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Entrainment range affected by the heterogeneity in the amplitude relaxation rate of suprachiasmatic nucleus neurons*

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Adaption of circadian rhythms in behavioral and physiological activities to the external light–dark cycle is achieved through the main clock, i.e., the suprachiasmatic nucleus (SCN) of the brain in mammals. It has been found that the SCN neurons differ in the amplitude relaxation rate, which represents the rigidity of the neurons to the external amplitude disturbance. Thus far, the appearance of that difference has not been explained. In the present study, an alternative explanation based on the Poincaré model is given which takes into account the effect of the difference in the entrainment range of the SCN. Both our simulation results and theoretical analyses show that the largest entrainment range is obtained with suitable difference in the case that only a part of SCN neurons are sensitive to the light information. Our findings may give an alternative explanation for the appearance of that difference (heterogeneity) and shed light on the effects of the heterogeneity in the neuronal properties on the collective behaviors of the SCN neurons.

Keywords: amplitude relaxation rate, entrainment range, heterogeneity

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1. Introduction

A master circadian clock located in the suprachiasmatic nucleus (SCN) regulates the circadian rhythm of physiological and behavioral activities to the external light–darkness cycle in mammals.[1,2] The SCN can be entrained to not only the natural 24 h cycle, but also an artificial cycle of non-24 h period. The range between the lowest period and the highest period of the external cycle that the SCN can be entrained to is called the entrainment range.[3] The entrainment range is a key indicator for the adaptability of the SCN to the alternation of external environment, which differs among species. For example, the entrainment range of the Nile grass mouse is from 22.5 h to 25.5 h, humans from 20.5 h to 29 h, and Rattus norvegicus from 23.5 h to 28.5 h.[4]

The SCN is composed of about twenty thousand autonomous neurons whose intrinsic periods range from 22 h to 28 h.[5–7] These neurons can be roughly organized into two subgroups, one named the ventrolateral part (VL) and the other named the dorsomedial part (DM). The SCN neurons are heterogeneous in the neuronal properties, including the sensitivity to light information, intrinsic period, and amplitude. The VL containing about 25% SCN neurons is sensitive to light information from the retina, and the DM composed of the rest SCN neurons is insensitive to the light information that is coupled to the VL.[8,9] The natural periods are also heterogeneous between SCN neurons, i.e., the DM neurons run faster than the VL neurons.[10] In addition, the neuronal amplitudes are also heterogeneous between the VL and the DM.[11–13] Although the neurons are heterogeneous, the SCN outputs a uniform robust 24 h rhythmic signal to regulate the body activities. This suggests that the neurons are coupled and synchronized to form an SCN network.[14,15] The coupling is mainly through the neurotransmitters, which are heterogeneous in the subgroups, including vasoactive intestinal polypeptide (VIP) in the VL, arginine vasopressin (AVP) in the DM, and Gamma aminobutyric acid (GABA) from the VL to the DM.[16,17]

Recently, a new neuronal property, called amplitude relaxation rate, which represents the rigidity of the oscillators to the external amplitude disturbance, has been found to differ between the SCN (central clock) and the peripheral clock.[18–20] The difference leads to the entrainment range of the former being narrower than that of the latter. The amplitude relaxation rate of the neuronal oscillators also differs within the SCN. The values of the amplitude relaxation rate vary in the range from 0.03 h^{-1} to 1 h^{-1} for the SCN neurons.[20] Thus far, the appearance of the heterogeneity (difference) in the amplitude relaxation rate of the SCN neurons has not been explained, and the effects of this heterogeneity have not yet been studied.

In the present study, an explanation for that appearance is given based on a Poincaré model,[20–27] where we consider the effect of the heterogeneity of the amplitude relaxation rate on the entrainment range. In the model, we assume that there is heterogeneity in the amplitude relaxation rate between the VL neurons and the DM neurons. For comparison, we examine the case of only the VL being sensitive to the light information and the case of both the VL and the DM being sensitive

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to the light information respectively. The rest of this paper is organized as follows. In Section 2, the Poincaré model is introduced to describe the SCN neuronal network exposed to an external light–darkness cycle. Then, we present the simulation results about the effects of the heterogeneity in the amplitude relaxation between the VL and the DM on the entrainment range in Section 3. In Section 4, theoretical analysis is given to confirm the simulation results. Finally, in Section 5, conclusion and discussion are presented.

2. Theoretical method

The Poincaré model is used to mimic the SCN network exposed to an external light–darkness cycle, which contains both phase and amplitude information of the neuronal oscillators.[20–27] Each neuronal oscillator is described by two variables x and y. All neurons form a global coupling network achieved by a mean field F. In this study, we consider the heterogeneity in the amplitude relaxation rate as well as in the sensitivity to light information between the VL and the DM. Subsequently, the SCN network can be described as follows:

$$\begin{aligned}
\dot{x}_i &= \gamma_i x_i(R-r_i) - \frac{2y_i\pi}{\tau} + gF + L_i \sin(\Omega t),\\
\dot{y}_i &= \gamma_i y_i(R-r_i) + \frac{2x_i\pi}{\tau}, \quad i = 1,2,\ldots,N,\\
F &= \frac{1}{N}\sum_{i=1}^{N} x_i,\\
r_i &= \sqrt{x_i^2+y_i^2},
\end{aligned} \tag{1}$$

where the subscript i represents the i-th oscillator, parameters γ_i, R, r_i, τ, g, L_i, N, Ω, and t represent the amplitude relaxation rate, intrinsic amplitude, coupled amplitude, natural period of the neuronal oscillator, coupling strength among the neurons, sensitivity to light, number of neurons in the SCN, frequency of external light–dark cycle, and time, respectively. The values of γ_i and L_i depend on the region in which the neuron is located. If the neuron i is located in the VL ($i \le PN$, P represents the proportion of neurons in the SCN that can directly receive light information), then $\gamma_i = A$ and $L_i = K_\mathrm{f}$ (here K_f represents the light intensity), otherwise $\gamma_i = B$ and $L_i = 0$ ($PN < i \le N$). Since the mean of the amplitude relaxation rates affects the entrainment range of the SCN,[28] we let $C = \frac{1}{N}\sum_{i=1}^{N}\gamma_i$ be a constant, that is, $C = PA + (1-P)B$. Without losing generality, the values of other variables are set to be $R = 1$ and $\tau = 24$. When all neurons are responsive to light information ($P = 1.0$), we set the coupling strength to be $g = 0.04$. No study has found whether the light intensity K_f is larger than the coupling strength g or not. Thus, the values of K_f are selected as 0.03 ($K_\mathrm{f} < g$), 0.04 ($K_\mathrm{f} = g$), and 0.05 ($K_\mathrm{f} > g$), respectively. Additionally, since the number of neurons being responsive to light in the case of $P = 0.5$ is half of the case of $P = 1.0$, the light intensity is selected as $K_\mathrm{f} = 0.06$, 0.08, and 0.1, and the coupling strength $g = 0.08$.

If the period T of the external light–dark cycle and the entrained period T_e of the neurons satisfy the relationship $\sqrt{\frac{1}{N}\sum_{i=1}^{N}(T_{\mathrm{e}_i} - T)^2} < \delta$, where $\delta = 0.00001$ h, we define that the SCN is synchronized or entrained to the external cycle. The entrainment range can be represented by the lower limit of entrainment (LLE), i.e., the shortest period of the external cycle to which the SCN can be entrained.[20] If the value of the LLE is larger, the entrainment range is smaller, and vice versa. In this paper, the heterogeneity is represented by the ratio d of the amplitude relaxation rate between the VL and the DM neurons ($d = A/B$). We mainly study the effect of ratio d on the LLE. If $C = A = B$, that is, the amplitude relaxation rates of the VL and DM neurons are equal, then the ratio is $d = 1$; if $A > B$, then $d > 1$; if $A < B$, then $d < 1$. It should be noted that we do not consider the heterogeneity in the amplitude relaxation rate of the neuronal oscillators within each region, in other words, the amplitude relaxation rates are identical within each region.

The method used for our numerical simulations is the fourth-order Runge–Kutta method with time steps of 0.01 h. In order to avoid the influence of transients, we ignore the first 5000000 time steps and use the next 100000 steps. The initial values of variables x_i and y_i for each oscillator are randomly selected from 0 to 1. We numerically simulate the cases of the number of oscillators being $N = 1000$ and $N = 40$, respectively, and found that the results are consistent. In the following sections, we take $N = 40$ as an example to show the results.

3. Simulation results

Exposed to a 22 h light–darkness cycle, illustrative examples for the effect of d on the entrainment of neurons with selected P values are shown in Fig. 1. It is visible that the effects of d are different between the cases of $P = 1.0$ (Figs. 1(a)–1(c)) and $P = 0.5$ (Figs. 1(d)–1(f)). If the parameter is $P = 1.0$, the entrainment is achieved when the ratio is $d = 1$, because the phase difference of each oscillator to the light–dark cycle is fixed over time (Fig. 1(b)). When the ratio is $d = 0.01$ (Fig. 1(a)) or $d = 100$ (Fig. 1(c)), neither the VL nor the DM is entrained to the external light–dark cycle, because the phase difference of each oscillator to the light–dark cycle fluctuates over time. However, if the parameter is $P = 0.5$, when the ratio is $d = 1$, both the VL and DM lose entrainment to the external cycle (Fig. 1(e)). Interestingly, each oscillator is entrained to the external cycle when the ratio is $d = 0.05$ (Fig. 1(d)) and not entrained when the ratio is $d = 100$ (Fig. 1(f)). Therefore, the ratio d affects the entrainment ability of the SCN, and the effect differs between the cases of $P = 1.0$ and $P = 0.5$.

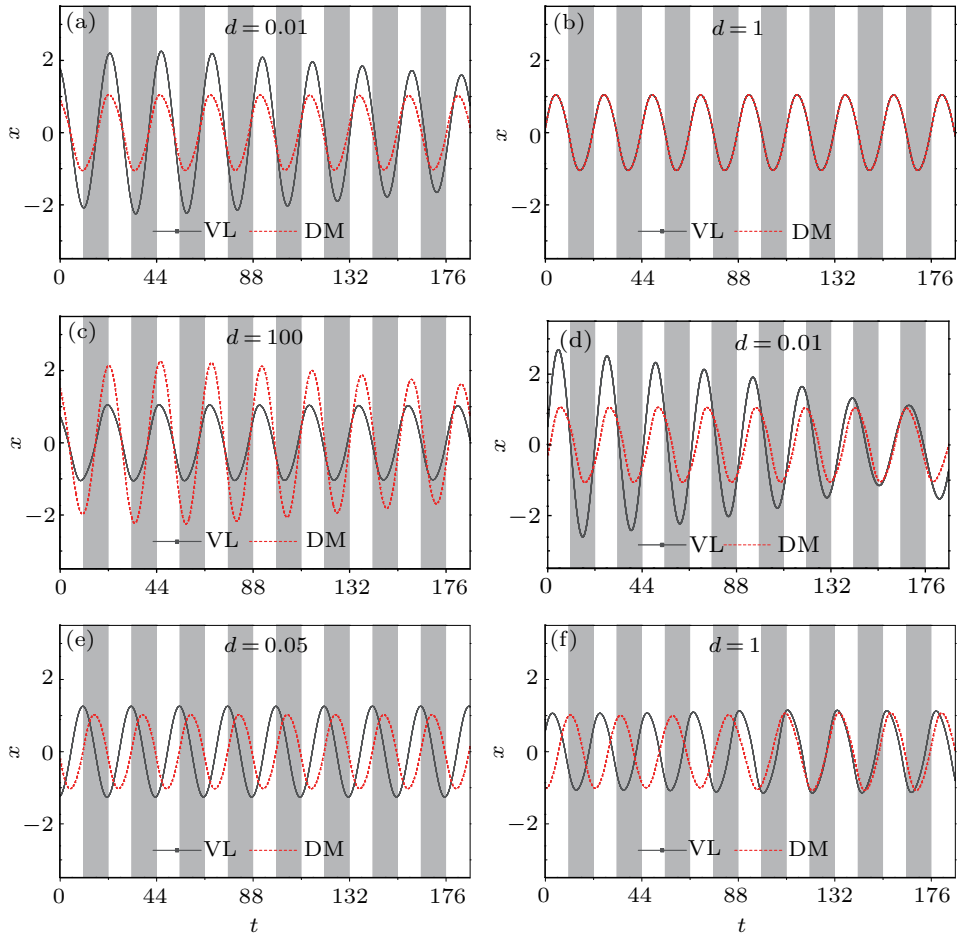


Fig. 1. The temporal evolutions of the VL and the DM with typical ratios d exposed to an external cycle of 22 h. The grey regions correspond to darkness and the white regions to light. The parameter P is the ratio of the light-sensitive neurons: (a)–(c) $P = 1.0$, (d)–(f) $P = 0.5$.

In order to systematically examine the effects of d, the relationship of LLE to d is shown in Fig. 2 in the cases of $P = 1.0$ (a) and $P = 0.5$ (b). It is visible that the relationship is parabolic-like for each light intensity K_f in both cases. In particular, the entrainment range increases (LLE decreases) with the increase of d when d is smaller than a critical value d_c, the entrainment range decreases (LLE increases) with the increase of d when d is larger than a critical value d_c, and the largest entrainment range is obtained when $d = d_c$. However, d_c differs between these two cases for each light intensity K_f, i.e., the critical value is $d_c = 1$ with $P = 1.0$ and $d_c = 0.47$ with $P = 0.5$.

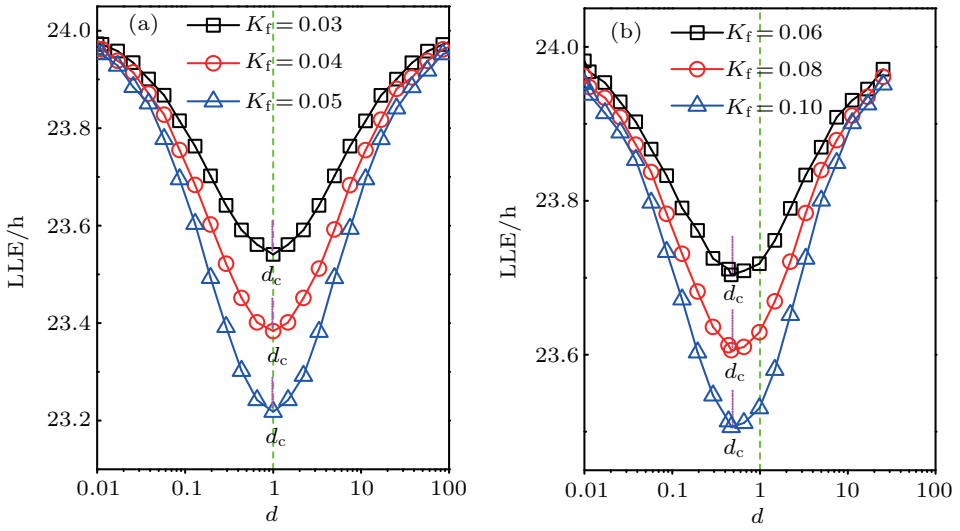


Fig. 2. The relationship between the ratio d and LLE in the cases of (a) $P = 1.0$ and (b) $P = 0.5$ with selected light intensity K_f. The coupling strength g is 0.04 and 0.08 in (a) and (b), respectively, and the mean of amplitude relaxation rate C is 0.01. The dotted pink lines indicate the trough d_c of the LLE and dashed green lines represent $d = 1$, respectively.

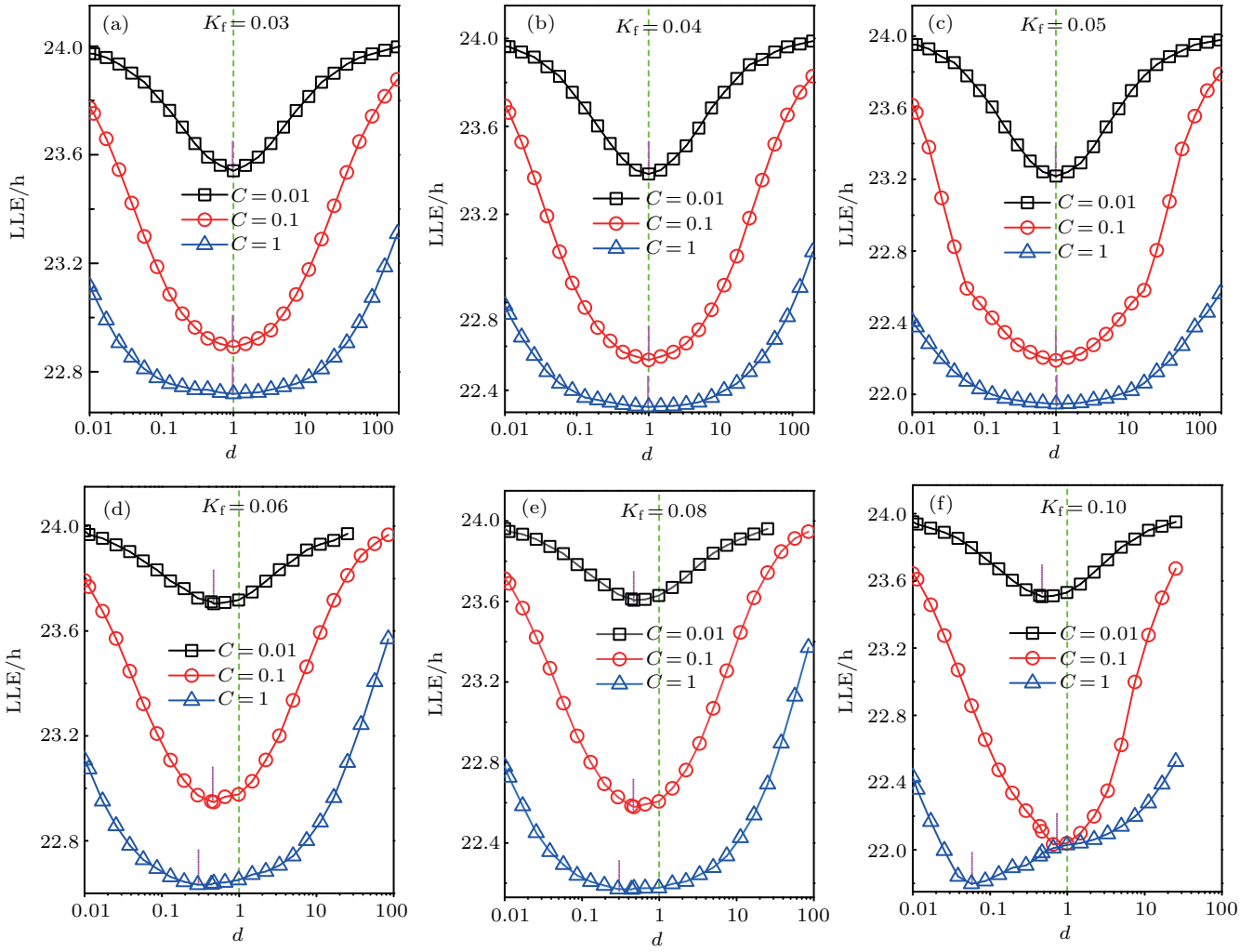


Fig. 3. The relationship between the LLE and the ratio d in cases of (a)–(c) $P = 1.0$ and (d)–(f) $P = 0.5$. The parameters C and P are the mean of amplitude relaxation rate and the ratio of the neurons being sensitive to light information, respectively. The coupling strength g is 0.04 in panels (a)–(c) and 0.08 in panels (d)–(f). The dotted pink lines indicate the trough d_c of the LLE and dashed green lines represent $d = 1$, respectively.

Next, we examine whether the relationship is affected by the mean of amplitude relaxation rates C. In addition to $C = 0.01$ in Fig. 2, $C = 0.1$ and $C = 1.0$ are investigated in Fig. 3. The results shown in Fig. 3 are consistent with those in Fig. 2. In detail, the relationship is also parabolic-like in the case of $P = 1.0$ or $P = 0.5$, and d_c also differs between these two cases, i.e., d_c is equal to 1 for $P = 1.0$ and d_c is apparently smaller than 1 for $P = 0.5$.

4. Analytical results

To explain the numerical simulations, the theoretical analyses are given as follows. Let $N = 2$, i.e., one oscillator a represents the VL and the other b represents the DM. The mean field is $F = (x_a + x_b)/2$. Then, equation (1) can be expressed as

$$\begin{aligned}
\dot{x}_a &= Ax_a(R - r_a) - \frac{2y_a\pi}{\tau} + \frac{x_a + x_b}{2}g + K_f\sin(\Omega t),\\
\dot{y}_a &= Ay_a(R - r_a) + \frac{2x_a\pi}{\tau},\\
\dot{x}_b &= Bx_b(R - r_b) - \frac{2y_b\pi}{\tau} + \frac{x_a + x_b}{2}g,\\
\dot{y}_b &= By_b(R - r_b) + \frac{2x_b\pi}{\tau}.
\end{aligned} \tag{2}$$

For simplicity, we convert Eq. (2) from Cartesian coordinates to polar coordinates. Let $x_a = r_a\cos\theta_a$, $y_a = r_a\sin\theta_a$, $x_b = r_b\cos\theta_b$, and $y_b = r_b\cos\theta_b$. Consequently, we obtain

$$\begin{aligned}
\dot{r}_a &= Ar_a(R - r_a) + \frac{r_a\cos^2\theta_a + r_b\cos\theta_b\cos\theta_a}{2}g\\
&\quad + K_f\sin(\Omega t)\cos\theta_a,\\
\dot{\theta}_a &= \omega - \frac{\cos\theta_a\sin\theta_a}{2}g - \frac{r_b\cos\theta_b\sin\theta_a}{2r_a}g\\
&\quad - \frac{K_f\sin(\Omega t)\sin\theta_a}{r_a},\\
\dot{r}_b &= Br_b(R - r_b) + \frac{r_a\cos\theta_a\cos\theta_b + r_b\cos^2\theta_b}{2}g,\\
\dot{\theta}_b &= \omega - \frac{r_a\cos\theta_a\sin\theta_b}{2r_b}g - \frac{\cos\theta_b\sin\theta_b}{2}g.
\end{aligned} \tag{3}$$

We use the averaging method proposed by Krylov and Bogoliubov and used in Refs. [29]–[31]. Let $\alpha = \langle\theta_b\rangle - \langle\theta_a\rangle$, $\phi_a = \theta_a - \Omega t$, and $\phi_b = \theta_b - \Omega t$. Then, we have

$$\langle\cos^2(\phi_a + \Omega t)\rangle = \frac{1}{2},$$

$$\begin{aligned}
&\langle\cos(\phi_b+\Omega t)\cos(\phi_a+\Omega t)\rangle = \frac{\langle\cos\alpha\rangle}{2},\\
&\langle\cos(\phi_a+\Omega t)\sin(\phi_a+\Omega t)\rangle = 0,\\
&\langle\cos(\phi_b+\Omega t)\sin(\phi_a+\Omega t)\rangle = -\frac{\langle\sin\alpha\rangle}{2},\\
&\langle\sin(\Omega t)\cos(\phi_a+\Omega t)\rangle = -\frac{\langle\sin\alpha\rangle}{2},\\
&\langle\sin(\Omega t)\sin(\phi_b+\Omega t)\rangle = \frac{\langle\cos\alpha\rangle}{2},
\end{aligned} \tag{4}$$

where $\langle\cdots\rangle$ represents the average value in one light–dark cycle. If the SCN neurons are entrained to the external cycle, we obtain $\dot{r}_a = \dot{r}_b = 0$ and $\dot{\theta}_a = \dot{\theta}_b = \Omega$. For simplicity, we keep the non-averaged sign of r_a, r_b, ϕ_a, and ϕ_b in the following. Note that θ has a smaller time scale than Ωt. Therefore, equation (4) can be turned into

$$\begin{aligned}
0 &= Ar_a(R-r_a)+\frac{r_a+r_b\cos\alpha}{4}g-\frac{K_{\rm f}\sin\phi_a}{2},\\
\Omega &= \omega+\frac{r_b\sin\alpha}{4r_a}g-\frac{K_{\rm f}\cos\phi_a}{2r_a},\\
0 &= Br_b(R-r_b)+\frac{r_a\cos\alpha+r_b}{4}g,\\
\Omega &= \omega-\frac{r_a\sin\alpha}{4r_b}g.
\end{aligned} \tag{5}$$

According to Eq. (5), in order to obtain the LLE ($\Omega_{\max}$), the light term $-\frac{K_{\rm f}\cos\phi_a}{2r_a}$ and the coupling term $-\frac{r_a\sin\alpha}{4r_b}g$ should be large, whereas $\frac{r_b\sin\alpha}{4r_a}g$ should be small. Therefore, there is a balance between $-\frac{r_a\cos\alpha}{4r_b}g$ and $\frac{r_b\sin\alpha}{4r_a}g-\frac{K_{\rm f}\cos\phi_a}{2r_a}$. To find the balance, two special cases are considered here, $K_{\rm f}\gg g$ and $K_{\rm f}\ll g$, respectively.

If $K_{\rm f}\gg g$, $-\frac{r_a\sin\alpha}{4r_b}g$ is much smaller than $-\frac{K_{\rm f}\cos\phi_a}{2r_a}$. Thus, $\Omega_{\max}$ depends on the smaller term $-\frac{r_a\sin\alpha}{4r_b}g$, where $\sin\alpha$ should be close to 1. Equation (5) is simplified to

$$\begin{aligned}
0 &= Ar_a(R-r_a)+\frac{r_a}{4}g+\frac{K_{\rm f}\sin\phi_a}{2},\\
\Omega_{\max} &= \omega-\frac{r_b}{4r_a}g-\frac{K_{\rm f}\cos\phi_a}{2r_a},\\
0 &= Br_b(R-r_b)+\frac{r_b}{4}g,\\
\Omega_{\max} &= \omega+\frac{r_a}{4r_b}g.
\end{aligned} \tag{6}$$

Because $K_{\rm f}\gg g$, $\cos\phi_a$ is a small term, where ϕ_a is close to $\pi/2$. Let $\cos\phi_a = \cos\phi_(\pi/2-\phi_{\hat{a}}) = \sin\phi_{\hat{a}}$, where $\phi_{\hat{a}}$ is a smaller value. Consequently, $\cos\phi_a\approx\phi_{\hat{a}}$ and $\sin\phi_a\approx 1$. Hence, the solutions for Eq. (6) are

$$\begin{aligned}
r_a &= \frac{r_0+\sqrt{r_0^2+2K_{\rm f}/A}}{2}\propto\delta,\\
r_b &= R+\frac{g}{4B}\equiv R+\frac{g}{4(1+\delta)}\propto\frac{1}{\delta},\\
\Omega_{\max} &= \omega+\frac{r_a}{4r_b}g\propto\delta,
\end{aligned} \tag{7}$$

where $r_0 = R+\frac{g}{4A}\equiv R+\frac{g}{4(1-\delta)}\propto\delta$. From Eq. (7), if δ is larger than 0, i.e., $d=A/B$ is smaller than 1, $\Omega_{\max}$ is larger than it if d is equal to 1. Therefore, we have proved that $d_{\rm c}$ is smaller than 1 in the case of $K_{\rm f}\gg g$.

If $K_{\rm f}\ll g$, $-\frac{r_a\sin\alpha}{4r_b}g$ is much larger than $-\frac{K_{\rm f}\cos\phi_a}{2r_a}$. Thus, $\Omega_{\max}$ depends on the smaller term $-\frac{K_{\rm f}\cos\phi_a}{2r_a}$, where $\cos\phi_a$ should be close to -1. Equation (5) is simplified to

$$\begin{aligned}
0 &= Ar_a(R-r_a)+\frac{r_a+r_b\cos\alpha}{4}g,\\
\Omega &= \omega+\frac{r_b\sin\alpha}{4r_a}g+\frac{K_{\rm f}}{2r_a},\\
0 &= Br_b(R-r_b)+\frac{r_a\cos\alpha+r_b}{4}g,\\
\Omega &= \omega-\frac{r_a\sin\alpha}{4r_b}g.
\end{aligned} \tag{8}$$

Because $K_{\rm f}\ll g$, $\sin\alpha$ is a small term. Thus, we have $\sin\alpha\approx\alpha$ and $\cos\alpha\approx 1$. Hence, the solutions for Eq. (8) are

$$\begin{aligned}
r_a &= R+\frac{g}{2A}\equiv R+\frac{g}{2(1-\delta)}\propto\delta,\\
r_b &= R+\frac{g}{2B}\equiv R+\frac{g}{2(1+\delta)}\propto\frac{1}{\delta},\\
\alpha &= -\frac{K_{\rm f}}{4gr_a},\\
\Omega_{\max} &= \omega-\frac{r_a}{4r_b}g\alpha\propto\frac{1}{r_b}\propto\delta.
\end{aligned} \tag{9}$$

From Eq. (9), if δ is larger than 0, i.e., $d=A/B$ is smaller than 1, $\Omega_{\max}$ is larger than it with d equal to 1. Therefore, we have proven that $d_{\rm c}$ is smaller than 1 in the case of $K_{\rm f}\ll g$.

5. Discussion and conclusion

It has been widely recognized that the entrainment range is a vital indicator for the adaptability of the SCN to an alteration of the external environment. Previous studies found that the entrainment range or adaptability is affected by the rigidity of the network, which is represented by the amplitude relaxation rate.[20] If the oscillator is more rigid than the other one, the amplitude relaxation rate is larger and the entrainment range is smaller. It has been found that the amplitude relaxation rate in the SCN is larger than that in the peripheral clock in that the entrainment range of the former is narrower than that of the latter.

In the SCN, it has also been found that the amplitude relaxation rate differs between neurons. In particular, the amplitude relaxation rate of SCN neurons is estimated in the range from 0.03 $\rm h^{-1}$ to 1 $\rm h^{-1}$. However, the appearance of that difference has not yet been explained, for which we try to give an alternative explanation in the present study when the entrainment range is taken into account. The heterogeneity is described by the ratio d of the amplitude relaxation rate between the VL and the DM here. We observed that it differs in the effect of the ratio d on the entrainment range between the cases of $P=1.0$ and $P=0.5$, in which both the VL and the DM are sensitive to the zeitgeber (time giver) and only the

VL are sensitive to the zeitgeber, respectively. When $P = 1.0$, the largest entrainment range is obtained with $d = 1$, in other words, there is no heterogeneity in the amplitude relaxation rate between the VL and the DM. Whereas $P = 0.5$, the largest entrainment range is obtained with $d < 1$, i.e., the amplitude relaxation rate for the VL neurons is smaller than that for the DM neurons. Therefore, the suitable heterogeneity of the amplitude relaxation rate in the SCN neurons leads to the maximal entrainment range when $P < 1.0$.

Our findings provide some suggestions for the experiments about distinct zeitgebers. When the zeitgeber is the temperature, all the SCN neurons are assumed to be sensitive to the zeitgeber ($P = 1.0$), and when the zeitgeber is the light, only a part of the SCN neurons are sensitive to the zeitgeber ($P < 1.0$).[20] It is interesting to examine the relationship between the entrainment range to the temperature and the entrainment range to the light, i.e., if the entrainment range to the temperature is large in one species, a question is raised whether the entrainment range to the light is also large in this species, and vice versa. Thus far, the entrainment range to the temperature is not obtained for most species in experiment. Hence, the relationship is unable to be obtained through experiment. From our current findings, we can predict that the relationship is parabolic-like, because the heterogeneity of the amplitude relaxation rate plays distinct roles in the entrainment range between these two zeitgebers.

In experiment, it has been found that the VL neurons are more likely to be affected by the external disturbance. For example, the amplitudes can differ after a sudden shift of the light–dark cycle of 6 h in the VL and the DM parts.[9] This implies that the amplitude relaxation rate is smaller for the VL neurons. In future, it would be interesting to calculate amplitude relaxation rates for the VL neurons and the DM neurons, respectively, in experiment. Our work may shed light on the appearance of the heterogeneity in the amplitude relaxation rate, and the effects of the heterogeneity in the neuronal properties on the entrainment of the SCN.

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