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Sustainment and Controlment of Noise-Induced Circadian Oscillations in *Neurospora*: Noise and External Signal Effects

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Abstract The effect of light noise on a *Neurospora* circadian clock system in the steady states is investigated. It is found that the circadian oscillations could be induced by light noise, leading to various resonance phenomena including internal signal stochastic resonance (ISSR) and ISSR without tuning in the system. The strength of ISSR could be significantly reinforced with the decrease of the distance of the control parameter to the Hopf bifurcation point of the system. The fundamental frequency of noise-induced circadian oscillations almost does not change with the increment of light noise intensity, which implies that the *Neurospora* system could sustain intrinsic circadian rhythms. In addition, the ISSR and ISSR without tuning could be both amplified, suppressed or destroyed by tuning the frequency or amplitude of external signal.

Keywords Neurospora · Circadian oscillation · Noise · External signal · Stochastic resonance

1 Introduction

Circadian clocks are ubiquitous in living organisms from unicellular plants to mammals including human beings [5, 33, 34]. The oscillations in circadian clocks (i.e., circadian rhythms) play an important role in making living organisms entrain to the 24-h cycle of environment, such that it allows an organism to build up an efficient organization of its daily activity. However, some individuals are difficult to entrain to environment and find themselves struggling with abnormalities of circadian clock, which may occur later or earlier than the usual circadian clock. For example, people with phase-advanced or phase-delayed sleep may encounter difficulties as a result of social requirements, e.g., work or school [27]. Therefore, it is very important for us to find a proper way in the theoretical studies to induce normal circadian rhythms and control the abnormal circadian rhythms. In living organisms,

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circadian rhythms are originated from a genetic control, where a clock protein exerts a repression on the transcription of its own gene [9, 36]. In general, the core mechanism can be described by a *Neurospora* circadian oscillator model [21], which is a typical representation of a class of mechanisms based on autoregulatory negative feedback loops on gene expression. Accordingly, the results, obtained in the *Neurospora* circadian oscillator system, could be extended to other circadian clock systems. Up to now, a lot of studies about the *Neurospora* have been developed [2, 8, 9, 14, 18]. For example, Gonze et al. [13] reported that the various dynamical behaviors, such as quasi-periodicity, entrainment, periods-doubling and chaos, could occur when the light–controlled parameter was periodically forced by light-dark cycles. Very recently, Hou et al. [18] demonstrated that internal noise could induce circadian oscillations and make the oscillations most ordered at an optimal system size in a *Neurospora* circadian clock system. However, to our knowledge, few works have reported that how environment noise, such as light fluctuation, and external signal influence circadian oscillations in a *Neurospora* circadian clock system.

It is well known that noise is unavoidable in real biological system, for example, fluctuations in temperature, light, and humidity can influence the oscillatory behaviors of biological systems. Since the discovery of stochastic resonance (SR) [3], the constructive role of noise has attracted increasing attraction in the last decades [1, 3, 11, 15, 28]. In the phenomenon of SR, the response of a system to a weak, external, and periodic signal is enhanced in the presence of background noise. At first, the cooperative effect of external signal and environment noise is originally considered as a necessary condition for occurrence of SR [12]. Later, the phenomenon of internal signal SR (ISSR) [19], which is also called autonomous SR [31], or coherent resonance [29], was found by replacing external signal with internal signal, i.e., noise-induced oscillations [19, 31] or intrinsic periodic oscillation [22, 37]. Emery et al. [10] pointed out that the fluctuation in light would be introduced into the clock system through *Drosophila* photoreceptors which could transduce light signals to the central oscillator. Yi et al. [35] stated that light fluctuations could give rise to circadian oscillations and the resonance behaviors in *Drosophila* oscillatory system.

In the present work, our attention is focused on studying the influences of light fluctuation for the internal signal transduction by using the mechanism of internal signal stochastic resonance (ISSR), and on controlling the resonance behaviors by modulating the external signal (ES) in a *Neurospora* circadian clock system. There exists many intriguing phenomena, including ISSR and ISSR without tuning in the system at various stable states.

2 Dynamical Model

Herein, in order to investigate the occurrence and transduction of the noise-induced oscillations, we employ a three-variable *Neurospora* model proposed by Gonze [14], which is depicted in Fig. 1. The core mechanism of this circadian rhythmicity relies on the negative regulation exerted by a clock protein (FRQ) on the transcription of clock gene (*frq*) into the clock gene messenger (mRNA), and the translation of mRNA leads to the synthesis of the clock protein. The time evolution of the three variables is governed by the following kinetic equations:

$$\begin{aligned}
\frac{d[M]}{dt} &= \upsilon_s \frac{K_I^n}{K_I^n + [P_N]^n} - \upsilon_m \frac{[M]}{K_M + [M]}, \\
\frac{d[P_C]}{dt} &= K_s[M] - \upsilon_d \frac{[P_C]}{K_d + [P_C]} - K_1[P_C] + K_2[P_N], \\
\frac{d[P_N]}{dt} &= K_1[P_C] - K_2[P_N].
\end{aligned} \tag{1}$$

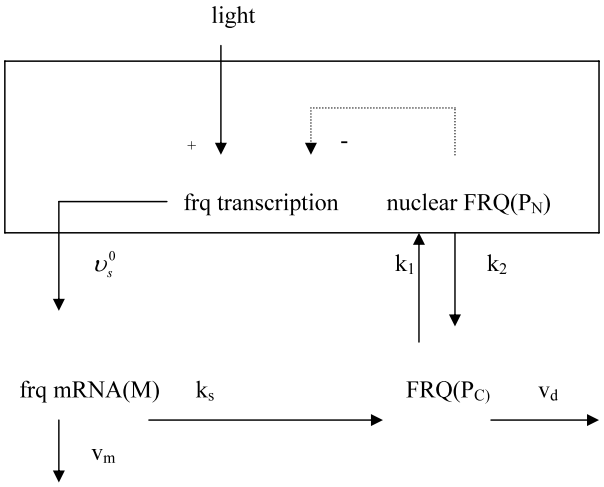


Fig. 1 Scheme of the model for circadian oscillations in Neurospora

Table 1 Parameter descriptions and values used in (1)

Parameter	Description	Value
υ_s	Transcription rate of the clock gene Control parameter	
kl	Threshold beyond which the nuclear protein repress the transcription of its gene	0.2 nM
n	Hill coefficient characterizing the repression	4
nm nMh^{-1}	Maximum rate of mRNA degradation	0.3
km	Michaelis constant related to mRNA degradation	0.2 nM
ks	Translation rate of mRNA to protein	2.0 h^{-1}
nsd h^{-1}	Maximum rate of protein degradation	1.5 nM
kd	Michaelis constant related to protein degradation	0.1 nM
$k1$	Transport rate of protein into the nucleus	0.2 h^{-1}
$k2$	Transport rate of protein out of the nucleus	0.2 h^{-1}

In (1), $[M]$, $[P_C]$, and $[P_N]$ denote the concentrations of the clock gene mRNA, of the cytosolic and nuclear forms of the clock protein, respectively. The parameter υ_s denotes the rate of *frq* transcription, which is called the light-controlled parameter because it increases with light intensity [13]. The other parameters relating to the physical properties of the model are listed in Table 1, and the reaction steps and corresponding transition rates involved in the model are listed in Table 2. Further detailed description and meaning of parameters about this model can be found in Refs. [13, 14, 18]. The system undergoes a supercritical Hopf bifurcation at $\upsilon_s^* = 0.257$. If $\upsilon_s < \upsilon_s^*$, the system is in a steady state, while $\upsilon_s > \upsilon_s^*$, the system is in an oscillatory state.

In this paper, light noise and external periodic signal are added to the light-controlled parameter υ_s. Then the first expression of (1) becomes:

$$\frac{d[M]}{dt} = [\upsilon_s^0 + \upsilon_s^0 D\xi(t) + A\sin(w_e t)]\frac{K_I^n}{K_I^n + [P_N]^n} - \upsilon_m \frac{[M]}{K_M + [M]}. \tag{2}$$

Table 2 Reaction steps and corresponding transition rates involved in the model

Reaction step	Description	Transition rate
$G \to M + G$	Transcription of the clock gene	$W_1 = a_1 V = \frac{\upsilon_s K_I^n}{K_I^n + [P_N]^n} V$
$M \to$	mRNA degradation	$W_2 = a_2 V = \frac{\upsilon_m [M]}{K_m + [M]} V$
$M \to P_C + M$	Translation of mRNA into protein	$W_3 = a_3 V = K_s [M] V$
$P_C \to$	Degradation of cytosolic protein	$W_4 = a_4 V = \frac{\upsilon_d [P_C]}{K_I + [P_C]} V$
$P_C \to P_N$	Transport of protein into the nucleus	$W_5 = a_5 V = K_1 [P_C] V$
$P_N \to P_C$	Transport of protein out of the nucleus	$W_6 = a_6 V = K_2 [P_N] V$

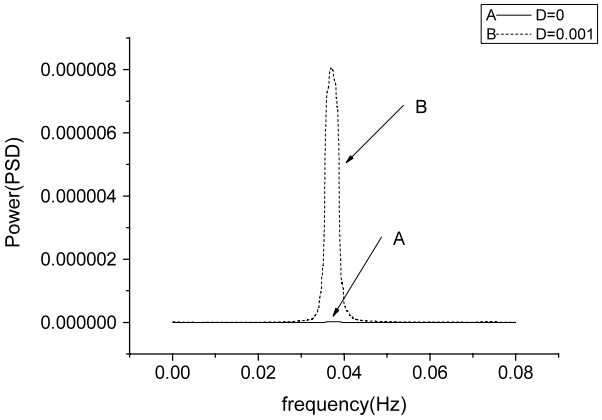


Fig. 2 The power spectrum density (PSD) of the clock gene mRNA at $\upsilon_s^0 = 0.256$ for various noise intensity. Other parameters are shown in Table 1

Where υ_s^0 is a constant value, at which the system lies in a steady state, i.e., the system does not exist circadian oscillation in the absence of external periodic signal and external noise. D is the intensity of Gaussian white noise $\xi(t)$ with zero mean value $\langle \xi(t) \rangle = 0$ and unit variance $\langle \xi(t)\xi(t+\tau) \rangle = \delta(\tau)$. A and w_e denote the amplitude and frequency of the external signal (ES), respectively.

3 Results and Discussion

Equations (1–2) are numerically solved by using Euler method and the time evolution of the system lasts 19 000 t.u. (time unit). To quantify the ISSR effect, the last 16 384 data points are used to obtain frequency spectra by fast Fourier transform. Based on the power spectrum, signal-to-noise ratio (SNR) is defined as $H(\Delta\omega/\omega_f)^{-1}$ [19], where H is the maximum peak height of the spectrum, ω_f is the principal peak frequency, and $\Delta\omega$ is the width of the peak at its half height. Each data is obtained by averaging 20 runs.

3.1 Independence of ISSR on External Signal

When only light noise is added to the *Neurospora* circadian clock system, there is a conspicuous peak in power spectral density (PSD) as shown in Fig. 2, which implies that circadian oscillations can be induced by light noise. It might be the reason that noise could draw

the system from the steady state into the oscillatory region, therefore circadian oscillations could occur and the output signal accordingly exhibits a Gaussian-expanded peak in the power spectrum [17].

The steady states for $\upsilon_s^0 = 0.256$ and 0.253 are chosen as examples to investigate the dynamical behaviors of the *Neurospora* system as shown in Fig. 3(a). The SNR curve for $\upsilon_s^0 = 0.256$ increases at first, reaches a maximum at the optimal noise $(D_{\text{opt}}) = 0.041$, and then decreases as noise intensity increases which qualitatively reflects the remarkable SR-like phenomenon of noise-induced circadian oscillations, i.e., internal signal stochastic resonance (ISSR), while the SNR curve for $\upsilon_s^0 = 0.253$ increases at first, and then displays a "plateau" above $D_{\text{opt}} = 0.101$ with the increment of light noise intensity, which is called ISSR without tuning [6] and suggests that the noise-induced circadian rhythms in the *Neurospora* system can be resistant to the high light fluctuation at appropriate control parameter. Figure 3(b) shows that the fundamental frequency of noise-induced oscillations (i.e., the fundamental frequency of IS) versus the noise intensity for $\upsilon_s^0 = 0.256$ and 0.253, respectively. It could be found that their fundamental frequencies almost do not change as the light noise increases, i.e., their values are about 0.035 Hz. One notes that the IS frequencies of other steady states also do not change with the light noise increasing, and the results are not shown here. The result implies that the *Neurospora* system could be resistant to the influences of light noise and sustain intrinsic circadian rhythms in a certain range of parameters.

Above results indicate that the circadian rhythms can be induced and optimized by light noise. For human being, the disorganized circadian oscillations could lead to circadian clock disorders and various syndromes, such as, phase-advanced or phase-delayed sleep syndromes [27]. The results obtained here might yield insights into the process of curing the circadian rhythms syndromes, e.g., some studies have shown that bright light exposure might correct the circadian rhythms syndromes [7, 32]. Furthermore, we expect that the results could be useful for further understanding other rhythms, such as cardiac, respiratory rhythms.

Now we intensively discuss the phenomenon of "ISSR without tuning" as exhibited in Fig. 3(a). The phenomenon of "ISSR without tuning" for noise intensity could be understood by means of the definition of the SNR as shown in Fig. 3(c), when the noise intensity is less than 0.101, the first factor H and the second factor $(\Delta w/w_f)^{-1}$ both increase with the increase of noise intensity, but H increases more quickly than $(\Delta w/w_f)^{-1}$, which leads to the increase of the SNR with increasing the noise intensity. However, when the noise intensity is equal to or larger than 0.101, H and $(\Delta w/w_f)^{-1}$ are almost constant, which results in the situation that the values of the SNR hardly change with the increase of the noise intensity.

The resonance behaviors have also been investigated for other steady states as shown in Fig. 4. It can be observed that the system at different control parameters would display various resonance behaviors. For example, the system exhibits ISSR for $\upsilon_s^0 \geq 0.254$ and ISSR without tuning for $\upsilon_s^0 < 0.254$. Furthermore, the strength of the resonance increases with the increment of υ_s^0. These phenomena might be explained as follows: with the increment of the control parameter υ_s^0, the distance between υ_s^0 and the Hopf bifurcation point υ_s^* decreases, so the chance for the system to pass across the distance to enter the oscillatory region would increase when the noise intensity is increased from zero, and accordingly the strength of the ISSR would be enhanced. These phenomena indicate that the distance between a steady state and the Hopf bifurcation point could play an important role in controlling the ISSR behaviors in the *Neurospora* system. It is worth mentioning that similar resonant effects at different excitation thresholds have been reported theoretically in Ref. [4] and experimentally in Refs. [16, 30].

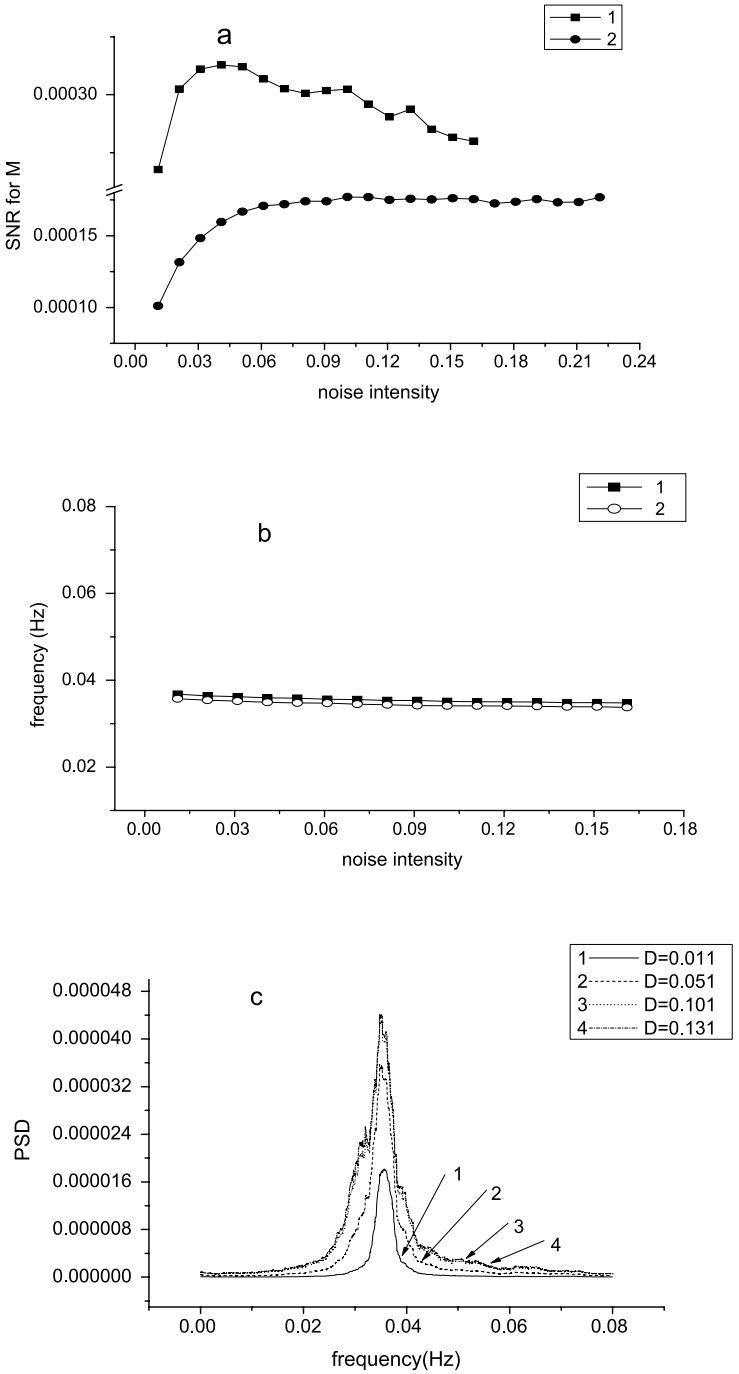


Fig. 3 **a** SNR for the clock gene mRNA vs. noise intensity at $\upsilon_s^0 = 0.256$ and 0.253; **b** The frequency for the clock gene mRNA vs. noise intensity at $\upsilon_s^0 = 0.256$ (*curve 1*) and 0.253 (*curve 2*); **c** The corresponding power spectrum density (PSD) of the clock gene mRNA at $\upsilon_s^0 = 0.253$ for various noise intensity. Other parameters are shown in Table 1

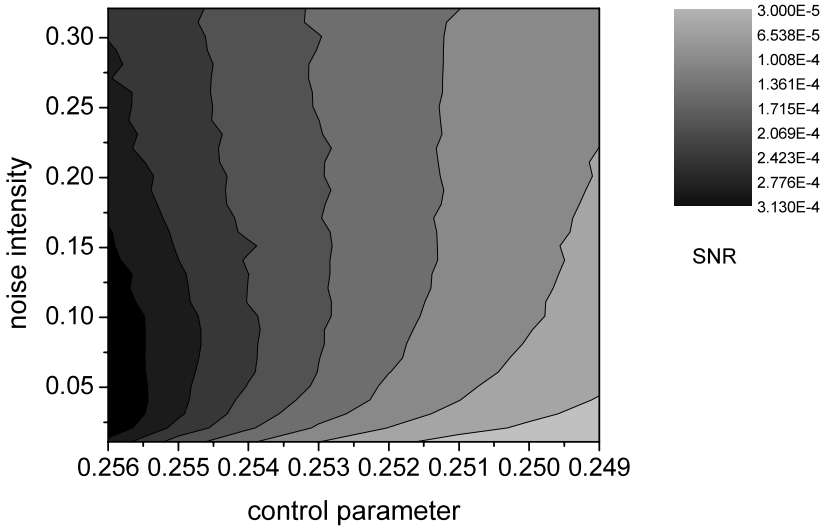


Fig. 4 The contour plot of SNR as a function of control parameter (υ_s) and noise intensity (D). Other parameters are shown in Table 1

3.2 Dependence of IISSR on External Signal

In Sect. 3.1, we demonstrate that the circadian oscillations (circadian rhythms) could be induced to occur by light noise. Especially, those who suffer from the abnormality of circadian rhythms would lead to various syndromes. Therefore, we expect to find a possible way to control the abnormal circadian rhythms. Gammaitoni et al. [11] reported that the SR phenomenon could be controlled by modulating the initial phases of the two signals in a modified Schmitt trigger. In the present work, we will try to control the circadian rhythms by modulating the amplitude (A) and frequency (w_e) of ES.

In Fig. 3(b), the fundamental oscillation frequency of the internal signal (IS) for $\upsilon_s^0 = 0.256$ and 0.253 are both about 0.035 Hz, i.e., $w_i = 0.035$ Hz. Herein, we will, respectively, investigate the phenomenon of ISSR at $\upsilon_s^0 = 0.256$ and 0.253 from the three cases: (1) $w_e < w_i$, $w_e = 0.001$, 0.003 and 0.004 Hz, (2) $w_e = w_i = 0.035$ Hz, (3) $w_e > w_i$, $w_e = 0.1$, 0.3 and 0.4 Hz. The ISSR behaviors in system at $w_e = 0.004$, 0.035 and 0.3 Hz are investigated as examples, respectively. In the first case ($w_e = 0.004$ Hz). The results are displayed in Fig. 5(a) for $\upsilon_s^0 = 0.256$ and Fig. 6(a) for $\upsilon_s^0 = 0.253$, respectively. In Fig. 5(a), the ISSR can only occur at $A = 0.001$, while occur at $A = 0.001$ and 0.005 in Fig. 6(a), which suggests that, when $w_e < w_i$, the influences of ES on the ISSR in the system at $\upsilon_s^0 = 0.256$ is larger than that at $\upsilon_s^0 = 0.253$. In the second case ($w_e = w_i = 0.035$ Hz). It can be observed from Fig. 5(c) and Fig. 6(c) that the ISSR can all occur at $A = 0.001$, 0.005 and 0.01 for two steady states, which implies the ES has the same influences on ISSR for two states. In the third case ($w_e = 0.3$ Hz). The ISSR can occur at various amplitudes of ES for $\upsilon_s^0 = 0.256$ as displayed in Fig. 5(e), while can not occur at any amplitudes for $\upsilon_s^0 = 0.253$ as shown in Fig. 6(e), which suggests that the influences of ES on ISSR in system at $\upsilon_s^0 = 0.253$ is larger than that at $\upsilon_s^0 = 0.256$. The results imply that, when $w_e > w_i$ and $w_e < w_i$, the cooperation effect between the external signal and light noise for two states is oppose to each other, while the same when $w_e = w_i$. Therefore, for the circadian rhythms of $\upsilon_s^0 = 0.256$, the

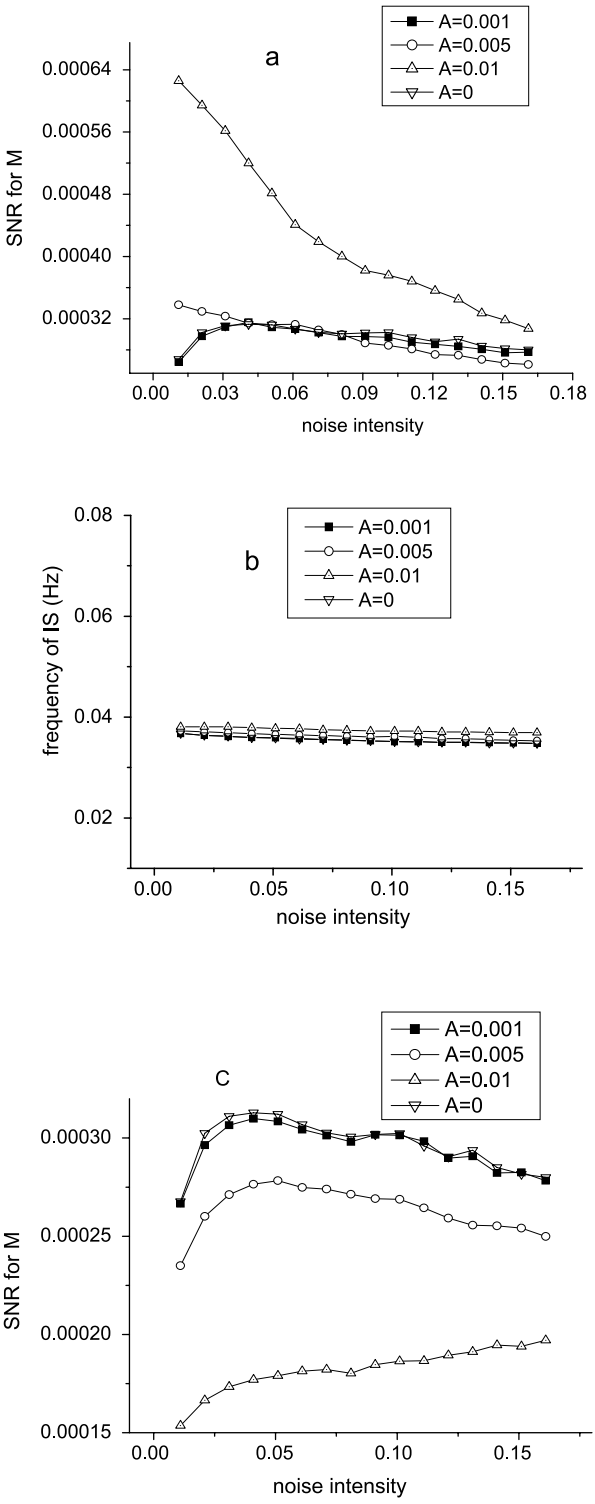
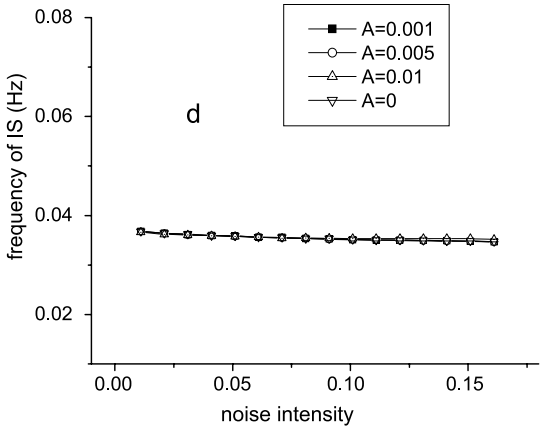
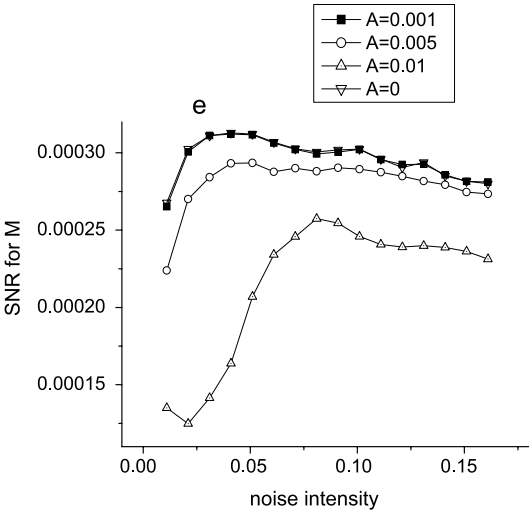
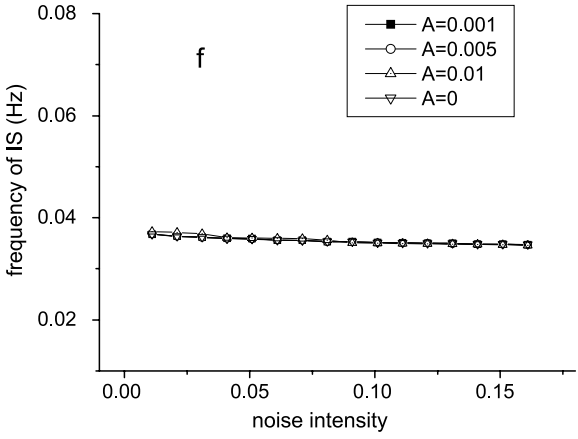


Fig. 5 SNR for the clock gene mRNA vs. noise intensity and the corresponding frequency shift of IS vs. noise intensity at different values of A for $\upsilon_s^0 = 0.256$. **a**–**b** $w_e = 0.004$ Hz; **c**–**d** $w_e = 0.04$ Hz; **e**–**f** $w_e = 0.3$ Hz. Other parameters are shown in Table 1

Fig. 5 (*continued*)







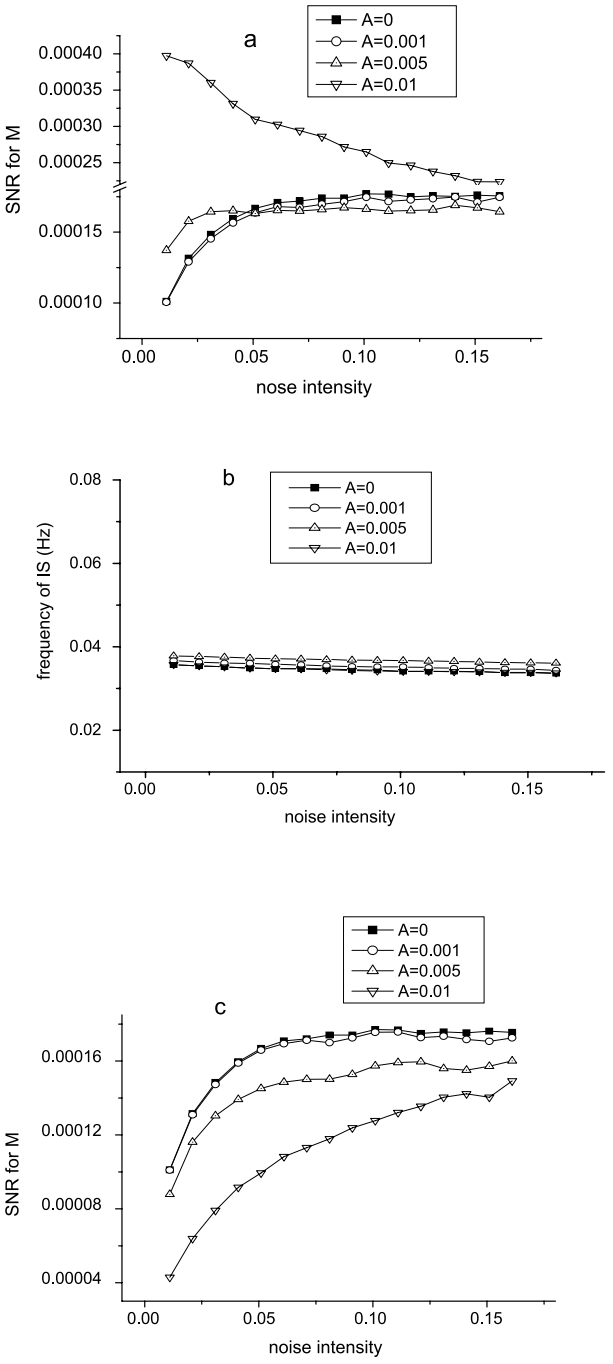
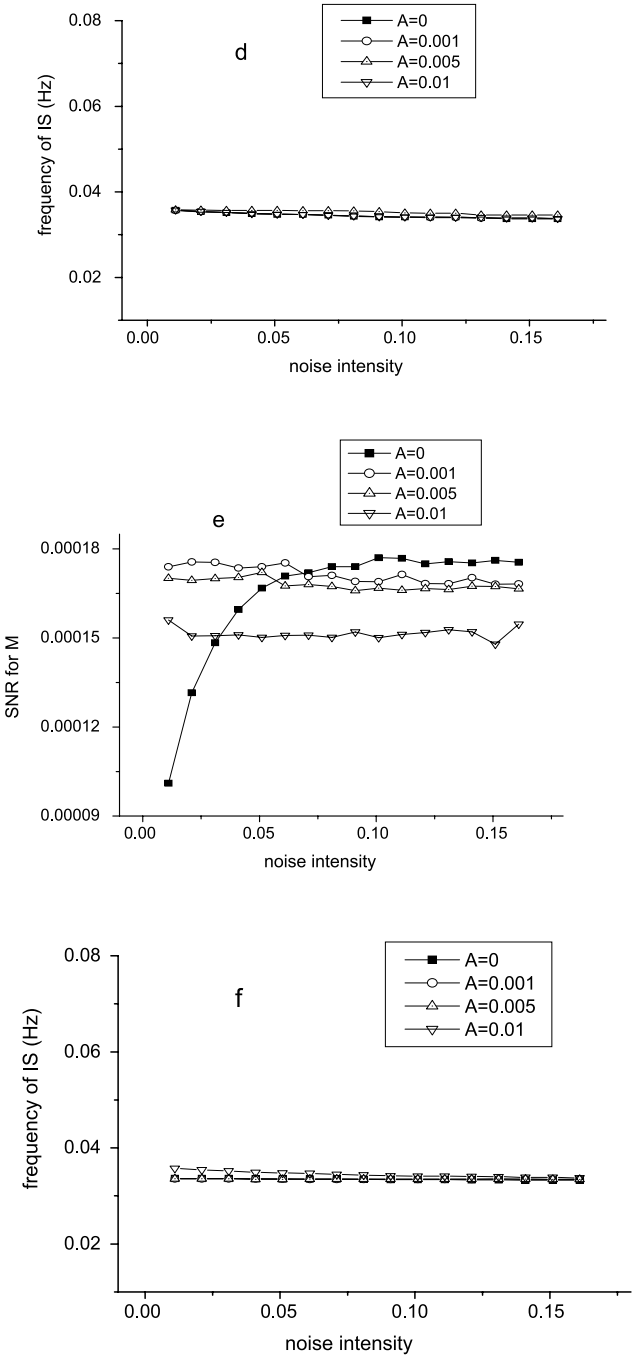


Fig. 6 SNR for the clock gene mRNA vs. noise intensity and the corresponding frequency shift of IS vs. noise intensity at different values of A for $\upsilon_s^0 = 0.253$. **a**–**b** $w_e = 0.004$ Hz; **c**–**d** $w_e = 0.04$ Hz; **e**–**f** $w_e = 0.3$ Hz. Other parameters are shown in Table 1

ES, of which its frequency is smaller than that of IS, is favorable for controlling circadian rhythms of system. Whereas, for the circadian rhythms of $\upsilon_s^0 = 0.253$, the ES frequency which is larger than IS frequency is preferred.

Fig. 6 (*continued*)



Furthermore, from Figs. 5(a), 5(c), 5(e) and 6(a), 6(c), 6(e), it can be found that the ISSR could be suppressed or destroyed by ES. It seems that the ES could play a negative role for ISSR in the *Neurospora* system, which is clearly different from the conclusions

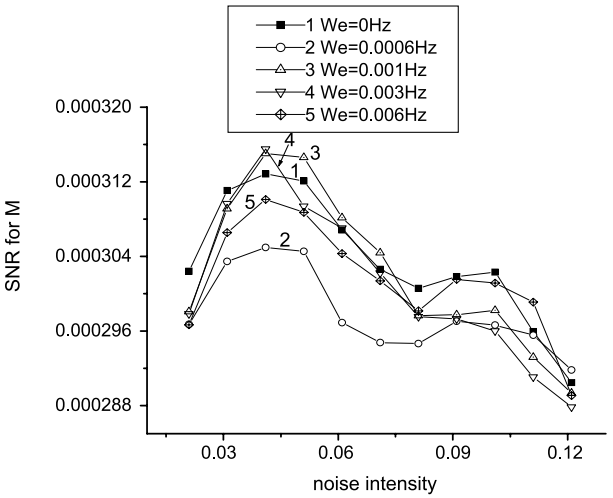


Fig. 7 SNR for the clock gene mRNA versus noise intensity in the case of $A = 0.001$ at different frequency of ES for $\upsilon_s^0 = 0.256$. Other parameters are shown in Table 1

in the previous work [23, 24, 26]. It might be the reason that the ES might destroy the optimal match between noise and nonlinearity in *Neurospora* system, leading to suppress ISSR or destroy ISSR. In order to further confirm the result that ES could play a negative role for ISSR in the *Neurospora* system, we investigated carefully the ISSR phenomenon at different frequency (w_e) with a fixed value of $A = 0.001$ for $\upsilon_s^0 = 0.256$ as shown in Fig. 7. One notes that the similar results are obtained for other A and the results are not shown here. From Fig. 7, It can be observed that, the ISSR is amplified at $w_e = 0.001, 0.003$ (Hz), suppressed at other frequency. That is to say, there may exist a frequency sensitivity range of ES for enhancing the ISSR, which is analogous to the results in the previous work [23, 24]. However, Li et al. [23, 24] reported that the frequency sensitivity range is near the frequency of the internal signal, and in the present work, the frequency sensitivity range is much less than the frequency of the internal signal. The aforementioned results might suggest that the ES might play different influences on the cooperative effect between the nonlinearity and noise for various systems, i.e., the ES of the optimal frequency or a frequency sensitivity range could make nonlinearity of the system cooperatively match with noise, which results in enhancing the ISSR in system, while ES with other frequency might suppress the optimal match between noise and nonlinearity of the system, leading to suppress or destroy the ISSR.

Additionally, from Figs. 5(b), 5(d), 5(f) and Figs. 6(b), 6(d), 6(f), it can be seen that the frequencies of IS are hardly shifted in the presence of the external signal, which implies that the internal signals of this *Neurospora* system could resistant to the influences of the ES, sustain intrinsic circadian rhythms and exhibit strong vitality. The results is in agreement with the Li's results [25] in calciumion oscillations, in which the frequencies of internal signal can not change with the increment of the noise intensity when the external signal is added to the system. We believe that the result could be helpful for us to further understand other phenomena such as signal detection and transduction in biological system [14, 18].

From the results in Figs. 5(a)–6(a), it can be found that the ISSR can occur at some amplitudes and can not occur at other amplitudes, we could supposed intuitively that there exists a critical amplitude (Ac) for occurrence ISSR at different frequency of ES i.e., when $A < Ac$, ISSR occurs and when $A > Ac$, the phenomenon of ISSR disappears. Here, the case of $\omega_e = 0.004$ Hz is selected to further investigate the aforementioned phenomenon and the

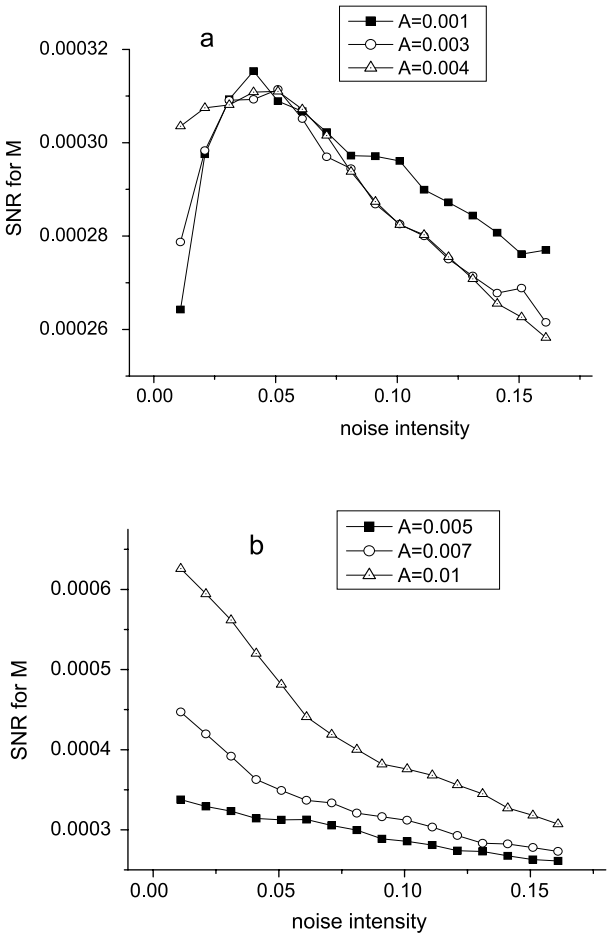


Fig. 8 SNR for the clock gene mRNA vs. noise intensity for $w_e = 0.004$ Hz at different values of A for $\upsilon_s^0 = 0.256$. Other parameters are shown in Table 1

results are shown in Fig. 8. When $A = 0$, 0.001, 0.003, 0.004, the ISSR could be exhibited in the system, while $A = 0.005$, 0.007, 0.01, the ISSR does not appear in the system, which illustrates that $A = 0.004$ is the optimal amplitude Ac for the occurrence of ISSR. It might be the reason that, the optimal matching between the time scale of noise and that of IS would be destroyed by a certain ES with the amplitude above the critical $Ac(0.004)$ or not by the ES with the amplitude below the critical $Ac(0.004)$. The results are in good agreement with the reports of Jung et al. [20] in bistable systems, Li et al. [24] in a coupled hormone system and Li et al. [23] in a model of energy transduction of molecular machinery. It is emphasized that the Ac values for other frequency are also investigated, and the results are not shown here.

4 Summary

The effect of light noise is investigated in the *Neurospora* circadian clock system, where the system is in various steady states. It is found that circadian oscillations could be induced by light noise. Interestingly, the remarkable ISSR could occur when $\upsilon_s^0 \geq 0.254$, ISSR without

tuning when $\upsilon_s^0 < 0.254$. Meanwhile, it is observed that the maximal SNR increases with the decrease of the distance of the control parameter to bifurcation point, implying that the distance could play a key role for controlling the ISSR behavior. Furthermore, whether there exists the ES or not, the fundamental frequencies of noise-induced circadian oscillations hardly change with the increment of light noise intensity, which indicates that the *Neurospora* system could be resistant to the light noise and sustain intrinsic circadian rhythms. In addition, the ES would play a key role in the process of controlling ISSR, i.e., when the ES is added to the *Neurospora* circadian clock system, the ISSR behavior could be amplified, suppressed or destroyed by adjusting the frequency (ω_e) and the amplitude (A) of ES. Moreover, the ES has different influences on the ISSR in the system at $\upsilon_s^0 = 0.253$ and 0.256, and there exists a critical amplitude (Ac) of ES for the occurrence of the ISSR. We believe that the present results are representation for a class of mechanisms based on autoregulatory negative feedback loops on gene express in vivo and are useful for inducement and control the circadian rhythms in other complex biological systems.

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