

Dependence of the entrainment on the ratio of amplitudes between two subgroups in the suprachiasmatic nucleus

Changgui Gu,^{1,2,*} Huijie Yang,¹ Johanna H. Meijer,² and Jos H. T. Rohling^{2,†}

¹*Business School, University of Shanghai for Science and Technology, Shanghai 200093, People's Republic of China*

²*Department of Molecular Cell Biology, Laboratory for Neurophysiology, Leiden University Medical Center, Leiden 2300RC, The Netherlands*



(Received 8 January 2018; revised manuscript received 8 May 2018; published 19 June 2018)

Organisms can be synchronized not only to the natural 24-h light-dark cycle but also to artificial non-24-h cycles. Interestingly, when the period of the cycle is far from 24 h, organisms may show complicated behavioral patterns. For example, exposed to a 22-h light-dark cycle, in behavioral activity of rats, a phenomenon called “dissociation” emerges, i.e., one periodic component shows a 22-h period and the other shows a period close to the endogenous period of the animal (around 24 h). It has been found that these two components are regulated by two subgroups of the suprachiasmatic nucleus (SCN), respectively, with the ventrolateral part regulating the 22-h component and the dorsomedial part regulating the other component. In the present study, based on a mathematical model, we will examine how the ratio of amplitudes between these two subgroups affects the entrainment of the SCN to the external 22-h light-dark cycle. Our results show that the dissociation happens when the ratio is smaller than 1 and the maximal entrainment (synchronization) ability of the SCN to the external cycle is obtained when the ratio is larger than 1. Our finding sheds light on the dissociation between the subgroups and suggests that the heterogeneity in the amplitudes alter the entrainment ability of the SCN.

DOI: [10.1103/PhysRevE.97.062215](https://doi.org/10.1103/PhysRevE.97.062215)

I. INTRODUCTION

Organisms have evolved to be synchronized (entrained) to the natural 24-h light-dark cycle. The physiology and behavior of organisms is thus nicely accustomed to the external cycle of light and darkness [1–3]. Despite being firmly entrained, living organisms are to some extent flexible and naturally predisposed to adjust to changes in environmental conditions, among others to changing regimes of light and darkness [3,4]. Some organisms are able to adjust to wider ranges of external light-dark cycles than others. For example, *Arvicanthus niloticus* can entrain to cycles ranging from 22.5 to 25.5 h, humans to cycles from 20.5 to 29.0 h, and *Rattus norvegicus* from 23.5 to 28.5 h [3]. The range of periods to which an organism can entrain is always limited and is called the *entrainment range*. This range can be determined experimentally and is an important indication for the adaptability of the animal to changes in external light-dark conditions. A large range of entrainment means that the oscillator may be too reactive, such as clocks in peripheral tissues, while a very narrow range of entrainment means that the oscillator may not be able to adapt to changes in environmental conditions at all [4]. The main clock keeps a balance between rigidity and reactivity and keeps its range of entrainment within certain boundaries.

Outside this entrainment range, animals do not synchronize to the external cycle and express periodic behavior that differs from the external period [5,6]. Under these conditions, more

complicated behavioral patterns can be observed. For example, rats exposed to a 22-h light-dark cycle may show two periodic components, one showing a 22-h period which is equal to the period of the external cycle and the other displaying a period around 24 h which is close to the endogenous period of the animal [6–9].

Experiments in rats have shown that these two periodic components are regulated by two subgroups of the main clock, the suprachiasmatic nucleus (SCN), which is located above the optic chiasma [6,9]. One subgroup is located in the ventrolateral (VL) part of the SCN, and this part directly receives light information from the retina [10,11]. The VL subgroup relays the light information to the other subgroup located in the dorsomedial (DM) part of the SCN. When exposed to a light-dark cycle with a period deviating from 24 h, such as 22 h, the VL part of the SCN follows the external cycle. However, the DM part, which obtains the external light information only indirectly through the VL part, cannot keep up with this period length and will fall back on its endogenous period of about 24 h.

The SCN contains about 20,000 neurons, of which 25% of all neurons are retinally innervated [7,10–12]. These neurons are mostly located in the ventrolateral part of the SCN, although nonretinal recipient cells are also present in this area. For the sake of simplicity, in this paper we will distinguish the VL part (which is mostly light-recipient) and the DM part (which is mostly non-light-recipient). Defined like this, 25% of all neurons constitute the VL and the other 75% of the neurons form the DM. The SCN neurons are coupled to form a network through neurotransmitters, such as vasoactive intestinal polypeptide (VIP) in the VL, arginine vasopressin (AVP) in the DM, and γ -aminobutyric acid (GABA), which

*Corresponding author: gu_changgui@163.com

†Corresponding author: J.H.T.Rohling@lumc.nl

plays an important role in the interaction between the VL and DM [13–15].

The SCN's responsiveness to light as well as the interplay between the light-responsive VL and the light-unresponsive DM influences the range of entrainment of the organism. We have shown previously that this range depends on the coupling strength between VL and DM, where a critical transition point determines if the entrainment is governed by the synchrony within the network or is controlled by the strength (the amplitude) of the network oscillations [16]. If the coupling between VL and DM is strong, then VL and DM will not dissociate and act as one oscillator. If the coupling within this single oscillator increases, the amplitude goes up, while if it decreases the amplitude goes down. In this case, the range of entrainment depends on the amplitude of the network: a higher amplitude means that only a strong zeitgeber is able to entrain the SCN, and thus a higher amplitude leads to a narrower range of entrainment [4]. If, however, the coupling between VL and DM is weak, then the range of entrainment depends on whether the DM neurons can be entrained by the VL neurons or not. If this is not the case, then a dissociation between VL and DM will occur, causing one component to entrain to the external cycle and one component oscillating at its endogenous period [6]. In this case, a higher coupling strength will lead to an increased range of entrainment [16]. Here the amplitude within the subgroups also plays an important role.

The amplitude within a subgroup in the SCN can be influenced by a number of factors, such as the amplitude of the single neurons, the synchrony between the neurons, and the proportion of arrhythmic to rhythmic neurons [8]. We have seen experimentally that the amplitudes in the VL and DM part can differ after a sudden shift of the light-dark cycle of 6 h [11]. We previously discussed the role of the ratio of arrhythmic neurons in both subregions of the SCN in entrainment, in the endogenous period of the SCN, and in the dissociation between the two subregions [8,17]. The proportion of arrhythmic neurons affects the amplitude of the subset that contains these cells. A higher proportion leads to a lower overall amplitude. An increase in the proportion of arrhythmic neurons in VL decreases the amplitude of VL and the influence on DM decreases. As a result, the DM dissociates faster from the VL-induced rhythm, negatively affecting the range of entrainment. DM can also impose its endogenous rhythm on VL. In this case the SCN will cycle with its endogenous period. If the proportion of arrhythmic neurons increases in DM, the amplitude of DM decreases and the influence on VL decreases. At some point, DM can no longer impose its rhythm on VL and VL will become entrained to the external cycle. If the proportion of arrhythmic neurons in DM increases even more, the amplitude of DM will become even lower and VL is able to entrain DM to the external cycle [8,17].

As the amplitude of the different subparts of the SCN is important for entrainment, we will systematically investigate the influence of the ratio between the amplitude of the VL and DM subgroups on the entrainment range of the SCN. By investigating the amplitude ratio between the VL and DM parts, we are able to generalize our conclusions and make our findings irrespective to differences in absolute amplitude between animals. For this study, we use a Poincaré model to model the neurons in the VL and DM parts of the SCN.

We use an artificial period of 22 h to assess under which conditions VL and DM dissociate and lose their entrainment. We find that the dissociation emerges only when the amplitude of the VL subgroup is not larger than the amplitude of the DM subgroup.

II. DESCRIPTION OF THE POINCARÉ MODEL

The Poincaré model is often used to describe the SCN network under the influence of an artificial external light-dark cycle with period T [4,16,18–24]. In the present study, the Poincaré model is composed of N nonidentical neuronal oscillators which differ in their intrinsic amplitudes. Each neuronal oscillator has two variables, x and y . The coupling between oscillators is modelled by a mean field F , which is the mean of x from all oscillators. The SCN network is described by the model as follows:

$$\begin{aligned}\dot{x}_i &= \gamma x_i(C_i - r_i) - \frac{2y_i\pi}{\tau} + gF + E_i, \\ \dot{y}_i &= \gamma y_i(C_i - r_i) + \frac{2x_i\pi}{\tau}, \quad i = 1, 2, \dots, N \\ F &= \frac{1}{N} \sum_{i=1}^N x_i,\end{aligned}\quad (1)$$

where the parameters γ , C_i , and τ represent the relaxation parameter, the intrinsic amplitude, and intrinsic period of the individual oscillator, respectively. The neuronal oscillators are coupled through the mean-field term gF , where g represents the coupling strength between neuronal oscillators within and between the VL and DM subgroups. The parameter r_i is the amplitude of the i th oscillator which reads:

$$r_i = \sqrt{x_i^2 + y_i^2}, \quad i = 1, 2, \dots, N. \quad (2)$$

The parameters C_i and E_i depend on the region of the neurons. If the neuron i is located in the VL region, i.e., $i \leq pN$, then $C_i = A$ and $E_i = K_f \sin(\Omega t)$, where p represents the ratio of the number of neurons responsive to the light information, and if the neuron i is in the DM region, i.e., $pN < i \leq N$, then $C_i = B$ and $E_i = 0$. The parameters Ω and t represent the frequency of the environmental cycle and time, respectively. K_f is the strength of the external light intensity. Let the mean of the intrinsic amplitudes for all SCN neurons be $C \equiv \frac{1}{N} \sum_{i=1}^N C_i$, in other words, $C \equiv pA + (1-p)B$. The mean amplitude C influences the entrainment range of the SCN [4]. In order to avoid the effects of C and focus on the study of the difference in intrinsic amplitudes between the VL and the DM, let the mean value C be constant in the present study. This means that the parameters A and B are correlated, i.e., B decreases with the increase of A and vice versa. For simplicity, we only consider the case where the amplitudes within each subgroup is identical for all neurons, being either A or B .

In the present study, the key parameter is the ratio in the neuronal amplitude between VL and DM ($d = \frac{A}{B}$). When the intrinsic amplitudes between the VL neurons and the DM neurons are equal ($A = B \equiv C$), the ratio is 1 ($d = 1$). When the intrinsic amplitude of the VL neurons is larger or smaller than the intrinsic amplitude of the DM neurons ($A > B$ or $A < B$), the ratio is $d > 1$ or $d < 1$, respectively. For instance,

for $p = 0.25$, the ratio is $d = 0.1$ with $A = \frac{4C}{31}$ and $B = \frac{40C}{31}$ and $d = 10.0$ with $A = \frac{40C}{13}$ and $B = \frac{4C}{13}$.

Here we examined the effect of the ratio d on the entrainment of the VL and the DM subgroups exposed to an external 22 h cycle. The parameters are set as $\gamma = 1 \text{ h}^{-1}$, $C = 1$, $g = 0.1 \text{ h}^{-1}$, $\tau = 23 \text{ h}$ throughout the present article. The other parameters are selected as the number of neurons $N = 400$, the light intensity $K_f = 0.05 \text{ h}^{-1}$, 0.10 h^{-1} , or 0.15 h^{-1} and the ratio of light-responsive neurons $p = 0.25$. We compare the case of $p = 0.25$ to the case when all neurons are responsive to light information ($p = 1.0$). In the case of $p = 1.0$, we assume that the difference between the two subgroups exists only in the intrinsic neuronal amplitudes but not in the light sensitivity of the neurons. Thus, in both subgroups, the neurons are responsive to light input, but 25% of the SCN neurons have an intrinsic amplitude that is A , and 75% has an intrinsic amplitude that is B . Note that, in the case of $p = 1.0$, the two subgroups are called by “subgroup 1” (SG1) and “subgroup 2” (SG2) in order to distinguish with the VL and the DM. Also, since in the case of $p = 1.0$, the number of neurons being responsive to light is 4 times as many as in the case of $p = 0.25$, the light intensity strength is reduced to $K_f = 0.03 \text{ h}^{-1}$, 0.04 h^{-1} , or 0.05 h^{-1} [8].

In order to test whether the effects of the ratio d on the entrainment range differs for different cases of p , we use a phase-response curve (PRC). The PRC is constructed by plotting the magnitude of the phase shifts after discrete light pulses (normally 1-h light pulse) are applied at different times across the circadian cycle under constant darkness [7]. Phase advances are plotted as positive numbers while phase delays are plotted as negative numbers. The maximal phase advance in the PRC is a measure for the ability of the SCN to entrain to external cycles with a period smaller than the endogenous period of the SCN, and the maximal phase delay in the PRC is a measure for the ability of the SCN to entrain to an external cycle with a period larger than the endogenous period of the SCN.

III. THE EFFECT OF DIFFERENCE IN THE AMPLITUDES BETWEEN TWO SUBGROUPS

Figure 1 shows illustrative examples for the effect of the ratio d on the entrainment of the SCN to an external cycle with a period of 22 h for $p = 1.0$ [Figs. 1(a)–1(c)] and $p = 0.25$ [Figs. 1(d)–1(f)]. When $p = 1.0$, the two subgroups are entrained to an external cycle with a period of 22 h only for $d = 1.0$ (b). For $d = 0.1$ (a) and for $d = 10.0$ (c) the periods of the subgroups deviate considerably from the period of the external cycle. This means that for $d = 0.1$ and for $d = 10.0$ the subgroups are both not entrained to the external 22-h cycle. When $p = 0.25$, the temporal evolutions of both subgroups differ from the case of $p = 1.0$. For $p = 0.25$ both VL and DM subgroups are entrained to the external 22 h cycle when $d = 10.0$ (f). For $d = 0.1$ (d) and $d = 1.0$ (e) something special happens. VL is entrained to the external 22 h cycle, while DM is not entrained, causing a dissociation between both subgroups in the SCN. For these examples, the strength of the light intensity for $p = 1.0$ is $K_f = 0.04 \text{ h}^{-1}$ and for $p = 0.25$ is $K_f = 0.1 \text{ h}^{-1}$.

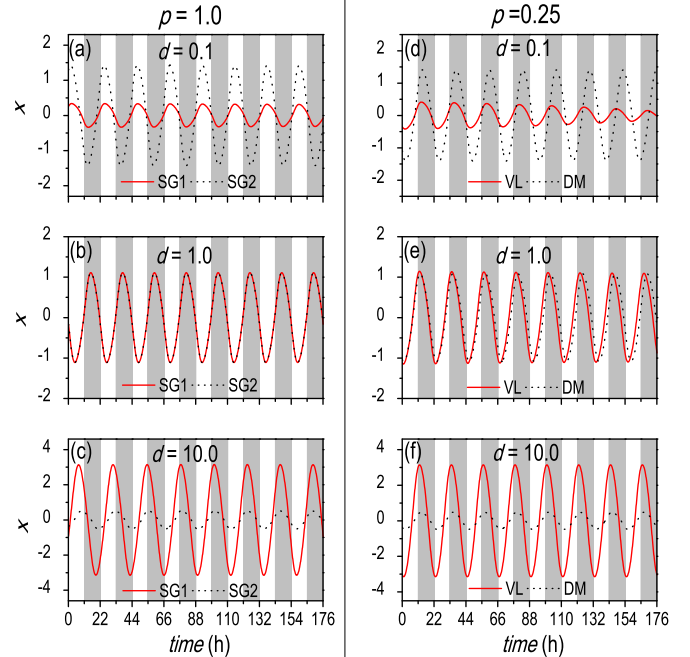


FIG. 1. The temporal evolutions of the SCN under the external 22-h cycle with different ratios d . The proportion of light responsive neurons is $p = 1.0$ [(a)–(c)] and $p = 0.25$ [(d)–(f)]. The y axis shows the amplitude of the subgroups of the SCN. SG1 and SG2 represent first and second subgroups that have different amplitudes, respectively [(a)–(c)]. The light intensity is $K_f = 0.04 \text{ h}^{-1}$ and $K_f = 0.1 \text{ h}^{-1}$ for the case of $p = 1.0$ and $p = 0.25$, respectively. The gray (white) area corresponds to the darkness (light).

Next the quantitative relationship between the period of each subgroup and the ratio d under the external 22-h cycle is examined for different light intensity strengths (K_f) in Fig. 2. Note that we used different light intensity strengths for $p = 1.0$ and $p = 0.25$ to account for the number of neurons that are responsive to the light input. When the light intensity is weak, both subgroups are not entrained to the external cycle for all values of d for both $p = 1.0$ (a) and $p = 0.25$ (d). The difference between the periods for both subgroups and the period of the external cycle (22 h) is minimal when the ratio is $d_c = 1.0$ for $p = 1.0$ (a) and $d_c \approx 3.0$ for $p = 0.25$ (d). This suggests that the maximal range of entrainment of the SCN is obtained at distinct values of d for different p , i.e., $d_c = 1.0$ for $p = 1.0$ but $d_c \approx 3.0$ for $p = 0.25$. When the light intensity is increased, the entrainment of each subgroup to the external cycle depends on the ratio d . In Figs. 2(b) and 2(e), the entrainment emerges around $d_c = 1.0$ for $p = 1.0$ or $d_c = 3.0$ for $p = 0.25$. If d is evidently larger or smaller than d_c , then the SCN loses entrainment to the external cycle. Interestingly, for $p = 0.25$, when the ratio is small ($d < 0.3$), the aforementioned dissociation between the VL and the DM emerges. This dissociation is not observed for $p = 1.0$. When the light intensity is larger, the range of d where the SCN is entrained to the external cycle is broader for both $p = 1.0$ [Fig. 2(c)] and $p = 0.25$ [Fig. 2(f)]. Also, the range of d where the VL dissociates from DM is broader for $p = 0.25$ [Fig. 2(f)].

We also investigate the case of $\gamma = 0.1 \text{ h}^{-1}$ (Fig. 3), and the results are consistent with those shown in Fig. 2. Note that

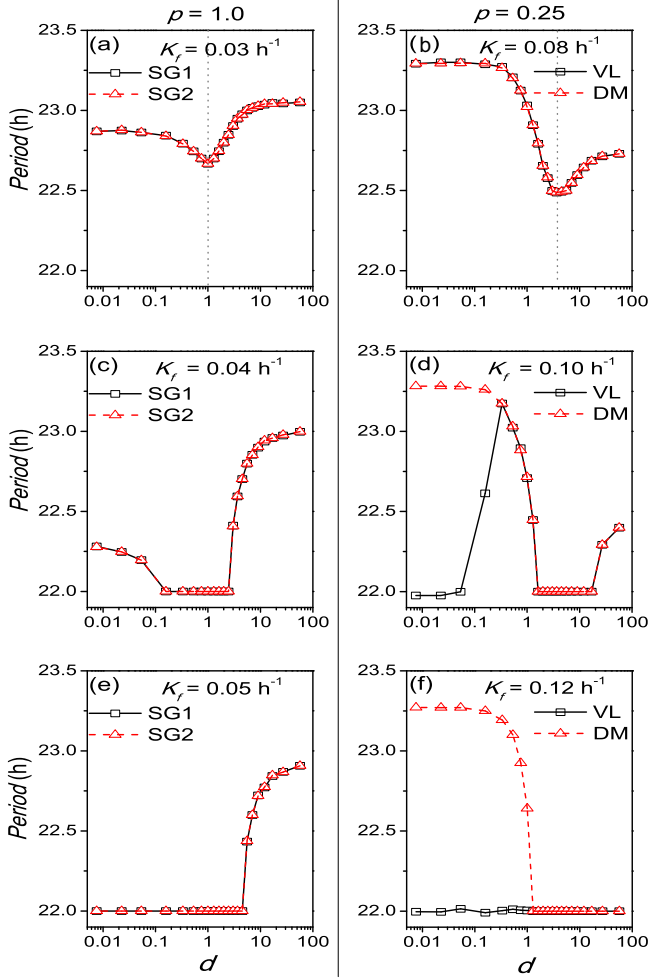


FIG. 2. The relationships between the periods of the two subgroups to the ratio d under an external 22-h cycle in the cases of $p = 1.0$ [(a), (c), and (e)] and $p = 0.25$ [(b), (d), and (f)]. SG1 and SG2 represent the first and second amplitude subgroups, respectively. K_f represents the light intensity. A dissociation between the VL and DM subgroup is seen in (d) and (f).

in order to visibly show the alternation from the unentrained to entrained state, the light intensities K_f is slightly different with Fig. 2.

In the previous figure we found a difference in maximal range of entrainment between $p = 1.0$ and $p = 0.25$. For $p = 1.0$ we saw a maximal range of entrainment when $d = 1.0$. For $p = 0.25$, this maximal range of entrainment was reached for $d \approx 3.0$. We test this finding by use of a phase-response curve (PRC) (Fig. 4). For $p = 1.0$ and $p = 0.25$, we used the values $d = 0.1, 1.0, 3.0$, and 10.0 . We find indeed that for $p = 1.0$, the value $d = 1.0$ shows the largest amplitude of the PRC, which indicates the highest range of entrainment (a). Also, for $p = 0.25$ we find a maximal amplitude PRC with $d = 3.0$ (b). Further, we examined the amplitude for the advance and delay part of the PRC for the whole range of values of d (c). Again, we observe that maximal entrainment range for $p = 1.0$ is reached when the ratio is $d = 1.0$, and the maximal entrainment range for $p = 0.25$ is reached when the ratio is $d \approx 3.0$. Except for

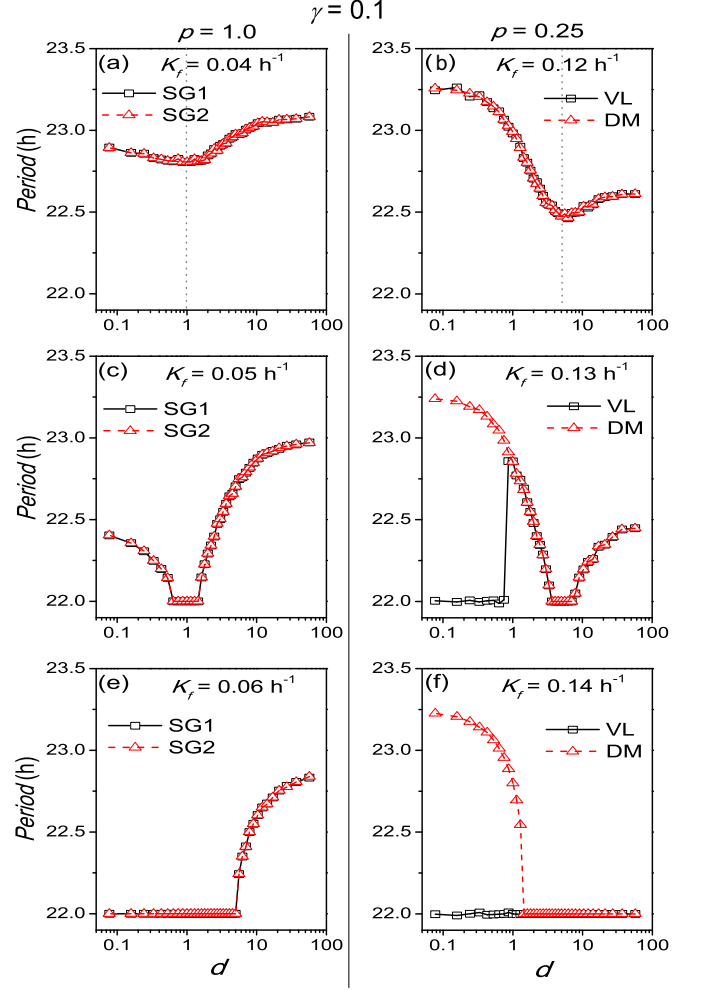


FIG. 3. The relationships between the periods of the two subgroups to the ratio d under an external 22-h cycle when the radial relaxation rate is $\gamma = 0.1 \text{ h}^{-1}$. SG1 and SG2 represent the first and second amplitude subgroups, respectively. K_f represents the light intensity. This figure corresponds to Fig. 2.

the explanation from PRC, we will show the analytical results in the next section.

IV. ANALYTICAL RESULTS

In order to distinguish the VL and the DM, Eq. (1) can be rewritten as follows:

$$\begin{aligned}
 \dot{x}_a &= \gamma x_a (A - r_a) - \frac{2y_a \pi}{\tau} + g[p x_a + (1-p)x_b], \\
 &\quad + K_f \sin(\Omega t), \\
 \dot{y}_a &= \gamma y_a (A - r_a) + \frac{2x_a \pi}{\tau}, \quad i = 1, 2, \dots, PN \\
 \dot{x}_b &= \gamma x_b (B - r_b) - \frac{2y_b \pi}{\tau} + g(p x_a + (1-p)x_b), \\
 \dot{y}_b &= \gamma y_b (B - r_b) + \frac{2x_b \pi}{\tau}, \quad i = PN + 1, PN + 2, \dots, N,
 \end{aligned} \tag{3}$$

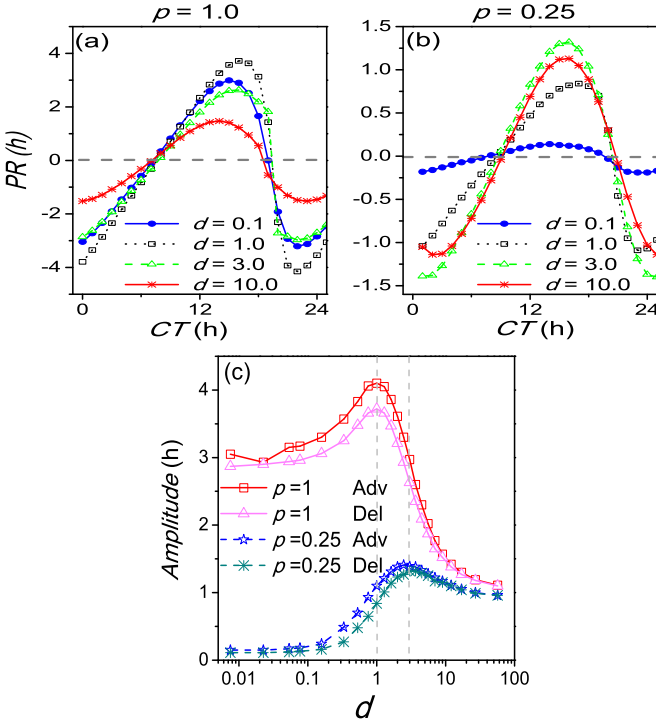


FIG. 4. The phase-response curve for different ratios d in the case of $p = 1.0$ (a) and $p = 0.25$ (b). CT and PR represent circadian time and phase response, respectively. In (c) the amplitudes for the delay zone and advance zone of the phase response curves for different proportions of light responsive neurons is plotted against the amplitude ratio d (c). Adv and Del represent the advance area and the delay area, respectively.

where the VL and the DM is represented by a and b , respectively, and the mean field F is the term $px_a + (1-p)x_b$. For convenience, Eq. (3) is transformed from Cartesian coordinates to polar coordinates. Let $x_a = r_a \cos \theta_a$, $y_a = r_a \sin \theta_a$, $x_b = r_b \cos \theta_b$, $y_b = r_b \sin \theta_b$. Substituting them into Eq. (3) and taking $A = \frac{Cd}{1-p+pd}$ and $B = \frac{C}{1-p+pd}$ into account, where d satisfies $d \geq 0$, we obtain

$$\begin{aligned} \dot{r}_a &= \gamma r_a \left(\frac{Cd}{1-p+pd} - r_a \right) + pr_a \cos^2 \theta_a g \\ &\quad + (1-p)r_b \cos \theta_b \cos \theta_a g + K_f \sin(\Omega t) \cos \theta_a, \\ \dot{\theta}_a &= \omega - \frac{(pr_a \cos \theta_a \sin \theta_a + (1-p)r_b \cos \theta_b \sin \theta_a)g}{r_a} \\ &\quad - \frac{K_f}{r_a} \sin(\Omega t) \sin \theta_a, \\ \dot{r}_b &= \gamma r_b \left(\frac{C}{1-p+pd} - r_b \right) + pr_a \cos \theta_a \cos \theta_b g \\ &\quad + (1-p)r_b \cos^2 \theta_b K \\ \dot{\theta}_b &= \omega - \frac{(pr_a \cos \theta_a \sin \theta_b + (1-p)r_b \cos \theta_b \sin \theta_b)g}{r_b}. \end{aligned} \quad (4)$$

If all the oscillators are entrained to the external cycle, then we obtain $\dot{r}_a = 0$, $\dot{r}_b = 0$, $\dot{\theta}_a = \Omega$, and $\dot{\theta}_b = \Omega$. Let $\theta_a = \Omega t + \phi_a$ and $\theta_b = \Omega t + \phi_b$. Considering the averaging method developed by Krylov and Bogoliubov as used in

Refs. [4,16,24,25], ϕ has a lower timescale than Ωt . Letting $\alpha = \langle \phi_b \rangle - \langle \phi_a \rangle$, we obtain

$$\begin{aligned} \langle \cos^2(\phi_a + \Omega t) \rangle &= \frac{1}{2}, \\ \langle \cos(\phi_b + \Omega t) \cos(\phi_a + \Omega t) \rangle &= \frac{\cos \alpha}{2}, \\ \langle \cos(\phi_a + \Omega t) \sin(\phi_a + \Omega t) \rangle &= 0, \\ \langle \cos(\phi_b + \Omega t) \sin(\phi_a + \Omega t) \rangle &= -\frac{\sin \alpha}{2}, \end{aligned} \quad (5)$$

where $\langle \cdot \rangle$ represents the average in one circadian cycle. For simplicity, we keep the nonaveraged notation r_a , r_b , ϕ_a , and ϕ_b in the rest of the article. Substituting Eq. (5) into Eq. (4) we obtain

$$\begin{aligned} 0 &= \gamma r_a \left(\frac{Cd}{1-p+pd} - r_a \right) + \frac{pr_a + (1-p)r_b \cos \alpha}{2} K \\ &\quad - \frac{K_f \sin \phi_a}{2}, \\ \Omega &= \omega + \frac{(1-p)r_b K \sin \alpha}{2r_a} - \frac{K_f \cos \phi_a}{2r_a}, \\ 0 &= \gamma r_b \left(\frac{C}{1-p+pd} - r_b \right) + \frac{pr_a \cos \alpha + (1-p)r_b}{2} g, \\ \Omega &= \omega - \frac{pr_a K \sin \alpha}{2r_b}. \end{aligned} \quad (6)$$

In the following, we will explain the effect of the ratio d on the entrainment of the SCN. Except for the phase-response curve, the entrainment ability can be also represented by the lower limit of entrainment of the SCN (LLE), which is the minimal T cycle the SCN can be entrained to. If the LLE is smaller than $T = 22$ h, then the SCN can be entrained to the $T = 22$ h cycle; if the LLE is larger than $T = 22$ h, then the SCN is incapable of being entrained to the $T = 22$ h cycle. Four conditions are considered, $d = 1.0$, $d = 1 + \delta$, $d = L$, and $d = L + \delta$, where δ is a small positive value and L is a very large positive value. If we find the LLE with $d = 1.0$ is larger than $d = 1.0 + \delta$, and the LLE with $d = L$ is smaller than $d = L + \delta$, i.e., the entrainment ability increases with the increase of d when d is around 1.0 and the entrainment ability decreases with the increase of d when d is very large, then this finding quantitatively explains why the maximal entrainment ability emerges when d is larger than 1 (e.g., $d \approx 3$) in Fig. 2. Note that the LLE is equal to $\frac{2\pi}{\Omega_{\text{LLE}}}$.

When the ratio is $d = 1$, Eq. (6) is as follows:

$$\begin{aligned} 0 &= \gamma r_a (C - r_a) + \frac{pr_a + (1-p)r_b \cos \alpha}{2} g - \frac{K_f \sin \phi_a}{2}, \\ \Omega &= \omega + \frac{(1-p)r_b g \sin \alpha}{2r_a} - \frac{K_f \cos \phi_a}{2r_a}, \\ 0 &= \gamma r_b (C - r_b) + \frac{pr_a \cos \alpha + (1-p)r_b}{2} g, \\ \Omega &= \omega - \frac{pr_a g \sin \alpha}{2r_b}. \end{aligned} \quad (7)$$

In order to achieve the maximal value of $\Omega = \Omega_{\text{LLE}}$, $\cos \phi_a$ should be close to -1 based on the second equation of Eq. (7). We assume $g \gg K_f$, and thus α is a small term.

Consequently, we obtain

$$\begin{aligned}
 0 &= \gamma r_a(C - r_a) + \frac{pr_a + (1-p)r_b}{2}g, \\
 \Omega_{LLE} &= \omega - \frac{(1-p)r_b g \alpha}{2r_a} + \frac{K_f}{2r_a}, \\
 0 &= \gamma r_b(C - r_b) + \frac{pr_a + (1-p)r_b}{2}g, \\
 \Omega_{LLE} &= \omega + \frac{pr_a g \alpha}{2r_b}. \tag{8}
 \end{aligned}$$

Accordingly, the solutions are as follows:

$$\begin{aligned}
 r_a = r_b &\equiv R = C + \frac{g}{2\gamma}, \\
 \alpha &= \frac{K_f}{gR}, \\
 \Omega_{LLE} &= \omega + \frac{pK_f}{2R}. \tag{9}
 \end{aligned}$$

When the ratio is $d = 1 + \delta$, based on Eq. (6) and similarly as Eq. (8), we obtain

$$\begin{aligned}
 0 &= \gamma r_a(C - Cp\delta + C\delta - r_a) + \frac{pr_a + (1-p)r_b}{2}g, \\
 \Omega_{LLE} &= \omega - \frac{(1-p)r_b g \alpha}{2r_a} + \frac{K_f}{2r_a}, \\
 0 &= \gamma r_b(C - Cp\delta - r_b) + \frac{pr_a + (1-p)r_b}{2}g, \\
 \Omega_{LLE} &= \omega + \frac{pr_a g \alpha}{2r_b}. \tag{10}
 \end{aligned}$$

From the first and third equations of Eq. (10) and the first equation of Eq. (9), qualitatively, we can define

$$\begin{aligned}
 r_a &= R(1 + \epsilon_1), \\
 r_b &= R(1 - \epsilon_2), \tag{11}
 \end{aligned}$$

where ϵ_1 and ϵ_2 are small positive values. Further, from the second and fourth equations of Eq. (10), we obtain

$$\begin{aligned}
 \Omega_{LLE} &\approx \omega - \frac{(1-p)g\alpha}{2} + \frac{K_f}{2R}(1 - \epsilon_1), \\
 \Omega_{LLE} &\approx \omega + \frac{pg\alpha}{2}. \tag{12}
 \end{aligned}$$

Thus, the results are

$$\begin{aligned}
 \alpha &\approx \frac{K_f(1 - \epsilon_1)}{gR}, \\
 \Omega_{LLE} &\approx \omega + \frac{pK_f}{2R}(1 + \epsilon_2). \tag{13}
 \end{aligned}$$

Comparing Eq. (13) with Eq. (9), we find that Ω_{LLE} is larger with $d = 1 + \delta$ than $d = 1$. Thus we have proven that the entrainment ability increases with the increase of d when d is around 1.

When the ratio d is very large ($d = L$), B is a small term compared to A and r_b is also a small term compared to r_a .

Consequently, Eq. (6) is reduced to:

$$\begin{aligned}
 0 &= \gamma r_a \left[\frac{C}{p} \left(1 - \frac{1-p}{Lp} \right) - r_a \right] + \frac{pgr_a}{2} - \frac{K_f \sin \phi_a}{2}, \\
 \Omega &= \omega - \frac{K_f \cos \phi_a}{2r_a}, \\
 0 &= \frac{pr_a \cos \alpha + (1-p)r_b}{2}g, \\
 \Omega &= \omega - \frac{pr_a K \sin \alpha}{2r_b}. \tag{14}
 \end{aligned}$$

Because $\frac{r_a}{r_b}$ is a very large value in the last equation of Eq. (14), the maximal value of Ω mainly depends on the second equation but not the last equation. In order to achieve the maximal value of Ω , $\cos \phi_a$ should be close to -1 in the second equation of Eq. (14). Consequently, Eq. (14) is

$$\begin{aligned}
 0 &= \gamma r_a \left[\frac{C}{p} \left(1 - \frac{1-p}{Lp} \right) - r_a \right] + \frac{pgr_a}{2}, \\
 \Omega_{LLE} &= \omega + \frac{K_f}{2r_a}, \\
 0 &= \frac{pr_a \cos \alpha + (1-p)r_b}{2}, \\
 \Omega_{LLE} &= \omega - \frac{pr_a K \sin \alpha}{2r_b}. \tag{15}
 \end{aligned}$$

The solutions are

$$\begin{aligned}
 r_a &\equiv R' = \frac{C}{p} \left(1 - \frac{1-p}{Lp} \right) + \frac{pg}{2\gamma}, \\
 \Omega_{LLE} &= \omega + \frac{K_f}{2r_a}, \\
 \alpha &= -\arctan \frac{pK_f}{g(1-p)r_a}, \\
 r_b &= \frac{pr_a \cos \alpha}{p-1}. \tag{16}
 \end{aligned}$$

Further, we examine the case of $d = L + \delta$. Based on Eq. (6) and similarly as Eq. (15), we obtain

$$\begin{aligned}
 r_a &= R' + \frac{C(1-p)}{p^2 L^2} \delta, \\
 \Omega_{LLE} &= \omega + \frac{K_f}{2r_a}, \\
 \alpha &= -\arctan \frac{pK_f}{g(1-p)r_a}, \\
 r_b &= \frac{pr_a \cos \alpha}{p-1}. \tag{17}
 \end{aligned}$$

From Eqs. (16) and (17), it is visible that Ω is smaller with $d = L + \delta$ than $d = L$. Thus, the relationship between Ω and d is negative when d is very large. Considering the positive relationship between Ω and d when d is around 1 as well, we have proven that the maximal entrainment ability emerges when d is larger than 1 instead of being equal to 1.

V. CONCLUSION AND DISCUSSION

In the present study, we examined how the entrainment of the SCN to an external 22-h cycle depends on the ratio between the amplitudes of the two subgroups VL and DM. The amplitudes of the subgroups depend (i) on the amplitude of the single neurons in the subgroup, (ii) on the synchrony of the neurons in that subgroup, and (iii) on the proportion of arrhythmic neurons in that subgroup. We show that a dissociation between the VL and DM subgroups [6] may depend on the amplitude ratio between the two groups. If only 25% of the neurons are responsive to light, and if the light intensity is larger than the coupling strength, then a dissociation between the two subgroups emerges only when the amplitude ratio is small, which means that the amplitude of the VL subgroup is not larger than the amplitude of the DM subgroup. Thus, entrainment in this case is only reached if the amplitude of the VL subgroup is larger than the amplitude of the DM subgroup.

Independent of the light intensity, the maximal range of entrainment of the SCN also differs between the two cases. If all neurons are responsive to light, then the maximum range of entrainment is achieved when the amplitude ratio is 1, which means that the amplitudes of both subgroups are the same. When only 25% of the neurons are responsive to light input, an amplitude ratio of approximately 3 gives the maximum range of entrainment, which means that the amplitude of the VL subgroup has to be about 3 times as high as the amplitude of the DM subgroup. Apparently, for different percentages of light-responsive neurons, there is an optimal amplitude ratio between the VL and DM subgroups for the range of entrainment. This may be different for different species. For diurnal species, for example, the percentage of neurons that are responsive to light is lower than in nocturnal rodents [26,27]; for instance, in the diurnal ground squirrel only 8.4% of the neurons were responsive to light [26].

In this study, the only difference between the VL neurons and the DM neurons is the sensitivity to light except for the amplitudes. The heterogeneity of the neurons themselves have been studied in our previous works. We examined the effect of this heterogeneity on the collective behavior of the neurons. In Ref. [28], we studied the effect of the difference of intrinsic neuronal amplitude between the VL and the DM on the synchronization of the SCN neurons under constant darkness, so without external light influence. In Ref. [29], the difference of intrinsic periods between the VL and the DM was taken into account. This difference induces an asymmetry of the entrainment range when the ratio of light-sensitive neurons is $p < 1$ (e.g., $p = 0.25$), while the asymmetry is absent when the ratio is $p = 1$. In Ref. [24], we considered the heterogeneity of intrinsic periods in all SCN neurons. The heterogeneity affects the entrainment range but not the asymmetry, i.e., with the increase of the heterogeneity, the entrainment range increases.

In the Supplemental Material [30], we also added heterogeneity in other parameters than light responsiveness for SCN neurons, including radial relaxation rates, intrinsic periods, and intrinsic amplitudes of neurons (Supplemental Figs. S1–S4) [30]. In Supplemental Figs. S1 and S2 [30], we introduced a new parameter d' which represents the ratio of radial relaxation

rate γ between the VL and the DM. We found that different with the amplitude ratio d , the entrainment ability decreases with the increase of the ratio d' , in other words, there is no parabolic relationship between the entrainment ability and d' when the proportion is $p = 0.25$. This shows that the ratio of different γ values between the VL and DM part does not lead to similar results as the amplitude ratio. The heterogeneity of the intrinsic periods and intrinsic amplitudes within groups is taken into account in Supplemental Figs. S3 and S4 [30], respectively. We found the relationship between the SCN period and d is not altered in these two figures compared with Fig. 2, when the SCN is exposed to a 22-h light-darkness cycle.

In this study, only the neurons that are activated by light were taken into account, and light-suppressed neurons were not. In nocturnal rodents, such as rats, only a small percentage of neurons are suppressed by light [27]. However, in diurnal animals, such as the degus, the percentage of neurons that is suppressed by light is much higher, namely almost 73% of all light-responsive neurons [27]. For these diurnal species only 6.8% of all neurons were activated by light, and 18.2% was suppressed by light. It would be interesting for future studies to investigate the influence of these suppressed neurons on the entrainment of the SCN. This would increase the dimensionality of the model from two groups of neurons to three groups of neurons, being the light-activated subpopulation, the light-suppressed subpopulation and the unaffected subpopulation of SCN neurons.

Note also that in this study we examined the ratio between the amplitudes of the two subgroups of the SCN, but not the absolute values of the amplitudes for both subgroups. These absolute amplitude values may differ between species, even between individual animals. By considering the amplitude ratio between the subgroups, we can disregard the actual amplitudes levels and still be able to determine entrainment properties of animals, because the amplitudes of different regions within the same animal are related. Depending on external conditions, there may occur a change in the amplitude ratio within the same animal. It is conceivable that the amplitude ratio between the VL and DM subgroups may change over seasons, for example. After a shift of the light-dark cycle of 6 h, a fast-shifting component and a slowly shifting component have been identified [15]. These components are likely the expression of a rapidly shifting population that is directly innervated by light and a light-unresponsive subpopulation of cells within the SCN. Immediately after the phase shift in the light-dark cycle, the fast-shifting, light-responsive subpopulation appeared to have a higher amplitude compared to the other subpopulation [11] (see Supplemental Fig. S5 in the Supplemental Material) [30]. After the phase-shift the ratio between VL and DM is not 1, as the amplitude of the light-responsive subpopulation is higher than the other subpopulation. It is possible that this ratio was already in place before the phase shift and is merely uncovered by the phase shift. However, this example shows clearly that the amplitudes between the different subgroups in the SCN may actually differ from each other. So, looking at the ratio between the amplitudes of the VL and DM part of the SCN can reveal information about the entrainment properties for a specific animal. This, in turn, may reveal differences between species and how this may be of functional importance to the proper working of the SCN.

To summarize, we found that the amplitude ratio between the VL and DM subgroup may be important for entrainment of the SCN. This paper reveals how the relative amplitude, together with light input, determines the entrainment range of the SCN. This model is testable by subjecting animals to a shifted light-dark cycle, followed by an analysis of phase shifts at the cellular level.

ACKNOWLEDGMENTS

The work is supported by the National Natural Science Foundation of China under Grants No. 11505114 and No. 10975099, the Program for Professor of Special Appointment (Oriental Scholar) at Shanghai Institutions of Higher Learning under Grants No. QD2015016 and No. D-USST02, and the Shanghai's Program for Constructing First-class Disciplinaries under Grant No. SHFCD-USST-SYS01.

-
- [1] C. S. Pittendrigh and S. Daan, *J. Comp. Physiol. A* **106**, 223 (1976).
- [2] C. S. Pittendrigh, *Annu. Rev. Physiol.* **55**, 17 (1993).
- [3] R. Refinetti, *Circadian Physiology* (CRC Press, Boca Raton, FL, 2006).
- [4] U. Abraham *et al.*, *Mol. Syst. Biol.* **6**, 438 (2010).
- [5] S. Usui, Y. Takahashi, and T. Okazaki, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **278**, R1148 (2000).
- [6] H. o. de la Iglesia *et al.*, *Curr. Biol.* **14**, 796 (2004).
- [7] C. Gu, Z. Liu, W. J. Schwartz, and P. Indic, *PLoS ONE* **7**, e36900 (2012).
- [8] C. Gu, H. Yang, and J. H. T. Rohling, *Phy. Rev. E* **95**, 032302 (2017).
- [9] M. D. Schwartz, C. Wotus, T. Liu, W. O. Friesen, J. Borjigin *et al.*, *Proc. Natl. Acad. Sci. USA* **106**, 17540 (2009).
- [10] H. S. Lee, J. L. Nelms, M. Nguyen, R. Silver, and M. N. Lehman, *Nat. Neurosci.* **6**, 111 (2003).
- [11] J. H. Rohling, H. T. vanderLeest, S. Michel, M. J. Vansteensel, and J. H. Meijer, *PLoS ONE* **6**, e25437 (2011).
- [12] J. H. Meijer and W. J. Schwartz, *J. Biol. Rhythms* **18**, 235 (2003).
- [13] S. J. Aton, C. S. Colwell, A. J. Harnmar, J. Waschek, and E. D. Herzog, *Nat. Neurosci.* **8**, 476 (2005).
- [14] L. P. Morin, *J. Biol. Rhythms* **22**, 3 (2007).
- [15] H. Albus, M. J. Vansteensel, S. Michel, G. D. Block, and J. H. Meijer, *Curr. Biol.* **15**, 886 (2005).
- [16] C. Gu, A. Ramkisoensing, Z. Liu, J. H. Meijer, and J. H. T. Rohling, *J. Biol. Rhythms* **29**, 16 (2014).
- [17] C. Gu, M. Tang, H. Yang, and J. H. T. Rohling, *Sci. Rep.* **6**, 37661 (2016).
- [18] C. Bodenstein, M. Gosak, S. Schuster, M. Marhl, and M. Perc, *PLoS Comput. Biol.* **8**, e1002697 (2012).
- [19] A. E. Granada, G. Bordyugov, A. Kramer, and H. Herzog, *PLoS ONE* **8**, e59464 (2013).
- [20] C. Schmal, J. Myung, H. Herzog, and G. Bordyugov, *Front. Neurol.* **6**, 94 (2015).
- [21] I. T. Tokuda, D. Ono, B. Ananthasubramaniam, S. Honma, K.-I. Honma, and H. Herzog, *Biophys. J.* **109**, 2159 (2015).
- [22] C. Gu, H. Yang, and Z. Ruan, *Phy. Rev. E* **95**, 042409 (2017).
- [23] C. Gu, H. Yang, and M. Wang, *Phy. Rev. E* **96**, 052207 (2017).
- [24] C. Gu, J. Xu, Z. Liu, and J. H. T. Rohling, *Phy. Rev. E* **88**, 022702 (2013).
- [25] A. Balanov, N. Janson, D. Postnov, and O. Sosnovtseva, *Synchronization: From Simple to Complex* (Springer-Verlag, New York, 2009).
- [26] J. H. Meijer, B. Rusak, and M. E. Harrington, *Brain Res.* **501**, 315 (1989).
- [27] Y-Y Jiao, T. M. Lee, B. Rusak, *Brain Res.* **817**, 93 (1999).
- [28] C. Gu and H. Yang, *Chaos* **27**, 093108 (2017).
- [29] C. Gu and H. Yang, *Chaos* **27**, 063115 (2017).
- [30] See Supplemental Material at <http://link.aps.org/supplemental/10.1103/PhysRevE.97.062215> for additional simulations for heterogeneity of SCN neurons.