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Synchronization Behaviors in Goodwin Oscillator Networks Driven by External Periodic Signals

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Abstract— **In this paper, we present a systematic approach based on harmonic balance method to study the induced oscillations in a class of Goodwin oscillator networks forced by external periodic signals. Analytical expressions on the dependence of the phases and amplitudes of network oscillations to those of forcing inputs are revealed. Based on those expressions, we further show that under some specific conditions, the amplitude and phase shift of synchronized oscillations in networks of Goodwin oscillators monotonically depend on the amplitude of exciting inputs. The theoretical results are then illustrated through some examples.**

I. INTRODUCTION

In mammals, the circadian timing system has a master clock network in suprachiasmatic nucleus (SCN) which coordinates the circadian rhythms and regulates the peripheral circadian clocks [1], [2], [3], [12], [15]. Moreover, the master circadian network is directly entrained by the daily Light-Dark cycle through the retina which shows an important property of the circadian system that it is entrainable by the periodic factors called zeitgebers in which light is the main zeitgeber [12], [18], [19], [20]. From the control system viewpoint, we can consider the circadian network as a dynamical system forced by an external periodic input representing the zeitgeber referred as the Light-Dark cycle in this paper. Without external inputs, that dynamical system itself exhibits an autonomous periodic oscillating pattern. Hence, a natural question raises up that how the oscillations produced by the system in presence of exciting periodic inputs look like. Particularly, it is worth seeing how the amplitudes and phases of induced oscillations in the system relate to those of exciting inputs.

Researches in biology community show that under the effect of Light-Dark signal, the oscillations in the circadian network are synchronized with frequency equal to the frequency of Light-Dark signal. Furthermore, there exists a phase shift between synchronized circadian oscillations and Light-Dark signal [2], [12], [13]. In [18], the phase shift was shown to be increasingly leading toward long periods and lagging toward short periods. There are also evidences from experiments, for example in older rats that to increase the amplitude of circadian oscillations to a desired level requires an increase in amplitude of Light-Dark signal [12]. However, the biological mechanisms under that phenomena have not been yet well understood, although there are some researches on circadian rhythms based on dynamical system theory. They mostly focus on the synchrony of circadian oscillations and only a few papers deal with the dependence of amplitude and phase shift of circadian oscillations to external inputs. [14] studied the synchronization of circadian oscillators described by a modified Goodwin model where the oscillators communicate through a mean-field. The research in [4] focused on how the period of circadian rhythm and the temperature compensation depend on the stability of FRQ-protein. The sync rate in a simple phase model which may be used for circadian network was investigated in [16]. Leloup et al. [5] investigated the effect of light's magnitude to the phase shift of circadian oscillations with some models of circadian rhythms in Drosophila and Neurospora, but no analytical relation was obtained.

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We present, in this paper, some analytical results on the relation between amplitude, phase shift of synchronized circadian oscillations and frequency, amplitude of periodic forcing inputs. The Goodwin model is used for circadian oscillators since it describes a biological process with a negative feedback loop which is shown to be one of the core molecular regulatory mechanisms for circadian oscillations [2], [13], [14]. In [17], a similar model was employed to study the collective frequency of inter-coupled circadian oscillators. In other words, [17] only focused on the frequency of autonomous oscillations in the circadian network and no results were obtained for the case that the circadian network is excited by external signals. Therefore, this paper contributes distinguishing results for the oscillations in the circadian network. Our first contribution is to provide analytical expressions on the dependence of amplitude and phase shift of circadian oscillations on those of external forcing inputs. Next, we prove that under some specific conditions, the amplitude and phase shift of induced oscillations are monotonically increasing functions of the amplitude of periodic forcing inputs. This interesting result may give new insights which are helpful for further studying the biological circadian rhythms. In the second half of the paper, we extend the analysis to the case when the forcing inputs include higher order harmonics. We then also derive explicit expressions for the amplitudes and phase shifts of higher order harmonics in the network oscillations in terms of amplitudes and phases of harmonic components in the forcing inputs. Hence, the previous analysis is strengthened since the forcing inputs are not purely sinusoidal.

The following notation and symbols will be used in the paper. $\mathbb{R}$ and $\mathbb{C}$ stand for the real and complex sets. $\mathbb{R}^n$, $\mathbb{R}^n_+$ and $\mathbb{C}^n$ are used to denote the set of real, positive real and complex $n \times 1$ vectors. Moreover, $\mathbf{1}_n$ denotes the $n \times 1$ vector with all elements equal to 1, and I_n denotes the $n \times n$ identity matrix. Lastly, for any vector $\nu = [\nu_1, \ldots, \nu_n]^T$, $\sin(\nu)$ means $[\sin(\nu_1), \ldots, \sin(\nu_n)]^T$ and similar notations are used for other functions in the paper.

II. Problem formulation

In this paper, we employ the Goodwin model for circadian oscillators [4], [5], [17] to investigate the circadian rhythms driven by daily Light-Dark cycle. This model was first proposed by Goodwin [10] and then modified by Griffith [11] as follows,

$$\begin{cases} \dfrac{dX}{d\tau} &= k_1 \dfrac{K^p}{K^p + Z^p} - k_4 X, \\ \dfrac{dY}{d\tau} &= k_2 X - k_5 Y, \\ \dfrac{dZ}{d\tau} &= k_3 Y - k_6 Z, \end{cases} \tag{1}$$

where X, Y, Z are concentrations of mRNA, its protein and inhibitor, respectively; k_1, k_2, k_3 are rates of transcription, translation and catalysis; k_4, k_5, k_6 are degradation rates of mRNA, its protein and inhibitor; the Hill function $\frac{K^p}{K^p+Z^p}$ represents a nonlinear effect of the inhibitor to the mRNA, K is a constant. Then by introducing the new variables,

$$\begin{aligned} &\mu = \sqrt[3]{\frac{K}{k_1 k_2 k_3}}, b_1 = \mu k_4, b_2 = \mu k_5, b_3 = \mu k_6, \\ &x = \frac{\mu^2 k_2 k_3 X}{K}, y = \frac{\mu k_3 Y}{K}, z = \frac{Z}{K}, t = \frac{\tau}{\mu}, \end{aligned} \tag{2}$$

we obtain a dimensionless mathematical model of a single circadian oscillator from above Goodwin model as follows,

$$\begin{cases} \dfrac{dx}{dt} &= f(z) - b_1 x, \\ \dfrac{dy}{dt} &= x - b_2 y, \\ \dfrac{dz}{dt} &= y - b_3 z, \end{cases} \tag{3}$$

where $f(z) = \dfrac{1}{1 + z^p}$. Using the Laplace transform, we further rewrite the Goodwin oscillator as the following system.

$$\begin{cases} z &= h(s)u, \\ u &= f(z), \end{cases} \tag{4}$$

where

$$h(s) = \frac{1}{(s + b_1)(s + b_2)(s + b_3)}. \tag{5}$$

In a population of SCN circadian neurons, neurons may interact with others through neurotransmitters such as VIP, GABA or by gap junctions [12], [13]. We here assume that the circadian neurons are interconnected through neurotransmitters but do not sense a common pool of neurotransmitters as in [14]. Hence, the dynamics of each circadian oscillator in the circadian network without external inputs is described as follows.

$$z_k = h(s) f(z_k) + \sum_{1 \le j \le n} A_{kj} f(z_j), k = 1, \ldots, n, \tag{6}$$

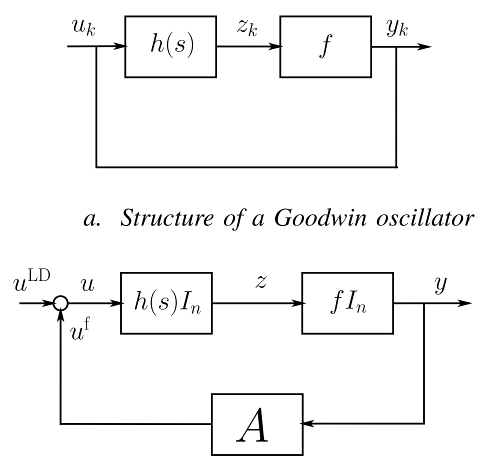
where $A_{kj}, k, j = 1, \ldots, n$ are coupling weights between circadian oscillators. Since the circadian clocks in SCN can be directly entrained by Light-Dark signal through the retinas, it is reasonable to argue that each circadian oscillator in SCN is forced by a same periodic input representing the Light-Dark signal. As a result, the whole network model in presence of Light-Dark inputs u^{LD} is written as follows.

$$\begin{cases} z &= H(s)u, \\ y &= \mathcal{F} z, \\ u &= Ay + u^{\mathrm{LD}}, \end{cases} \tag{7}$$

where

$$\begin{aligned} u &= \begin{bmatrix} u_1 & u_2 & \ldots & u_n \end{bmatrix}^T = u^{\mathrm{f}} + u^{\mathrm{LD}} = Ay + u^{\mathrm{LD}}, \\ u^{\mathrm{f}} &= \begin{bmatrix} u_1^{\mathrm{f}} & u_2^{\mathrm{f}} & \ldots & u_n^{\mathrm{f}} \end{bmatrix}^T, \\ u^{\mathrm{LD}} &= \hat{u} \mathbf{1}_n, \\ y &= \begin{bmatrix} y_1 & y_2 & \ldots & y_n \end{bmatrix}^T, \\ z &= \begin{bmatrix} z_1 & z_2 & \ldots & z_n \end{bmatrix}^T, \end{aligned}$$

and $A = (A_{kj})_{k,j=1,\ldots,n}$ is the weighted coupling matrix, $H(s) = h(s) I_n$, $\mathcal{F} = f I_n$, $\hat{u}$ represents the Light-Dark signal, $u_k^{\mathrm{f}}, k = 1, \ldots, n$ describes the feedback input to the k-th oscillator formed by interacting with other oscillators in the network. Figure 1 shows the block diagram of the network described in (7).



a. Structure of a Goodwin oscillator

b. Structure of the network

Fig. 1. Network model of interconnected Goodwin oscillators

For simplicity, let $\hat{u}(t) = \kappa \sin(\omega t), \kappa > 0$ where $\omega > 0$ is the frequency of Light-Dark signal. This sinusoidal form of Light-Dark signal is utilized to take into account the variability of light intensity during a day. Hence, κ has a physical meaning of maximum intensity of the light during a day. Our problem here is to find out how the natural oscillations in the nonlinear circadian system are changed by the effect of external periodic Light-Dark signal. It is obvious that the problem in this paper is different from the work in [17] since the results in [17] were obtained for autonomous oscillations in circadian networks without external inputs, i.e., without u^{LD}. Thus, the results presented in subsequent sections theoretically contribute some advances to the study of circadian rhythms.

III. Harmonic Balance Analysis of Circadian Oscillations forced by Light-Dark inputs

Suppose that the intrinsic oscillations in the network of Goodwin oscillators, i.e., without external input u^{LD}, are sinusoidal with natural frequency $\omega_0 > 0$. Using the phase oscillator model, it was shown [6] that if the frequency ω of the forcing inputs is close to the intrinsic frequency ω_0 of network oscillations and amplitudes of the forcing inputs are sufficiently large then the frequency of induced network oscillations will be entrained to ω. Since phase model of oscillators is not utilized in this paper, we ignore the details of the frequency entrainment and assume hereafter that the frequency of induced network oscillations is equal to that of forcing inputs, i.e., ω. Then let $z_k(t)$ be described in the following form,

$$z_k(t) = \alpha_{0k} + \alpha_{1k}\sin(\omega t + \varphi_k), k = 1, \dots, n. \quad (8)$$

Accordingly, using the describing function method [7] to approximate the nonlinearity f, the output $y_k(t)$ can be written as follows,

$$y_k(t) = \sigma_{0k}\alpha_{0k} + \sigma_{1k}\alpha_{1k}\sin(\omega t + \varphi_k), k = 1, \dots, n. \quad (9)$$

The describing functions $\sigma_{jk}, j = 0, 1, k = 1, \dots, n$ can be considered as the gains of the nonlinearity f as the inputs are the zero and first-order harmonics and the outputs are approximated by zero and first-order harmonics, respectively. They are computed [7] as follows for $k = 1, \dots, n$,

$$\begin{aligned} \sigma_{0k} &= \frac{2}{\pi\alpha_{0k}}\int_0^{\pi} f(\alpha_{0k} + \alpha_{1k}\sin(t))dt, \\ \sigma_{1k} &= \frac{2}{\pi\alpha_{1k}}\int_0^{\pi} f(\alpha_{0k} + \alpha_{1k}\sin(t))\sin(t)dt. \end{aligned} \quad (10)$$

Let us denote

$$\left\{ \begin{aligned} \alpha_0 &= \left[\alpha_{01}, \dots, \alpha_{0n}\right]^T, \\ \alpha_1 &= \left[\alpha_{11}e^{i\varphi_1}, \dots, \alpha_{1n}e^{i\varphi_n}\right]^T, \\ \varphi &= \left[\varphi_1, \dots, \varphi_n\right]^T, \end{aligned} \right. \quad (11)$$

the bias vector, phasor vector and phase vector of the signal $z(t)$, and

$$\left\{ \begin{aligned} \Sigma_0 &= \mathrm{diag}\,(\sigma_{0k})_{k=1,\dots,n}, \\ \Sigma_1 &= \mathrm{diag}\,(\sigma_{1k})_{k=1,\dots,n}, \end{aligned} \right. \quad (12)$$

the matrices of describing functions. Then we can represent the signals $z(t)$ and $y(t)$ as following phasor vectors

$$\left\{ \begin{aligned} z &= \alpha_0 + \alpha_1, \\ y &= \Sigma_0\alpha_0 + \Sigma_1\alpha_1. \end{aligned} \right. \quad (13)$$

Consequently, substituting (13) into (7) and using harmonic balance method [7], [9], we obtain the following harmonic balance equations.

$$\left\{ \begin{aligned} \left[I_n - h(0)A\Sigma_0\right]\alpha_0 &= 0, \\ \left[I_n - h(i\omega)A\Sigma_1\right]\alpha_1 &= h(i\omega)\kappa\mathbf{1}_n. \end{aligned} \right. \quad (14)$$

Denote $\phi(s) = 1/h(s)$ which is a generalized frequency variable [8], then (14) is equivalent to

$$\left\{ \begin{aligned} \left[\phi(0)I_n - A\Sigma_0\right]\alpha_0 &= 0, \\ \left[\phi(i\omega)I_n - A\Sigma_1\right]\alpha_1 &= \kappa\mathbf{1}_n. \end{aligned} \right. \quad (15)$$

Next, we propose a condition for the synchronization of circadian oscillators under the effect of Light-Dark signal and how phases and amplitudes of circadian oscillations depend on those of Light-Dark signal.

Proposition 1: Consider the network of circadian oscillators driven by Light-Dark signals (7) with sufficiently high amplitude and frequency close to intrinsic frequency of circadian oscillators. The following statements hold.

(i) **(Sync condition)** If the weighted coupling matrix A has an eigenvector $\mathbf{1}_n$ then the circadian oscillations in the network are expected to synchronize at frequency ω of Light-Dark signals.

(ii) The phase and amplitude dependence of circadian oscillations to Light-Dark signal can be calculated as follows,

$$\left\{ \begin{aligned} \left[\phi(0) - \lambda\hat{\sigma}_0\right]\hat{\alpha}_0 &= 0, \\ \left[\phi(i\omega) - \lambda\hat{\sigma}_1\right]\hat{\alpha}_1 e^{i\hat{\varphi}} &= \kappa, \end{aligned} \right. \quad (16)$$

with $\varphi = \hat{\varphi}\mathbf{1}_n, \Sigma_0 = \hat{\sigma}_0 I_n, \Sigma_1 = \hat{\sigma}_1 I_n,\ \varphi, \Sigma_0, \Sigma_1$ are defined in (11)–(12), λ is the eigenvalue of A corresponding to the eigenvector $\mathbf{1}_n$.

Proof: Due to the limitation of space, we omit the proof here. ∎

Remark 1: The sync condition in Proposition 1 sounds artificial from a practical point of view. However, if the circadian oscillators are diffusively interconnected as usually considered in literature [17] then the interconnection matrix A is in the form of a Laplacian matrix and hence A always has an eigenvector $\mathbf{1}_n$. Thus, our assumption is reasonable.

It should be noted that two equations in (16) are scalar, so they can be numerically solved to obtain the values of the phase shift $\hat{\varphi}$, amplitude $\hat{\alpha}_1$ and bias $\hat{\alpha}_0$ of induced circadian oscillations. The first equation in (16) shows that the bias $\hat{\alpha}_0$ only depends on λ and $\phi(s)$ which are the network's properties and $\hat{\alpha}_0$ does not depend on Light-Dark signal. Hence in the following we explore in more details the second equation to see how the phase shift $\hat{\varphi}$ and amplitude $\hat{\alpha}_1$ of induced circadian oscillations vary according to the change in the amplitude κ and frequency ω of Light-Dark signal. We have

$$\phi(i\omega) = b_1b_2b_3 - (b_1+b_2+b_3)\omega^2 + i\omega(b_1b_2+b_2b_3+b_3b_1-\omega^2).$$

Therefore, the second equation in (16) is equivalent to the following two equations,

$$\begin{aligned} \big[(b_1b_2b_3 - (b_1+b_2+b_3)\omega^2 - \lambda\hat{\sigma}_1)^2 + \\ \omega^2(b_1b_2+b_2b_3+b_3b_1-\omega^2)^2\big]\hat{\alpha}_1^2 &= \kappa^2, \end{aligned} \quad (17)$$

$$-\frac{\omega(b_1b_2+b_2b_3+b_3b_1-\omega^2)}{b_1b_2b_3 - (b_1+b_2+b_3)\omega^2 - \lambda\hat{\sigma}_1} = \tan(\hat{\varphi}). \quad (18)$$

Equation (17) shows the dependence of amplitude $\hat{\alpha}_1$ of induced circadian oscillations to amplitude κ and frequency ω of Light-Dark signal. The essential question here is how the increase or decrease on amplitude $\hat{\alpha}_1$ of induced circadian oscillations caused by the increase or decrease of Light-Dark signal's amplitude. The following proposition provide an answer for that question.

Proposition 2: The amplitude $\hat{\alpha}_1$ of induced synchronized circadian oscillations is a monotonically increasing function of the amplitude κ of Light-Dark signal if the following conditions hold:

C1. $[b_1b_2b_3 - (b_1 + b_2 + b_3)\omega^2]\lambda > 0$,
C2. $\kappa^2 > 16\lambda^2 f^2(\hat{\alpha}_0)/\pi^2 + \omega^2(b_1b_2 + b_2b_3 + b_3b_1 - \omega^2)^2\alpha_*^2$,
where $\alpha_* > 0$ satisfying

$$\begin{aligned}&[b_1b_2b_3 - (b_1 + b_2 + b_3)\omega^2]\alpha_* \\ &= \frac{2\lambda}{\pi}\int_0^{\pi} f(\hat{\alpha}_0 + \alpha_* \sin(t))\sin(t)dt.\end{aligned} \tag{19}$$

Proof:
Due to limitation of space, we ignore this proof here. ■

Remark 2: If one of the conditions C1 or C2 is violated, says C1 then $\hat{\alpha}_1$ would not increase as κ increase. For example, let us select b_1, b_2, b_3 and ω such that $b_1b_2b_3 - (b_1 + b_2 + b_3)\omega^2 > 0$ and choose $\lambda < 0$. Then from the proof of Proposition 2, $\left[b_1b_2b_3 - (b_1 + b_2 + b_3)\omega^2\right]\hat{\alpha}_1$ is positive and monotonically increasing w.r.t $\hat{\alpha}_1$ and $-\lambda\hat{\sigma}_1\hat{\alpha}_1$ is positive and monotonically decreasing w.r.t $\hat{\alpha}_1$. Hence, if the decrease of $-\lambda\hat{\sigma}_1\hat{\alpha}_1$ is greater than the increase of $\left[b_1b_2b_3 - (b_1 + b_2 + b_3)\omega^2\right]\hat{\alpha}_1$ as $\hat{\alpha}_1$ increase then $\left[b_1b_2b_3 - (b_1 + b_2 + b_3)\omega^2 - \lambda\hat{\sigma}_1\right]\hat{\alpha}_1$ is not always a monotonic function of $\hat{\alpha}_1$. Thus, our result in Proposition 2 is meaningful in the analysis of Goodwin oscillator networks driven by external periodic signals.

Remark 3: From the result of Proposition 2, we may fix the frequency of Light-Dark signal and vary its amplitude to see the corresponding response of the amplitude of induced circadian oscillations. Hence, this study may be helpful for further understanding and exploring the relationship between amplitudes of realistic circadian rhythms and Light-Dark signal.

The following proposition shows a circumstance where the phase shift $\hat{\phi}$ is a monotone function of the amplitude κ of Light-Dark signal.

Proposition 3: The phase shift $\hat{\varphi}$ is a monotonically increasing function of the amplitude κ of Light-Dark signal if $\omega^2 > b_1b_2 + b_2b_3 + b_3b_1$, $\lambda < 0$ and the condition C2 in Proposition 2 is satisfied. In constrast, if $b_1b_2b_3/(b_1 + b_2 + b_3) < \omega^2 < b_1b_2 + b_2b_3 + b_3b_1$, $\lambda > 0$ and the condition C2 in Proposition 2 is satisfied then the phase shift $\hat{\varphi}$ is a monotonically decreasing function of the amplitude κ of Light-Dark signal

Proof: The outline of this proof is as follows. We can show that $\int_0^{\pi} f(\hat{\alpha}_0 + \hat{\alpha}_1 \sin(t))\sin(t)dt$ is positive and monotonically decreasing with respect to $\hat{\alpha}_1$. Therefore, $\hat{\sigma}_1 = \frac{2}{\pi\hat{\alpha}_1}\int_0^{\pi} f(\hat{\alpha}_0 + \hat{\alpha}_1 \sin(t))\sin(t)dt$ is positive and a monotonically decreasing function of $\hat{\alpha}_1$. Then if the condition C2 in Proposition 2 is satisfied and other conditions in the proposition are fulfilled then we will obtain $\hat{\varphi}$ as a monotonically increasing or decreasing function of the amplitude κ of Light-Dark signal. ■

Remark 4: It can be seen from Propositions 2 and 3 that if the frequency and amplitude of Ligh-Dark signal satisfy some specific conditions then the induced circadian oscillations are stronger, i.e., their amplitudes increase as the amplitude of Light-Dark signal increase but the phase shift of induced circadian oscillations is also increase, i.e., they response more slowly. It implies that there is a tradeoff between the amplitude and the phase shift of circadian oscillations under the effect of external Light-Dark input. This point may be useful in the clinical application of light for treating some diseases related to circadian rhythms [12].

Example 1: Consider a network of 20 circadian oscillators (3) with dimensionless parameters $b_1 = 0.5, b_2 = 1, b_3 = 1.5$ and the interconnection matrix A is randomly generated such that it admits $\mathbf{1}_{20}$ as one of its eigenvectors. With this interconnection matrix, the autonomous oscillations in the circadian network are shown in Figure 2. It is obviously that the autonomous circadian oscillations are not synchronized. Moreover, the frequency of autonomous oscillations can be observed to be 1.66.

Next, we assume that each circadian oscillator is driven by a normalized Light-Dark signal $u^{\mathrm{LD}} = 2\sin(t)$. Then, we obtain a synchronized oscillating pattern in the circadian network with frequency equal to the frequency of driven signals as displayed in Figure 3. This clearly shows the statement in Proposition 1.

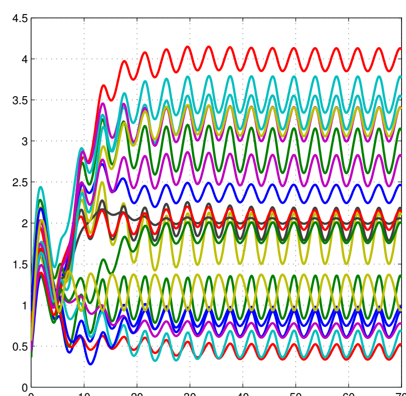


Fig. 2. Autonomous oscillations in a randomly interconnected network of circadian oscillators.

Example 2: We consider a network of 20 circadian oscillators (3) with b_1, b_2, b_3 are the same as in Example 1. The interconnection matrix A is generated such that it has an eigenvector $\mathbf{1}_{20}$. Moreover, we assume that each circadian oscillator is driven by a sinusoidal signal u^{LD} representing the normalized Light-Dark signal. Then we attempt to verify

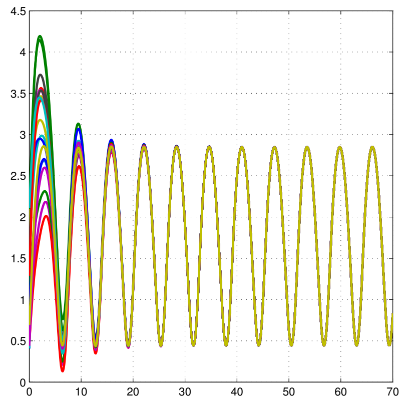


Fig. 3. Synchrony in a randomly interconnected network of circadian oscillators by a sinusoidal Light-Dark input.

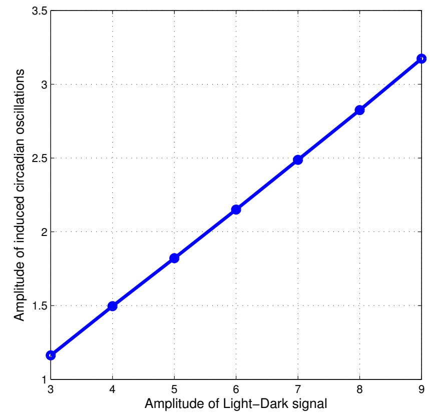


Fig. 4. Monotonicity of amplitude of synchronized circadian oscillations to amplitude of Light-Dark signal.

the monotonicity of the amplitude of induced synchronized circadian oscillations with respect to the amplitude of Light-Dark signal u^{LD}. To do so, we first check the conditions C1–C2. Choosing the normalized frequency of Light-Dark signal u^{LD} to be 1, then the eigenvalue λ of A corresponding to the eigenvector $\mathbf{1}_{20}$ must be negative to satisfy the condition C1. Let $\lambda = -1$ then the condition C2 is equivalent to $\kappa^2 > 16f^2(\hat{\alpha}_0)/\pi^2 + 3.0625\alpha_*^2$, where α_* is obtained from (19), i.e.,

$$-2.25\alpha_* = \frac{-2}{\pi}\int_0^{\pi} f(\hat{\alpha}_0 + \alpha_* \sin(t))\sin(t)dt. \qquad (20)$$

By choosing the Hill coefficient p to be 2, the right hand side of (20) can be analytically expressed in terms of $\hat{\alpha}_0$ and α_*. Subsequently, solving $\hat{\alpha}_0$ from (16) and α_* from (20), we can obtain the minimum value of κ such that the condition C2 is satisfied. Note that this value is less than 3, so in simulation we will increase κ starting from 3 and record the corresponding amplitude $\hat{\alpha}_1$ of induced synchronized circadian oscillations. Figure 4 displays the simulated values of κ and $\hat{\alpha}_1$. We then clearly see that $\hat{\alpha}_1$ is a monotonically increasing function of κ.

IV. External inputs with higher order harmonics

In the previous section, we have considered the circadian oscillations under the effect of Light-Dark signals modeled by sinusoidal inputs. However, the real sun light's changes during a day or during different seasons may not follow the shape of exact sinusoidal signals but instead the form of periodic signals containing higher-order harmonic components as well as the first one. Therefore, in the following we assume that the Light-Dark signal includes the harmonics up to m-th order, i.e.,

$$u^{\mathrm{LD}} = \kappa_0 + \kappa_1\sin(\omega t + \zeta_1) + \ldots + \kappa_m \sin(m\omega t + \zeta_m), \quad (21)$$

where $\kappa_0, \kappa_1, \ldots, \kappa_m > 0$ are the bias and amplitudes of harmonic components, $\zeta_1, \ldots, \zeta_m$ are the phases of harmonic components, respectively.

Suppose that the natural frequency of circadian oscillators is close to the frequency ω of Light-Dark signal and the amplitudes of harmonic components are sufficiently high, then the oscillating frequency of circadian oscillators is entrained to ω. Accordingly, assume that the induced oscillations in the circadian network also compose of higher-order harmonic components up to m-th order as follows.

$$\begin{aligned} z_k(t) &= \alpha_{0k} + \alpha_{1k}\sin(\omega t + \varphi_{1k}) + \ldots \\ &\quad + \alpha_m \sin(m\omega t + \varphi_{mk}), k = 1, \ldots, n, \\ y_k(t) &= \sigma_{0k}\alpha_{0k} + \sigma_{1k}\alpha_{1k}\sin(\omega t + \varphi_{1k}) + \ldots \\ &\quad + \sigma_{mk}\alpha_m \sin(m\omega t + \varphi_{mk}), k = 1, \ldots, n, \end{aligned} \qquad (22)$$

where $\sigma_{0k}, \sigma_{1k}, \ldots, \sigma_{mk}, k = 1, \ldots, n$ are describing functions which can be calculated [7] similarly to (10). Then, we obtain the following result when Light-Dark signal includes higher order harmonics.

Proposition 4: Consider the network of circadian oscillators (7) driven by Light-Dark signals (21) with sufficiently high amplitudes and frequency close to intrinsic frequency of circadian oscillators. Suppose that the circadian oscillations are under the form (22). The following statements hold.

(i) If the interconnection matrix A between circadian oscillators has an eigenvector $\mathbf{1}_n$ then the circadian oscillations in the network are expected to synchronize at frequency ω of Light-Dark signals, i.e.,

$$\begin{aligned} \alpha_{01} &= \cdots = \alpha_{0n} = \hat{\alpha}_0, \\ \alpha_{11} &= \cdots = \alpha_{1n} = \hat{\alpha}_1, \ldots, \\ \alpha_{m1} &= \cdots = \alpha_{mn} = \hat{\alpha}_m, \\ \varphi_{11} &= \cdots = \varphi_{1n} = \hat{\varphi}_1, \ldots, \\ \varphi_{m1} &= \cdots = \varphi_{mn} = \hat{\varphi}_m. \end{aligned} \qquad (23)$$

(ii) The phase-shift as well as the amplitude dependence of circadian oscillators to Light-Dark signal can be calculated as follows.

$$\begin{cases} [\phi(0) - \lambda\hat{\sigma}_0]\,\hat{\alpha}_0 &= \kappa_0, \\ [\phi(i\omega) - \lambda\hat{\sigma}_1]\,\hat{\alpha}_1 e^{i\hat{\varphi}_1} &= \kappa_1 e^{i\zeta_1}, \\ \vdots & \\ [\phi(im\omega) - \lambda\hat{\sigma}_m]\,\hat{\alpha}_m e^{i\hat{\varphi}_m} &= \kappa_m e^{i\zeta_m}, \end{cases} \qquad (24)$$

where $\sigma_{01} = \cdots = \sigma_{0n} = \hat{\sigma}_0, \sigma_{11} = \cdots = \sigma_{1n} = \hat{\sigma}_1, \ldots, \sigma_{m1} = \cdots = \sigma_{mn} = \hat{\sigma}_m$, λ is the eigenvalue of A corresponding to the eigenvector $\mathbf{1}_n$.

Proof: This proof can be obtained similarly to the proof of Proposition 1, so we ignore it here for brevity. ■

Example 3: Consider a network of 20 circadian oscillators with the same b_1, b_2, b_3 and the randomly generated interconnection matrix A such that it admits $\mathbf{1}_{20}$ as one of its eigenvectors as in Example 1.

We assume that each circadian oscillator is driven by a normalized Light-Dark signal represented by $u^{\mathrm{LD}} = 2\sin(t) + 3\sin(2t + 2\pi/5) + 5\sin(3t + 3\pi/7)$. Then the induced circadian oscillations in the network are exhibited in Figure 5. We can see that the circadian oscillations still synchronize at the frequency of normalized Light-Dark signal and they contain higher order harmonics instead of having only zero and first order harmonics. Employing Theorem 4, we can approximate the harmonic components including zero, first and higher order ones in the circadian oscillations based on those of Light-Dark signal.

As seen in Figure 2, the autonomous circadian oscillations are of different frequency, asynchronous and seem to contain only zero and first order harmonic components. However, under the effect of external Light-Dark signal, the oscillations in the circadian network are completely changed in their frequency, amplitudes and phases.

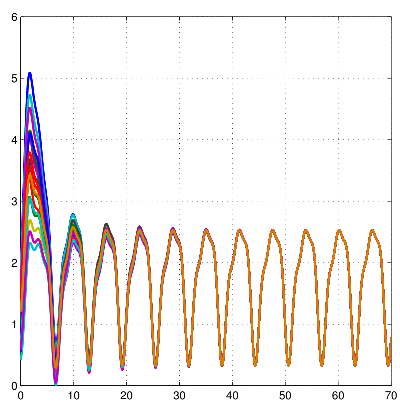


Fig. 5. Synchrony in a randomly interconnected network of circadian oscillators by a periodic Light-Dark input with higher order harmonics.

V. CONCLUSION

An approach based on the harmonic balance method has been proposed to study the circadian oscillations in a network of Goodwin oscillators forced by periodic Light-Dark inputs. We show how the phases and amplitudes of circadian oscillations depend on those of driving Light-Dark inputs. We then explore the monotonicity of the amplitude and phase shift of induced oscillations with respect to the amplitude of Light-Dark input. In a further step, the effect of Light-Dark input with higher order harmonics to circadian oscillations is investigated in a similar manner which reveals the relation between the amplitudes and phases of harmonics in circadian oscillations and thoses of Light-Dark signal. The obtained results may give some new insights to the study of biological circadian rhythms.

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