Circadian Oscillators and Phase Synchronization under a Light-Dark Cycle

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Abstract: This paper aims to analyze the circadian behavior of the population of suprachiasmatic nucleus (SCN) neuron by light-dark cycle. Self-sustained oscillation is generated in individual SCN neuron by a molecular regulatory network. Cells oscillate with different periods, but the SCN neurons display significant synchronization under the effect of the light-dark (LD) cycle. We present a model for a population of circadian oscillations in the SCN. We show that synchronization can be entrained by a 24-h LD cycle. The results of this paper establish not only a theoretical foundation, but also a quantitative basis for understanding the essential cooperative dynamics.

Keywords: SCN neuron; Circadian rhythm; Self-sustained oscillator; Phase synchronization

1 Introduction

In mammals, physiological and behavioral circadian rhythms are controlled by a pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus[1, 2]. Daily rhythms in behavior, physiology and metabolism are controlled by endogenous circadian clocks. At the heart of these clocks is a circadian oscillator that keeps circadian time, which is entrained by environmental cues such as light and activates rhythmic outputs at the appropriate time of day. Circadian clocks regulate rhythmic phenomena in animals, plants, fungi and even some prokaryotes. The circadian oscillator must maintain synchrony with environmental cycles to drive behavioral, physiological and metabolic outputs at the appropriate time of day.

Daily environmental cycles of light, temperature, food and social interactions are all capable of entraining circadian oscillators, but light is generally considered to be the strongest and most pervasive factor. In nature conditions, the circadian clock is subject to alternation of days and nights and in response to this cycling environment, phase-locks to the LD cycle, enabling the body to follow a 24-h rhythm. It has been shown that isolated individual neurons are able to produce circadian oscillations, with periods ranging from 20 to 28 hours[3, 4].

In this article, we mainly analyze the circadian oscillator and the effect of the LD cycle from mathematical angle. A mathematical model to describe the behavior of a population of SCN neurons is presented. The single cell oscillator is described by a three-variable model similar to the widely used Goodwin model that was able to simulate physiological oscillations on the basis of a negative feedback. This model, based on the negative feedback loop, accounts for the core molecular mechanism leading to self-sustained oscillations of clock genes.

First of all, we analyze the stability of the single cell model and give the sufficient conditions to have stable equilibrium point and periodic solution. Then under the condition of periodic solution, we show
that, the models of cells with different parameter values, whose individual periods are different. Finally, we show the effect of a LD cycle from theoretical and numerical aspects. The LD cycle entrains phase synchronization and all the cells have the same periods 24-h.

2 Model of self-sustained oscillation in a SCN neuron

To simulate circadian oscillations in single mammalian cells, we resort to a three-variable model, based on the Goodwin oscillator\[5\]. In this model, a clock gene mRNA ($X$) produces a clock protein ($Y$) which, in turn, activates a transcriptional inhibitor ($Z$). The latter inhibits the transcription of the clock gene, closing a negative feedback loop. In the original model\[5\], sustained oscillations could be obtained only by choosing a steep feedback function, with a high Hill coefficient\[6\]. This constraint is due to the linear terms used for the degradation steps. In circadian clocks, protein degradation is controlled by phosphorylation, ubiquitination and proteasomal degradation and thus it is reasonable to assume Michaelian kinetics. Many other biological models\[7, 8\] rely on Michaelian functions as well. Here, we advise the model of an individual cell as following:

\[
\begin{align*}
\dot{X} &= \frac{v_1 K^n_1}{K^n_1 Z^n} - \frac{v_2 X}{K_2 + X}, \\
\dot{Y} &= k_3 X - \frac{v_4 Y}{K_4 + Y}, \\
\dot{Z} &= k_5 Y - \frac{v_6 Z}{K_6 + Z}.
\end{align*}
\]

(1)

where $v_1, v_2, v_4, v_6, K_1, K_2, K_4, K_6, k_3, k_5$ are parameters.

In this version, self-sustained oscillation can be obtained for a Hill coefficient of $n = 4$. The variable $X$ represents mRNA concentration of a clock gene, per or cry; $Y$ is the resulting protein, PER or CRY; and $Z$ is the active protein or the nuclear form of the protein (inhibitor). This model is closely related to those proposed by Ruoff and Rensing\[9\], Leloup and co-workers\[8\], or Ruoff and co-workers\[10\] for the circadian clock in Neurospora.

3 The analysis of self-sustained oscillation in model (1)

According to the result of biological experiment, we know that there exists self-sustained oscillation in model (1) generated by circadian oscillator. Therefore, the dynamics of model (1) should be analyzed. Firstly we will show the existence and uniqueness of the equilibrium point of system Eq.(1).

Let the right hand of Eq.(1) be zero, then we have

\[
\frac{v_1 K^n_1}{K^n_1 Z^n} - \frac{v_2 X}{K_2 + X} = 0
\]

(2)

\[
k_3 X - \frac{v_4 Y}{K_4 + Y} = 0
\]

(3)

\[
k_5 Y - \frac{v_6 Z}{K_6 + Z} = 0
\]

(4)

It’s obvious that $(0, 0, 0)$ is not the solution of Eq.(2), Eq.(3) and Eq.(4). The following equation can be derived from Eq.(2), Eq.(3) and Eq.(4) by the knowledge of elementary mathematics.

\[
\frac{v_1}{v_2 K^n_1 K_2} Z^n + \frac{v_1}{v_2 K_2} - \frac{1}{K_2} = \frac{k_3}{v_4} + \frac{K_4 k_5}{v_4 v_6} K_6 K_4 + \frac{k_3 k_5}{v_4 v_6} 1 Z \geq 0
\]

(5)

Regarding the right hand and left hand of equal mark of Eq.(5) respectively as the function of $Z$ and $Z \geq 0$, we can easily see that there is one and only one solution of Eq.(5). That is to say the system Eq.(1) has one and only one equilibrium point $\bar{P}(\bar{X}, \bar{Y}, \bar{Z})$. 

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Let $Q$ denote the Jacobin matrix at $\bar{P}$ of Eq. (1)

$$
Q = \begin{pmatrix}
\frac{K_2v_2}{(K_2 + X)^2} & 0 & -\frac{nv_1K_1^nZ^{n-1}}{(K_1^n + Z^n)^2} \\
\frac{v_4K_4}{(K_4 + Y)^2} & 0 & -\frac{v_6K_6}{(K_6 + Z)^2} \\
0 & 0 & -\frac{v_8K_8}{(K_8 + W)^2}
\end{pmatrix}
$$

and $\det(\lambda I - Q) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$, then we have:

$$
a_1 = \frac{K_2v_2}{(K_2 + X)^2} + \frac{v_4K_4}{(K_4 + Y)^2} + \frac{v_6K_6}{(K_6 + Z)^2} > 0
$$

$$
a_2 = \frac{K_2v_2K_4v_4}{(K_2 + X)^2(K_4 + Y)^2} + \frac{K_4v_2K_6v_6}{(K_2 + X)^2(K_6 + Z)^2} + \frac{v_4K_4v_6K_6}{(K_4 + Y)^2(K_6 + Z)^2} > 0
$$

$$
a_3 = \frac{K_2v_2K_4v_4K_6v_6}{(K_2 + X)^2(K_4 + Y)^2(K_6 + Z)^2} + \frac{nv_1K_1^nK_3K_5Z^{n-1}}{(K_1^n + Z^n)^2} > 0
$$

Hence, from Routh-Hurwitz criterion, the equilibrium point $\bar{P}$ of Eq. (1) is asymptotically stable if the following conditions hold:

$$
a_1a_2 - a_3 > 0
$$

and Hopf bifurcation will appear when

$$
a_1a_2 - a_3 = 0
$$

Now we conclude the foregoing analysis as the following theorem for the single cell without the effect of LD cycle.

**Theorem 1.** The system Eq. (1) has one and only one equilibrium point. Furthermore, if the parameters of Eq. (1) satisfy $a_1a_2 - a_3 > 0$, then the equilibrium point is asymptotically stable. And if $a_1a_2 - a_3 = 0$, then Hopf bifurcation appears.

This theorem tells that the parameter values of model (1) must satisfy the conditions above when we study the circadian phenomenon of SCN. Under these conditions, if we consider the SCN colony, in which the models of different cells have different parameter values, then the self-sustained oscillators restrained from Hopf-bifurcation of these models will have different periods. Here we take ten cells as an example. We take the the same parameter values for the ten models except $v_1, k_3, k_5$ and furthermore $v_1 = k_3 = k_5$ whose values are given by Tab.1. The other values are $K_1 = K_2 = K_4 = K_6 = 1; n = 4; v_2 = v_4 = v_6 = 0.35$. These values are validated to satisfy $a_1a_2 - a_3 < 0$. By simulation, we get Fig.1 and Fig.2.

In Fig.1 we give the time evolution of the first variables of ten cells. Although every cell expresses periodic solution, their periods and wave forms are different. Fig.2 shows the different individual periods of ten cells where the abscissa axis refers to the serial number of cells and the ordinate axis refers to periods. From Fig.2, we can see that the individual periods of different cells are different and they range from 23.5-h to 25.1-h. From the report of [11], we know that the periods of different cells arrange from 20h to 28h.

<table>
<thead>
<tr>
<th>$n$</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
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<td>0.61</td>
<td>0.62</td>
<td>0.63</td>
<td>0.64</td>
<td>0.65</td>
<td>0.66</td>
<td>0.67</td>
<td>0.68</td>
<td>0.69</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Tab.1 The values of $v_1$ in ten models. $n$ represents the $n$-th cell.

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Figure 1: The time evolution of $x_i(t)$ for $i = 1, 2, \ldots, 10$.

Figure 2: The profile of ten cells’ periods.

4 The effect of LD cycle and phase synchronization

In the natural environment, circadian clocks are subjected to alternation of light and darkness. This external cycle entrains the oscillations precisely to a 24-period. Here we will give the theoretic analysis of the effect of a light-cycle by using a square-wave function for the light term, $L$. The term $L$ switches from $L = 0$ in dark phase to $L = L_0$ in light phase. That is to say

$$L(t) = \begin{cases} L_0 & t \in [24k, 24k + 12), \\ 0 & t \in [24k + 12, 24(k + 1)). \end{cases}$$

where $k$ is a natural number. By Fourier series expansion, $L(t)$ can be rewritten as

$$L(t) \sim L_0 - \frac{2L_0}{\pi} \sum_{k=0}^{\infty} \frac{1}{2k+1} \sin \left( \frac{(2k+1)\pi t}{12} \right)$$

The evolutions equations for the population composed of $N$ cells under the effect of day-light cycle are then written as

$$\begin{cases} \dot{X}_i = v_1 \frac{K_1^+}{K_1^+ + Z_i} - v_2 \frac{X_i}{K_2 + X_i} + L, \\ \dot{Y}_i = k_3 X_i - v_4 \frac{Y_i}{K_4 + Y_i}, \\ \dot{Z}_i = k_5 Y_i - v_6 \frac{Z_i}{K_6 + Z_i}. \end{cases} \quad (7)$$

where $i = 1, 2, \ldots, N$, and when $L_0 = 0$, the system $(7)$ has self-sustained oscillation.

At the first place we will give a proposition as follows.

**Proposition 1.** The periodic external forcing added on the right side of Eq.(7) is composed by the constant part and the periodic part with zero mean. The oscillators have the same period as that of the periodic external forcing, if the constant part can make Eq.(8) have an asymptotically stable equilibrium point but Eq.(1) has an unstable equilibrium point.

Let us consider the autonomous part of system $(7)$:

$$\begin{cases} \dot{X} = v_1 \frac{K_1^+}{K_1^+ + Z} - v_2 \frac{X}{K_2 + X} + L_0, \\ \dot{Y} = k_3 X - v_4 \frac{Y}{K_4 + Y}, \\ \dot{Z} = k_5 Y - v_6 \frac{Z}{K_6 + Z}. \end{cases} \quad (8)$$
Now, we analyze the equilibrium point of Eq. (8). Using the same method as the last section, the similar equation can be educed.

\[
\frac{2v_1K_1^n}{(2v_1-L_0)K_1^n-L_0Z^n} = 3 + \frac{k_3k_2}{v_4} + \frac{k_3k_5K_4}{v_4v_6} + \frac{k_3k_5K_4K_6}{v_6v_4} \cdot \frac{1}{Z} > 0
\] (9)

According to the elementary mathematic knowledge, we know that when \(L_0 < 2v_1\), the Eq.(9) has one and only one positive solution. So the System (8) has one and only one equilibrium point \(P_0(X_0, Y_0, Z_0)\). Then we have:

\[
a'_1 = \frac{K_2v_2}{(K_2 + X_0)^2} + v_4K_4(Y_0)^2 + \frac{v_6K_6}{(K_0 + Z_0)^2} > 0
\]

\[
a'_2 = \frac{K_2v_2K_4v_4}{(K_2 + X_0)^2(K_4 + Y_0)^2} + \frac{K_2v_2K_6v_6}{(K_2 + X_0)^2(K_6 + Z_0)^2} + \frac{v_4K_4v_6K_6}{(K_4 + Y_0)^2(K_6 + Z_0)^2} > 0
\]

\[
a'_3 = \frac{K_2v_2K_4v_4K_6v_6}{(K_2 + X_0)^2(K_4 + Y_0)^2(K_6 + Z_0)^2} + \frac{nv_1K_1^nK_3K_5Z_0^{n-1}}{(K_1^n + Z_0^n)^2} > 0
\]

By Routh-Hurwitz criterion, the equilibrium point \(P_0\) of Eq.(8) is asymptotically stable if the following condition hold:

\[
a'_1a'_2 - a'_3 > 0
\]

Summarizing the foregoing analysis, we get that when \(L_0\) satisfies

\[
\begin{align*}
L_0 < 2v_1, \\
a'_1a'_2 - a'_3 > 0.
\end{align*}
\] (10)

the system (8) has one and only one equilibrium point \(P_0\), and \(P_0\) is asymptotically stable.

Fig.3 and Fig.4 show the shifts from periodic solution to stable equilibrium point. The value of \(L_0\) of Fig.4 satisfies the condition Eq.(10)

Now, let us consider system (7) under the condition of Eq.(10).

\[
\begin{align*}
\dot{X}_i &= v_1 \frac{K_1^n}{K_1^n + Z_0^n} - v_2 \frac{X_i}{K_2 + X_i} + \frac{L_0}{2} - \frac{2L_0}{\pi} \sum_{k=0}^{\infty} \frac{1}{2k+1} \sin \left( \frac{(2k+1)\pi t}{12} \right), \\
\dot{Y}_i &= k_3X_i - v_4 \frac{Y_i}{K_4 + Y_i}, \\
\dot{Z}_i &= k_5Y_i - v_6 \frac{Z_i}{K_6 + Z_i}.
\end{align*}
\] (11)

according to the proposition, all the oscillators have the same period which is 24-h the period of the LD cycle. Fig.5 shows the periodic evolution of \(X_i\) with the same parameter values as Fig.1 with \(L_0 = 0.09\). Fig.6 gives the comparison of periods of ten different cells. From Fig.5 and Fig.6, we can see that every cell has not only the uniform period but also the same phase and only the amplitudes are different. That is to say these cells get a special phase synchronization but not complete synchronization.

At last, we give the detailed outline to solve periodic solution as follows.

Rewriting Eq.(11) as follows:

\[
\dot{x} = f(x) + p(t) = f(x) + M - \varepsilon \tilde{p}(t) = \tilde{f}(x) - \varepsilon \tilde{p}(t)
\] (12)

where \(x = (X, Y, Z)^T, f(x) = (v_1 \frac{K_1^n}{K_1^n + Z_0^n} - v_2 \frac{X}{K_2 + X}, k_3X - v_4 \frac{Y}{K_4 + Y}, k_5Y - v_6 \frac{Z}{K_6 + Z})^T, M = (\frac{L_0}{2}, 0, 0)^T, \tilde{f}(x) = f(x) + M, \tilde{p}(t) = (\sum_{k=0}^{\infty} \frac{1}{2k+1} \sin \left( \frac{(2k+1)\pi t}{12} \right), 0, 0)^T \) and \(0 < \varepsilon = \frac{2L_0}{\pi} < 1\).

Let the solution of Eq.(12) be

\[
x = x_0 + \varepsilon x_1 + \varepsilon^2 x_2 + \varepsilon^3 x_3 + \cdots
\]

where \(\tilde{f}(x_0) = 0\). Substituting \(x\) into Eq.(12) and taking Taylor expansion for \(f(x)\), by comparing the coefficients of \(\varepsilon^i, i = 1, 2, 3 \cdots\) we have

\[
\dot{x}_1 = Ax_1 - \tilde{p}(t),
\] (13)
Figure 3: The time evolution of $X$. Parameter values are $v_1 = k_3 = k_5 = 0.7; K_1 = K_2 = K_4 = K_6 = 1; n = 4; v_2 = v_4 = v_6 = 0.35; L_0 = 0$.

Figure 4: The time evolution of $X$. Parameter values are the same as those of Fig.3 except $L_0 = 0.4$.

Figure 5: The time evolution of $x_i(t)$ for $i = 1, 2, \ldots, 10$.

Figure 6: The profile of ten cells’ periods.

$$\dot{x}_2 = Ax_2 + \frac{1}{2}x_1^T D^2 f(x_0)x_1, \quad (14)$$

$$\vdots$$

$$\dot{x}_n = Ax_n + g(x_0, x_1, x_2, \ldots, x_{n-1}), \quad (15)$$

where $A = Df(x_0)$ and $g(x_0, x_1, x_2, \ldots, x_{n-1})$ is the polynomial of $x_0, x_1, x_2, \ldots, x_{n-1}$.

From Eq.(13), we have

$$x_1 = ce^{At} - e^{At} \int e^{-As} \bar{p}(s) ds \quad (16)$$

$$= ce^{At} + \sum_{k=0}^{\infty} \frac{A^{-1}}{2k+1}(\sin \frac{(2k+1) \pi t}{12}, 0, 0)^T + \frac{A^{-2} \pi}{12} (\cos \frac{(2k+1) \pi t}{12}, 0, 0)^T$$

$$\left(1 + \frac{(2k+1)^2}{12^2} \pi^2 A^{-2}\right)^{-1} \quad (17)$$

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Since $x_0$ is asymptotically stable, the first part of the right side converges to zero. The second part is a sum of infinite series, each term of which is 24-periodic. Then let us consider the infinite series.

$$\sum_{k=0}^{\infty} \left( \frac{A^{-1}}{2k+1} \right) (\sin \frac{(2k+1)\pi t}{12}, 0, 0)^T + \frac{A^{-2}\pi}{12} (\cos \frac{(2k+1)\pi t}{12}, 0, 0)^T (1 + \frac{(2k+1)^2}{144}\pi^2 A^{-2})^{-1}$$

$$\leq \sum_{k=0}^{\infty} \left( \frac{A^{-1}}{2k+1} \right) ||(\cos \frac{(2k+1)^2}{144}\pi^2 ||A^{-2}||)^{-1}$$

$$= \sum_{k=0}^{\infty} \left( \frac{A^{-1}}{2k+1} \right) \frac{144}{(2k+1)^2 \pi^2}$$

From the last inequality, we can see that the infinite series is convergent with $\frac{1}{(2k+1)^2}$. So $x_1$ is 24-periodic after a long time.

From Eq.(14), we have

$$x_2 = e^{At} + e^{At} \int e^{-As} \frac{1}{2} x_1^T D^2 f(x_0) x_1 ds$$  \hspace{1cm} (18)$$

Substituting Eq.(17) into Eq.(18), we get that $x_2$ has similar form to $x_1$ which is the sum of a term convergent to zero and a infinite series which is convergent with at least $\frac{1}{(2k+1)^2}$ and 24-periodic. At most, a constant part will appear in $x_2$ compared with $x_1$. So $x_2$ is also 24-periodic after a long time. With similar method we can analyze $x_n$, $n = 3, 4, \cdots$, which are also 24-periodic. Thus

$$x = x_0 + \varepsilon x_1 + \varepsilon^2 x_2 + \varepsilon^3 x_3 + \cdots$$

is 24-periodic. Besides, if all of $x_i$ are uniformly bounded, then the right side is convergent.

5 Discussion and conclusion

When $L_0$ is not large enough, that is to say, when the system Eq.(8) still has a limit cycle, some oscillators probably can not get the special phase synchronization which has the same phase and period but different amplitude. Fig.7 shows this situation. In Fig.7, the oscillators have the same parameter values as those in Fig.5 and the eleventh has the parameter values as follows: $v_1 = k_2 = k_5 = 0.7; K_1 = K_2 = K_4 = K_6 = 1; n = 4; v_2 = v_4 = v_6 = 0.35; L_0 = 0.002$. In this figure ten oscillators get phase synchronization and the eleventh does not phase synchronize with the others. From this fact, we can see that when the light is strong enough, most of the cells can get phase synchronization, but when the light is weak, some cells can not get phase synchronization.

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In this paper, we have introduced a molecular model for the regulatory network underlying the circadian oscillations in the SCN. We investigated the property of the isolated individual cell behavior and gave sufficient conditions for stable equilibrium point and Hopf-bifurcation. Then we analyzed the effect of a LD cycle. We presented the theoretical explanation for the 24-h clock entrained by a LD cycle. That is to say, the isolated cells with different individual periods get phase synchronization if the light satisfies some condition.

It seems that the results above tell us that the cells can get phase synchronization in SCN only with the effect of the LD cycle. Naturally, you may ask why these cells must take interaction by neurotransmitters. In fact, the phase synchronization can be obtained only when the parameter values satisfy Eq.(10), which limits the range of $L_0$ greatly. From Fig.7 we can see that when $L_0$ does not satisfy Eq.(10), phase synchronization can not be obtained. The limitation of $L_0$ causes the limitation of the range of periods of self-sustained oscillators which can get phase synchronization. Thus many cells can not get phase synchronization only with the effect of the LD cycle, what’s more, the dynamics of these cells may be much complex. Once the number of this kind of cells is large enough, then the normal circadian rhythm will be destroyed. Therefore, it’s necessary to consider the interactions of cells. About the interaction we will give more detailed analysis in the next paper.

For the next step, we will study the coupled oscillators by the interaction between cells and the corporate effect of interaction and LD cycle. We will also consider the effect of random factors.

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