# Noise-Induced Coherence in Multicellular Circadian Clocks

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ABSTRACT In higher organisms, circadian rhythms are generated by a multicellular genetic clock that is entrained very efficiently to the 24-h light-dark cycle. Most studies done so far of these circadian oscillators have considered a perfectly periodic driving by light, in the form of either a square wave or a sinusoidal modulation. However, in natural conditions, organisms are subject to nonnegligible fluctuations in the light level all through the daily cycle. In this article, we investigate how the interplay between light fluctuations and intercellular coupling affects the dynamics of the collective rhythm in a large ensemble of nonidentical, globally coupled cellular clocks modeled as Goodwin oscillators. On the basis of experimental considerations, we assume an inverse dependence of the cell-cell coupling strength on the light intensity, in such a way that the larger the light intensity, the weaker the coupling. Our results show a noise-induced rhythm generation for constant light intensities at which the clock is arrhythmic in the noise-free case. Importantly, the rhythm shows a resonancelike phenomenon as a function of the noise intensity. Such improved coherence can be only observed at the level of the overt rhythm and not at the level of the individual oscillators, thus suggesting a cooperative effect of noise, coupling, and the emerging synchronization between the oscillators.

## INTRODUCTION

Circadian rhythms pervade higher organisms, from the molecular level of the proteins involved in the circadian generation process, to the behavioral level underlying the activity of the whole organism and its interaction with the environment. In mammals, the circadian pacemaker is located in the suprachiasmatic nuclei (SCN) of the hypothalamus, consisting in two paired nuclei containing ~10,000 neurons each. The activity of these neurons is controlled by a genetic circuit that generates an oscillatory behavior for a certain set of clock genes. Experimental techniques such as tagging of clock proteins with fluorescence proteins or bioluminescent assays allow time-resolved studies of the biochemical clock inside the SCN cells, revealing the presence of autonomous rhythms in the individual SCN neurons (1,2). Thus, the circadian activity of the SCN emerges from the interaction of many individual circadian clocks (3–6), which can be entrained by periodic light modulation such as that produced by the natural day-night cycle.

Interestingly, under constant light conditions the SCN cells are only able to produce self-sustained oscillations provided the illumination level is low enough: for increasing light, the circadian clock undergoes a transition from a rhythmic to an arrhythmic behavior (7). Remarkably, this transition from the free-running rhythmic behavior to the arrhythmic one only occurs at the global level (in the mean activity of all cells), while the individual clock cells remain in the oscillatory state. Recent in vitro experiments in explanted mouse SCN (8) have shown that while, in the rhythmic regime, the oscillating clock protein concentration is synchronized among the clock cells, in the arrhythmic regime the cells preserve their oscillatory behavior but lose their synchronization, oscillating with different phases and eigen-frequencies (due to intercell variability).

Thus, circadian rhythmicity at the organism level emerges via a synchronization transition. The fact that increasing light leads to arrhythmicity, and hence to synchronization loss (8), suggests that illumination may have a repressive influence on the strength of coupling among clock cells (9), i.e., the stronger the light, the weaker the coupling. In this scenario, under constant darkness (DD), the single-cell oscillators are strongly coupled, and hence they are synchronized and phase-locked. For higher light levels, coupling is reduced, and eventually the cells lose their synchronization.

Simulations of theoretical models of multioscillator systems have shown (9–12) that just by controlling the internal coupling one can simulate the main properties of a circadian system: modulation of the free running period as a function of coupling strength, entrainment to cyclic changes in coupling, phase response curves, etc. Additionally, if one assumes that coupling is directly controlled by light, the system behaves more realistically and responds to light changes very similarly to real systems, exhibiting properties such as induction of arrhythmicity (as explained above) and plasticity (adaptation of the circadian clock to slow external changes, e.g., during the season or through aging). It obeys the Aschoff rules (according to which nocturnal animals respond to constant light (LL) with a longer free-running period than to constant darkness (DD), whereas the opposite is true in diurnal animals). This suggests that coupling might be a key element in the control and generation of the characteristic properties of any circadian system. The assumption of a light-controlled coupling

*Submitted October 24, 2008, and accepted for publication February 2, 2009.*

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Editor: Arthur Sherman.



0006-3495/09/05/3573/9 $2.00

doi: 10.1016/j.bpj.2009.02.031

does not exclude, but rather complements, the well-known direct effect of light in the individual cells, by emphasizing the importance of synchronization phenomena for the emergence of circadian rhythmicity. Therefore, knowing how light-driven variations in coupling affect the functionality of the circadian system is of great theoretical and practical interest for chronobiology.

In natural conditions, the light levels acting upon an organism (and thus driving their SCN) will be affected by a certain amount of random fluctuations. It is well known that noise may play a constructive role in nonlinear systems, by enhancing coherent (periodic) behavior near bifurcations and phase transitions (13). Here we are interested in studying whether random fluctuations in the lighting profile are able to evoke a sustained circadian rhythmicity in the multicellular clock, under conditions for which the clock is arrhythmic in the absence of noise. The phenomenon is known as coherence resonance (CR) in the stochastic dynamics literature (14). Since the phenomenon occurs close to the rhythmic-arrhythmic transition under constant light, we assume that the only relevant influence of light into the system is through the interoscillator coupling. The direct effect of light on the clock cells can be expected to play a more important role in the case of entrainment to a light-dark cycle. That case, in which noise can be expected to help through a stochastic resonance effect, is not considered below. Assuming that the illumination is related with the coupling strength, we will consider that the noise globally affects the strength of coupling among the oscillators.

The aim of the manuscript is twofold. On the one hand, we discuss a novel mechanism through which noise can have a constructive effect on circadian oscillators, and make an experimental prediction whose potential verification would clarify the assumption of a light-dependent coupling between the circadian oscillators in the SCN. Previous theoretical studies have addressed the effect of noise on genetic oscillators (15–18), and some have proposed an ordering influence of noise on circadian clocks at the single-cell level (19–24). Motivated by the fact that circadian rhythmicity is a collective phenomenon, here we conjecture, in contrast to those previous studies, that noise in the illumination affects the collective rather than the single-cell dynamics of the multicellular clock. To that end, in the next section we introduce the circadian model that we use in our study, which is based on the well-known Goodwin oscillator, extended to account for intercell chemical coupling whose strength depends on the illumination level. Next, we show that this model exhibits a transition in the mean field from a rhythmic to an arrhythmic dynamics. Then we report that noise induces circadian rhythm generation, in a resonant way, as an effect based on the light-dependent coupling.

On the other hand, from a general stochastic dynamics perspective, this study deals with a system of globally coupled nonlinear oscillators affected by noise in the coupling strength. Several previous works dealing with the effect of noise in coupled oscillators have assumed that random fluctuations affect the local phase dynamics (25–27). Here we consider, in contrast, that noise acts upon the coupling between the oscillators, while their individual dynamics are not affected by fluctuations. This situation has been previously studied in relation with noise-enhanced multistability (28), but it is not at all clear whether noise-induced collective coherence can emerge under these conditions. Our results in the circadian model described above show that this is the case. To demonstrate the generality of these results, we present, in the Supporting Material, an analytic study of synchronization induced by global noise in the coupling for the prototypical Kuramoto model. The article ends with a discussion of the applicability of these results to an experimental setting, and of their biological significance.

## The circadian model

We model the circadian pacemaker at the basic genetic level by using a large ensemble of globally coupled nonidentical Goodwin oscillators. The Goodwin model (29) describes circadian oscillations in single mammalian cells by means of three variables. As shown schematically in Fig. 1, a clock gene mRNA ($X$) produces a clock protein ($Y$) which activates a transcriptional inhibitor ($Z$) and in turn inhibits the transcription of the clock gene. All three variables build up a closed negative feedback loop. Gonze et al. (30) replaced the linear degradation by a nonlinear Michaelis-Menten term to overcome the unnaturally high Hill coefficients required for self-oscillations. Additionally, they also introduced a global coupling term depending on the concentration of a synchronizing factor (a neurotransmitter) in the extracellular medium,

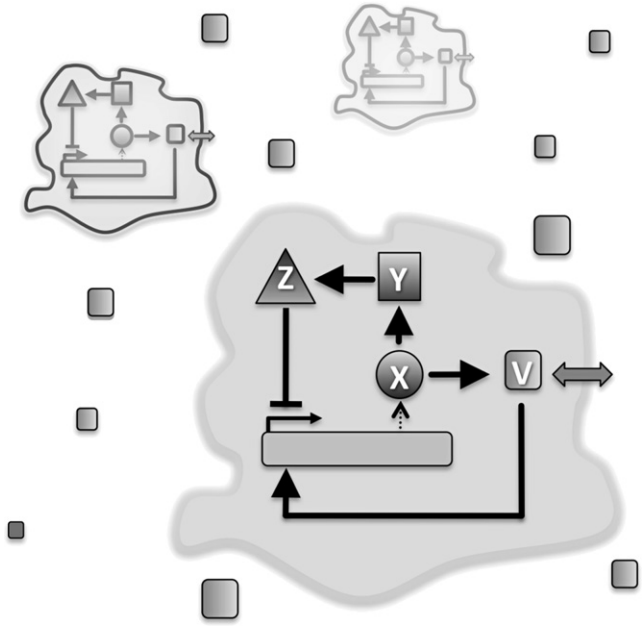


FIGURE 1 Scheme of the core clock genetic network and the diffusive cell-to-cell communication mechanism assumed in the model.

and assumed fast dynamics of the small neurotransmitter molecules in the extracellular medium. Recent experimental evidence (31) supports the assumption of a chemical (rather than, for instance, electrical) mechanism of intercell communication among SCN neurons as a synchronization factor. Possible mechanisms for the SCN communication could involve neurotransmitters (32,33), emphatic communication (direct cell-to-cell electrical influences) (34,35), intercellular chemical gradients ($Ca^{2+}$, glutamate, aspartic) (36), gas diffusible agents (NO, CO) (37–39), chemical fluxes through gap junctions (40,41), special adhesive membrane proteins (42,43), or electrical gradients (44,45). In the model below, we simplify the partially unknown signaling cascade by a small signaling molecule ($V$) which couples the individual oscillators in a diffusive way. The different effective membrane permeabilities for the in- and outflux implement the various possible steps in the signaling cascade. Note, however, that the signaling is more complicated than normal diffusion.

Because of this assumption, the mean signaling molecule concentration positively influences the clock gene concentration. Under these conditions, the resulting model is

$$\frac{dX_i}{dt} = \nu_x \frac{K_t^n}{K_t^n + Z_i^n} - \delta_x \frac{X_i}{K_x + X_i} + \nu_c \frac{\alpha V_i}{K_c + \alpha V_i}, \quad (1)$$

$$\frac{dY_i}{dt} = \nu_y X_i - \delta_y \frac{Y_i}{K_y + Y_i}, \quad (2)$$

$$\frac{dZ_i}{dt} = \nu_z Y_i - \delta_z \frac{Z_i}{K_z + Z_i}, \quad (3)$$

$$\frac{dV_i}{dt} = \nu_v X_i - \delta_v \frac{V_i}{K_v + V_i} - \eta(V_i - QF), \quad (4)$$

and describes the dynamics by means of concentrations in arbitrary units. Here the index $i$ denotes the different cells, and $V_i$ represents the internal signaling molecule concentration of cell $i$. The production rates are represented by $\nu_i$, the degradation rates by $\delta_i$, and $K_i$ values are Michaelis constants. As mentioned above, the release of signaling molecule is supposed to be fast compared to the circadian timescale, which results in an average external signaling molecule level, represented by a mean field $F$,

$$F = \frac{1}{N}\sum_{i=1}^{N} V_i. \quad (5)$$

Gonze et al. (30) considered that the clock gene $X_i$ was directly activated by the mean field $F$. In contrast, here we distinguish between the intracellular signaling molecule, $V_i$, which directly activates expression of $X_i$ (Eq. 1) and whose dynamics is given by Eq. 4, and the extracellular signaling molecule $F$. This coupling mechanism is similar to the one suggested by García-Ojalvo et al. (46) for intercell communication of synthetic gene oscillators via a small autoinducer molecule. In this case, the parameter $Q$ describes the influx of external signaling molecule back into the cell. The fact that the SCN is a relative small and highly dense area with short distances between the cells allows us to simplify the cell-to-cell communication by mean-field coupling.

In models 1–5, the coupling between the individual cell oscillators is determined by the membrane permeability $\eta$ and the relative signaling molecule influx $Q$. We assume in what follows that light affects the signaling molecule influx, and thus we will consider $Q$ as the parameter driving the synchronization transition. The diversity in the eigenfrequencies of the individual oscillators was modeled by rescaling the production and degradation rate constants ($\nu_i$ and $\delta_i$) by a scaling factor $\tau_i$, $i = 1, \ldots, N$, different for each cell. The value of these factors $\tau_i$ is drawn randomly from a normal distribution of mean $\overline{\tau} = 1.0$ and standard deviation $\sigma_\tau$.

Normally, a direct positive influence of the external light on the clock gene transcription $X$ is assumed, which is modeled by an additional term in Eq. 1 (30,47). Under constant light conditions, the direct impact of light on the clock gene transcription would lead to a constant time offset of the transcription rate, but cannot lead to synchronization, and thus it is not relevant for the effect discussed below under LL conditions. Therefore, we exclude that well-accepted pathway of the light in this model, and consider an alternative mechanism in the form of a light-dependent coupling. In the case of entrainment and phase resetting by light pulses, the direct light influence on the clock gene becomes relevant and may mask the alternative synchronization mechanism via the light-dependent coupling. Experiments under constant light give the opportunity for us to investigate this hypothetical second pathway of the light influence on the clock.

## Generation of an overt rhythm through synchronization

In a certain parameter range, the Goodwin model exhibits self-sustained oscillations. In the absence of coupling, the oscillations are uncorrelated, with different periods due to the diversity $\sigma_\tau$ and to different initial phases. For sufficiently large ensembles, the mean response of the oscillators is mostly flat, showing no periodicity despite each oscillator having a clear periodic behavior. This state can be associated with an arrhythmic behavior of mice under constant (and relatively high) illumination levels (8). An increase of the coupling parameter $Q$ leads to the onset of synchronization among the oscillators, and a period close to the mean period of the different individual oscillators appears in the mean field. This self-sustained rhythm generation in the mean field is the manifestation of a circadian overt rhythm in the organism under constant darkness. Stronger coupling leads to a more pronounced synchronization: the behavior of the oscillators becomes more similar, and in parallel, the

amplitude of the mean field increases until a complete synchronization is reached (in the case of perfectly identical oscillators): all cells behave identically to each other and to the mean field. This synchronization effect is the basis of the emergence of coherence in this model, because the rhythm in the mean field is generated by an approximately synchronous dynamics of the individual oscillators. Therefore, we first investigate the transition from the nonsynchronized to the synchronized state as $Q$ increases (i.e., the light decreases). We measure the degree of synchronization $R_{\mathrm{syn}}$ by the ratio of the variance of the mean field to the mean variance of each oscillator (46), defined as

$$R_{\mathrm{syn}} = \frac{\langle \overline{Y}^2 \rangle - \langle \overline{Y} \rangle^2}{\frac{1}{N}\sum_{i=1}^{N} \left( \langle Y_{\mathrm{i}}^2 \rangle - \langle Y_{\mathrm{i}} \rangle^2 \right)}, \tag{6}$$

where the brackets denote time averaging, and the overbar represents an average over oscillators, so that the mean clock protein concentration $\overline{Y}$ is

$$\overline{Y} = \frac{1}{N}\sum_{i=1}^{N} Y_{\mathrm{i}}. \tag{7}$$

According to what we said above, the fully desynchronized state results in $R_{\mathrm{syn}} = 0$, whereas the complete synchronization in the case of identical oscillators corresponds to $R_{\mathrm{syn}} = 1$. Values $R_{\mathrm{syn}}$ close to zero (one) describe states of weak (partial) synchronization. Unless stated explicitly, we use these parameters: $N = 10,000$, $n = 4$, $\nu_{\mathrm{x}} = 0.7$, $\nu_{\mathrm{y,\,z}} = 0.7$, $\nu_{\mathrm{v}} = 0.35$, $\nu_{\mathrm{c}} = 0.4$, $\delta_{\mathrm{x,\,y,\,z}} = 0.35$, $\delta_{\mathrm{v}} = 1$, $K_{\mathrm{t,\,c,\,x,\,y,\,z,\,v}} = 1$, $\alpha = 0.5$, and $\eta = 5$.

Fig. 2(*top*) plots the synchronization degree $R_{\mathrm{syn}}$ versus the coupling parameter $Q$ for various values of the diversity coefficient $\sigma_\tau$. The bottom panel shows the period of the mean field, calculated from the main peak of the power spectrum. The figure shows a transition from the nonsynchronized (arrhythmic, $R_{\mathrm{syn}} \approx 0$) to the synchronized (rhythmic, $R_{\mathrm{syn}} \approx 1$) state as the coupling $Q$ increases, for all diversities $\sigma_\tau$. As the diversity $\sigma_\tau$ increases, the transition point shifts to higher coupling strengths. Note also that a relevant characteristic of this model is that the free-running period depends on the coupling strength. This effect, which influences the behavior of the system under noise, as discussed below, might be a defining feature that could help in validating the model experimentally.

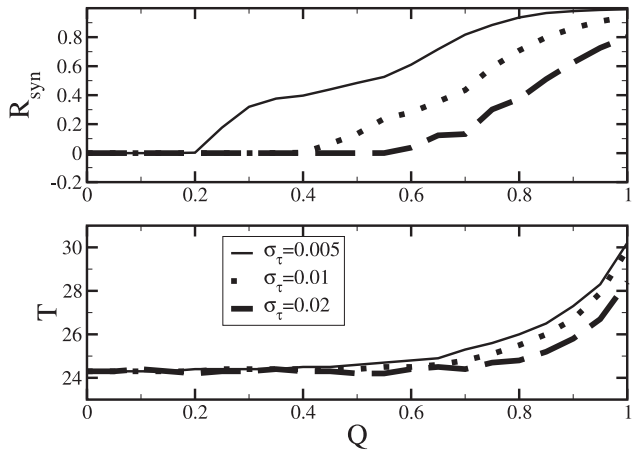


FIGURE 2 Transition from the nonsynchronized to the synchronized state by increasing coupling $Q$ in an ensemble of Goodwin oscillators with Gaussian-distributed diversity, and in the absence of noise. Parameters are given in the text.

## The overt rhythm and the quantification of noise-induced coherence

The mean field of the clock gene $\overline{Y}$ exhibits a sinusoidal dynamics due to the strongly harmonic dynamics of the single Goodwin oscillators. On the other hand, the overt rhythm, which corresponds to, e.g., the motor activity or the body temperature of the organism, has a strongly nonlinear pulse shape. To mimic the experimental results, we calculate the overt rhythm $Y_{\mathrm{or}}$ in the model from the dynamics of the clock protein concentration $Y_{\mathrm{i}}$ by means of

$$Y_{\mathrm{or}} = \frac{1}{N}\sum_{i=1}^{N} [Y_{\mathrm{i}}\Theta(Y_{\mathrm{i}} - Y_{\mathrm{th}})], \tag{8}$$

where $\Theta$ is the Heaviside function. Thus, we assume that only oscillators above a certain threshold $Y_{\mathrm{th}}$ (chosen equal to 0.4 in our case) contribute to the overt rhythm (9). The overt rhythm is qualitatively similar to the mean field (i.e., they have the same rhythmicity) but with more nonlinear elongation and larger amplitude. The use of the overt rhythm as an observable does not affect the results presented below: the CR effect can also be found in the dynamics of the mean field, and does not depend on the arbitrarily chosen threshold $Y_{\mathrm{th}}$. Thus, the overt rhythm is not essential for the noise-induced rhythmicity, but it converts the mean field to a more naturally observed pulsed shape, with fast jumps from rest to activity and vice versa (see Fig. 5 below).

We determine the coherence of the overt rhythm by means of the decay time of the envelope of the autocorrelation function, defined as the time needed by that envelope to decay 30%. The resulting correlation time $\tau_{\mathrm{c}}$ is a measure for the regularity of the rhythm. Qualitatively comparable results can be observed by calculating the coherence time from of the mean field $\overline{Y}$, or by considering the sharpness of the power spectral peak of the overt rhythm or of the mean field.

## Coherence resonance in an ensemble of circadian Goodwin oscillators

Light affects the circadian oscillators and leads under natural day-night conditions to an entrainment to the external driving. Following Díez-Noguera (9), we assume that light has an inhibitory influence on the coupling strength between the cellular oscillators, i.e., an increase in light reduces the

coupling strength. We considered several functional relations between the illumination level and the coupling strength; the noise-induced transition from the nonsynchronized to the synchronized state shown below is unaffected by the specific form of this relation. In what follows, we consider for simplicity a direct relationship between light and $Q$ for our qualitative model. Therefore, a random illumination would correspond to replacing the coupling $Q$ in Eq. 4 by $Q = Q_0 + \xi(t)$. Consequently, that equation governing the signaling molecule dynamics has to be replaced by

$$\frac{dV_i}{dt} = \nu_v X_i - \delta_v \frac{V_i}{K_v + V_i} - \eta[V_i - (Q_0 + \xi(t))F]. \quad (9)$$

The global noise term $\xi(t)$ is assumed to be Gaussian, with zero mean and intensity $\sigma_m^2$ defined by the correlation $\langle \xi(t)\xi(t+\tau)\rangle = \sigma_m^2 \delta(\tau)$. This noise is multiplicative, due to its dependence on the state variable representing the external signaling molecule concentration, $F$. The noise is assumed global because light presumably affects all clock cells similarly.

One of the mechanisms through which CR arises is through a noisy precursor of a Hopf bifurcation (48,49). Therefore, in what follows we fix the value of the coupling strength $Q$ just before the onset of the synchronization transition, in the arrhythmic regime. Under these conditions, random fluctuations in the coupling (i.e., in the external light) allow the cells to surpass momentarily the bifurcation onset and kick the system into the rhythmic regime. A sudden transition (with a steep slope) from the arrhythmic to the rhythmic dynamics enhances the CR effect. On the other hand, for large couplings ($Q > 0.7$) the period of the overt rhythm is seen to depend strongly on $Q$, which is destructive for CR, since the dynamical variability in $Q$ leads to a large variability of the period of the mean response and thus to the reduction of its coherence. Hence, that range of coupling values should be avoided when looking for CR.

As discussed above, we fix the mean coupling $Q_0$ just before the onset of synchronization (Fig. 2), and study the coherence level as the intensity $\sigma_m^2$ of the global noise $\xi(t)$ increases. Fig. 3 plots the synchronization level (*top panel*), as defined by Eq (6), and the coherence level (*bottom panel*), given by the decay time of the autocorrelation function of the overt rhythm, for increasing noise $\sigma_m^2$ and small diversity $\sigma_\tau = 0.005$. Whereas the synchronization increases monotonically with the noise intensity $\sigma_m^2$, the coherence shows a clear resonancelike behavior with a well-pronounced maximum at an optimal noise level—in this case, $\sigma_{m,opt}^2 \approx 0.04$. As expected, an increasing amount of global noise synchronizes the oscillators, which initially leads to an increase in the coherence of the overt rhythm. As the noise intensity increases further, however, synchronization keeps increasing (since all oscillators are driven globally by the noise), but the coherence of the signal decays. Thus, coherence and synchronization are different effects: synchronization is needed for the emergence of coherence, but it is not sufficient. This leads to a CR, which can be seen qualitatively in the dynamics of the overt rhythm but not on that of the individual oscillators. The stochastic nature of the CR effect requires a long time series to obtain statistically significant results. For the figures shown here, we used a long time series of 800,000 h, which cover >33,000 cycles of the circadian oscillators. Furthermore, each simulation started from random initial conditions of the oscillator variables, and a different random distribution of the diversity with standard deviation $\sigma_\tau$.

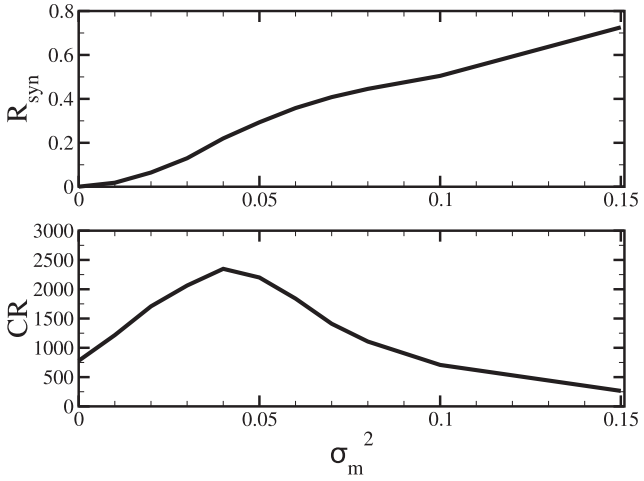


FIGURE 3 Synchronization coefficient (*top*) and coherence level (*bottom*) in a normally distributed ensemble of 10,000 cells for increasing noise. $Q_0 = 0.15$ and $\sigma_\tau = 0.005$, other parameters are given in the text.

The dynamics corresponding to the results of Fig. 3 is shown in Fig. 4, which presents double actograms for three different noise levels, and in Fig. 5, which shows the corresponding time traces of a few individual oscillators (*shaded lines*), the mean field (*dashed line*) and the over rhythm (*solid line*). In Fig. 4, the value of the overt rhythm is color-coded, while both the $x$ and $y$ axes represent time. The $x$ axis runs from 0 to twice a reference time $T_{ref}$, while the $y$ axis represents the number of circadian cycles, up to ~800 cycles of the total time series. In the case of the natural day-night rhythm, $T_{ref}$ can be chosen equal to the period of the external driving, i.e., 24 h. Since we do not have an external period in our case, we fix $T_{ref}$ to a value close to the free-running period ($T_{ref} = 24.5$). In the absence of noise (*left plot* in Fig. 4), the amplitude of the oscillations in the overt rhythm is very small, and thus almost imperceptible. The individual cells are oscillating, but in an incoherent way (Fig. 5 *a*). Stronger noise enhances the coupling, and so increases the amplitude of the overt rhythm (middle plot in Fig. 4 and Fig. 5 *b*). The optimal noise intensity arises as a compromise between a strong coupling (and hence enhanced synchronization and large amplitude of the overt rhythm), and a low destructive influence of the stochastic fluctuations, which reduce the coherence. For large noise levels (*right plot* in Fig. 4 and Fig. 5 *c*), the coherence of

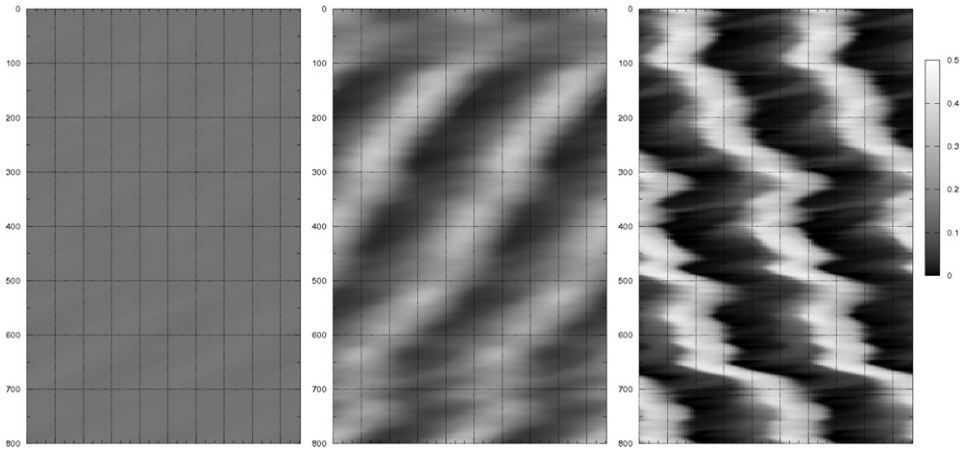

FIGURE 4 Double actograms of the overt rhythm with a reference period $T_{ref} = 24.5$, for three different noise intensities, corresponding to significant points of Fig. 3. The noise intensities are (*left* to *right*) $\sigma_m^2 = 0.0$, 0.04, and 0.1, respectively.

the individual oscillators becomes dominated by the fluctuations, and the resulting loss of regularity is also reflected in the global rhythm.

Fig. 4 also shows that the noise intensity $\sigma_m^2$ affects the average period of the overt rhythm: the larger the noise intensity, the longer the free-running period under LL conditions. This is due to the nonlinear relationship between the coupling $Q$ and the free-running period of the ensemble (Fig. 2, *bottom*), which causes a stronger mean impact of the positive noisy fluctuations of the coupling than the negative ones, leading to a shift of the mean period by noise.

The noise-induced coherence shown above is also present for higher diversity between the oscillators, provided the average coupling is tuned appropriately. This is shown in Fig. 6 for $\sigma_\tau = 0.01$ and $Q_0 = 0.25$ (Fig. 6 *a*) and for $\sigma_\tau = 0.02$ and $Q_0 = 0.4$ (Fig. 6 *b*). In the first case, an improvement of the coherence by a factor of two is observed between the noise-free situation and the optimal noise intensity ($\sigma_{m,opt}^2 \approx 0.05$). Both the absolute coherence and its relative improvement factor decrease with increasing diversity, as revealed by a comparison between these results and those presented above in Fig. 3. The dynamics of the overt rhythm in this high-diversity situation (corresponding to Fig. 6 *a*) is shown in the double actograms of Fig. S2 in the Supporting Material. The less coherence at optimal noise $\sigma_{m,opt}^2 \approx 0.05$ is reflected in the double actogram (*middle plot* in Fig. S2) by shorter straight lines and more zigzags compared to the small-diversity situation (*middle plot* in Fig. 4). The increased diversity thwarts the emergence of synchronization (compare to the *y* axes of the *top panels* of Figs. 3 and 6) and thus the coherence level.

For larger diversities, the transition from the arrhythmic to the rhythmic state occurs at larger coupling strengths (see, e.g., Fig. 2), for which the average period depends strongly on $Q$. In that case, fluctuations lead effectively to an even higher variability among the oscillators, which hinders the coherence. The situation is shown in Figs. 3 and 6 for three different levels of diversity. From those plots, one can see that as the diversity increases, the optimal coherence occurs for smaller values of $R_{syn}$.

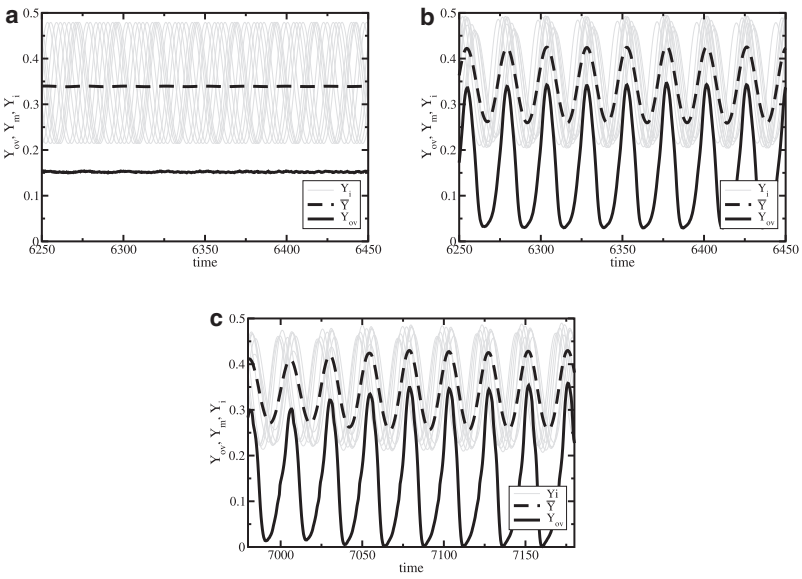


FIGURE 5 Time series corresponding to the double actograms in Fig. 4 with the same parameters: $Q_0 = 0.15$ and $\sigma_\tau = 0.005$. The noise intensities are: (*a*) $\sigma_m^2 = 0.0$, (*b*) 0.04, and (*c*) 0.1. The thin shaded lines show 10 out of 10,000 time traces of the individual clock protein concentrations $Y_i$. The solid line depicts the overt rhythm $Y_{ov}$ and the dashed line the mean clock protein concentration $\overline{Y}$.

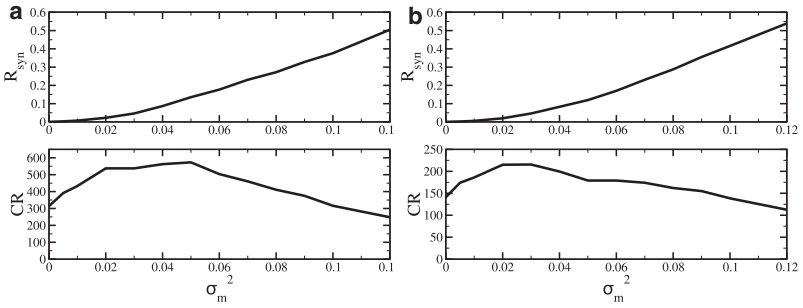


FIGURE 6 Synchronization coefficient (*top*) and coherence level (*bottom*) in an ensemble of 10,000 cells by increased noise. (*a*) $Q_0 = 0.25$, $\sigma_\tau = 0.01$, and (*b*) $Q_0 = 0.4$, $\sigma_\tau = 0.02$. Corresponding double actograms of the overt rhythm for the parameter set in panel *a* are shown in Fig. S2.

## Influence of temporal noise correlation

The concept of white uncorrelated noise is a theoretical idealization. Only in the case of very small correlation time of the noise—compared to the deterministic timescale of the biological system—is the white-noise approximation reasonable. In the case of the entrainment of circadian oscillations by light, fluctuations in the illumination level under natural conditions vary in timescales ranging from seconds to hours, corresponding to fast changes in the environment due to the organism's activity and slow variations due to meteorological conditions (such as clouds), respectively. The influence of these very different timescales of the noisy fluctuations on the entrainment of the circadian clock is not clear. Therefore, we now investigate how the noise-induced circadian rhythm generation described above is affected by the noise-correlation time $\tau_{nc}$. To that effect, we replace the white-noise term $\xi(t)$ in Eq. 9 by an Ornstein-Uhlenbeck noise $\xi_{ou}(t)$, a widely used paradigm for colored noise (50), with zero mean and intensity $\sigma_m^2$ defined by the correlation $\langle \xi_{ou}(t)\xi_{ou}(t') \rangle = \sigma_m^2 \frac{1}{2\tau_{nc}} e^{-|t-t'|/\tau_{nc}}$. The correlation time $\tau_{nc}$ determines the memory of the noisy fluctuations.

Fig. 7 shows how the resonancelike noise-induced rhythmicity arising in the case of small diversity (Figs. 3 and 4) is affected by the noise correlation $\tau_{nc}$. First, it can be seen clearly that the noise-induced rhythm persists in the case of colored noise: a certain noise intensity $\sigma_m^2$ optimizes the rhythm generation for nonzero $\tau_{nc}$. Second, noise correlation reduces the resonance effect in particular and the rhythmicity in general: the best results arise in the case of white noise, and an increasing noise correlation $\tau_{nc}$ diminishes the effect. Our circadian model is therefore much more susceptible to fast fluctuations. One can thus conclude from these modeling results that long correlated fluctuations influence the rhythm generation much less than short ones. From these results, we can conjecture that an experimental observation of the predicted noise-induced rhythmicity would be more likely if the noise added upon the illumination has a correlation time as small as possible.

## DISCUSSION

Herein we have modeled the effect of noise in the illumination acting upon a multicellular circadian clock under constant illumination conditions. Assuming that the most important effect of light in these conditions is through the intercellular coupling, such noise leads to a randomly fluctuating coupling coefficient among the individual circadian clocks. Such stochastic driving has been implemented by means of a modified version of the Goodwin model. Our numerical simulations show that global noise indeed enhances synchronization, which is a necessary condition for multicellular circadian coherence to emerge. Moreover, we have also shown that for large noise coherence is lost, thus leading to a CR phenomenon that exists in a broad parameter range.

The effect is based on the transition of the mean field from an arrhythmic state (in which the mean field exhibits a steady state) to a rhythmic state (of self-sustained oscillations in the mean field) by increasing the coupling coefficient. If the system is placed in the arrhythmic regime but close to the transition to the rhythmic regime, random fluctuations in the coupling, representing light fluctuations, push the system partially and randomly into the rhythmic regime and hence evoke an improved coherent response. The specific form of the transfer function between the coupling parameter and light is not important for the effect to arise.

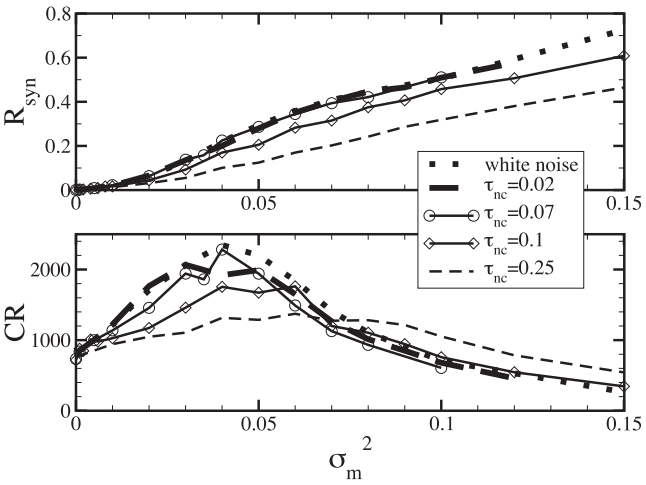


FIGURE 7 Synchronization coefficient (*top*) and coherence level (*bottom*) in a normally distributed ensemble of 10,000 cells for increasing noise for different noise correlation times $\tau_{nc}$. The fixed $Q_0 = 0.15$ and $\sigma_\tau = 0.005$ correspond to Fig. 3; other parameters are given in the text.

The noise-induced rhythmicity becomes manifest in both the mean field of all variables and in the overt rhythm. It is interesting to note that the noise-improved coherence and rhythm generation arise even in the case of weak synchronization, i.e., even when the individual genetic oscillators still have large dynamical variations among them, they are able to generate conjointly a precise rhythm.

Our model assumes that the intercellular coupling is global, given the structural characteristics of the SCN, which is a relatively small and dense area with short distances between the clock cells. We expect, however, that the effect reported here also holds for local coupling, provided the network is sufficiently large and strongly coupled. A detailed investigation of the influence of the network structure and topology would be of general physical interest, but is beyond the scope of this work. Additional general investigations should also consider the influence of diversity on the noise-induced coherence, given, for instance, the recent results by Tessone et al. (51), who have shown that diversity in a coupled network can enhance the coherence.

One may ask about the generality of this phenomenon as a way to address its plausibility in biological systems. Since noise-enhanced synchronization is, as mentioned earlier, a necessary condition, we have examined the universality of the proposed mechanism from this perspective by studying the simplest scenario one can possibly envision: two noisy-coupled Kuramoto phase oscillators (see Supporting Material). These results support the fact that the role played by global fluctuations in the coupling of oscillators is to advance the onset of synchronization with respect to the deterministic case thus indicating the generality of the phenomenon we introduced herein.

Higher organisms such as rats are known to exhibit an arrhythmic state under constant light conditions, and a self-generated internal rhythmicity in constant darkness. Our modeling results could be proved by behavior experiments with mice or rats under constant light conditions. First, one should detect the threshold for the transition from the rhythmic to the arrhythmic regime by increasing the light intensity slowly over several days. Second, the constant light intensity should be fixed in the arrhythmic region, just before the transition to the rhythmic regime. Third, one should add fast fluctuations to the constant light. Our results predict that just before the transition to the rhythmic regime, a circadian rhythm would arise from random fluctuations in the illumination, despite the mean light intensity would evoke arrhythmic response in the absence of noise. This would indicate that the circadian clockwork might have evolved to employ in a beneficial way the unavoidable sources of external random fluctuations to which they are subject.

## SUPPORTING MATERIAL

Two figures are available at http://www.biophysj.org/biophysj/supplemental/S0006-3495(09)00575-X.

E.U. acknowledges financial support from the Alexander von Humboldt Foundation, J.B. acknowledges support by Ministerio de Educación y Ciencia (grant No. FIS2006-01197) and Departament d'Universitats, Recerca i Societat de la Informacio (project No. 2005-SGR/00653), A.D.-N. from Ministerio de Ciencia y Tecnología, Spain (project No. BFI 200303489), and J.G.-O. from the Ministerio de Educacion y Ciencia (Spain, project ORDEN and I3 program) and from Instituto de Salud Carlos III (Spain, project No. RD07/0060/0017). This work has also been supported by the European Commission (project GABA, FP6-NEST contract No. 043309).

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