TOPICAL REVIEW — Statistical physics and complex systems

Collective behaviors of suprachiasm nucleus neurons under different light–dark cycles*

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The principal circadian clock in the suprachiasm nucleus (SCN) regulates the circadian rhythm of physiological and behavioral activities of mammals. Except for the normal function of the circadian rhythm, the ensemble of SCN neurons may show two collective behaviors, i.e., a free running period in the absence of a light–dark cycle and an entrainment ability to an external T cycle. Experiments show that both the free running periods and the entrainment ranges may vary from one species to another and can be seriously influenced by the coupling among the SCN neurons. We here review the recent progress on how the heterogeneous couplings influence these two collective behaviors. We will show that in the case of homogeneous coupling, the free running period increases monotonically while the entrainment range decreases monotonically with the increase of the coupling strength. While in the case of heterogenous coupling, the dispersion of the coupling strength plays a crucial role. It has been found that the free running period decreases with the increase of the dispersion while the entrainment ability is enhanced by the dispersion. These findings provide new insights into the mechanism of the circadian clock in the SCN.

Keywords: suprachiasm nucleus, light–dark cycle, free running period, entrainment range

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1. Introduction

In mammals, the circadian rhythm of physiological and behavioral activities is regulated by a principal circadian clock located in the suprachiasm nucleus (SCN) of the hypothalamus.[1–4] The SCN is bilaterally situated above the optic chiasm, composed of right SCN and left SCN.[5,6] In the condition of sunlight, the SCN controls the circadian rhythm of mammals. In addition, the SCN has two main features, as follows. In the absence of a light–dark cycle (typically under constant darkness or under constant light), the SCN keeps the free running period close to but not exactly 24 h,[7–9] i.e., maintaining a rhythmic cycle of approximately 24 h in the absence of the light–dark cycle. When there is an external light–dark cycle named the T cycle (the period T is not necessary 24 h), the SCN is able to be entrained to the T cycle,[10,11] i.e., the ability to entrain to the external light–dark cycle. Experiments have shown that both the free running period and the entrainment range are different from one species to another. For instance, the free running period is around 24.1 h for a Sudanian grass rat, 23.8 h for a southern flying squirrel, 22.9 h for a deer mouse, and 24.2 h for the human being. The entrainment range is from 22.9 h to 25.3 h for a Sudanian grass rat, from 23.5 h to 24.9 h for a southern flying squirrel, from 22.5 h to 25.1 h for a deer mouse, and from 21.5 h to 28.6 h for the human being.[3] An interesting question is how the ensemble of neurons within the SCN produces the wide range of collective behaviors.[4,12,13]

The SCN neurons have an intrinsic property of self-oscillation with periods ranging from 22 h to 28 h, which is the key to maintaining the circadian rhythm.[14,15] The molecular mechanism of the self-oscillation is based on the feedback loop of transcriptional and translational control. There are several key genes involved in the feedback loop, i.e., Per, Cry, Clock, and Bmal1.[16,17] This feedback loop can be simply described as follows. A clock gene mRNA upregulates the clock protein, and the clock protein upregulates the clock inhibitor, then the clock inhibitor downregulates the clock gene mRNA. Thus, the clock gene mRNA, the clock protein, and the clock inhibitor in a neuron constitute a negative feedback loop.[16]

The individual neurons in SCN run with different intrinsic periods, but the output period of the SCN is uniform. This implies that the neurons are coupled to form a network, and synchronize to produce a common period. Many works have focused on the coupling mechanism between neurons within the SCN. Experiments revealed that the neurons are coupled mainly through transmitters, e.g., Gamma aminobutyric acid (GABA), vasoactive intestinal polypeptide (VIP), arginine vasopressin (AVP), and so on.[18–21] These neurons are functionally and physically coupled into two subgroups within each side of the SCN (right/left SCN),[22–25] i.e., a ventrolateral part

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(VL) containing 25% SCN neurons and a dorsomedial part (DM) possessing the remaining neurons. The VL charges for receiving light information from the retinohypothalamic tract (RHT), and relays the light information to the DM. The neurons located in the VL mainly produce VIP, and the neurons situated in the DM mostly express AVP.[18–20] The communication between the VL and the DM is relied on GABA.[19] However, the coupling mechanism of left SCN and right SCN is still unclear.[26] Figure 1 shows the schematic diagram of the interaction within the SCN and the input/output of the SCN.

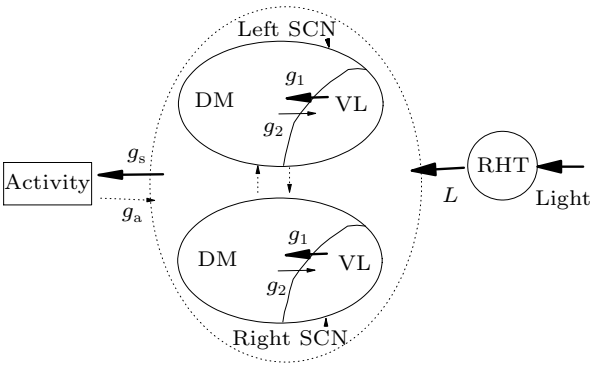


Fig. 1. Interaction within SCN and intput/output of SCN. Here L denotes the strength of light information, and g represents the coupling strength. The light information from RHT is received by the VL containing 25% SCN neurons, and then the VL relays this information to the DM composed of 75% SCN neurons. Both the VL and the DM take part in the regulation of the circadian rhythm of activity. The arrows represent the directed couplings, and the thickness denotes the coupling strength. The coupling strength g_1 from the VL to the DM is much stronger than the coupling strength g_2 from the DM to the VL, while the coupling between the left SCN and the right SCN is still unclear. The coupling strength g_s from the SCN to the behavioral activity is larger than the feedback strength g_a.

The SCN is a heterogeneous network where the VL neurons are sensitive to light information but the DM neurons are not. Physically, the size of the VL neurons is smaller than that of the DM neurons, and the VL neurons are positioned denser than the DM neurons.[4] Since the sensitive ability to VIP (or AVP) varies between the VL neurons and the DM neurons, and the influence of the VL neurons to the DM neurons is more than that of the DM neurons to the VL neurons, these factors result in heterogenous coupling strengths. The influence of this heterogenous coupling has been recently addressed by Gu *et al.* from two aspects, i.e., the mean coupling strength and its dispersion.[27–29]

It is found that the homogeneous coupling between the neurons plays a key role in determining the free running period and the entrainment ability of the SCN. The free running period increases as the coupling strength increases.[30–32] While the entrainment range is negatively related to the coupling strength.[11,33] Recently, Gu *et al.* considered the heterogeneous coupling and found that in addition to the mean value of coupling strengths, the dispersion of coupling strengths also plays an important role in determining the free running period and the entrainment ability of the SCN.[27,29] In the following sections, we will review the effect of the heterogenous coupling on the collective behaviors of the SCN in detail. The rest of the paper is organized as follows. In Section 2, we will summarize the experimental findings under four kinds of light–dark cycles, i.e., constant darkness, constant light, the 24 h light–dark cycle, and the T cycle. Then, in Section 3, we will discuss the theoretical explanations of the experiment findings by a modified Goodwin model. Finally, we provide a discussion and give a conclusion in Section 4.

2. Experimental findings under different light–dark cycles

Owing to the multiple recording methods, experiments can investigate the circadian rhythm from three levels: tissue level, organismal level, and supra-organismal level. The research at the tissue level is mainly focused on the concentration of gene expression *in vitro*, for example Per mNRA of a single neuron measured by bioluminescence.[5,34,35] At the organismal level, the animal behavior is often used as the recording marker, including wheel running, movements, and drinks.[36,37] Another marker used at the organismal level is the multi neuronal unit activity (MUA), which plants an electrode into the brain and records the neuronal activity within the SCN *in vivo*.[38,39] At the supra-organismal level, the social interaction between animals is considered, where the animal behavior is often recorded as a marker of the circadian rhythm.[40]

With these recording methods, in order to explore the network structure of the SCN, the multiple light conditions are applied. Compared to other operations, e.g., anatomy or drug application, there is little physical damage on the SCN exposed to light. Furthermore, there are several kinds of light conditions in nature. For example, there is perpetual day (perpetual night) at the poles, which corresponds to the constant light (constant darkness) in experiments. The photoperiod varies among seasons, especially in the regions of high latitudes. Jet lag happens to travelers across time zones and in shift works. We introduce here the experimental results on the SCN under four kinds of light–dark cycles as follows.

2.1. Constant darkness

It has been reported that there is a circadian rhythm in mammals even in the absence of a light–dark cycle,[7–9] indicating that there is an endogenous clock in mammals. Under constant darkness, it is interesting to find that the free running period changes from one species to another. Recently, studies revealed that this diversity also exists in age, ethnicity, and so on.[41,42] To show the changing process in activity patterns, this locomotor activity is usually displayed in the double-plot actogram (double means 24 h times 2) in the field of circadian

rhythm. As an example, figure 2 shows a schematic illustration of the double-plot actogram under constant darkness, where the x axis represents the external time, the y axis denotes the number of continuous days, and the red dots indicate the activity onset. It is visible that the activity onset is not shifted in Fig. 2(a), but delayed in Fig. 2(b) every day. Thus, the free running period is 24 h in Fig. 2(a) while it is larger than 24 h in Fig. 2(b).

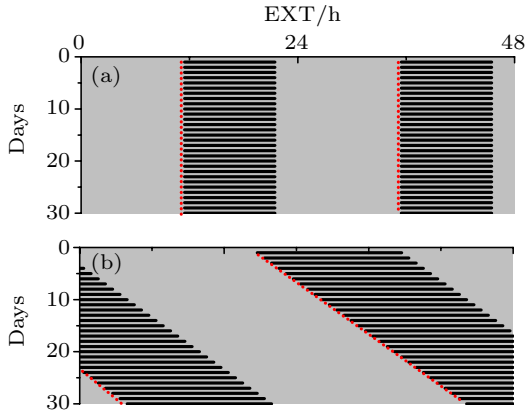


Fig. 2. Locomotor activity of one mouse under constant darkness in a double-plot actogram, where the x axis represents the external time, the y axis denotes the number of continuous days, and the red dots indicate the activity onset. (a) The free running period is 24 h and the external time of activity onset is a constant 11 h. (b) The free running period is larger than 24 h and the activity onset is delayed every day. This figure is made from artificial data.

In MUA studies *in vivo*, the SCN shows a strong rhythm under constant darkness, as found in the 24 h light–dark cycle (light 12 h and dark 12 h in one cycle).[43] There is a high synchronization between the neurons and the strong rhythm in a single neuron oscillation under both constant darkness and 24 h light–dark cycle conditions.[44,45] These studies suggest that the neurons are coupled very well under constant darkness.

2.2. Constant light

Another form of absence of a light–dark cycle is in constant light conditions, such as the arctic ground squirrels. Exposed to constant light, animals may show three kinds of behavioral activities recorded by wheel running.[1,5,46,47] In the first one, animals keep free running with a period larger than 24 h. In the second one, the 24 h activity dissociates into two 12 h activity components which are 12 hs apart or in anti-phase (this phenomenon is called phase-splitting), thus the total activity exhibits a 12 h rhythm. In the third one, animals lose their activity rhythm. The free running and the phase-splitting behaviors under constant light are shown in Fig. 3. To further understand the rhythm regulation of the SCN to behavior activities, researchers investigated the circadian rhythm of the SCN tissue *in vitro*.

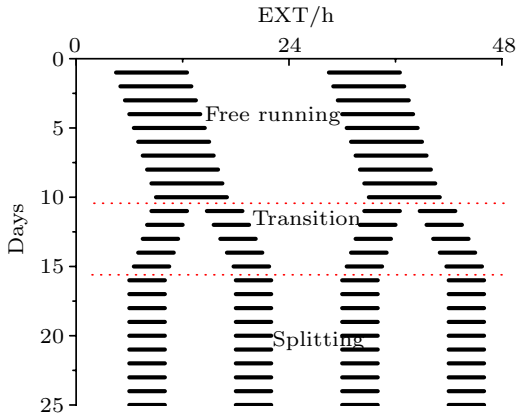


Fig. 3. Locomotor activity of one hamster under constant light in a double-plot actogram, where the x axis represents the external time, and the y axis denotes the number of continuous days. In the first 10 days, the animal shows the free running behavior with a period larger than 24 h. Then in the next 5 days, there emerge two activity bouts within one day, which depart from each other gradually. In the last 10 days, the phase difference between the two bouts is stable and equals to 12 h. This figure is made from artificial data.

In the case of phase-splitting, researchers found that the behavioral activity shows a 12 h rhythm because of the anti-phase between the left SCN and the right SCN. Within each side of the SCN from the same animal, the concentration of Per mRNA is recorded in one slice. Within each slice, the neurons are in-phase and high synchrony, thus the whole slice shows a high amplitude oscillation with a period equal to 24 h. Between the slices of right and left SCNs, the phase difference is 12 h, i.e., anti-phase. Furthermore, the ablation of one side of the SCN causes the disappearance of one activity component, and the animal activity restores the 24 h circadian rhythm.[6] Thus, one activity component is regulated by one side of the SCN.

In the case of maintaining a 24 h circadian rhythm, there is no phase difference between the left SCN and the right SCN. Within the left or right SCN, the presence of high synchrony between the neurons leads to a large amplitude of the slice. Thus, the output of the whole SCN shows a pronounced 24 h rhythm, as found under constant darkness.

In the case of disappearance of the rhythm, there are two alternative explanations. One is that the rhythm of a single neuron oscillator vanishes,[1] and the other is that the synchrony between the neurons is lost.[46]

2.3. 24 h light–dark cycle

For mammals, the most crucial function of the SCN is to maintain synchronization to the external 24 h light–dark cycle. Most mammals have evolved to exhibit a stable phase difference to the external 24 h light–dark cycle. For instance, mice are active during the night-time, and human beings are active during the daytime. The difference between the free running period and 24 h contributes to the stable phase difference, i.e., animals with a free running period of less than 24 h are active during the night-time (they are called nocturnal animals)

and animals with a free running period of larger than 24 h are active during the daytime (they are called diurnal animals).[48] For the human being, the free running period is around 24 h.[8] Thus, people with a free running period of less than 24 h wake up early, and prefer to work in the morning. These people are called "morning types". On the other hand, people with a free running period of larger than 24 h sleep late, and prefer to work in the evening. These people are called "evening types".[49] Unfortunately, some people are in lack of a stable phase difference to the 24 h light–dark cycle on account of their free running period being far from 24 h.[50,51]

The stable phase difference between the internal circadian clock and the external 24 h cycle may be disturbed by jet-lag across different time zones or in factory or hospital shift work that many people have suffered. After traveling to a new time zone, the VL will be quickly adjusted to the new 24 h cycle, while the DM will remain in the phase of the previous 24 h cycle at the beginning and then be gradually adjusted to the new 24 h cycle. The amount of adjusting time depends on the difference between the time zones, i.e., roughly 1 h time difference takes 1 day to be adjusted.[23,52,53] Moreover, the process of adjustment also proves that the VL directly receives the light information and relays it to the DM.

2.4. T cycle

The SCN can be entrained not only to the 24 h light–dark cycle, but also to an artificial T cycle, where T denotes the period of the cycle. The artificial T cycle can provide some realistic significance. First, the rotation periods reflected by the light–dark cycle of other planets are not 24 h. For instance, the rotation period of Mars is 24.7 h. Second, the rotation period of Earth is gradually increased during its evolution. Third, mathematically, the free running period (τ) of one species is set as 1, and 24 h is set as $T'_{24} = 24/\tau$. Due to the variation of the free running periods among species, the normalized period T'_{24} will also vary among species. Thus, the T'_{24} is not a constant among species.

Most animals are able to be entrained to the 24 h cycle. While for the T cycle, an animal may perform two kinds of behavioral activities. One is that the animal may display the same period as the T cycle. This phenomenon is called the entrainment to the T cycle.[10,11,54] The other is that the period of the animal remains different from the T cycle, thus the animal loses the entrainment to the T cycle.[55,56] The range of T cycle for an animal to be entrained is called the entrainment range. In mice, the SCN can be entrained in the range from a 22 h cycle to a 28 h cycle. The entrainment range varies among species. The entrainment range can be also influenced by external conditions such as the light intensity and the wave form of the light–dark cycle (e.g., square wave, sine wave).[57,58]

If the external T cycle is in the entrainment range, the SCN will remain synchronized. If the T cycle is out of the entrainment range, the SCN will lose the synchronization and its ability of being entrained to the T cycle partially or fully.[55,56] For example, under the T cycle of 22 h, the behavioral activity of a rat shows two components, see Fig. 4. One component shows a 22 h period, which is the same as the period of the external T cycle, and the other shows a 24 h period, which is close to the free running period under constant darkness. Recently, experiments found that the 22 h component is regulated by the VL, and the 24 h component is controlled by the DM.[56] Thus, under the external T cycle of 22 h, there is a desynchronization between the VL and the DM.

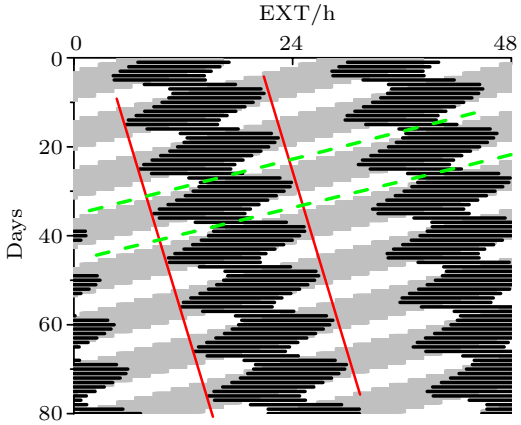


Fig. 4. Locomotor activity under the T cycle of 22 h in double-plot actogram, where the x axis represents the external time, the y axis denotes the number of continuous days, and the grey region corresponds to darkness. There are two activity components which are represented by red solid and green dash lines, respectively. The period of the red solid lines is close to 24 h, while the period of the green dash lines equals to 22 h. This figure is made from artificial data.

3. Theoretical explanations based on heterogeneous couplings

To explain the above experimental findings, much attention has been paid to the phenomena of collective behaviors of the SCN, such as the free running periods under constant darkness, phase-splitting under constant light, and entrainment to a T cycle, which emerge from the ensemble of neurons with different intrinsic periods. An SCN neuron may be regarded as a limit cycle oscillator, which is based on the gene translation-transcriptional feedback loop. Such behavior of the limit cycle has been well described by the Goodwin model for individual SCN neurons, which has three variables.[27–29,31,59–64] For simplicity, the Kuramoto model and the Poincaré model have also been included for analysis.[11,27,28,30,65] Previously, the coupling between the neurons was assumed to be homogeneous and calculated by the mean-field method. However, the above experiment findings have revealed that the coupling between neurons is heterogeneous. For example, it was pointed

out that the coupling from the VL to the DM is dominant, and the inverse coupling from the DM to the VL is relatively weak. In addition, the sensitive abilities of the neurons to transmitters are non-identical. The neurons located in the VL are sensitive to VIP, while the neurons situated in the DM are sensitive to AVP. Therefore, recent works have focused on the influence of the heterogeneous coupling. In this section, we will briefly introduce these theoretical works.

3.1. A modified Goodwin model

The Goodwin model has been widely used in studying the circadian rhythm of mammals.[27–29,31,59–64] In this model, a single SCN neuron is represented by three variables, i.e., a clock gene mRNA, a clock protein, and a transcriptional inhibitor. This Goodwin model is usually used for the case of homogeneous coupling. To consider the case of heterogeneous coupling, a modified Goodwin model has been provided for N coupled neurons and can be written as

$$\begin{aligned}
\dot{x}_i &= \alpha_1 \frac{k_1^n}{k_1^n + z_i^n} - \alpha_2 \frac{x_i}{k_2 + x_i} + \alpha_c \frac{g_i F}{k_c + g_i F} + L_i, \\
\dot{y}_i &= k_3 x_i - \alpha_4 \frac{y_i}{k_4 + y_i}, \\
\dot{z}_i &= k_5 y_i - \alpha_6 \frac{z_i}{k_6 + z_i}, \\
\dot{V}_i &= k_7 x_i - \alpha_8 \frac{V_i}{k_8 + V_i}, \quad i = 1, 2, \ldots, N, \\
F &= \frac{1}{N} \sum_{i=1}^{N} V_i, \qquad (1)
\end{aligned}$$

where x_i, y_i, and z_i constitute a negative feedback loop in the clock cell i, x, y, and z indicate a clock gene mRNA, a clock protein, and a transcriptional inhibitor, respectively, F performs as a mean field, L_i denotes the light information strength from RHT, and g_i is regarded as the coupling strength and describes the sensitivity of neuron i to one transmitter (for instance VIP). Note that both the coupling strength g_i and the light term L_i is heterogenous based on the findings from experiments. When we set $g_i = g_c$ and $L_i = L_c$, model (1) will return to the original Goodwin model. The schematic diagram of the modified Goodwin model is illustrated in Fig. 5 under constant darkness.

In Eq. (1), the main differences among the non-identical neurons are represented by the heterogenous coupling strength g_i. This kind of heterogenous coupling strength can be characterized by the mean value $\langle g \rangle$ of the coupling strength and its standard deviation δ (named dispersion). In addition, the heterogenous light term L_i is also taken into account. Experiments show that only the SCN neurons situated in the VL are sensitive to light information, while the neurons in the DM are not sensitive to light information. The DM will obtain the light information through the transmitter, i.e., coupling. Thus, the light term L_i can be represented by

$$\begin{aligned}
L_i &= K_f, \quad \mathrm{mod}(t, T) < T/2, \quad i = 1, 2, \ldots, pN, \qquad (2) \\
L_i &= 0, \quad \mathrm{mod}(t, T) \geq T/2, \quad i = 1, 2, \ldots, pN, \qquad (3) \\
L_i &= 0, \quad i = pN+1, pN+2, \ldots, N,
\end{aligned}$$

where p represents the ratio of the number of neurons sensitive to light information to the total number of SCN neurons, thus pN is the number of SCN neurons in the VL which are sensitive to light information, and K_f is the light intensity. We will mainly use this modified Goodwin model to explain the experiment findings in the following subsections.

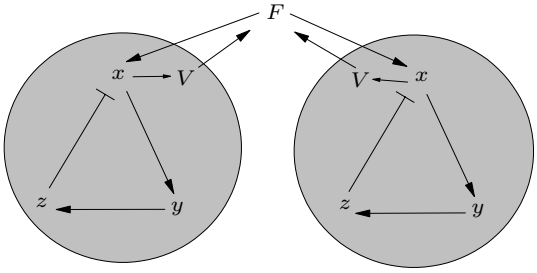


Fig. 5. Schematic diagram of the Goodwin model composed of two neuron oscillators under constant darkness, where x, y, and z constitute a negative feedback loop in one clock cell, and x, y, and z represents a clock gene mRNA, a clock protein, and a transcriptional inhibitor, respectively. The oscillators are coupled through the mean field F, and F is defined as the mean value of the transmitters which are induced by the clock gene mRNA x.

3.2. Free running under constant darkness

Under constant darkness, the free running period of mammals changes from one species to another. This variation may come from two aspects. One is the different distributions of the intrinsic periods of individual neurons for different species, the other is the different couplings for different species. For the first aspect, a recent work shows that the standard deviation (dispersion) of the distribution of the intrinsic periods has little effect on the free running periods.[30] For the second aspect, several theoretical works have proved that the free running period increases as the coupling strength increases.[27,31] In addition, the amplitude of the SCN network goes up with the increase of the coupling strength.[31] Figure 6(a) shows the relationship between free running period τ and coupling strength $\langle g \rangle$ when the dispersion $\delta = 0$, which is a monotonously increasing relationship.

Except for the coupling strength, it is found that the distribution of the coupling strength among neurons will also influence the free running period. Figure 6(b) shows how the dispersion (standard deviation) of the coupling strength influences the free running period.[27] It is easy to see that the free running period τ monotonically decreases with the increase of the dispersion δ. Noticing that we have $L_i = 0, \quad i = 1, 2, \ldots, N$ in Eq. (2) under constant darkness, there is no difference between the VL and the DM. Thus, the results in

Figs. 6(a) and 6(b) work for both the neurons in the VL and the DM.

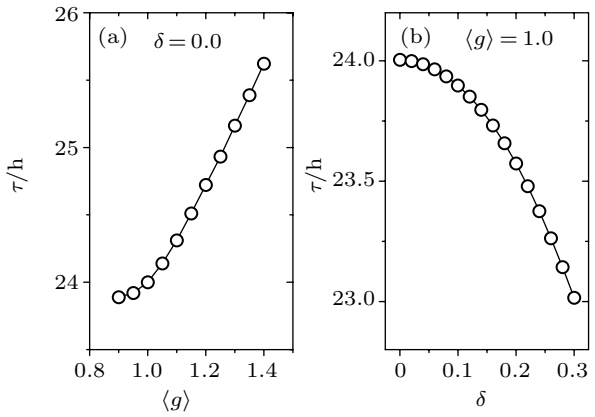


Fig. 6. Dependence of free running period τ on the mean coupling strength $\langle g \rangle$ and its dispersion δ. (a) The free running period τ versus the mean coupling strength $\langle g \rangle$ for $\delta = 0$; (b) the free running period τ versus the dispersion δ for $\langle g \rangle = 1.0$. This figure is reproduced from Figs. 1 and 2 in Ref. [27], the parameters are set as those used in Ref. [27].

3.3. Phase-splitting under constant light

Under constant light, the presence of phase-splitting between the left SCN and the right SCN inspires the theoretical research on its mechanism. The article [65] assumed that the feedback of the behavioral activity is crucially involved in phase-splitting based on the modified Kuramoto model. Recently, experiments[38,39] found that the activity indeed has a feedback to the SCN, while the feedback delay is unclear. There are three coupling interaction terms to one neuron oscillator in Ref. [65], i.e., the interactions from the same side of the SCN neurons, from the other side of the SCN, and the feedback of the behavioral activity. The feedback is assumed to have a time delay of several hours. We apply these assumptions to the modified Goodwin model,[28] where the mean field F of Eq. (1) is modified into

$$\begin{aligned} F_1 &= \frac{a}{N}\sum_{i=1}^{N_1} V_i + \frac{b}{N}\sum_{i=N_1+1}^{N} V_i + \frac{c}{N}\sum_{i=1}^{N} V_{i,-\tau}, \\ F_2 &= \frac{b}{N}\sum_{i=1}^{N_1} V_i + \frac{a}{N}\sum_{i=N_1+1}^{N} V_i + \frac{c}{N}\sum_{i=1}^{N} V_{i,-\tau}, \end{aligned} \tag{4}$$

where indices '1' and '2' represent the right SCN and the left SCN, respectively. The parameters a, b, and c represent the coupling weights from the same group, a different group, and the part due to the time delay, respectively, and satisfy the relationship $(a+b)/2+c=1$. τ represents the time delay of the behavioral activity feedback. We find that there are three kinds of collective behaviors of SCN neurons in Eq. (4), including phase-splitting (anti-phase) between the right SCN and the left SCN, in-phase synchronization between the right SCN and the left SCN, and the amplitude death of the SCN neurons. Figure 7 shows the results, where panels (a), (b), and (c) represent the cases of in-phase synchronization, phase-splitting, and amplitude death of the SCN, respectively. In fact, these three kinds of behaviors correspond to the free running, phase-splitting, and loss of rhythm found in animals, respectively. Furthermore, the feedback term also influences the period of the in-phase synchronization, which is consistent with the influence of exercise on the SCN period in mice.[66]

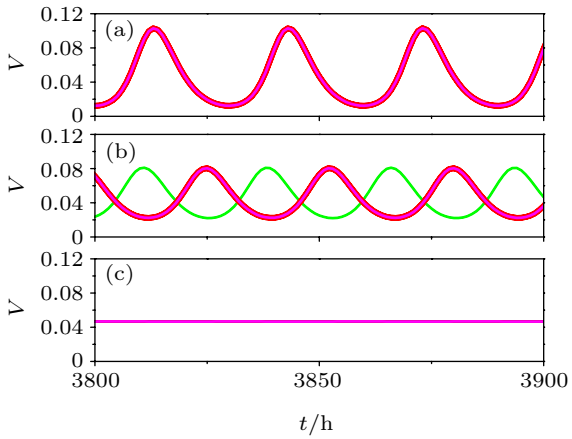


Fig. 7. Three kinds of collective behaviors of the SCN neurons:[28] (a) in-phase synchronization between the left SCN and the right SCN; (b) phase-splitting (anti-phase) between the left SCN and the right SCN; (c) amplitude death of the SCN neurons. The parameters are $a = 1.64$, $b = 0.32$, and $c = 0.02$ in panel (a); $a = 1.64$, $b = 0.16$, and $c = 0.1$ in panel (b); and $a = 1.16$, $b = 0.28$, and $c = 0.28$ in panel (c). The parameters are set as those used in Ref. [28].

In addition, the dispersion δ of the coupling strength distribution has been investigated in Ref. [28]. It was found that the dispersion δ has little effect on the three kinds of collective behaviors of the SCN neurons, but that it does have an influence on the SCN period.

3.4. Entrainment to T cycle

The entrainment ability of the SCN neurons to an external T cycle can be influenced by several intrinsic parameters such as the coupling strength g,[11,33] the dispersion δ of the coupling strength distribution,[29] the ratio p of the number of light-sensitive neurons to the total number of SCN neurons,[29,67] and the dispersion μ of the distribution of single neuron intrinsic periods.[30] To check how these parameters influence the entrainment, we first consider the case of the SCN under a special T cycle condition $T = 22$ h (11 h light alternating with 11 h darkness) and focus on the effect of p. We find that both the periods of the VL and the DM can be easily entrained to $T = 22$ h, i.e., the external T cycle.[29] Then, we consider the case of $T = 26$ h (13 h light alternating with 13 h darkness). Surprisingly, we find that with the increase of p, the period of the DM is not entrained to $T = 26$ h but separated away from it. Figure 8(a) shows the result where the diamonds and circles represent the periods of the VL and the DM, respectively. From Fig. 8(a), we see that the period of the VL can be easily frequency-locked to the external period when p is small, whereas the period of the

DM will linearly decrease with the increase of p until a critical p_c. There is a jumping transition at $p = p_c$ where the period of the DM jumps from 20.8 h to 26 h. The period of the DM will be entrained to the external period once $p > p_c$. Then, an interesting question arises: what is the mechanism for this jumping transition? To understand the jumping transition better, we check how the oscillation amplitudes of the DM oscillators change with p. By checking the behaviors of x_i in Eq. (1), we find that the oscillators in the DM are almost synchronized. Thus, we let $\langle X\rangle = \frac{1}{(1-p)N}\sum_{i=1+pN}^{N} x_i$ represent the oscillations in the DM. Figures 8(b)–8(e) show the oscillations for $p = 0.02, 0.2, 0.408, 0.42$, respectively. It is easy to see that the amplitude of $\langle X\rangle$ is significantly reduced with the increase of p and reaches its minimum at the transition point of $p_c \approx 0.408$. This reduction of amplitude makes the neurons of the DM lose their intrinsic property and thus they can be entrained to the external 26 h cycle.

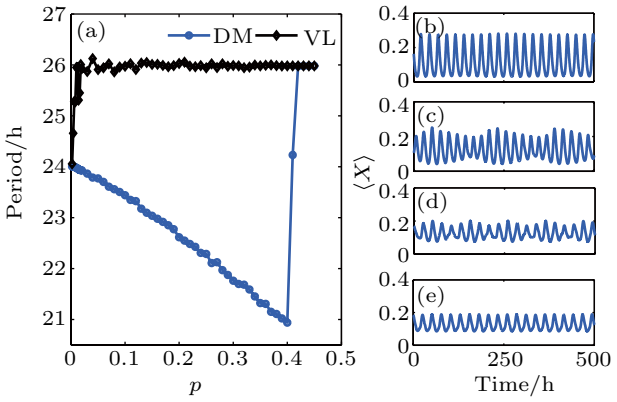


Fig. 8. The evolution of VL and DM subgroups for different parameter p during a 26 h cycle, where the parameters are taken as $N = 500$ and $K_f = 0.02$. (a) Periods of VL and DM versus p, where the diamonds and circles represent the periods of VL and DM, respectively. (b)–(e) The oscillations of $\langle X\rangle$ for $p = 0.02, 0.2, 0.408, 0.42$, respectively.

In summary, the entrainment abilities for $T = 22 < 24$ and $T = 26 > 24$ are different. For a fixed p, an interesting quantity will be the range between the lower limit of entrainment ($T < 24$) and the higher limit of entrainment ($T > 24$), called the entrainment range. When the external light–dark cycle is outside this entrainment range, the SCN neurons will lose their synchronization and thus the T cycle cannot be successfully entrained to the DM. For simplicity, either the lower limit of entrainment (LLE) or the higher limit of entrainment (HLE) is often used to represent the entrainment range, provided that the LLE and the HLE are symmetrically distant from the free-running period.[11,30] For example, the entrainment range is from 23.5 h (LLE) to 24.9 h (HLE) for Peromyscus leucopus, from 22.8 h to 26.5 h for Mus musculus, from 21.5 h to 28.6 h for Homo sapiens, and from 14.9 h to 32.4 h for Eutamias sibiricus. We may use the LLE 23.5 h to represent the entrainment range from 23.5 h to 24.9 h for Peromyscus leucopus and the same way for other animals.

The coupling is found to be crucial in the entrainment of a circadian clock to a T cycle. In Refs. [11] and [33], the external signal was temperature, and the entrainment ranges of the SCN (master clock) and the lung (peripheral clock) were compared in the case of a homogeneous coupling strength. The experiment results showed that the wider entrainment range exists in the peripheral clock, and the narrower entrainment range exists in the master clock.[11] Since the coupling strength of the SCN neurons is stronger than that of the lung cells, it was concluded that the entrainment range decreases with the increase of the coupling strength. This conclusion has been confirmed by the simulations and theoretical results based on the Poincaré model.[11] An interesting question is, besides the temperature signal, what about other external signals for the SCN, such as the light signal?

Based on the Poincaré model and the Goodwin model, Gu *et al.* recently found that the dependence of the entrainment range on the coupling strength can be influenced by the parameter p.[30,67] The Poincaré model has the following form:

$$\begin{aligned}
\dot{x}_i &= \gamma x_i(A_0 - r_i) - \frac{2y_i\pi}{\tau\sigma_i} + gF + L_i,\\
\dot{y}_i &= \gamma y_i(A_0 - r_i) + \frac{2x_i\pi}{\tau\sigma_i}, \quad i = 1,2,\ldots,N,\\
F &= \frac{1}{N}\sum_{i=1}^{N} x_i,
\end{aligned} \tag{5}$$

where γ is the relaxation parameter, A_0 and $\tau\sigma_i$ represent the amplitude and the intrinsic period of an individual oscillator in the absence of a light–dark cycle, $r_i = \sqrt{x_i^2 + y_i^2}$, and σ_i satisfies a normal distribution with mean value 1 and deviation μ. The L_i represents the light signal and is defined as

$$L_i = \begin{cases} K_f \sin(\Omega t), & i = 1,2,\ldots,pN,\\ 0, & i = pN+1, pN+2,\ldots,N, \end{cases} \tag{6}$$

where K_f and Ω represent the light intensity and the angular frequency of the light–dark cycle, respectively. Figure 9 shows the results of Eqs. (5) and (6). From Fig. 9, we see that for $p = 1$, the LLE decreases with the increase of the coupling strength. For $p < 1$, the relationship between the LLE and the coupling strength is represented by a unimodal curve with a maxima at $g_c \approx 0.08$, indicating that there is an optimal coupling for the entrainment. In the situation of $g \geq g_c$, the relationship is positive, while in the situation of $g < g_c$, the relationship is negative.

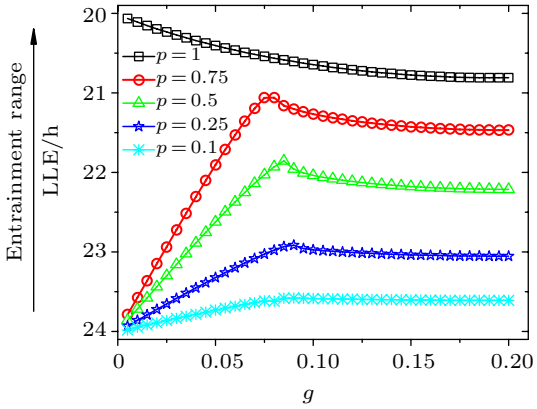


Fig. 9. The entrainment range of the SCN versus coupling strength under different ratios p in the case of homogeneous coupling strength. It is noticed that the entrainment range decreases with the increase of the coupling strength when $p = 1$. When $p < 1$, there is an optimal entrainment range at $g_c \approx 0.08$. In the situation of $g \geq g_c$, the relationship is positive, while in the situation of $g < g_c$, the relationship is negative. This figure is reproduced from Fig. 1 in Ref. [67]. The light intensity is $K_f = 0.01$, and the other parameters are chosen as those used in Ref. [67].

In addition to the coupling strength, it is found that the dispersion μ also influences the entrainment range LLE. Figure 10 shows the results where all neurons are sensitive to light ($p = 1$). From Fig. 10, we see that the entrainment range LLE increases with the increase of dispersion μ, indicating that increasing μ is beneficial for the entrainment range. This result also works for the case of $p < 1$ and has been confirmed by the theoretical analysis in Ref. [30]. Thus, it may provide a new clue to explain the variation of entrainment ranges between species.

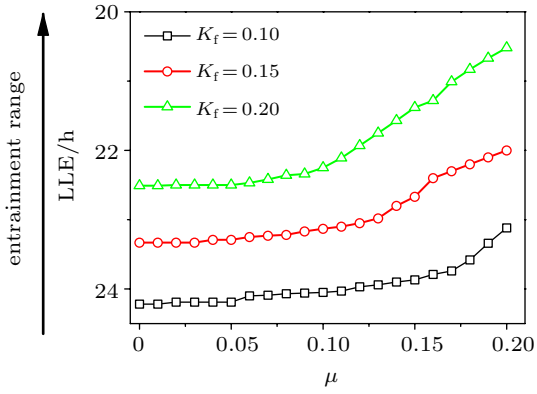


Fig. 10. The influence of dispersion μ on the lower limit of entrainment of the SCN, where all neurons are sensitive to light ($p = 1$). This figure is reproduced from Fig. 2 in Ref. [30]. Three kinds of light intensities K_f are considered, and the other parameters are chosen as those used in Ref. [30].

4. Discussion and conclusion

In this review, we have summarized the collective behaviors of the heterogeneous SCN neurons based on the experimental findings and pointed out that they can be classified into three aspects by the light–dark cycles, i.e., constant darkness, constant light, and different T cycles including the 24 h cycle. These three aspects are mainly focused on the diversity of the free-running periods, phase-splitting, and entrainment ability, respectively. Then, we discussed how the modified Goodwin model can be applied to all three aspects. We revealed that these collective behaviors of the SCN neurons can be influenced not only by the heterogenous intrinsic properties of the neurons but also by the heterogenous couplings through transmitters among the neurons, in contrast to the previous theoretical works only on the effect of the homogenous coupling strength.

For the case of constant darkness, the neurons in the VL and the DM are treated as the same. The free-running period τ is influenced by both the mean coupling strength $\langle g \rangle$ and the dispersion δ. The τ increases with increasing $\langle g \rangle$ but decreases with the increase of δ. For the case of constant light, the left SCN and the right SCN neurons show an anti-phase synchronization and thus can be used to explain the phase-splitting phenomenon observed in mammals. Interestingly, this phase-splitting behavior is not influenced by the dispersion δ. For the case of different T cycles, the main concern is focused on the entrainment ability. All the animals are used to a 24 h cycle of circadian rhythm. When the T cycle is not a 24 h cycle, the entrainment abilities for $T > 24$ and $T < 24$ will be different and can be described by the lower limit of entrainment and the higher limit of entrainment, respectively. Similar to the case of constant darkness, the entrainment range can also be influenced by both the mean coupling strength $\langle g \rangle$ and the dispersion δ or μ. However, there are two differences between these two cases. The first one is that τ monotonously increases with increasing $\langle g \rangle$ while there is an optimal $\langle g \rangle$ for the LLE. The second one is that τ decreases with the increase of δ but the LLE increases with increasing δ or μ.

In addition to the heterogenous couplings, the effect of the heterogenous intrinsic properties of the neurons on the SCN behaviors are also discussed here. We considered the effect of the ratio of the number of light-sensitive neurons to the total number of SCN neurons. On one hand, the ratio influences the entrainment range, i.e., it increases with the ratio. On the other hand, the ratio also affects the relationship between the entrainment range and the coupling strength, i.e., the relationship remains negative when ratio = 1 but becomes a unimodal curve when ratio < 1. These results may shed light on the field of circadian rhythm.

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