Entrainment Analysis in Goodwin-Type Nonlinear 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 entrained oscillations in a class of Goodwin-type oscillator networks forced by external periodic signals consisting of high order harmonics. First, a necessary condition and a conjecture for entrainment of network oscillations are presented. Next, the authors reveal an estimation for the profile of entrained oscillations in one situation and the monotone dependence of the amplitude and phase shift of entrained oscillations to the external input in other contexts. The theoretical results are then illustrated through some examples including a practical model for circadian rhythm in Neurospora crassa.

Key Words : measurement, control, systems and information, system integration, industrial applications.

1. Introduction

Circadian rhythm is an interesting example of biological oscillations which appears in many species of living organisms such as bacterial [1], the fungus Neurospora [2], Drosophila [3], and mammals [4]–[6]. It is now well known that there are cellular clocks inside the living organisms which can autonomously generate such circadian oscillations. Due to that internal clocks, the living creatures adjust their behaviors and adapt themselves to the changes of the outside environment. One of the most important features of the circadian clocks is that they can be entrained by periodic factors in the environment called zeitgebers [6]–[8]. This remarkable property of circadian rhythm therefore becomes a very important research topic to understand its underlying mechanisms. The sources of zeitgebers can be natural or artificial for instance the daily light, temperature or food, among which the daily light is a main zeitgeber for the circadian network [6]–[9]. From the control system viewpoint, we can consider the circadian network as a dynamical system forced by an external periodic input representing the zeitgeber. 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 the 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. Therefore, the goal of this paper is to find out the answers for those problems and we will refer the daily light as the zeitgeber for the circadian system.

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 [5],[6],[10]–[12]. The master circadian network is shown to be directly entrained by the daily Light-Dark cycle through the retina to coherently oscillate with period equal to Light-Dark period since circadian oscillators autonomously oscillate but their periods are not exactly 24 hrs [4],[6]. Furthermore, there exists a phase shift between synchronized circadian oscillations and Light-Dark signal [4],[6],[7],[11]. In [7], the phase shift was observed to be increasing and positive for long periods, decreasing and negative for short periods. There are also evidences from other 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 [6]. However, the biological mechanisms under that phenomena have not yet been well understood. Leloup et al.[3] 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.

On the other hand, the theoretical researches for nonlinear oscillator networks excited by exogenous periodic signals have several limitations. First, most researches focus on autonomous, nearly sinusoidal oscillations without taking into account external inputs or higher order harmonics [2],[13],[14]. Second, some studies consider external periodic inputs but only for single nonlinear oscillators, e.g. [15]. Third, the nonlinear oscillator networks excited by external periodic inputs have been investigated but only for the frequency synchronization problem, moreover the oscillators are usually assumed to be globally coupled or weakly nonlinear oscillators to obtain phase model of oscillators [8],[15],[16].

This paper aims at investigating the entrainment in Goodwin-type nonlinear oscillator networks excited by a periodic external signal. The main contribution of this paper is on the properties of entrainment, i.e., the relations between the amplitudes, phases of the entrained oscillations in the network and those of the external input. More specifically, the authors show that under some conditions, we may obtain the monotone relations between the entrained oscillations and the external periodic input,
which in some senses are coincident with biological experiment results. Furthermore, based on the harmonic balance method, a necessary condition on the interconnections among oscillators in the network is revealed and a conjecture on the efficiency of the external periodic input such that the entrainment occurs.

Note that the results in [17] were obtained for third-order Goodwin model and some results are imprecise whereas the results derived in this paper are more general and correct the ones in [17]. Since negative feedback loop is one of the core molecular regulatory mechanisms for circadian oscillations [4,11,13], the Goodwin model is reasonable for studying the circadian network and the obtained results may be helpful for further understanding and investigating the circadian oscillations. An example in which the parameters from a biological model of circadian oscillations in [18] is employed to emphasize this point.

The paper is organized as follows. In Section 2, a class of Goodwin-type nonlinear oscillator networks is presented. We then introduce a motivating example in Section 3 followed by definitions of periodic oscillations, synchronization and entrainment. Next, a necessary condition and a conjecture on the efficiency for entrainment are proposed. Subsequently, the entrainment properties are studied in Section 5. In Section 6, a network of 3rd-order Goodwin oscillators used to model the circadian network is investigated and the simulations for a practical model of circadian oscillation in Neurospora crassa presented to demonstrate the theoretical results. Lastly, our main results are summarized in Section 7.

The following notation and symbols will be used in the paper. The symbol $I_n$ denotes the $n \times n$ identity matrix. Lastly, for any vector $v = [v_1, \ldots, v_n]^T$, $\sin(v)$ means $[\sin(v_1), \ldots, \sin(v_n)]^T$ and similar notations are used for other functions in the paper.

2. Goodwin-Type Nonlinear Oscillator Networks

2.1 Model of a Goodwin-Type Nonlinear Oscillator

In this paper, we consider a class of nonlinear oscillator networks consisting of the so-called generalized Goodwin-type oscillators of qth-order ($q \geq 3$) expressed as

$$
\begin{align*}
\frac{dx_1}{dt} &= k_1 \frac{K^p}{K^p + X_q} - k_{q+1} X_1,
\frac{dx_2}{dt} &= k_2 X_1 - k_{q+2} X_2,
& \vdots \\
\frac{dx_q}{dt} &= k_q X_{q-1} - k_{2q} X_q.
\end{align*}
$$

(1)

This model is a generalization of the classical 3rd-order Goodwin model in [2,3,19,20] to represent a process with nonlinear negative feedback which may be found for instance in biochemical networks. The physical meanings of variables and parameters may be explained as follows: $X_1, X_2, \ldots, X_q$ are the concentrations of chemicals; $k_1, k_2, \ldots, k_{2q}$ are the rates of reactions; the Hill function $\frac{K^p}{K^p + X_q}$ represents a nonlinear effect of the last chemical to the first one, and $K$ is a constant. Then, introducing new variables as

$$
\begin{align*}
\eta &= \left[ \begin{array}{c} K \\ k_1 k_2 \cdots k_q \end{array} \right], \quad b_1 = \eta k_{q+1}, \ldots, b_q = \eta k_{2q}, \\
x_1 &= \eta^{-1} k_2 \cdots k_q X_1, \quad x_2 = \eta^{-2} k_3 \cdots k_q X_2, \\
& \vdots \\
x_q &= \frac{X_q}{K}, \quad t = \frac{\tau}{\eta},
\end{align*}
$$

(2)

leads to the dimensionless mathematical model of a single Goodwin-type oscillator as follows,

$$
\begin{align*}
\frac{dx_1}{dt} &= f(x_q) - b_1 x_1, \quad f(x_q) = \frac{1}{1 + x_q^2}, \\
\frac{dx_2}{dt} &= x_1 - b_2 x_2, \\
& \vdots \\
\frac{dx_q}{dt} &= x_{q-1} - b_q x_q.
\end{align*}
$$

(3)

Using the Laplace transform, we further rewrite the dimensionless Goodwin-type oscillator as

$$
\begin{align*}
z &= h(s) u, \\
u &= f(z),
\end{align*}
$$

(4)

where $z$ is used to denote $x_q$ and

$$
h(s) = \frac{1}{(s + b_1)(s + b_2) \cdots (s + b_q)}.
$$

(5)

2.2 Model of Oscillator Networks

Assuming now that the oscillator network includes $n$ interconnected Goodwin-type oscillators, where the input of the $k$th oscillator is given by

$$
u_k = \sum_{j \in \mathbb{N}} A_{kj} f(z_j) + w, \quad k = 1, \ldots, n,
$$

(6)

where $A_{kj}, k, j = 1, \ldots, n$ are coupling weights between oscillator $k$ and other oscillators. This means that the input of each oscillator is the summation of a linear combination of the output of other oscillators $y_j = f(z_j)$ and the external input $w$. Figure 1 shows the block diagram of the network described above.

Fig. 1 Network model of interconnected Goodwin-type oscillators.

Consequently, under the effect of the same external input $w$, the whole network model is described as follows,

$$
\begin{align*}
z &= H(s) u, \\
y &= \mathcal{F} z, \\
u &= A y + w I_n,
\end{align*}
$$

(7)

where $H(s) = h(s) I_n$, $\mathcal{F} = f I_n$ and

$$
\begin{align*}
u &= [u_1 \ u_2 \ \ldots \ \ u_q]^T, \\
y &= [y_1 \ y_2 \ \ldots \ \ y_n]^T, \\
z &= [z_1 \ z_2 \ \ldots \ \ z_n]^T.
\end{align*}
$$
3. Entrainment in Goodwin-Type Oscillator Networks

3.1 Periodic Oscillations, Synchronization and Entrainment

We here present the definitions of periodic oscillations, synchronization and entrainment used in this paper so that they are clearly distinguished.

Definition 1. (Periodically oscillating signal) A signal \( x(t) \), at steady state, is called a periodically oscillating signal with a period \( T(>0) \) if \( T \) is the smallest value satisfying \( \lim_{t \to \infty} [x(t+T)−x(t)] = 0 \). Moreover, \( \omega = 2\pi/T \) is called the frequency of that oscillation.

Definition 2. (Synchronization) A network system represented by (7) is said to be synchronized if all the outputs \( y_k(t) \), \( k = 1, \ldots, n \) are periodically oscillating signals with same frequency, phase, and amplitude.

Definition 3. (Entrainment) A network system represented by (7), which is excited by an external, periodically oscillating input \( w(t) \), is said to be entrained by \( w(t) \), if it is synchronized and the frequency is equal to that of \( w(t) \).

The definition of synchronization from Definition 2 is sometime called full synchronization in some other papers. That is because they consider “weaker synchronizing” scenarios where only the frequencies or frequencies and phases of oscillators are the same. On the other hand, from Definition 2 and 3, synchronization and entrainment are different. A network of periodic oscillators need not to be synchronized but they are still able to be entrained by an external, periodically oscillating signal.

Therefore, in this paper, we attempt to find the properties of the entrainment and the conditions for non-synchronized interconnected oscillators such that they are entrained by an exogenous input.

3.2 Motivating Example

In order to make the goals of this paper more clear we here illustrate a motivating numerical example, in which the autonomous oscillations in the network are asynchronous and then the network oscillations are entrained under the excitation of an external periodic input.

Consider a network (7) of 50 5th-order Goodwin-type oscillators with the dimensionless parameters \( b_1 = b_2 = b_3 = b_4 = b_5 = 1, p = 10 \) and a randomly generated interconnection matrix \( A \) such that it admits \( \mathbf{1}_{50} \) as one of its eigenvectors. Figure 2 shows the autonomous oscillations in this network, which are asynchronous. In addition, the intrinsic frequency of the autonomous oscillations is 0.69.

Consequently, suppose that each 5th-order Goodwin-type oscillator is excited by a common periodic signal with higher order harmonics as follows,

\[
 w(t) = 5 + 4 \sin(0.5t) + 7 \sin(t + \frac{4\pi}{11}) + 9 \sin(1.5t + \frac{6\pi}{7}).
\]

Here, the frequency of external input is close to the autonomous frequency of network oscillations and the amplitudes of harmonic components in the external input are high. Then, the resulting oscillations in the network are displayed in Fig. 3. We can observe that the induced oscillations not only synchronize at the frequency 0.5 of external signal but also contain higher order harmonics instead of having only zero and first order harmonics.

Now, we consider another situation where the elements of above matrix \( A \) are randomly perturbed which has no longer an eigenvector \( \mathbf{1}_{50} \). However, the external input is kept the same as above. Then Fig. 4 shows that the forced oscillations in the network are not synchronized.

From these simulation results, a couple of questions raise up. First, how to explain the entrainment of network oscillations in the presence of the external periodic input, or in other words what are the conditions for the entrainment of the oscillator network by an external periodic input? Second, how to evaluate or compute the entrained oscillations in the network? The answers for those questions will be sequentially given in the succeeding sections.

4. Entrainment Condition

This section is devoted to the conditions for occurring the entrainment. Let us consider the external periodic input including the harmonics up to \( m \)th order represented by
amplitudes of harmonic components; \( \omega \) is the frequency; \( \kappa_0, \kappa_1, \ldots, \kappa_m > 0 \) are the bias and amplitudes of harmonic components; \( \zeta_1, \ldots, \zeta_m \) denote the phases of harmonic components. Accordingly, assume that the frequency of induced oscillations in the Goodwin-type oscillator network is entrained to \( \omega \), and the induced oscillations \( z_k(t) \) and \( y_k(t) \) can be approximated by the following periodic signals composed of higher-order harmonic components up to \( n \)th order,

\[
\begin{align*}
z_k^{(m)}(t) &= \sigma_{0k} + \sigma_{1k} \sin(\omega t + \varphi_{1k}) + \cdots + \sigma_{nk} \sin(n\omega t + \varphi_{nk}), \\
y_k^{(m)}(t) &= \sum_{j=1}^{m} \sigma_{jk} \sin(\omega t + \varphi_{jk}) + \cdots + \sigma_{nk} \sin(n\omega t + \varphi_{nk}), \quad k = 1, \ldots, n,
\end{align*}
\]

where \( \sigma_{0k} \) and \( \sigma_{jk} \), \( j = 1, \ldots, m \) are describing functions which can be calculated [21] by

\[
\begin{align*}
\sigma_{0k} &= \frac{1}{\pi \alpha_{0k}} \int_0^{\pi} f(\alpha_{0k} + \cdots + \alpha_{nk} \sin(mt)) dt, \\
\sigma_{jk} &= \frac{1}{\pi \alpha_{jk}} \int_0^{\pi} f(\alpha_{0k} + \cdots + \alpha_{nk} \sin(mt)) \sin(jt) dt.
\end{align*}
\]

Denote

\[
\begin{align*}
\alpha_0 &= [\alpha_{01}, \ldots, \alpha_{0m}]^T, \\
\alpha_j &= [\alpha_{j1} e^{i\varphi_{1j}}, \ldots, \alpha_{jm} e^{i\varphi_{mj}}]^T, \quad j = 1, \ldots, m, \\
\Sigma_0 &= \text{diag}(\sigma_{0k})_{k=1,\ldots,n}, \\
\Sigma_j &= \text{diag}(\sigma_{jk})_{k=1,\ldots,n}, \quad j = 1, \ldots, m.
\end{align*}
\]

Then, we can represent the signals \( z^{(m)}(t), y^{(m)}(t) \) and \( w(t) \) by phasor vectors as follows:

\[
\begin{align*}
z^{(m)} &= [\alpha_0 + \alpha_1 + \cdots + \alpha_m]^T, \\
y^{(m)} &= \Sigma_0 \alpha_0 + \Sigma_1 \alpha_1 + \cdots + \Sigma_m \alpha_m, \\
w &= \kappa_0 + \kappa_1 e^{i\varphi_1} + \cdots + \kappa_m e^{i\varphi_m}.
\end{align*}
\]

Introducing \( \phi(x) := 1/\hbar(x) \), which is the generalized frequency variable [22], then we have

\[
\phi(i\omega) = (i\omega)^q + \beta_1 (i\omega)^{q-1} + \cdots + \beta_q (i\omega)^1 + \beta_{q+1},
\]

where

\[
\beta_k = \sum_{i,j=1}^{n} b_i b_j \cdots b_q; k = 1, \ldots, q.
\]

Consequently, substituting (11) into (7) and balancing harmonic components, we can obtain the following harmonic balance equations:

\[
\begin{align*}
\phi(0)I_n - A \Sigma_0 \alpha_0 &= \kappa_0 I_n, \\
\phi(i\omega)I_n - A \Sigma_j \alpha_j &= \kappa_j e^{i\varphi_j} I_n, \quad j = 1, \ldots, m.
\end{align*}
\]

Then, the following proposition shows a necessary condition for entrainment in the network (7).

**Proposition 1.** If the entrainment occurs in network (7) and the harmonic balance equation (13) is satisfied then the interconnection matrix \( A \) representing the couplings among Goodwin-type oscillators must have an eigenvector \( I_n \).

**Proof.** As the entrainment occurs, (13) leads to

\[
\begin{align*}
\phi(0)I_n - A \Sigma_0 \alpha_0 &= \kappa_0 I_n, \\
\phi(i\omega)I_n - A \Sigma_j \alpha_j &= \kappa_j e^{i\varphi_j} I_n, \quad j = 1, \ldots, m.
\end{align*}
\]

where \( \sigma_{01} = \cdots = \sigma_{0m} = \sigma_{11} = \cdots = \sigma_{kn} = \sigma_{jk} = \kappa_0 = \kappa_1 = \cdots = \kappa_m = \kappa_j = \varphi_{1j} = \cdots = \varphi_{mj} = \varphi_j, \ j = 1, \ldots, m. \) This is in turn equivalent to the following equations:

\[
\begin{align*}
A \Sigma_0 \alpha_0 &= \kappa_0 I_n, \\
A \Sigma_j \alpha_j e^{i\varphi_j} &= \kappa_j e^{i\varphi_j} I_n, \quad j = 1, \ldots, m.
\end{align*}
\]

It can immediately deduce from (15) that \( I_n \) is an eigenvector of \( A \).

Unfortunately, we cannot show the sufficiency for the entrainment. However, we may raise in the following conjecture by employing similar ideas in [15] for a single oscillator forced by periodic inputs.

**Conjecture 1.** If the frequency of the external periodic input \( w(t) \) is close to the natural frequency of network oscillations, the amplitude of the external input is sufficiently large, and the interconnection matrix \( A \) has an eigenvector \( I_n \), then the network (7) is entrained by the external input \( w(t) \).

It can be seen from the conjecture that the condition in Proposition 1 is not only necessary but also sufficient. However, to obtain the entrainment, we need two more conditions as stated in Conjecture 1. Some simulation results presented in Section 6.4 provide an evidence for supporting this conjecture.

### 5. Properties of Entrainment

Suppose that the network (7) is entrained by the external periodic input \( w(t) \). Let \( \lambda \) be the eigenvalue of \( A \) corresponding to the eigenvector \( I_n \), then we obtain from (15) that

\[
\begin{align*}
\phi(0) - \lambda \Sigma_0 \alpha_0 &= \kappa_0, \\
\phi(i\omega) - \lambda \Sigma_j \alpha_j &= \kappa_j e^{i\varphi_j} \quad j = 1, \ldots, m.
\end{align*}
\]

It is generally hard to solve the harmonic balance equations in (16). Nevertheless, we will show in Section 5.1 that an explicit estimation for the entrained network oscillations could be obtained in a certain situation. For other cases, Section 5.2 reveals the monotonic dependence of network oscillations on the external input, which bring useful information on entrained oscillations, though we could not explicitly approximate them.
5.1 Case 1: A Has an Eigen-Pair (0, 1<sub>e</sub>)

In this case, the harmonic balance equations in (16) becomes
\[
\begin{align*}
\phi(0)\hat{a}_0 & = \kappa_0, \\
\phi(i\omega j)\hat{a}_j e^{i\phi_j} & = \kappa_j e^{i\phi_j}, \ j = 1, \ldots, m. \\
\end{align*}
\]
(17)

Let us denote \(\rho_j = \phi_j - \zeta_j\) the phase shifts between the \(j\)th-order harmonics in the network oscillations and the external input, and \(\phi_{R,j}, \phi_{I,j}\) the real and imaginary parts of \(\phi(i\omega_j), \ i, j = 1, \ldots, m\), respectively, then (17) is equivalent to
\[
\begin{align*}
\phi(0)\hat{a}_0 & = \kappa_0, \\
[\phi_{R,j} + i\phi_{I,j}]\hat{a}_j e^{i\phi_j} & = \kappa_j, \ j = 1, \ldots, m. \\
\end{align*}
\]
(18)

The following proposition gives us an estimation of the entrained network oscillations.

**Proposition 2.** Suppose that network (7) is entrained by the external input of the form (8) and the network oscillations can be approximated as in (9). Then their amplitudes and phases can be estimated as follows:
\[
\hat{a}_j = \frac{\kappa_j}{\sqrt{\phi_{R,j}^2 + \phi_{I,j}^2}}, \ j = 1, \ldots, m. \\
\phi_j = \zeta_j - \tan(\phi_{I,j}/\phi_{R,j}), \ j = 1, \ldots, m. \\
\]
(19) (20)

**Proof.** Note that \(\phi_{R,j}\) and \(\phi_{I,j}\) can be easily calculated from (12) for every \(j = 1, \ldots, m\). Subsequently, (18) are equivalent to
\[
\begin{align*}
[\phi_{R,j}^2 + \phi_{I,j}^2]\hat{a}_j^2 & = \kappa_j^2, \\
-\frac{\phi_{I,j}}{\phi_{R,j}} & = \tan(\rho_j), \\
\end{align*}
\]
which lead to (19) and (20). \(\square\)

Since \(\sqrt{\phi_{R,j}^2 + \phi_{I,j}^2} > 0\), we immediately obtain the following corollary from Proposition 2.

**Corollary 1.** The following two statements hold.

(i) The amplitude \(\hat{a}_j\) of the \(j\)th-order harmonic components in the entrained network oscillations is a monotonically increasing function of the amplitude \(\kappa_j\) of the \(j\)th-order harmonic component in the driving signal.

(ii) The phase shift \(\rho_j\) between the \(j\)th-order harmonic components in the entrained network oscillations and in the exciting input is a constant with respect to the changes of the amplitude \(\kappa_j\).

Proposition 2 theoretically contributes an explicit estimation for the profile of any harmonic order in the network oscillations as they are entrained by the external input (8) within the context that the interconnection matrix \(A\) has an eigen-pair \((0, 1<sub>e</sub>)\). This analysis result would give us a strong basis for designing oscillator networks in real applications.

5.2 Case 2: A Has an Eigen-Pair \((\lambda, 1<sub>e</sub>)\), \(\lambda \neq 0\)

In this scenario, we are not able to obtain an explicit estimation of the entrained network oscillations as in the previous case. Hence, we aim at verifying the monotonic dependence of the entrained oscillations to the external input as it is varying. As a result, even though we do not know precisely the profile of entrained oscillations but at least we may know how they change with respect to the external input.

For simplicity, we only consider the case of sinusoidal external inputs, i.e.,
\[
w(t) = \kappa_0 + \kappa_1 \sin(\omega t + \zeta_1).
\]

Subsequently, under some mathematical manipulations, the describing function \(\hat{\sigma}_1\) can be rewritten as
\[
\hat{\sigma}_1 = \frac{1}{\pi\hat{a}_1} \int_{0}^{\pi} f(\hat{a}_0 + \hat{a}_1 \sin(t)) \sin(t) dt, \\
= \frac{1}{\pi\hat{a}_1} \int_{0}^{\pi} [f(\hat{a}_0 + \hat{a}_1 \sin(t)) - f(\hat{a}_0 - \hat{a}_1 \sin(t))] \sin(t) dt.
\]

Note that \(\hat{a}_0\) should be greater than or equal to \(\hat{a}_1\) to guarantee that \(\hat{a}_0 + \hat{a}_1 \sin(t)\) and \(\hat{a}_0 - \hat{a}_1 \sin(t)\) are non-negative since the Hill function is only defined in the interval \([0, +\infty)\). Therefore, we can see from the above equation that \(\hat{\sigma}_1 < 0\), since \(\hat{a}_0 + \hat{a}_1 \sin(t) > \hat{a}_0 - \hat{a}_1 \sin(t) > 0\) with \(t \in [0, \pi]\) and the Hill function \(f\) is monotonically decreasing.

Consider the harmonic balance equation in (16) associated with the 1st harmonic component,
\[
[\phi(\omega) - \lambda\hat{\sigma}_1]\hat{a}_1 e^{i\phi_1} = \kappa_1 e^{i\phi_1}.
\]
(22)

Then (22) is equivalent to
\[
[\phi_{R,1} - \lambda\hat{\sigma}_1 + i\phi_{I,1}]\hat{a}_1 e^{i\phi_1} = \kappa_1. \\
\]
(23)

Note that \(\phi_{R,1}\) and \(\phi_{I,1}\) can be easily calculated from (12), and hence (23) is equivalent to
\[
\begin{align*}
[\phi_{R,1} - \lambda\hat{\sigma}_1]^2 + \phi_{I,1}^2 \hat{a}_1^2 & = \kappa_1^2, \\
-\frac{\phi_{I,1}}{\phi_{R,1} - \lambda\hat{\sigma}_1} & = \tan(\rho_1), \\
\end{align*}
\]
(24) (25)

The proposition below shows the second monotonic property of the entrainment in the Goodwin-type oscillator networks under the following assumption.

- **Assumption 1.** The integral in the describing function \(\hat{\sigma}_1\) is a monotonically decreasing function of \(\hat{a}_0\) and \(\hat{a}_1\).

**Proposition 3.** Suppose that Assumption 1 is satisfied. Then, the amplitude \(\hat{a}_1\) of the 1st harmonic components in the entrained network oscillations is a monotonically increasing function of the amplitude \(\kappa_1\) of the 1st harmonic component in the driving signal if the following condition holds,
\[
\lambda > 0. \\
\]

**Proof.** We obtain from Assumption 1 that the describing function \(\hat{\sigma}_1\) is a monotonically decreasing function of \(\hat{a}_1\) since \(\frac{1}{\hat{a}_1}\) is positive and monotonically decreasing with respect to \(\hat{a}_1\). Accordingly, the following two cases occur if the condition C1 is satisfied.

**Case 1:** \(\phi_{R,1} > 0\) and \(\lambda > 0\): We can deduce from Assumption 1 that \(-\lambda\hat{\sigma}_1\hat{a}_1\) is positive and monotonically increasing with respect to \(\hat{a}_1\), and hence \([\phi_{R,1} - \lambda\hat{\sigma}_1]\hat{a}_1\) is monotonically increasing with respect to \(\hat{a}_1\). Moreover, we have

\(^1\) See the Appendix for the validation of this assumption.
Thus, we can conclude from both Case 1 and Case 2 that \( \hat{\alpha}_1 \) is monotonically decreasing with respect to \( \hat{\alpha}_1 \). Computing similarly to Case 1, we have
\[
\min_{\hat{\alpha}_1 \in (0, +\infty)} \left[ \phi_{R1} - \lambda \hat{\alpha}_1 \right] \hat{\alpha}_1 = -\infty, \quad \max_{\hat{\alpha}_1 \in (0, +\infty)} \left[ \phi_{R1} - \lambda \hat{\alpha}_1 \right] \hat{\alpha}_1 = 0.
\]

Thus, we can conclude from both Case 1 and Case 2 that \( (\phi_{R1} - \lambda \hat{\alpha}_1)^2 \hat{\alpha}_1^2 \) is monotonically increasing with respect to \( \hat{\alpha}_1 \) in \([0, +\infty)\). In addition, we have
\[
\max_{\hat{\alpha}_1 \in (0, +\infty)} \left[ (\phi_{R1} - \lambda \hat{\alpha}_1)^2 \hat{\alpha}_1^2 \right] \hat{\alpha}_1 = +\infty,
\]
\[
\min_{\hat{\alpha}_1 \in (0, +\infty)} \left[ (\phi_{R1} - \lambda \hat{\alpha}_1)^2 \hat{\alpha}_1^2 \right] \hat{\alpha}_1 = 0.
\]

On the other hand, \( \phi_{S1}^2 \hat{\alpha}_1^2 \) is always a monotonically increasing function of \( \hat{\alpha}_1 \) in \([0, +\infty)\). Thereupon, if condition C1 is satisfied, \( \kappa_1^2 = \left( (\phi_{S1} - \lambda \hat{\alpha}_1)^2 + \phi_{S1}^2 \right) \hat{\alpha}_1^2 \) is monotonically increasing with respect to \( \hat{\alpha}_1 \), i.e., \( \hat{\alpha}_1 \) is a monotonically increasing function of \( \kappa_1 \). This completes the proof. \( \square \)

**Example 1:** Consider the same network (7) of 50 5th-order Goodwin-type oscillators as in the motivating example. We here attempt to verify the monotonicity of the amplitude \( \hat{\alpha}_1 \) on the amplitude \( \kappa_1 \) of the first harmonic components in the network oscillations and the external signal. Let the external signal be
\[
w(t) = 7 + \kappa_1 \sin(0.5t),
\]
where \( \kappa_0 \) is fixed at 7 and \( \kappa_1 \) is increased from 1 to 7. We then measure the amplitude \( \hat{\alpha}_1 \) of the induced network oscillations and illustrate the dependence of \( \hat{\alpha}_1 \) on \( \kappa_1 \) in Fig. 5. It is seen that \( \hat{\alpha}_1 \) is monotonically increasing with respect to \( \kappa_1 \). We also observe that \( \hat{\alpha}_0 \) is almost constant in the simulation, in particular \( \hat{\alpha}_0 \approx 4 \). Moreover, these values of \( \hat{\alpha}_0 \) and \( \hat{\alpha}_1 \) belong to the region plotted in Fig. A.1 in the Appendix.

![Monotonicity of the amplitude of network oscillations to the amplitude of exciting signal.](image)

Next, we introduce the third monotonic property of the entrainment in the Goodwin-type oscillator networks.

**Proposition 4.** Suppose that Assumption 1 is satisfied. Then the phase shift \( \rho_1 \) of the 1st harmonic component in the entrained network oscillations is a monotonic function of the amplitude \( \kappa_1 \) of the 1st harmonic component in the external driving signal as indicated in the following table, where \( - \) and \( + \) mean negative and positive, respectively; \( \uparrow \) and \( \downarrow \) mean monotonically increasing and decreasing, respectively.

<table>
<thead>
<tr>
<th>( \lambda )</th>
<th>( \phi_{R1} )</th>
<th>( \phi_{S1} )</th>
<th>( \rho_1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(\uparrow)</td>
</tr>
<tr>
<td>(-)</td>
<td>(-)</td>
<td>(+)</td>
<td>(\downarrow)</td>
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<tr>
<td>(+)</td>
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<td>(+)</td>
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<td>(+)</td>
<td>(\uparrow)</td>
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<tr>
<td>(+)</td>
<td>(+)</td>
<td>(\downarrow)</td>
<td>(\downarrow)</td>
</tr>
</tbody>
</table>

Proof. It is seen from the proof of Proposition 3 that the describing function is negative and monotonically decreasing with respect to \( \hat{\alpha}_1 \). On the other hand, \( \tan(\rho_1) \) is a monotone function of \( \rho_1 \), hence it can be deduced from (25) that \( \rho_1 \) is a monotonic function of \( \hat{\alpha}_1 \) and whether that function is increasing or decreasing depends on the signs of \( \phi_{R1}, \phi_{S1} \), and \( \lambda \). Then, making a sign table yields the results as in Table 1. \( \square \)

### 6. A Special Case: Circadian Networks

#### 6.1 Model of Circadian Networks

In this section, we particularly pay attention to circadian networks in which the circadian oscillators are represented by the classical 3rd-order Goodwin model [19],[20] to investigate the effects of zeitgebers to circadian oscillations. The critical point here is that the model is simple but it captures the essential features that benefit the study of the entrainment of circadian oscillations such as the containment of a negative feedback loop and the simplification of formulation [23].

A network of 3rd-order Goodwin oscillators is represented by (7) with
\[
h(s) = \frac{1}{(s + b_1)(s + b_2)(s + b_3)}. \tag{26}
\]

Since the 3rd-order Goodwin oscillator network is a special case of the generalized model (7), all the results derived in the previous sections are also applied here. However, we still recall the important results with details for 3rd-order Goodwin model and introduce an important property of the entrainment which has not been addressed for generalized Goodwin-type oscillator networks. In addition, a practical model of circadian rhythm in *Neurospora crassa* adopted from [18] is employed in the simulation to clearly demonstrate the theoretical results.

For simplicity, let us consider the zeitgeber to be sinusoidal, i.e.,
\[
w(t) = \kappa_0 + \kappa_1 \sin(\omega t + \zeta_1). \tag{27}
\]
and suppose that the circadian network is entrained by the zeitgeber (27). Consequently, the harmonic balance equations for entrained oscillations are written as
\[
\begin{aligned}
\left[ \phi(0) - \lambda \hat{\alpha}_0 \right] \hat{\alpha}_0 &= \kappa_0, \\
\left[ \phi(i\omega) - \lambda \hat{\alpha}_1 e^{i\phi_0} \right] \hat{\alpha}_1 e^{i\phi} &= \kappa_1.
\end{aligned} \tag{28}
\]

We note that \( \phi(i\omega) \) is represented by
Proposition 5. Suppose that the interconnection matrix $A$ is a Laplacian matrix. Then, the phase shift $\rho_1$ of entrained oscillations in the circadian network (7) with $n = 3$ is a monotonically decreasing function of the frequency $\omega$ of the zeitgeber, in particular the Light-Dark signal. Note that the relation between the phase shift and the frequency of the zeitgeber has a significant importance in the study of circadian oscillations [23]. This relation has been observed in biology but its underlying mechanism is still unclear. Recently, Granada et al. present a theoretical study on the relation between the entrainment phase of circadian oscillations and the zeitgebers [23]. Nevertheless, the mathematical models utilized in [23] are different from ours. The interesting point here is that the obtained result agrees with the result in [23] even though our model is different.

Proof. Since all Laplacian matrix has eigenvalue $\lambda = 0$ we obtain from (31) that
\[
\tan(\rho_1) = \frac{\omega (b_1 b_2 b_3 + b_1 b_3 - \omega^2)}{b_1 b_2 b_3 - (b_1 + b_2 + b_3) \omega^2} = \frac{\omega (\beta_2 - \omega^2)}{\beta_1 - \beta_1 \omega^2}.
\]
Denote $g(\omega) = \frac{\omega (\beta_2 - \omega^2)}{\beta_1 - \beta_1 \omega^2}$. We have
\[
\frac{dg(\omega)}{d\omega} = \frac{\beta_1 \omega^3 + (\beta_2 \beta_1 - 3\beta_3) \omega^2 + \beta_2 \beta_1}{(\beta_1 - \beta_1 \omega^2)^2}.
\]
Employing Cauchy-Schwarz inequality gives us
\[
(b_1 b_2 + b_2 b_3 + b_3 b_1)(b_1 + b_2 + b_3) \geq 9 b_1 b_2 b_3
\]
\[
\Leftrightarrow \beta_2 \beta_1 \geq 9 \beta_3.
\]
Consequently, we can write
\[
\beta_1 \omega^3 + (\beta_2 \beta_1 - 3 \beta_3) \omega^2 + \beta_2 \beta_1 = \beta_1 (\omega^3 + \omega (\omega^2 + \omega^2)),
\]
where $\omega_1 + \omega_2 = \beta_2 \beta_1 - 3 \beta_3 > 0$ and $\omega_1 \omega_2 = \frac{\beta_2 \beta_1}{\beta_1} > 0$.
This leads to a fact that $\omega_1 > 0$ and $\omega_2 > 0$. As a result, $\beta_1 (\omega^3 + \omega (\omega^2 + \omega^2)) > 0 \forall \omega$. Thus, $\frac{dg(\omega)}{d\omega} > 0 \forall \omega$, i.e., $g(\omega)$ is a strictly monotonically increasing function of $\omega$. Note that tan is monotonically increasing, and hence we see from (33) that $\rho_1$ is a monotonically decreasing function of $\omega$. □

Remark 1. It should be noted in [23] that the authors consider the entrainment phase $\psi$, which is equal to the difference between the phase of zeitgebers and the phase of induced circadian oscillations. This quantity in fact is equal to $-\rho_1$ in this paper. We then obtain immediately from Proposition 5 that the entrainment phase $\psi$ is a monotonically increasing function of $\omega$. Furthermore, let us denote $T$ and $T_z$ the period of autonomous circadian oscillations and the period of zeitgebers, respectively, then the period mismatch $T_z - T = \frac{2\pi}{\omega_1} - \frac{2\pi}{\omega_2}$ is monotonically increasing with respect to $\omega$. Hence, the entrainment phase $\psi$ is a monotonically increasing function of the period mismatch $T_z - T$. This result agrees with the observations in [7], [23], [24]. Therefore, our result supports the biological evidences and may be helpful for further investigating the circadian oscillations.

6.3 General Case

Likewise in Section 5.2, we assume here that the integral in the describing function $\hat{\sigma}_1$ is a monotonically decreasing function of $\hat{a}_0$ and $\hat{a}_1$. Moreover, we can also show that $\hat{\sigma}_1 < 0$. The following corollaries show the monotonic dependence of the amplitudes and phases of entrained circadian oscillations to the amplitude of the zeitgeber in the 3rd-order Goodwin oscillator networks.

Corollary 2. The amplitude $\hat{a}_1$ of entrained circadian oscillations is a monotonically increasing function of the amplitude $\kappa_1$ of the zeitgeber if the following condition holds:
\[
C_2. \ [b_1 b_2 b_3 - (b_1 + b_2 + b_3) \omega^2] \lambda > 0.
\]

Corollary 3. The phase shift $\rho_1$ of the 1st harmonic component in the entrained network oscillations is a monotonically function of the amplitude $\kappa_1$ of the zeitgeber as indicated in Table 2, where $-\downarrow$ and $+\uparrow$ mean negative and positive, respectively; $\uparrow$ and $\downarrow$ mean monotonically increasing and decreasing, respectively.

Proof. This corollary can be proved similarly to Proposition 4 with a note that $\frac{b_1 b_2 b_3}{b_1 + b_2 + b_3} < b_1 b_2 b_3 + b_1 b_3$ holds, and hence we can deduce that $\hat{\phi}_R < 0$ if $\phi_1 < 0$ and $\phi_R > 0$ leads to $\phi_1 > 0$. Therefore, the cases corresponding to $\hat{\phi}_R > 0$, $\phi_1 < 0$ cannot occur. □

Table 2 Monotonic dependence of the phase shift to the zeitgeber in networks of 3rd-order Goodwin oscillators.

<table>
<thead>
<tr>
<th>$\lambda$</th>
<th>$\hat{\phi}_R$</th>
<th>$\phi_1$</th>
<th>$\phi_R$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$-\downarrow$</td>
<td>$-\downarrow$</td>
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<tr>
<td>$-\downarrow$</td>
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<tr>
<td>$+\uparrow$</td>
<td>$+\uparrow$</td>
<td>$+\uparrow$</td>
<td>$-\downarrow$</td>
</tr>
</tbody>
</table>
6.4 Numerical Example

Consider a network of 50 circadian oscillators with \( h(s) \) given in (26) and the original parameters are adopted from [18] for the model of circadian oscillations in *Neurospora crassa* as follows: \( k_1 = 1, k_2 = 1, k_3 = 1, k_4 = 0.2, k_5 = 0.2, k_6 = 0.1, K = 1, p = 9 \). These parameters corresponds to autonomous circadian oscillations with period 22.3 hours. Hence, we can compute the dimensionless parameters to be \( b_1 = 0.2, b_2 = 0.2, b_3 = 0.1 \). We assume that the network has the same structure as in Example 1, i.e., the interconnection matrix in the whole network is \( A = I_2 \otimes A_1 + L \otimes I_0 \). Then \( A_1 \) is randomly generated such that it admits \( I_{10} \) as one of its eigenvectors and the associated eigenvalue is 15, while \( L \) is chosen to be a Laplacian matrix as in Example 1. As a result, the interconnection matrix in the whole network \( A \) has one eigenvector \( I_{50} \) and the associated eigenvalue is 15.

To demonstrate the amplitude condition of the external input for entrainment, we first simulate the autonomous oscillations in the network, i.e., without the zeitgeber and then simulate the oscillator network forced by a sinusoidal zeitgeber with period equal to 24 hours \( w(t) = k_0 + k_1 \sin \left( \frac{2\pi}{24} t \right) \), where \( k_0 \) and \( k_1 \) are subjected to be gradually changed. Then Fig. 6 shows the simulation results with different values of \( k_0 \) and \( k_1 \). It can be observed that the autonomous oscillations are asynchronous and when \( k_0 \) and \( k_1 \) increase from 0.001 to 0.004, the induced oscillations in the network are not synchronized. Afterward, the induced network oscillations are synchronized as \( k_0 \) and \( k_1 \) are equal to 0.006 and they are synchronized as we continually increase \( k_0 \) and \( k_1 \). Thus, the amplitude of the zeitgeber should be large enough to make the network oscillations entrained as stated in Conjecture 1.

Next, we attempt to verify another condition on the frequency of the zeitgeber which should be close enough to the natural frequency of the autonomous network oscillations so that there exist induced oscillations in the network under the effect of the zeitgeber. To do so, we apply a sinusoidal zeitgeber \( w(t) = 0.1 + 0.1 \sin(\omega t) \) with oscillating period changes from 3 hours to 28 hours to the oscillator network. The simulation results are displayed in Fig. 7 in which the first subplot exhibits the asynchronous autonomous network oscillations and the next two subplots with period of the zeitgeber to be 3 hours and 5 hours shows that there are no oscillations in the network though the output of oscillators converge to a same value. The sequent subplots reveal that as we increase the period of the zeitgeber, the oscillations occur in the network. In addition, they are synchronized and their frequency changes respectively to the variance on the period of the zeitgeber. More specifically, the period of induced network oscillations is exactly equal to \( (\omega - \frac{2\pi}{24}) \).

Then the induced circadian oscillations in the network are exhibited in Fig. 9. We can see that the circadian oscillations still synchronize at the frequency of the zeitgeber and they contain higher order harmonics instead of having only zero and first order harmonics.

### 7. Conclusion

A systematic approach based on the harmonic balance
networks should be considered.

orously treated and more general model of nonlinear oscillator works, the subiological experiments and hence they may give some new in-

grily, our theoretical results agree with the observations from 

results can be utilized to investigate the e-

Neurospora crassa 

oscillations, for example in 

tors. Since this model can be used to describe the circadian 

have been shown for a network of 3rd-order Goodwin oscilla-

work oscillations have been derived. Then more specific results 

riodic external inputs. Specifically, a necessary condition and 

method has been proposed to study the entrainment in nonlinear 

networks of generalized Goodwin-type oscillators driven by pe-

periodic external inputs. Specifically, a necessary condition and a conjecture for entrainment have been introduced. Then the 

profile estimation and monotonic properties of entrained net-

Fig. 8 Monotonicity of the phase shift of entrained circadian oscillations to the period of the zeitgeber.

Fig. 9 Synchrony in a randomly interconnected network of Neurospora crassa circadian oscillators by a periodic zeitgeber with higher or-

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[1] M.J. Rust, S.S. Golden, and E.K. OShea: Light-driven changes in energy metabolism directly entrain the cyanobacterial circa-


**Appendix**

- **Assumption 1.** The integral in the describing function $\hat{\sigma}_1$ is a monotonically decreasing function of $\hat{\alpha}_0$ and $\hat{\alpha}_1$.

![Graph](image)

Fig. A.1 An example of the describing function $\hat{\sigma}_1$ calculated with $\hat{\alpha}_0, \hat{\alpha}_1 \in [0, 10]$.

This assumption seems to be conservative from a theoretical point of view but we observe from many simulations that this assumption is satisfied with the bias $\hat{\alpha}_0$ and the amplitude of the 1st-order harmonic $\hat{\alpha}_1$ in some intervals. An example of such an interval of $\hat{\alpha}_0$ and $\hat{\alpha}_1$ is shown in Fig. A.1 where $\hat{\alpha}_0$ and $\hat{\alpha}_1$ belong to the interval [0, 10] and the Hill coefficient $p$ is taken to be 9. We can observe that there exist some regions of $\hat{\alpha}_0$ and $\hat{\alpha}_1$ such that in which $\hat{\sigma}_1$ is monotonically decreasing, for instance near the upper right corner in the figure. Hence, Assumption 1 is employed in for analysis in this paper.

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