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Stochastic resonance in circadian rhythms

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Abstract The effect of fluctuations in the two-variable discrete delay model proposed earlier by us [1] for the circadian rhythm of the fungal species *Neurospora Crassa* is studied. We have investigated the effect of parametric and additive noise in two different regimes namely, steady-state and Period-1 regimes. It is found that under the influence of noise coherent oscillations are generated in the steady-state. Oscillations are preserved and robust to a wide range of noise intensity in the Period-1 regime. The oscillations in both these regimes are always found to be close to the circadian period (21.5 h). Coherence resonance is observed when parametric or velocity additive noise is added near the Hopf bifurcation. Finally, the implications of fluctuations in circadian rhythms are discussed.

Keywords *Neurospora Crassa* · Stochastic resonance · Parametric noise · Delay

1 Introduction

One of the fundamental properties of biochemical systems in cells is the preservation of viability under conditions of stress and environmental fluctuations. All biochemical systems are subject to fluctuations. These fluctuations may stem from varying environmental conditions, or from the interaction of biochemical networks. The effect of fluctuations on the dynamical behavior of the system depends on its source. Broadly, it can be classified into two types: (1) Type-P noise and (2) Type-V noise [2]. Type-P noise arises from the environmental perturbations of the system parameters, e.g., the

effect of light on the photosynthesis of plants and the imperfect input control in biochemical systems. Type-V acts on the state variables of the system. Fluctuations in the temperature may cause a change in the reaction velocity. This can also be called velocity-additive noise. In many metabolic systems, the chemical species that play an important role in determining the dynamics of the system are present in different cellular compartments. The incomplete mixing of these species may give rise to fluctuations. Further, the fluctuations in environmental temperature of metabolic systems may induce changes in the velocity of enzymatic reactions abruptly.

It is well known that the interplay between deterministic non-linear dynamics and noise can lead to non-trivial phenomena such as noise-induced transition [3] and stochastic resonance [4]. In the case of noise-induced transition, the noise takes the system from one state to another new state and the system remains in the new state even after the noise is removed from it. Stochastic resonance is the amplification of a weak signal by the simultaneous application of a weak periodic signal and noise. Further, the amplification of the weak signal persists as long as the noise with certain intensity is applied to the system. Many workers have paid considerable attention to the counter intuitive phenomena of stochastic resonance, in which noise plays a constructive role [5]. Recently, it has been shown that non-linear systems in the presence of noise can display stochastic resonance-like behavior, even without the external periodic signal [6–8]. These phenomena are called autonomous SR, coherence resonance, or internal signal stochastic resonance (ISSR). ISSR was first discovered by numerically investigating the model that exhibits saddle-node (SN) bifurcation [6]. When the control parameter is modulated near the saddle-node bifurcation point by noise, noise-induced coherent oscillations (NICO) and noise-induced shift in frequency occur. This is ascribed to the non-uniformity of the limit cycle. It is possible to quantify the intensity of noise that can bring about coherent oscillations by determining its signal-to-noise (SNR) ratio from the power spectrum. SNR is used as a measure of the coherence of the oscillations. It is measured by the relative height of the peak in the power spectrum. The more appropriate

This article is dedicated to Professor Karl Jug on the occasion of his sixtyfifth birthday.

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measure of SNR is $h/\delta\omega$, where $\delta\omega$ is the width of the peak at the height $h/2$. Later, Xin and co-workers demonstrated numerically [9, 10] and experimentally [11] the occurrence of NICO in BZ reaction.

One of the major motivations of SR studies is its applications in biology, especially in neuronal [12] and circadian systems [13]. The effect of noise on biological rhythms has been studied previously both experimentally and theoretically by Beck et al. [13]. These authors have studied the influence of noise on endogenous rhythmicity in the special case of photosynthesis oscillations in plants performing crassulacean acid metabolism (CAM). These authors showed that noise plays a constructive role, giving rise to coherence resonance in the rhythmicity of CO_2 intake and uptake in cell vacuole.

The goal of the present investigation is to study the effect of noise in the two-variable delay model of circadian rhythms of the fungal species *Neurospora crassa* proposed by us [1]. The basic idea behind the model is that the dynamical effects of complex networks can be represented by time-delayed variables. This delay model exhibits rich dynamics such as quasiperiodicity and chaos apart from circadian oscillations of period 21.5 h. In this model, we have introduced noise in two distinct regimes: (1) steady-state (2) Period-1 regime. It is found that in both these regimes, oscillations close to the circadian period are retained. Based on these observations, we conclude that noise plays a constructive role in not only amplifying the signal (where, in genetic networks it is the increase in protein concentration) but also maintains the circadian period with almost constant amplitude.

This paper is organized in the following way. Section 2 briefly describes the biological circuit and the mathematical model with time delay. Section 3 describes the effect of noise near the steady-state when Type-P noise is introduced. Section 4 describes the effect of Type-V noise near Hopf bifurcation and in the periodic regime and our main findings are summarized in Sect. 5.

2 Brief description of Delay model

In the *Neurospora* frq- wc-based circadian loop, two transcription factors, WHITE COLLAR-1 (WC-1) and WC-2, form heterodimeric complexes WCC, to activate the transcription of frequency [frq] gene [14–17], whereas the two forms of the FREQUENCY (FRQ) protein form homodimeric complexes that feedback to repress the transcription of FRQ, by interacting with WCC complexes [18–25]. In addition to its role in repressing FRQ transcription, the FRQ protein positively regulates protein levels of WC-1 and WC-2, thereby forming a positive feedback loop interlocked with a negative feedback loop [16, 23, 25]. Hence, the two important clock genes are FRQ and *wc-1* genes. We have in our delay model considered only the protein–protein interaction of FRQ and WC-1 and not the DNA–protein interactions. Thus, ours is a reduced model consisting of only two dynamical variables, namely FRQ and WC-1 proteins.

The dynamics is described by the following set of delay differential equations:

$$\frac{dr_1(\theta)}{d\theta} = \frac{q_1}{1 + r_1(\theta - \epsilon_1)^n} + \frac{r_2(\theta - \epsilon_2)}{q_2 + r_2(\theta - \epsilon_2)} - q_3 r_1 \quad (1)$$

$$\frac{dr_2(\theta)}{d\theta} = \frac{q_4 r_1(\theta - \epsilon_3)}{q_5 + r_1(\theta - \epsilon_3)} - q_6 r_2 \quad (2)$$

Here, all quantities are reduced to dimensionless variables and constants. r_1 and r_2 are the FRQ and WC1 protein concentrations and θ is the dimensionless time. The first term on the rhs of Eq. (1) represents the rate of self-repression of FRQ, the second term the activation of FRQ by WC1, and the last term the first-order degradation of FRQ. Similarly, in Eq. (2), the first term on the rhs is the rate of activation of WC-1. The repression and activation processes are taken to be time delayed, the delays being denoted by $\epsilon_{1,2,3}$. The delays represent the time involved in various intermediate steps such as translation, phosphorylation, transport into nucleus, complexation etc. n is the so-called Hill's coefficient representing the degree of co-operativity of the FRQ repression process. q_1, \dots, q_6 are dimensionless constants.

In the present simulation, the following parameter values have been used: q_1 is taken as a variable parameter to simulate different values of light intensity. $q_2 = 6; q_3 = 0.15; q_4 = 1; q_5 = 6; q_6 = 0.2; n = 4; \epsilon_{1,2,3} = 16$ and q_1 is the light-sensitive variable parameter. Here, θ represents the dimensionless time. The above system of delay differential equations was solved and the corresponding bifurcation diagram constructed with q_1 as the bifurcation parameter using the software DDEBIF-TOOL [26] (See Fig. 1).

The bifurcation diagram can be interpreted in the following way. The stable node corresponds to the synthesis of constant protein concentration, while stable limit cycle corresponds to both the synthesis and destruction of protein levels. In the experimental system, proteins are both synthesized and destroyed. So, the constant protein concentration

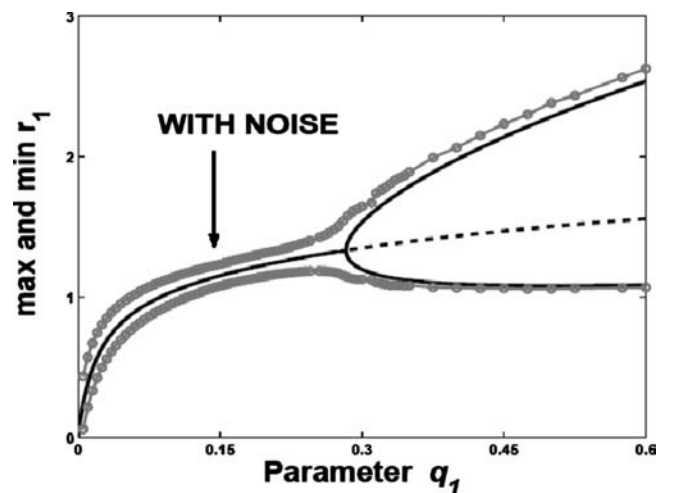


Fig. 1 Effect of Type-P noise on the bifurcation diagram of *Neurospora Crassa*: dark line is the bifurcation diagram without noise for parameter q_1 . The grey plot is the same diagram with Type-P noise intensity $D_p = 0.1$.

may correspond to a pathological or mutant system. Since in our model we have considered only the wild type and not any mutant phenotypes, there should be always some fluctuating protein concentration ever present in the system. The fluctuations can be introduced by converting the system of delay differential equation into stochastic delay differential equation. It is possible to quantify the intensity of noise that can bring about coherent oscillations with circadian period by determining the SNR ratio. A plot of SNR versus noise intensity gives a non-monotonic behavior, which is a signature of stochastic or coherence resonance. The noise intensity at which SNR attains its maximum gives the amount of noise that can be introduced in the system where noise plays a constructive role and above which the system is swamped by noise.

With the above facts in mind, the dynamics of the oscillator driven by external noise near the Hopf bifurcation as well as in other regimes are investigated. A Gaussian noise, $\eta(\theta)$, is introduced into the system, with $\langle \eta(\theta) \rangle = 0$ and $\langle \eta(\theta) \eta(\theta - \theta') \rangle = 2D \delta(\theta - \theta')$ with D being the noise intensity. Noise is added to the system in the following two different ways:

- (1) Type-P, i.e., parametric noise is added to the light sensitive parameter q_1 as $q_1 = q_0 + \eta(\theta)$, where q_0 is the steady-state value of q_1 in the absence of noise.
- (2) Type-V, i.e. velocity noise is added to both velocity component r_1 and r_2 .

$$\frac{dr_1}{d\theta} = f(r_1, r_2; p) + \eta_1(\theta) \quad (3)$$

$$\frac{dr_2}{d\theta} = g(r_1, r_2; p) + \eta_2(\theta). \quad (4)$$

Here, f and g represent the right-hand side of Eqs. 3 and 4, with q_0 taken at the steady-state value. Noise terms $\eta_1(\theta)$ and $\eta_2(\theta)$ have intensities D_{v1} and D_{v2} , respectively. The noise intensity is denoted as D_{v12} when added to both the components simultaneously.

- (3) The simultaneous effect of Type-P and Type-V noise is also studied.
- (4) Finally, the effect of Type-V noise in the periodic regime is also investigated.

In the following sections, the results of these studies are discussed.

3 Effect of Type-P noise near the Hopf bifurcation

To study the effect of noise when the system is close to the Hopf bifurcation, the control parameter q_0 was chosen to be in the vicinity of the supercritical Hopf bifurcation i.e., at 0.265, which is a stable node (Fig. 1). It is then perturbed by a Gaussian noise with noise intensity D_p . For $D_p = 0$, the deterministic oscillation is absent as the system is at a stable node. When D_p is increased to a certain level, oscillations start appearing (Fig. 2.a). Further, a broad peak in the power spectrum is seen, indicating the occurrence of NICO (Fig. 2.b).

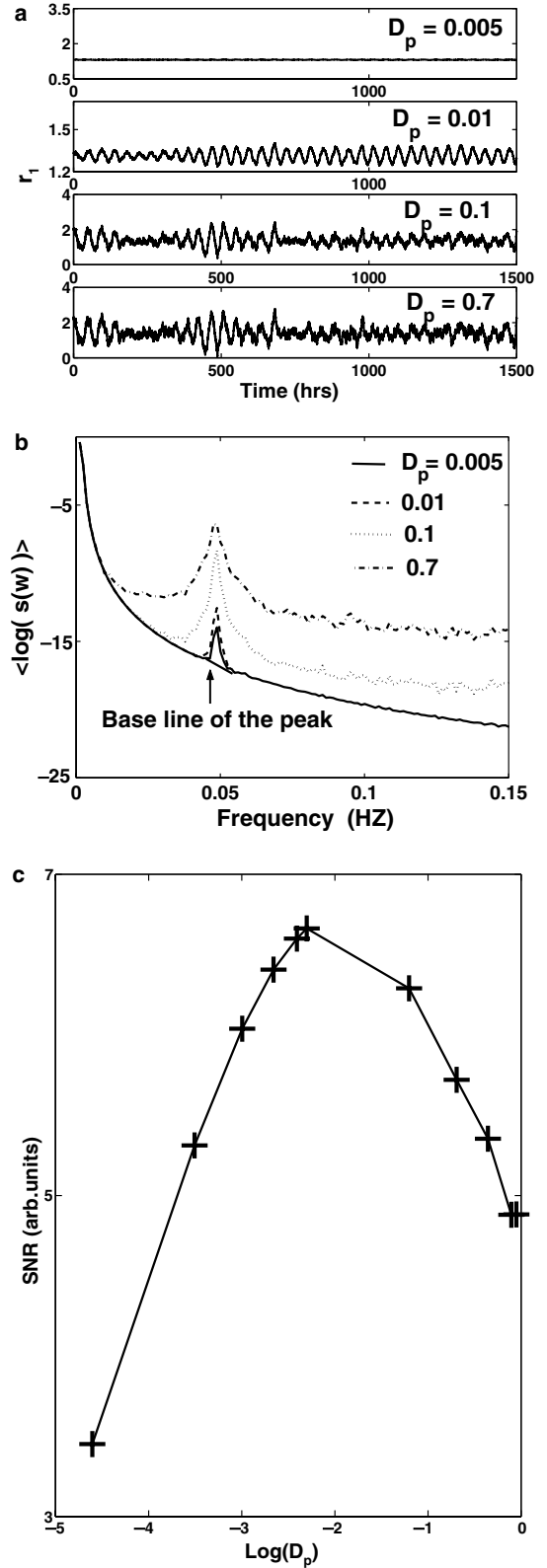


Fig. 2 Stochastic resonance in *Neurospora Crassa*. (a) typical time series of the delay equations activated by various noise intensity when added to the parameter q_1 . (b) the corresponding power spectrum and the height is measured from base line shown in the panel. (c) plot of SNR versus D_p .

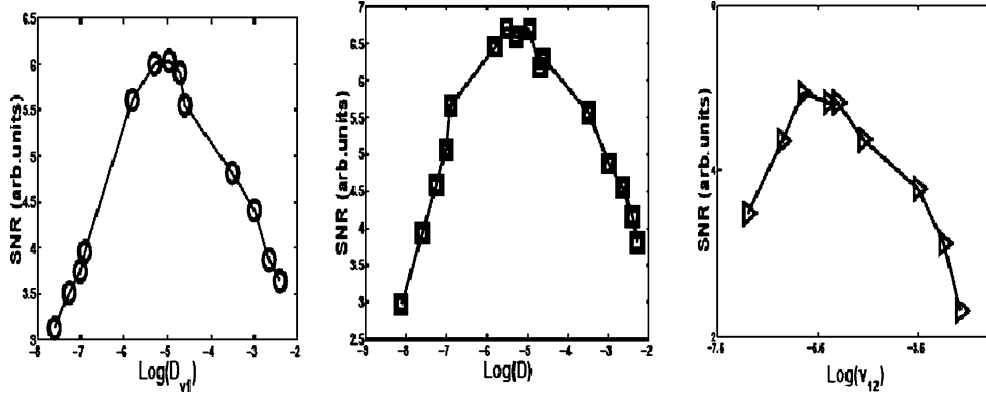


Fig. 3 Signal-to-noise-ratio versus logarithm of noise intensity added as in Eq. 3 (left panel), as in eq. 4 (middle panel) and simultaneously as in Eqs. 3 and 4 (right panel)

The increment in noise intensity enhanced the NICO strength, which reaches a maximum and finally gets swamped in the noise background. This behavior is the signature of stochastic resonance. Fig. 2.a shows a typical part of the time series of noise-induced oscillations for various noise intensity. Fig. 2.b shows the typical power spectrum that was obtained by averaging over 100 independent runs. Fig. 2.c shows the plot of SNR versus D_p .

The reason for the occurrence of noise-induced oscillations is that noise lets the system randomly visit the oscillatory region. The coherence of noise-induced oscillations produces an expanded peak in the Fourier spectrum. In conventional SR with an external periodic signal, the noise-induced oscillations produce delta-like peaks in the Fourier spectrum [5]. Here, the term SNR is used to express the coherence of the oscillations. It is measured as $h/\delta\omega$ taking $\delta\omega$ to be uniform and h as the height from the base of the peak.

The most important aspect of NICO is that in the deterministic model, oscillations are not present in the parameter range considered in the absence of noise. However oscillations arise in that range as noise is introduced (See Fig. 1). Further, the period of the noise-induced oscillations (21.05 h) is found to be close to the circadian period of *Neurospora* (21.5 h). This is the noise-induced frequency shift and may be due to the non-uniformity of the limit cycle [See Ref. 6]. Thus, noise creates a new oscillatory dynamical regime where it is a stable node in the absence of noise. As the bifurcation parameter q_0 is increased from a lower value, the amplitude of the oscillations is increased and close to the original bifurcation point the amplitude is appreciably large. This can also be seen in Fig. 1.

4 Effect of Type-V noise near the Hopf bifurcation

Type-V i.e., velocity-additive noise is added to the system and the stochastic delay equations are integrated by means of the stochastic Euler method. The stochastic Euler method [27] is given by

$$x(\theta + \Delta\theta) = x(\theta) + \Delta\theta f(x) + \sqrt{\Delta\theta} \eta(\theta), \quad (5)$$

where $\Delta\theta$ is the time step and $\eta(\theta)$ the Gaussian noise of intensity D . Noise is added to velocity components separately as well as simultaneously as shown in Eqs. 3 and 4. In all these three cases, we observe stochastic resonance. The plots of SNR versus noise intensity D_{v1} , D_{v2} , and D_{v12} are shown in Fig. 3. There is a non-monotonic behavior for SNR with the increase in noise intensity, suggesting the occurrence of stochastic resonance. Thus, Type-V noise also induces NICO. Furthermore, when noise is added to both the parameter and the velocity component simultaneously, stochastic resonance is observed. A 3-D plot of SNR versus the noise intensity D_{v12} and D_p is shown in Fig. 4. This clearly shows that stochastic resonance occurs over a wide range of noise levels in the parameter as well as velocities.

4.1 Effect of Type-V noise on Period-1 oscillation

The system studied in the earlier sections is the single threshold system associated with the Hopf bifurcation and the occur-

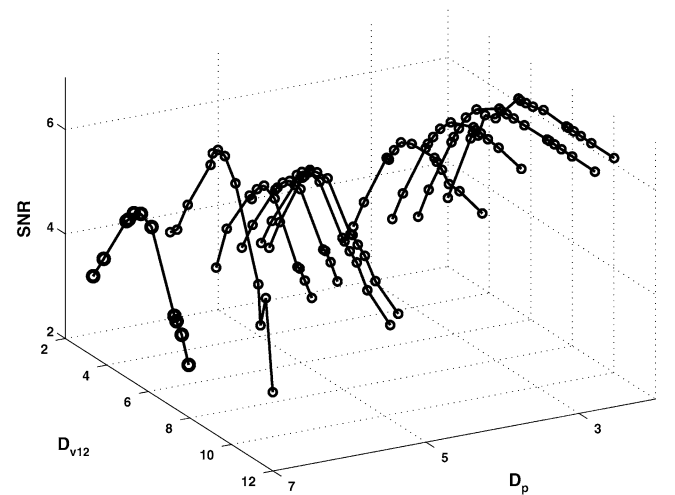


Fig. 4 Signal-to-noise-ratio for Type-P (noise intensity- D_p) and Type-V (noise intensity- D_{v12}) noise added simultaneously to both components and the maximum of SNR and its corresponding D_p and D_{v12}

rences of ISSR are closely related to NICO generated by crossing bifurcations. Recently, ISSR has been observed by a simulation of Belousov–Zhabotinskii (BZ) reaction model, in which the dynamical region of periodic regime was subjected to additive Gaussian white noise [28]. In the three-variable BZ reaction model, Type-V noise was added separately to the three equations. In all the three cases, for the Ce(IV) variable, ISSR occurred without crossing of any bifurcation regime. ISSR occurs because of the intrinsic Period-1 oscillation of the non-linear system. This type of stochastic resonance is called as explicit ISSR because the signal is the intrinsic deterministic Period-1 oscillation of the system.

In the present study, Type-V noise is added to the Period-1 dynamical regime of the *N. crassa* to look for the occurrence of explicit ISSR. Noise is added as per Eqs. 3 and 4 in the Period-1 dynamical regime to each velocity component separately as well as simultaneously to both the components. When the noise intensity is modulated, it is found that the circadian system did not exhibit any explicit ISSR. There is no change in SNR in all the cases up to high noise levels. This is shown in Fig. 5. The oscillation is robust and no synergetic effect is seen between the noise and the deterministic system. This points to the fact that in the Period-1 regime the system is robust for a wide range of noise intensities. Only for very large noise intensities SNR falls drastically (Fig. 5), which may correspond to a pathological system.

5 Summary and conclusions

Random fluctuations are ever present in the biological system either due to the perturbation from external environment (External noise) or due to the presence of low molecular numbers (Internal noise). We have studied in this paper the effect of external noise both on the parameter and on velocity equation in the delay model for the circadian rhythm of *N. crassa*. Noise-induced coherent oscillations (NICO) are observed when Type-P and Type-V noise are added to the

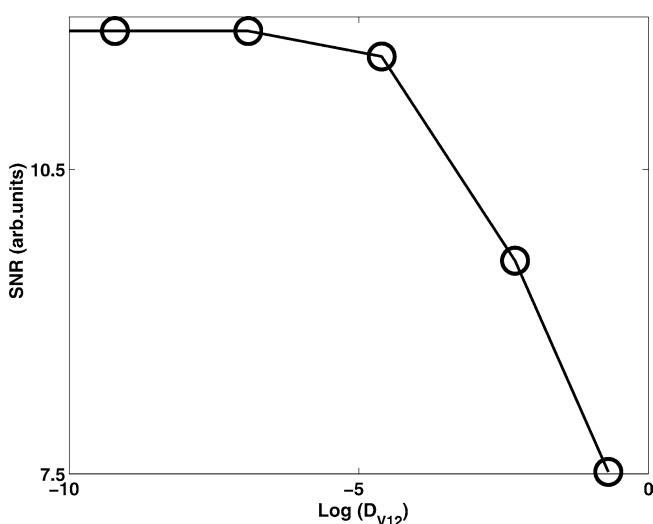


Fig. 5 Signal-to-noise-ratio for Type-v noise added to Eqs. 3 and 4. simultaneously in the periodic regime

two-variable delay model for the circadian rhythms of fungal species *N. crassa*, when present in the non-oscillatory stable steady-state. Both types of noise give rise to internal signal stochastic resonance (ISSR). However stochastic resonance is absent when applied to the period-1 dynamical regime, i.e., explicit internal signal stochastic resonance (EISSR) is absent. The average power spectrum in all these cases showed that the period of the circadian rhythms is always close to the natural period even in the presence of noise.

It is not surprising to find that noise brings about coherent oscillations and thereby exhibits stochastic resonance, as it is well documented in the literature. But what is surprising is that irrespective of the type of noise added to the system, coherent oscillations close to circadian period of *N. Crassa* i.e., 21.5 h is always maintained. Further, when noise is added to the Period-1 regime, it is found to be robust for a wide range of noise intensities, suggesting that the system always tries to retain its circadian period even under drastic fluctuations.

From this study, it is clear that one can use the concept of stochastic resonance to quantify the amount of noise that the system can tolerate while maintaining its periodicity. These conjectures remain to be verified by experimentation. Two important aspects remain to be taken up in future work. In the present work, noise is introduced with a constant delay. It is well documented in the literature that feedbacks and delays [29] reduce the fluctuations. It is also well known that delays can make a stable system unstable and vice versa [30] and will be worthwhile to study the effect of variations in delay that occurs in positive and negative feedback loops in conjunction with noise. Another interesting aspect that remains to be studied is the effect of noise that couples different circadian cells under the influence of 12:12 LD cycle, which may bring about synchronization. Synchronization has been extensively studied in many physical, chemical, and neural systems in terms of both deterministic and random dynamical system theories (See ref [31] for a comprehensive survey), but very little in chronobiology. Synchronization of the endogenous circadian rhythm to exogenous LD cycle is a very important aspect that may have several implications in physiological disorders like non-24 h sleep-wake syndromes [32].

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