_i' which have the added noise terms as $X_i \to X_i + \gamma\xi_i$ and $X_i' \to X_i' + \gamma\xi_i$ become synchronized for appropriate strength of the noise, namely γ. The noise itself is taken to be uncorrelated and Gaussian distributed, $\langle \xi_i \xi_j \rangle = \delta_{ij}$[38]. It should be noted that noise synchronization can be nonmonotonic: If the two systems become correlated at a critical value γ_c, then for smaller values $\gamma < \gamma_c$, X_i and X_i' are of course uncorrelated, but above a second threshold $\gamma > \gamma_u$ the added noise dominates and any notion of synchrony loses meaning.

It has been shown recently[39−40] that time-delay can induce "relay" synchronization. Systems that are not mutually coupled but instead are both coupled to a third can show either in-phase or out–of–phase synchrony. This form of coupling results in novel temporal patterns, and can give rise to long-range information transfer in a group of oscillators[31]. Such effects are particularly important in spatially extended systems when coupling can involve time-delay. At a phenomenological level, signals are transmitted via diffusive processes which naturally have a finite velocity. The evolution of such systems can be studied either through delay–differential equations, or through appropriately adapted stochastic simulation techniques[21,31,36]. We have studied such relay synchronization in a population of delay–coupled oscillators[41].

4 Results

To investigate the synchrony in a group of cells, we can either couple them sequentially or simultaneously, namely in series or in parallel. We first present results for the former strategy in the D. melanogaster network, using pairwise direct coupling via per. Shown in Figure 2 are the results from our simulations of N=5 cells using direct coupling via P_2, which is switched on at $t = 1000$ hr, and it can be seen that subsequent to this time, the coupling is very effective in bringing about synchrony. The left inset shows M_p in cells 1 and 2 before and after coupling, and the right one shows the desynchronized and synchronized regimes. In the regime $t \leq$ 1000 hrs the time series of the per mRNA, namely M_p populations in the different cells evolve in an uncorrelated fashion. The left inset shows the dependence of the populations on each other, and as synchrony emerges, the dependence becomes linear. The phase difference $\Delta\phi$ of pairs of signals is shown in the right inset, evolving randomly with time in the desynchronized regime, and fluctuating about a constant value once synchrony kicks in. Analogous results for N. crassa using frq as the driving molecular species have also been obtained[41].

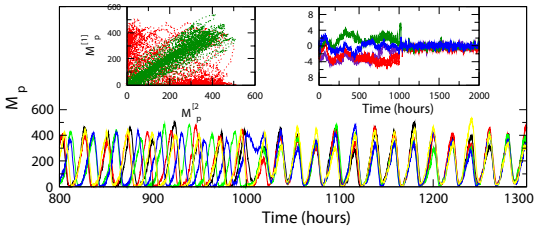

Figure 2 Plot of per mRNA (M_p) populations as a function of time in the case of D. melanogaster

Synchrony mediated through exchange coupling is also effective in the two cases, and our results are presented in Figure 3 for N. crassa for different values of the exchange reaction rate c. The upper left panel show the dynamics of F_N for two coupling constant $c = 0.01$ and 0.3 respectively. For small c the dynamics is uncorrelated, and at higher c synchrony emerges. The critical value of the coupling at which synchrony emerges is shown as a function of the cellular volume in the lower right panel in Figure 3. The similarities of this behaviour with a phase transition requires further investigation[41].

When cells are coupled by the mean field coupling strategy, the correlation between them is stronger and more rapid. Comparison is made with direct coupling, and the results are shown in Figure 4 for D. melanogaster. Shown in the upper left panel is the dynamics of nuclear per proteins, P_N, from two cells (1 and 2) out of 5 coupled in the mean-field scheme. Comparison with results from direct coupling is reported in upper right panel. The lower left panel shows the emergence of the synchronization manifold when coupling is turned on, and the

right panel show the phase difference as a function of time. Figure 5 presents analogous results for N. crassa: The simulation is of 5 cells coupled through the mean-field, and results are shown for the nuclear frq protein, F_N variation from cells 1 and 5. Synchronization occurs faster and oscillations in the synchronous state have smaller fluctuations. This may be due to the fact that as the number of communicating molecular species increases, information is transmitted more rapidly.

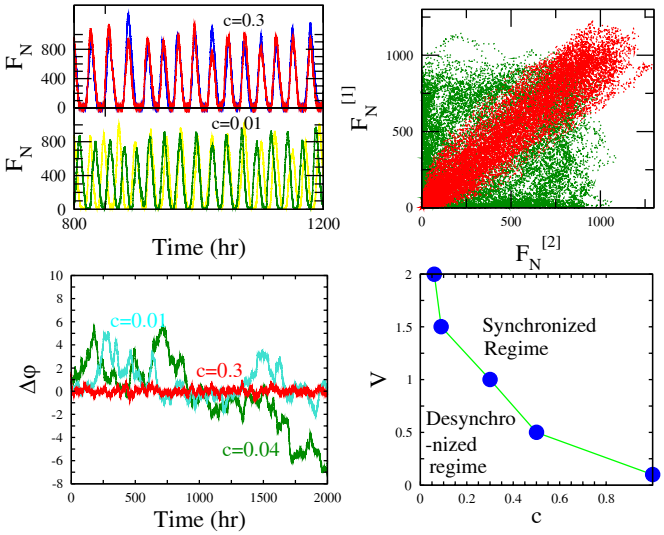

Figure 3 Plot of F_N in two N. crassa nuclei coupled by the exchange of M_F

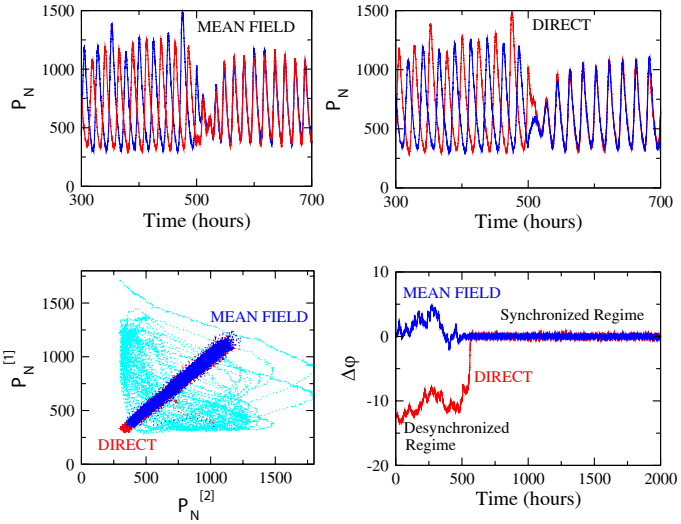

Figure 4 Synchronization of PER in D. melanogaster cells via mean-field and direct coupling

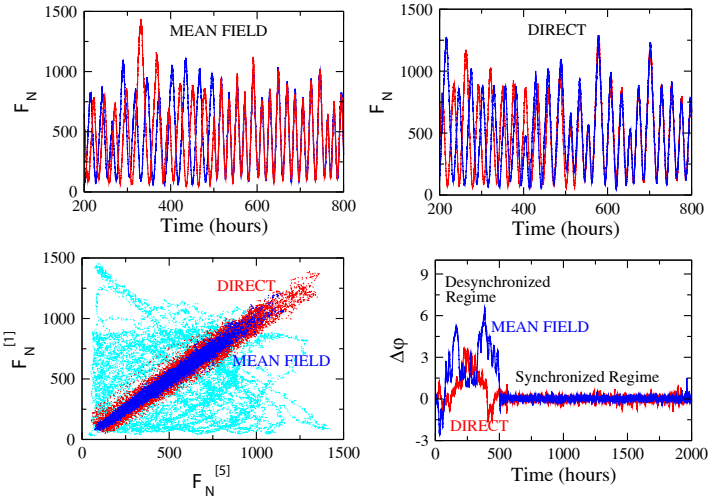

Figure 5 As in Figure 4, but for the case of N. crassa

With delay coupling, both in- and out-of-phase behaviour results. Shown in Figure 6 are results for coupling five oscillators in series; the upper two panel show the variation of nuclear per in cells 1 and 5 as a function of time at coupling constant c=0.1. Here M_P is taken as the coupling molecular species. For delay t_d=25, cells 1 and 5 are synchronized (upper left pannel) while for t_d=80, their dynamics is uncorrelated (upper right panel) at $c = 0.2$. The lower panels are as in Figure 4. For delay t_d=80, dynamics is uncorrelated, but for shorter delay t_d=25 the cells get synchronized. Similar results are obtained for the case of N. crassa: Synchronization is obtained for t_d=49 while on increasing the delay to t_d=80 the dynamics gets uncorrelated as can be seen in Figure 7 where c has been taken to be 0.1.

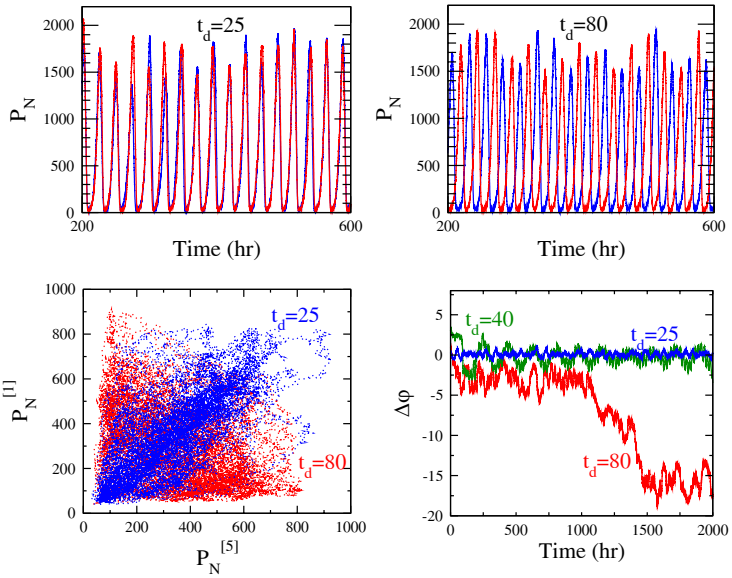

Figure 6 Dynamics of P_N when the coupling involves time–delay

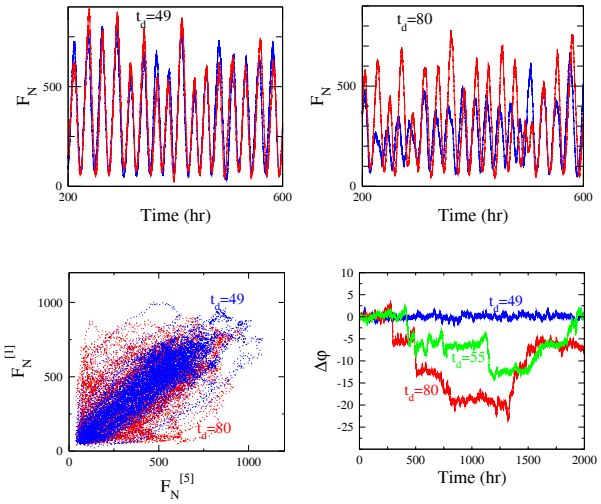

Figure 7 As in Figure 6, but for the case of N. crassa

The results of external noise mediated coupling for two cells in D. melanogaster are shown in Figure 8. The top and middle panels are for noise strengths $\gamma = 1.4 \times 10^{-2}$ (synchronous oscillations) and 8×10^{-2} (desynchronized oscillations), respectively. The bottom panel shows the phase difference for various noise strengths indicating synchrony only for intermediate noise strengths. Prior to the introduction of this noise the oscillations are uncorrelated, but as soon as noise is introduced, they synchronize. If the strength of the noise exceeds a critical value, though, the oscillatory behavior of the dynamics is vitiated (as can be seen for γ=8×10^{-2}). The lowermost panel shows the phase differences for different values of γ, showing synchronized and unsynchronized behaviour. Similar results are found for the case of N. crassa (shown in Figure 9) although the couplin
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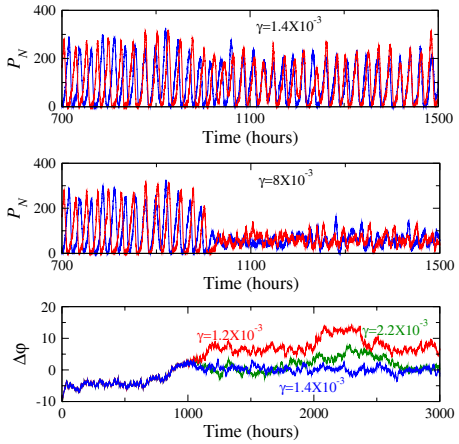

Figure 8 Plot of P_N as a function of time in two D. melanogaster cells coupled by common external noise

We thus observe that the coupling strategies discussed in Section 3 are successful in synchronizing groups of cells in an efficient manner. Global or mean–field coupling is, in a sense, the most robust method that ensures that all the individual oscillators essentially guide each other into a coherent state. Note also that by suitably altering the coupling and delay parameters, arbitrary temporal patterns can be obtained so that it is possible to ensure that groups of cells have complex oscillations. Furthermore, weak noise can enhance correlation of an ensemble of stochastic oscillators. However, if the strength of the noise is too large, synchrony is lost.

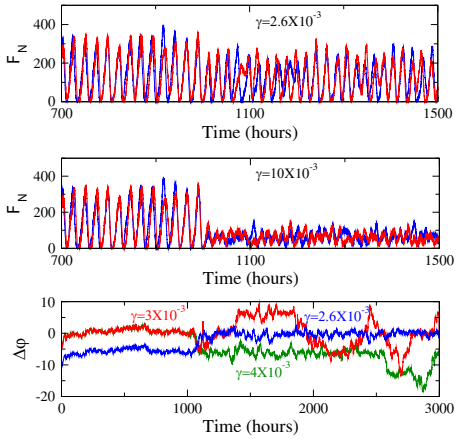

Figure 9 As in Figure 8, but for the case of N. crassa

5 Concluding Remarks

We have investigated the emergence of synchrony in a group of cells through different coupling mechanisms. Using circadian oscillator models that have been developed for D. melanogaster and N. crassa and which share a basic common mechanism, we have examined different forms of coupling that are plausible at the molecular level, and furthermore, which cause a rapid synchronization in the dynamics. Explicit incorporation of time–delay results in relay synchrony between cells with both in– and out–of–phase dynamics (or any other desired relative phase motion) being possible. An important aspect of the present work is that we do not consider dynamical models perse, but instead treat the individual stochastic processes and couple the different oscillators through elementary reactions. Thus, the effect of both internal and external noise is incorporated in the models.

The case of mean–field coupling is of particular significance since a large number of cells can easily be brought into synchrony through the use of small diffusible molecules, for instance via metabolites. As the number of such species increases, the rate of synchronization also increases. The study of such processes—which are likely to be operative, for instance, in situations where a population of unicellular organisms form a colony—may cast more light on the dynamics of phenomena such as quorum sensing[40]. Our observation that the addition of weak noise in an ensemble of cells can lead to synchrony gives addition evidence to the current belief that noise can enhance information processing.

The efficiency of a given mechanism to induce synchrony depends on a variety of factors such as the system parameters and their degree of variability, to name two. While we have

found that mean–field coupling brings about synchrony most rapidly in the present examples, this may not hold generally, and other mechanisms maybe more efficient in other contexts. However, given the importance of synchronous dynamics in a number of biological systems, a study of the manner in which different systems can show a concerted temporal response is of fundamental importance and relevance. Our ongoing studies[41] are devoted to a more complete understanding of the effect of both internal and external noise in the synchronization of cellular and subcellular processes.

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