Mathematical Biosciences and Engineering, 16(4): 1893–1913.
DOI: 10.3934/mbe.2019092
Received: 13 December 2018
Accepted: 14 February 2019
Published: 07 March 2019

http://www.aimspress.com/journal/MBE

Review

Heterogeneity of neuronal properties determines the collective behavior of the neurons in the suprachiasmatic nucleus

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Abstract: Circadian rhythms have been observed in behavioral and physiological activities of living things exposed to the natural 24 h light-darkness cycle. Interestingly, even under constant darkness, living organisms maintain a robust endogenous circadian rhythm suggesting the existence of an endogenous clock. In mammals, the endogenous clock is located in the suprachiasmatic nucleus (SCN) which is composed of about 20,000 neuronal oscillators. These neuronal oscillators are heterogeneous in their properties, including the intrinsic period, intrinsic amplitude, light information sensitivity, cellular coupling strength, intrinsic amplitudes and the topological links. In this review, we introduce the influence of the heterogeneity of these properties on the two main functions of the SCN, i.e. the free running rhythm in constant darkness and entrainment to the external cycle, based on mathematical models where heterogeneous neuronal oscillators are coupled to form a network. Our findings show that the heterogeneities can alter the free running periods under constant darkness and the entrainment ability to the external cycle for the SCN by controlling a fine balance between flexibility and robustness of the clock. These findings can explain experimental observation, e.g., why the free running periods and entrainment abilities are different between species, and shed light on the heterogeneity of the SCN network.

Keywords: circadian rhythms; mathematical modeling; coupling; neuronal network; entrainment range; free running period; synchronization

1. Introduction

In almost all living beings on earth, including humans, behavioral activities and physiological processes in the body exhibit circadian (24-h or daily) rhythms that are synchronized to the natural 24 h light-dark cycle to which all life on earth is exposed [1]. Nocturnal animals are awake during the dark period and asleep during the light period, while diurnal animals, such as humans, are active during daytime and sleep at night. Physiological parameters, such as hormones, are also active at certain times in the 24-h cycle that most benefit the organism. For example, the 'sleep hormone' melatonin rises just before going to sleep to help the organism fall asleep[2,3]. Interestingly, these circadian rhythms pertain when external conditions change. If an animal is exposed to constant darkness conditions, i.e., no light is presented to the animal at all during the 24-h period, the animal still shows a free-running rhythm, i.e., a daily pattern of activity that has a period close to 24-h [4,5]. This means that the animal must have an internal circadian clock that generates a rhythm of approximately 24-h, even in the absence of external input, and which regulates all peripheral circadian clocks in the body [6]. In mammals, the endogenous clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus, which is situated just above the optic chiasm, and is composed of about 20,000 self-oscillating neurons [1,7,8]. The circadian rhythms of the SCN neurons originate from a genetic negative feedback loop within each individual neuron [9]. For a precise and consistent output of the clock as a whole by means of neurotransmitters to other brain areas, these cells must be organized in such a way that they are not randomly active throughout the period. This would result in a non-periodic output signal for the ensemble of cells. To organize the activity of the individual cells in such a way that the clock as a whole has a consistent and precise output pattern [10], the cells interact and form network configurations, containing specialized cellular subgroups [1].

To accommodate the external light-dark cycles, the internal clock is able to entrain, or synchronize, to this external cycle. As such, this clock receives input from light-sensitive retinal ganglion cells in the eyes through the retinal hypothalamic tract [11]. The clock must be flexible in order to adjust to different seasons, and to enable adjusting to shifted light-dark regimes after transatlantic travel. However, the clock must not be too flexible, because we do not want to experience a jet lag every time we switch on the light at night. This delicate balance between flexibility and rigidity makes the circadian clock an interesting topic for studying oscillator properties in biological systems.

One oscillator property that can be investigated is the range of periods to which the clock is able to entrain [12,13]. In experiments the external period can be artificially changed to a period T, which can be longer or shorter than 24-h. If the period T becomes too short or too long, the animal will not be able to entrain to these artificial light-dark cycles. The shortest artificial period to which the animal can entrain is called the lower limit of entrainment (LLE), while the longest period to which the animal can entrain is called the upper limit of entrainment (ULE) [13]. The range between the LLE and ULE is called the entrainment range of that species. This entrainment range differs between species. For example, for a Sudanian grass rat it ranges from 22.9 h to 25.3 h, for a southern flying squirrel from 23.5 h to 24.9 h, for a deer mouse from 22.5 h to 25.1 h, and for the human being from 21.5 h to 28.6 h [14]. When, in experimental conditions, the period T of the external light-dark cycle is set to a value that is outside the entrainment range for a certain species, complicated entrainment patterns emerge. For example, if Wistar rats are exposed to a light-dark cycle with a period of 22 h, a phenomenon called "dissociation" arises, i.e., the behavioral activity of the rat exhibits two periodic

components, of which one follows the external 22 h-period, while the other follows the period of the internal clock, which is close to 24 h [15].

The oscillatory behavior of the SCN as a whole depends upon the collective activity of the SCN neurons. These neurons show oscillations themselves, although the oscillatory properties are heterogeneous. Three oscillatory phenotypes have been observed for SCN neurons: self-sustained oscillatory neurons, damped oscillatory neurons and neurons that do not show oscillatory behavior, the so-called arrhythmic neurons [16,17]. For the oscillatory neurons, either self-sustained or damped, the intrinsic periods differ and roughly range from 22 h to 28 h [8]. Also the amplitudes are heterogeneous among SCN neuronal oscillators [18], as well as the relaxation rates [17,19], which represent the rigidity of the oscillators to an external perturbation.

The SCN neurons organize themselves in specialized functional subgroups, according to their neuronal properties. For example, approximately 25% of the SCN neurons are directly sensitive to the light information from light-sensitive retinal ganglion cells, and relay the light information from the eyes to the remaining 75% of the SCN neurons that are not light-sensitive [20]. The group of light-sensitive neurons is located in the ventrolateral (VL) region of the SCN, while there are no light-sensitive neurons in the dorsomedial (DM) region of the SCN. Although there are also light-insensitive neurons present in the VL part of the SCN, for simplicity we divide the SCN into a light-sensitive region, which we call VL and is comprised of 25% of the SCN neurons, and a light-insensitive DM region, comprising of the remaining 75% of the neurons. When exposed to light pulses during darkness, the VL neurons respond immediately [21]. After a transatlantic flight, when entering a new light-dark schedule, the VL subgroup shifts its phase immediately to the new light-phase, while the DM subgroup gradually transitions from the phase of the previous light-dark cycle to the phase of the new light-dark cycle [22]. Also, when rats are exposed to a T-cycle of 22 h, the 22 h component of the behavioral activity is regulated by the VL cell-subgroup, while the 24 h component is regulated by the DM subgroup [23]. Moreover, when the VL and the DM are separated in vitro, the DM runs faster than the VL [24].

However, there is still a lively debate on the differences between VL and DM neuronal subgroups about whether or not the difference in the amplitudes of *Period* gene expression exists. It was reported that the amplitudes of *Period* gene expression for VL neurons are zero (damped oscillatory neurons or arrhythmic neurons) but the amplitudes of DM neurons are not, in other words, the amplitudes depend on the location of the neurons [18]. Conversely Webb AB, et al. found that neuronal amplitudes of *Period* gene expression are independent of the location of the neurons [16]. In particular, the three phenotypes of neurons were observed in both the VL and the DM, and the proportion of each phenotype is not visibly different between these two subgroups.

The question now raised is how this heterogeneity in the SCN, which manifests itself in group and neuronal differences, is able to produce a robust SCN rhythm, which maintains a fine balance between flexibility and rigidity. Experiments found that the synchronization between SCN neurons plays a key role in the generation of this rhythm [25,26]. If the neurons are well synchronized, the rhythm is robust, but less flexible, while if the neurons are more distributed in phase, the rhythm is less robust, but the flexibility increases. This synchronization between the neurons is determined by the network organization of the SCN, i.e. how the neurons in the SCN are connected to each other [1]. The network organization emerges from the coupling between the neurons, predominantly through neurotransmitter release. The neurons in the SCN can be divided into neuronal subgroups depending on neurotransmitter release and sensitivity, which adds to the heterogeneity in the SCN. The main

neurotransmitters used in the SCN to establish the network organization within the SCN are vasoactive intestinal polypeptide (VIP), arginine vasopressin (AVP) and γ-amino butyric acid (GABA) [27–29]. Neurons in the VL region mainly use VIP to communicate among each other, but also DM neurons are sensitive to VIP produced by the VL neurons. The DM neurons mainly use AVP to communicate with each other. GABA is used mainly for the long-range communication between the VL and DM subgroups. It has been shown that the VL region has a larger influence on the DM than vice versa, although the DM region does have influence on VL neurons as well, i.e., the coupling from the VL to the DM is much larger than the coupling from the DM to the VL [1,20,24,30,31]. In other words, the coupling strength is heterogeneous between the VL neurons and the DM neurons. The interaction within the SCN and the input from the retina is summarized in Figure 1.

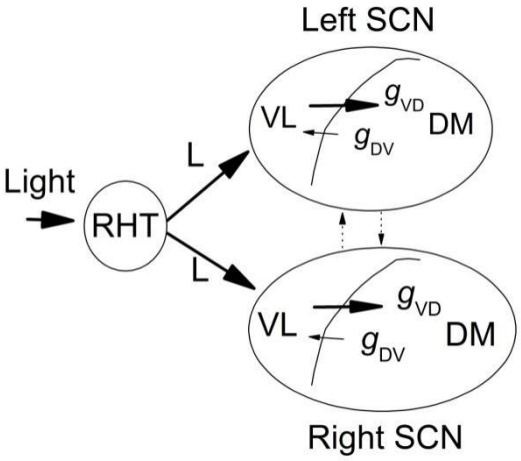

Figure 1. Schematic overview of main interacting pathways of the SCN and its input. *L* denotes the strength of the light input pathway of the SCN which is received by light-sensitive neurons located in the ventro-lateral part of the SCN (VL). Between the VL and dorso-medial (DM) region of the SCN, *g* denotes the coupling between both regions, where the thickness of the arrow indicates the strength of the coupling. RHT represents retinal hypothalamic tract.

The heterogeneity of the neuronal properties mentioned above affects the collective behavior of the SCN neurons, such as the free running rhythms under constant darkness and entrainment to the external light-darkness cycle, by changing the network configuration. For example, the dissociation between the VL and the DM under a 22 h external cycle is due to the heterogeneity in the sensitivity to light between the VL and the DM [23]. However, limited by the experimental technology, it is hard to quantitatively calculate the degree of heterogeneity as well as analyze the effects of the heterogeneity on the collective behaviors from experiments. By using mathematical models, this effect can be quantitatively predicted. In the next section, mathematical models that have been used to describe the SCN network are introduced. Then, based on the models, the effects of the heterogeneity in the SCN are presented in Section III. Finally, conclusions are drawn and discussed in Section IV.

2. Methods

Two types of models are typically used to describe the circadian clock, including the biophysical models (mechanistic models) and the generic models (phenomenological models). The former type captures transcriptional regulation, such as the models [32–34], where one neuronal oscillator is composed of multiple variables (16, about 70 and 7, respectively). Here, we focus on the simplest biophysical model, a Goodwin model, where one neuronal oscillator is represented by three variables [35]. The Goodwin model describes the transcriptional translational feedback loop of individual neurons in a mathematical manner, where interaction to other neurons is possible through the influence on one of the parameters of the model [35]. The latter type includes a Poincaré model and a Kuramoto model. The Poincaré model describes the oscillatory neurons purely in terms of phase and amplitude [13]. The Kuramoto model is purely based on the phase of the oscillators, and focuses on interaction between the different oscillatory units [36]. Here the Goodwin model, the Poincaré model and the Kuramoto model will be described in more mathematical detail. Importantly, the parameters that are used in the different models to investigate heterogeneous properties of the SCN are explored for each model separately.

2.1. Goodwin model

One single Goodwin oscillator is composed of three variables, being a clock gene and protein, and a transcriptional inhibitor which constitutes the generic negative feedback. The neuronal oscillators are coupled through a mean field representing the neurotransmitters. The model composed of N SCN neuronal oscillators is shown in Eq (1) and Figure 2.

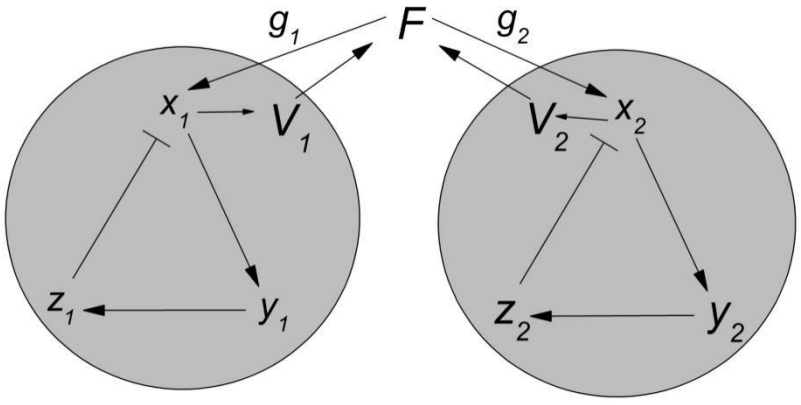

Figure 2. Schematic diagram of the Goodwin model with $N = 2$ (without external light input). The variables x (clock gene mRNA), y (clock protein) and z (a transcriptional inhibitor) constitute a generic negative feedback loop within one clock cell. The variable V is neurotransmitter concentration which is assumed to be induced by x. The oscillators are coupled through a mean field F, which is defined as the mean value of the neurotransmitters V.

$$\begin{aligned}
\frac{dx_i}{dt} &= \mu_i(\alpha_1 \frac{k_1^n}{k_1^n + z_i^n} - \alpha_2 \frac{x_i}{k_2 + x_i}) + \alpha_c \frac{gF}{k_c + gF} + L_i, \\
\frac{dy_i}{dt} &= \mu_i(k_3 x_i - \alpha_4 \frac{y_i}{k_4 + y_i}), \\
\frac{dz_i}{dt} &= \mu_i(k_5 y_i - \alpha_6 \frac{z_i}{k_6 + z_i}), \\
\frac{dV_i}{dt} &= \mu_i(k_7 x_i - \alpha_8 \frac{V_i}{k_8 + V_i}), \\
F &= \frac{1}{N}\sum_{i=1}^{N} V_i,
\end{aligned} \tag{1}$$

where subscript i denotes the i-th oscillator, and the variables x_i, y_i, z_i and V_i represents a clock gene mRNA, clock protein, transcriptional inhibitor and neurotransmitter concentration, respectively, of the i-th oscillator. F describes a mean field input to all oscillators and is constituted of all V_i (V_i is assumed to be produced by x_i [35,37]). The coupling strength g and light intensity L_i represents the sensitivity of the oscillator to this mean field and the light responsiveness term, respectively. The values of other parameters are set as given in Ref. [35,38]. The temporal evolutions of variables are shown in Figure 3. All variables show robust circadian rhythms of the same period. Note that, the parameters g, L and N are used to represent the coupling strength, light responsiveness term and the total number of SCN neurons, respectively, throughout this review article.

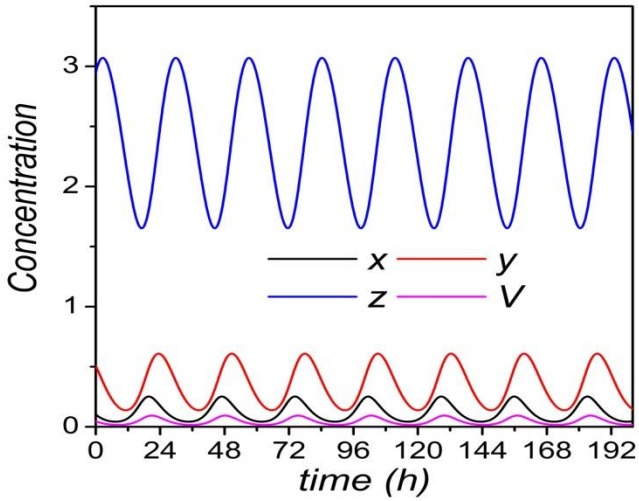

Figure 3. Temporal evolutions for the four variables of one randomly selected Goodwin oscillator without external light input. The number of neurons is set to be N = 100, and the other parameters are set as given in Ref. [35,38].

2.2. Poincaré model

For simplicity and for theoretical analysis, a generic model, the Poincaré model is also used to describe the SCN network. One single Poincaré oscillator is represented by two variables *x* and *y*, which contains amplitude and phase information.

$$\begin{aligned}\frac{dx_i}{dt} &= \lambda x_i(a_i - r_i) - \frac{2\pi\mu_i}{\tau} y_i + gF + L_i,\\ \frac{dy_i}{dt} &= \lambda y_i(a_i - r_i) + \frac{2\pi\mu_i}{\tau} x_i,\end{aligned} \tag{2}$$

where the subscript i represents the i-th oscillator, and parameters λ, a_i and τ represent the amplitude relaxation rate, intrinsic amplitude and natural period of the neuronal oscillator, respectively. F is a mean field of x_i, i.e. $F = \frac{1}{N}\sum_{i=1}^{N} x_i$. r_i is the actual amplitude of the i-th oscillator, which is defined as $r_i = \sqrt{x_i^2 + y_i^2}$. The phase θ_i is defined as $\theta_i = atan\ \frac{y_i}{x_i}$.

2.3. Kuramoto model

Another simple model is the Kuramoto model, which contains only the phase information. The model containing the intrinsic periods τ and the actual phase θ is represented as follows.

$$\dot{\theta}_i = \frac{2\pi\mu_i}{\tau} + \frac{g}{N}\sum_{j=1}^{N}\sin(\theta_j - \theta_i) + L_i. \tag{3}$$

2.4. Defining heterogeneity

To include heterogeneity in the models, a number of parameters were introduced in mathematical models. Only the VL subpopulation is sensitive to light input, while the DM subpopulation is not [38]. Neuronal oscillators can be heterogeneous in their intrinsic period, their intrinsic amplitude and their susceptibility to the coupling signals of other neurons in biophysical models [16,35,37,39] and generic models [40–43]. Finally, the network organization, or topology, can also affect how subpopulations influence each other in biophysical models [33,44–46] and generic models [47,48]. Here we will explore these different sources of heterogeneity in the Goodwin model, the Poincaré model and the Kuramoto model, respectively.

The light responsiveness term L_i differs between the VL neurons ($1 \le i \le pN$) and the DM neurons ($pN < i \le N$) in all models (Eqs (1–3)), where the parameter p represents the proportion of light-responsive SCN neurons. The heterogeneity can be represented by p. If p is equal to 0 (or 1), all neurons are insensitive (or sensitive) to the light information. For the DM neurons, L_i is equal to zero independent of either daytime or nighttime in each model. For the VL neurons, L_i is also equal to 0 in night time (mod (t, T) $> \frac{T}{2}$) for the Goodwin model, but in daytime (mod (t, T)$\le \frac{T}{2}$) L_i is equal to K_f for the Goodwin model. The light term is $K_f \sin(\Omega_e t)$ in the Poincaré model, and

$K_f \sin(\Omega_e t - \theta_i)$ in the Kuramoto model for both daytime and nighttime, where the parameter K_f and Ω_e represent the light intensity and the frequency of the external light cycle, respectively. The light responsiveness terms differ between models, because the typical forms of light responsiveness terms for the latter two models are selected for the convenience of theoretical analyses.

In order to induce heterogeneity in the intrinsic neuronal periods, a coefficient μ_i is introduced for each model, which is drawn from a normal distribution with a mean equal to 1 and a standard deviation δ. Consequently, the intrinsic neuronal periods satisfy a normal distribution around 24 h. In particular, a larger value of μ_i corresponds to smaller intrinsic periods for node *i*, and vice versa. The deviation δ stands for the heterogeneity in the neuronal intrinsic periods, i.e. if δ is 0, there is no heterogeneity and with the increase of δ the heterogeneity increases.

Heterogeneity in intrinsic neuronal amplitude has been investigated for neuronal subpopulations. We assume that, within the VL and DM subpopulations, the intrinsic amplitudes of the neuronal oscillators are identical ($a_i = a_j,\ 1 \le i,j \le pN;\ a_k = a_l, pN < k,l \le N$), but between the VL and DM subpopulations the intrinsic amplitudes are different. The difference in intrinsic amplitude of the VL and DM subpopulations was achieved in two different ways. First, the intrinsic amplitudes of the neuronal oscillators can be both larger than 0. The ratio ($a_i/a_j,\ 1 \le i \le pN$ and $pN < j \le N$) or the difference ($a_i - a_j = 0,\ 1 \le i \le pN$ and $pN < j \le N$) in the amplitudes between the VL neurons and the DM neurons represent the heterogeneity in intrinsic amplitudes in the Poincaré model. If the ratio is 1 or the difference is 0, there is no heterogeneity. If the ratio is far from 1 or the difference is far from 0, the heterogeneity is large. In the second case, the heterogeneity is represented by the proportion of the number of non-rhythmic neurons to the number of neurons within the same subgroup (note that the non-rhythmic neurons have amplitudes of 0). In particular, for the Goodwin model, the hill coefficient and the degradation rate of the clock gene are set to be $n = 3$ and $\alpha_2 = 0.5$, respectively, for non-rhythmic neurons [46], and for Poincaré oscillators, the intrinsic amplitude is set to $a = 0$ for non-rhythmic neurons. Note that for the Kuramoto model only phase information is given and amplitude is not defined.

Heterogeneity in the cellular coupling strength was defined by a coefficient ε_i which is drawn from a normal distribution with a mean equal to 1 and a standard deviation σ. The deviation σ signifies the heterogeneity. This coefficient ε_i, which value is randomly assigned to each neuron, is multiplied with the coupling strength *g* for each model.

The network organization, or network topology, also affects how two subpopulations interact. In the SCN network the neurons can be viewed as the nodes of the graph, while the interactions between the neurons can be viewed as the edges/links of the graphs. We introduced a number of directed edges between VL and DM. Accordingly, the mean field *F* in Eq. (1) and (2) is altered and is now specifically defined for each individual oscillator, being

$$F_i = \frac{1}{E_i}\sum_{j=1}^{N} e_{ji} x_j \,, \tag{4}$$

where e_{ji} represents whether there is an edge from the node *j* to node *i*. If there is an edge, e_{ji} is equal to 1, otherwise it is 0. E_i is the number of neighbors to node *i* ($E_i = \sum_{j=1}^{N} e_{ji}$).

If the number (M_{VD}) of directed edges from the VL to the DM is larger than the number (M_{DV}) of directed edges from the DM to the VL, the VL is able to more strongly influence the DM than vice versa [49]. Thus, the heterogeneity is then represented by the ratio ($\rho = M_{DV}/(M_{DV} + M_{VD})$), which is derived from the SCN network structure. If the ratio ρ is 0.5, there is no heterogeneity; if the ratio is larger than 0.5, the VL has a stronger influence on the DM than vise versa. The network type within VL or DM is a directed Newman-Watts network, and the edges between subgroups are randomly selected, i.e., the neurons in one subgroup are randomly linked to the neurons of the other subgroup.

3. Results

In this section the effects of heterogeneity of (mathematical) parameters of the oscillators in the SCN are explored. For each parameter, mathematical simulations have been performed using at least one of the aforementioned models and the simulation results have been compared to actual experimental results. The mathematical analyses have provided insights into how these parameters influence the behaviors of the SCN.

3.1. The effects of the heterogeneity in the sensitivity to the zeitgeber

Whereas only a subpopulation of the neurons in the SCN are sensitive to the external light signal through the action of glutamate and pituitary adenylate cyclase-activatingpolypeptide (PACAP) [50–52], all SCN neurons are sensitive to temperature pulses [13]. Or, in other words, the SCN reacts in a homogeneous way towards temperature pulses, while it reacts heterogeneously to light input. Hence, the mechanism of SCN entrainment is potentially different between different zeitgebers (time-givers), for example the light-dark cycle and the temperature cycle. Based on the Poincaré model, it was found that the relationship between the entrainment range of the SCN and the coupling strength is opposed in a homogeneous situation where all neurons are sensitive to the zeitgeber ($p = 1$), as with temperature (see Figure 4) [13] If the coupling strength between the neurons increases, the entrainment range becomes smaller. It was found that in the heterogeneous case, when only a subpopulation of the neurons is sensitive to the zeitgeber ($p < 1$), for example light, and the other subpopulation is not, the relationship between coupling strength and entrainment range becomes more complicated [53]. A critical coupling strength between the oscillatory neurons emerges above and below which differences in entrainment occur. Below this critical coupling strength, the entrainment range increases with increasing coupling strength, while if the coupling strength is above this critical value, an increase in coupling strength induces a decrease in entrainment range, similar to the homogeneous situation. Therefore, the heterogeneity in the sensitivity to the zeitgeber affects the mechanism of the SCN entrainment.

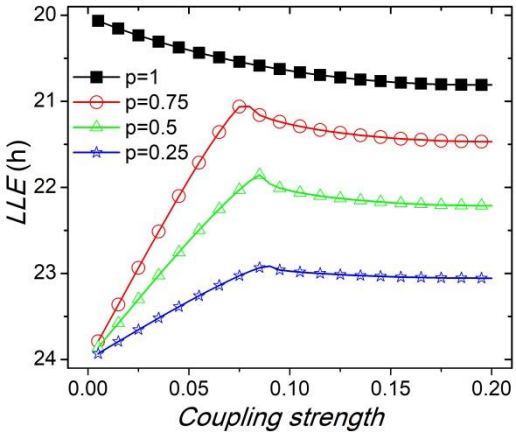

Figure 4. The relationship of the entrainment range (represented by the lower limit of entrainment, LLE) to coupling strength for situations where the zeitgeber is homogeneous ($p = 1$), e.g. temperature (closed boxes), or heterogeneous ($p < 1$), e.g., light (open symbols). In the homogeneous situation, the entrainment range monotonically decreases with increasing coupling strength, while in the heterogeneous situation a critical value exists where the relationship between the entrainment range and the coupling strength reverses. Below this value, increasing coupling strength leads to increased entrainment range, and above this value the entrainment range decreases with increasing coupling strength. Note that smaller LLE corresponds to larger entrainment range, thus the direction of y-axis is reversed. This figure is simulated from the Poincaré model and modified from Ref. [53].

Outside the entrainment range, for example when the animal is exposed to a 22 h light-dark cycle, a dissociation between the two major regions of the SCN (the VL and DM regions) may emerge. The emergence of this dissociation is affected by the heterogeneous action of light in the SCN. Similar to experimental results, both the Poincaré model and the Goodwin model showed that the period of the VL is adjusted to the external 22 h period of light and darkness, while the period of the DM is close to the free running period (Figure 5) [54,55]. For homogeneous zeitgebers, when all the neurons are sensitive to the zeitgeber, neither models show the dissociation between VL and DM occur. In order to induce the dissociation between both subpopulations, it suggests that the minimum proportion of the neurons sensitive to the light should be around 25% [54], which is consistent with experimental findings [20,56]. Interestingly, the heterogeneous action of light in the SCN is unable to cause dissociation between VL and DM when exposed to a cycle of 26 h, which is symmetrical to the cycle of 22 h around the cycle of 24 h. This suggests an asymmetry in the entrainment range around the free running period.

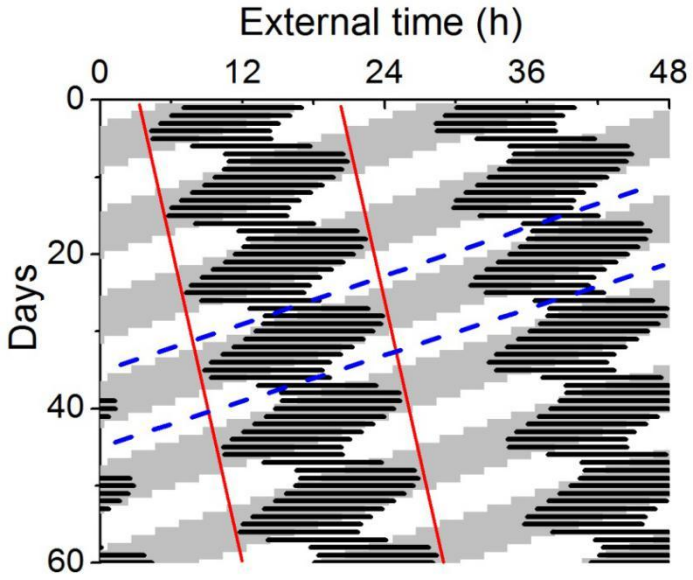

Figure 5. Simulated locomotor activity with tow dissociated components for a 22 h light-dark cycle. The blue dashed line indicates the component with a period of 22 h which is regulated by the VL and the red solid line indicates the component that follows the free running period and is regulated by the DM. This figure is made from the simulation data of the Poincaré model exposed to a 22 h light-dark cycle.

3.2. The effects of the heterogeneity in the intrinsic neuronal periods

In the Poincaré model, we found that heterogeneity in intrinsic periods of neurons affect the entrainment range. It was reported that an increase of the heterogeneity widens the entrainment range [57]. In addition, heterogeneous intrinsic neuronal periods alter the symmetry of the entrainment range. The lower limit of entrainment (LLE) and the upper limit of entrainment (ULE) are not always symmetrical with respect to the free running period (τ). The Kuramoto model was introduced to explain this asymmetry [58]. We found that the difference in the intrinsic periods between the VL (τ_V) and the DM (τ_D) can lead to this asymmetry. If the intrinsic period of DM neurons is smaller than the intrinsic period of the VL neurons ($\tau_D < \tau_V$), the asymmetry in entrainment range $(\tau - LLE) < (ULE - \tau)$ is observed.

The heterogeneity in the neuronal intrinsic periods has also been found to play a role in the amplitude of the endogenous rhythm for the SCN network, where the heterogeneity has different consequences between strongly coupled neuronal networks and weakly coupled networks [59]. Intuitively, if the coupling strength is strong ($g = 1.0$) between the neurons, the amplitude of the SCN network is monotonically decreasing when the heterogeneity of intrinsic periods increases (Figure 6). In particular, the increase of the heterogeneity leads to a decrease of the synchronization degree between the SCN neurons and, with that, reduces the amplitude for the SCN network. When the coupling strength between the neurons is weak, the relationship of the amplitude for the SCN network and the heterogeneity is parabolic-like. As observed in [38], with weak coupling ($g = 0.8$), for homogeneous intrinsic periods, so when all neurons have the same intrinsic period, the amplitude of the circadian rhythm is close to zero. When the intrinsic periods become heterogeneous, slowly

the network will obtain a circadian rhythm as the amplitude increases. The maximal amplitude for the SCN network is reached for a certain degree of heterogeneity in these intrinsic periods. When the heterogeneity increases above this threshold value, the amplitude of the rhythm decreases again with increasing heterogeneity. In the case of weak coupling (or in the absence of coupling strength, such as isolated neurons), the neurons lose their rhythm and the amplitudes can be defined as zero [17]. Proper heterogeneity of the intrinsic periods leads to some neurons (with larger intrinsic periods) to self-oscillate and these self-oscillating neurons will then synchronize the non-self-oscillating neurons, and the amplitude of the network rhythm increases. With the increase of the heterogeneity after the critical value (peak of the red line in Figure 6), the synchronization degree between neurons is decreased, so the amplitude of the network is reduced.

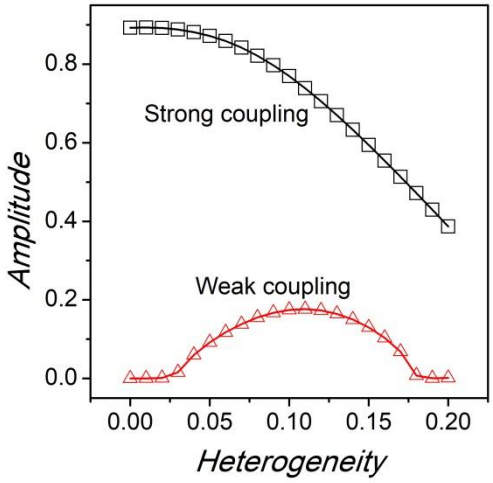

Figure 6. The relationship between the amplitude of the SCN network and the heterogeneity in the intrinsic neuronal periods in the case of strong coupling (the coupling strength $g = 1.0$) and the case of weak coupling ($g = 0.8$), respectively. For strong coupling the amplitude of the rhythm monotonically decreases when the heterogeneity increases. For weak coupling, a complex situation arises, where a certain heterogeneity of neuronal periods is necessary to obtain a rhythm (the amplitude starts to go up), but when the heterogeneity becomes too large, the rhythm amplitude decreases again. This figure is adapted from Ref. [59] based on the Goodwin model.

3.3. The effects of the heterogeneity in the intrinsic neuronal amplitudes

To investigate the influence of heterogeneity between the VL and DM subgroups on the SCN rhythm, a difference in intrinsic amplitudes between the two subgroups was first introduced as a source of heterogeneity. We found that the heterogeneity of the intrinsic amplitudes of the two subgroups improves the synchronization between the VL and DM subgroups [60]. One intuitive explanation is that the subgroup with larger amplitudes dominates the other subgroup. This same heterogeneity of amplitudes between both subgroups also affects the entrainment range to external light-dark cycles. A parabolic-like relationship exists between the entrainment range and the degree of heterogeneity, which is quantified by the difference in amplitude between both subgroups [61]. In

particular, if the heterogeneity is equal to some critical value, the maximal entrainment range is obtained. If the heterogeneity is smaller than this critical value, the entrainment range increases with the increase of the heterogeneity, and if the heterogeneity is larger than the critical value, the entrainment range decreases with the increase of the difference.

Furthermore, when defining the heterogeneity as the ratio of the VL amplitude to the DM amplitude, the emergence of a dissociation between both subgroups is affected when exposed to a 22 h light-dark cycle [55]. If the ratio is smaller than this critical value, the dissociation emerges, and if the ratio is larger than or equal to the critical value, the dissociation is not observed (Figure 7). This means that a dissociation can only occur if the amplitude of the light-sensitive VL subgroup is too small to entrain the DM subgroup to its period. If the amplitude of the VL subgroup is large enough, the dissociation between the subgroups disappears and the SCN as a whole will be entrained to the external 22 h cycle of light and darkness. Also in this case, a parabolic-like curve exists, with a critical value indicating the maximal range of entrainment [61].

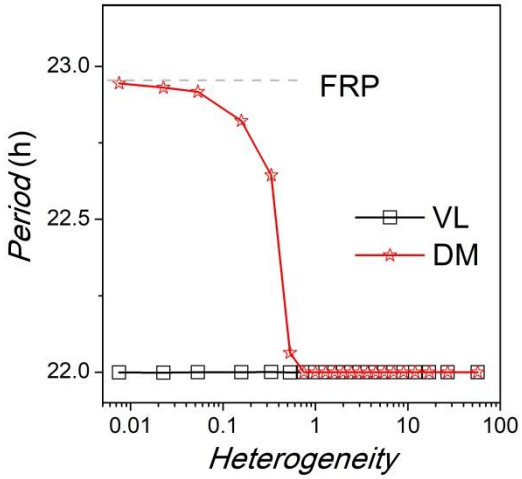

Figure 7. The period of the VL and the DM depends on the ratio of intrinsic neuronal amplitudes (heterogeneity), when exposed to a 22 h light-dark cycle. FRP means the endogenous (free running) period of the SCN. The DM subgroup will run only at the FRP, and dissociate from the VL subgroup when the ratio of the amplitudes is below a certain threshold. Above this threshold, entrainment occurs. This figure is modified from Ref. [55] based on the Poincaré model.

Secondly, the heterogeneity in amplitude of the VL and DM subgroup is represented by the ratio of the number of the arrhythmic neurons to the total number of neurons within the same subgroup. The arrhythmic neurons do not contribute to the amplitude of the subgroup as their amplitude is zero. It was found that the role of the arrhythmic neurons in the entrainment range of the SCN depends on their region [62]. If all the arrhythmic neurons are located in the VL, the entrainment range widens with the increase of the ratio of arrhythmic neurons. However, if they are in the DM, the entrainment range narrows with the increase of this ratio. Additionally, the role of the arrhythmic neurons in the dissociation between VL and DM subgroups also relies on the their region [63]. If all the arrhythmic neurons are located in the VL, the dissociation happens when the ratio is larger than a critical value, and

if all the arrhythmic neurons are located in the DM, the dissociation disappears when the ratio is larger than a critical value. This, again is due to the fact that the amplitude of the VL subgroup with respect to the amplitude of the DM subgroup is leading in the occurrence of a dissociation between the two.

3.4. The effects of the heterogeneity in the cellular coupling strength

Neurons are heterogeneous with respect to neurotransmitter release and susceptibility, amongst others depending on their location in the SCN. This heterogeneity can be modeled by assuming heterogeneous coupling strengths for the neurons in the SCN. If these coupling strengths between the neurons become more heterogeneous, both the Goodwin model and the Kuramoto model show that this leads to a reduction of the free running periods [64].

The coupling strength of neurons is correlated with the intrinsic periods of the neurons [39]. VL neurons of rats have a relatively smaller coupling strength and longer intrinsic periods, while DM neurons have a larger coupling strength paired with shorter intrinsic periods [24,27–29]. Thus, we reexamined the effects of the heterogeneity in the coupling strength on the free running periods [65]. We found that the effects depend on the relationship of the coupling strengths and the intrinsic neuronal periods. In particular, in the case of negative relationship, the free running period increases with the increase of the heterogeneity in coupling strengths. In the case of positive relationship, the free running period decreases with the increase of the heterogeneity in coupling strengths.

3.5. The effects of the heterogeneity in the network structure

The heterogeneity in the network structure is represented by the ratio between the numbers of directed links between the VL to the DM ($M_{DV}/(M_{DV}+M_{VD})$). This ratio is between 0.5 and 1, and if it is higher than 0.5 the number of links from VL to DM is higher, which means that VL has more influence on the DM. As shown before, if VL dominates DM enough, VL is able to synchronize the DM region to the external light-dark cycle, even if this cycle diverges from 24 h. When VL dominates DM, synchronization between both regions increases, and, as such, increases the synchronization within the SCN. We found that the ratio plays a role in the synchronization of the SCN neurons [66]. Based on both the Kuramoto model and the Goodwin model, we found if the ratio is close to 1, the synchronization degree for SCN neurons is large, and if the ratio is close to 0.5, the synchronization degree is small. As it is known that in short photoperiod the neurons in the SCN are more synchronized than in long photoperiods [67]. Therefore, a ratio close to 1 could correspond to the condition of short photoperiod, and the ratio close to 0.5 could correspond to the condition of long photoperiod, and this network heterogeneity may provide an alternative explanation why the SCN neurons are better synchronized under short photoperiod than under long photoperiod.

The exact type of SCN network is unknown so far. Several network types, including a scale-free network (BA network), a small-world network (NW network), a random network (ER network) as well as an all-to-all network were taken into account in our study [68]. We examined the effect of the network type on the collective behavior of the SCN neurons when the coupling strength is weak. We observed that in the scale-free network, the amplitude for the SCN is largest among these network types (Figure 8). This scale-free network is also the most heterogeneous network of these networks. Therefore, the heterogeneity of the network structure increases the amplitudes for the SCN.

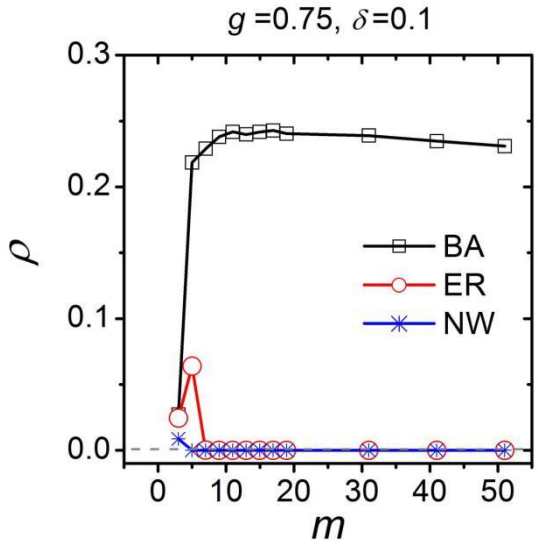

Figure 8. The effects of the network type on the SCN amplitude ρ. As reported in the reference [38], the amplitude of the SCN is zero in the all-to-all network when the coupling strength g < 0.8, which is indicated by the dashed gray line here. The parameters m and δ represent the average node degree (the number of links per node) and the heterogeneity in the intrinsic neuronal periods, respectively. This figure is modified from Ref. [68] based on the Goodwin model.

4. Conclusion and discussion

In the present review, we ask the question what mechanisms are necessary for the SCN to retain a good balance between flexibility to adjust to sudden changes of the external light-dark cycle, and rigidity to retain a stable rhythm in a noisy environment. With use of mathematical models we were able to investigate oscillator and network properties that play a role to uphold this balance.

One measurable oscillator property that is an important indication for the adaptability of an animal to changes in the light-dark cycle is the range of periods to which an animal is able to entrain, also called the *entrainment range*. A large range of entrainment characterizes a reactive clock, while a small range of entrainment fits with a more rigid clock. The main circadian clock situated in the SCN keeps the entrainment range within certain boundaries [13], thus keeping a fine balance between flexibility and rigidity. Outside the entrainment range some species show a dissociation of two components in their behavioral rhythm. One component follows the period of the external light-dark cycle, while the other component oscillates according to its endogenous period [15]. This measurable property enlightens the structure of the network, more specifically the interaction between two main regions inside the SCN. Between species and between animals it has been shown that there are differences in entrainment range and rhythm dissociation [14]. By understanding the mechanisms behind these properties, we can distinguish oscillator properties, such as amplitude [55,61,62], intrinsic period and relaxation rate [57,69], and coupling strength [53,64,65], between species based on these differences in entrainment range and rhythm dissociation.

The amplitude of the oscillations and the coupling strength within the SCN play key roles in the characterization of the measurable clock properties. Amplitude and coupling strength can not easily

be measured using experimental techniques. To be able to investigate their influence on the measurable clock properties, modeling is an important tool.

The SCN is a multi-oscillator structure, where the oscillators are grouped according to cell-type and, partly, location. The complex nature of multi-oscillator systems sometimes give non-intuitive results of experimental findings. For example, if the VL and DM are treated as oscillatory subgroups, the entrainment range of the animal depends on the interactions between those subgroups. If the coupling strength between both oscillatory subgroups is large, above a certain threshold, VL and DM will not dissociate and operate as one oscillator. In this case, increased coupling leads to higher amplitude of the SCN, which means that to entrain the SCN to an external light-dark cycle that deviates from the endogenous, free running, rhythm, the zeitgeber must be strong. It becomes more difficult to entrain the SCN to a period that is further away from its endogenous rhythm, and therefore the range of entrainment becomes narrower for stronger oscillators [13]. However, if the coupling strength between both oscillatory subgroups is below the previously mentioned threshold, the range of entrainment depends on whether or not the internal synchrony between VL and DM can be retained, and either VL can drive DM into following the externally imposed cycle or DM can drive VL into cycling at its endogenous period. This depends on the strength of the oscillators, as determined by their amplitude and the coupling strength. Also the ratio of directed links between VL and DM may cause VL to drive the DM rhythm [66]. If the internal synchrony can not be held, a dissociation between both oscillators will occur, with one component entrained to the external cycle (VL) and one component oscillating at its endogenous period (DM). In the case of weak coupling, an increased coupling strength will lead to a larger range of entrainment, because both oscillators will be synchronized and not dissociate for a broader range of entrainment periods [53,55].

The main difference between the VL and DM subgroups is that the VL subgroup is considered to contain the neurons that are directly responsive to the external light input, while the DM neurons are not. The VL neurons follow the external light-dark period because of this direct influence of light, while the DM neurons prefer to tick in their endogenous rhythm. The entrainment range depends upon the amplitude ratio between both subgroups, for example, if 25% of the neurons is light-sensitive (in VL), then the amplitude of VL must be about 3 times higher than the amplitude of DM to reach the maximum range of entrainment [55]. The amplitude of one oscillatory unit, consisting of multiple neurons, is determined by (i) the amplitude of the individual oscillatory neurons in the unit, (ii) the synchrony between the neurons in the subgroup, and (iii) the proportion of non-oscillatory neurons with respect to oscillatory neurons in the subgroup [53,61]. It appears that different group sizes of VL and DM result in different amplitude ratios for maximum entrainment ranges, which could explain the differences between species, where diurnal animals often have a lot less light-responsive neurons in the SCN [55].

To summarize, we have shown that the heterogeneity in the SCN may be important to keep a fine balance between flexibility and rigidity of the rhythm. Furthermore, the heterogeneity in circadian properties of different species may be a result of slightly different oscillator and network parameters. In the present review, we introduce different types of heterogeneity for the SCN neurons and for the network. We mainly treat these different types of heterogeneity in the SCN in isolation, but we also discuss several combinations of two of these types together. The combination of two types of heterogeneity may lead to different collective behavior of the SCN neurons or the network compared to one isolated type of heterogeneity. In Ref. [58], two types of heterogeneity are considered, the heterogeneity in light-sensitivity and the heterogeneity in intrinsic neuronal periods.

If both are present, the asymmetrical entrainment range of the SCN can be observed, and if only the light-sensitivity or the intrinsic neuronal period is heterogeneous and the other is not, a symmetrical entrainment range is observed. In Ref. [64], the free running periods are negatively related to the dispersion of the coupling strengths, when only coupling strength is heterogeneous. If two types of heterogeneity are considered simultaneously, i.e., heterogeneity in coupling strength as well as heterogeneity in intrinsic neuronal period, the relationship of the free running periods to the dispersion of the coupling strength is more complicated [65]. In particular, if the neurons with larger periods have smaller coupling strengths, the relationship is negative, and if the neurons with larger periods have larger coupling strength, the relationship is positive. Therefore, taking into account combinations of two types of heterogeneity, opposite results may be shown from the case of one single type of heterogeneity. In future studies we desire to examine the effects of a combination of two or more types of heterogeneity on the collective behavior of the circadian clock.

Acknowledgment

This article is supported by the National Natural Science Foundation of China under Grants Nos. 11875042, 11505114, 11805128 and No. 10975099.

Conflict of interest

The authors declare there is no conflict of interest.

References

1. D. K. Welsh, J. S. Takahashi and S. A. Kay, Suprachiasmatic nucleus: cell autonomy and network properties, *Annu. Rev. Physiol.,* **72** (2010), 551–577.
2. G. Zerbini, T. Kantermann and M. Merrow, Strategies to decrease social jetlag: reducing evening blue light advances sleep and melatonin, *Eur. J. Neurosci*., (2018).
3. A. Slomski, Melatonin Improves Sleep in Patients With Circadian Disruption, *JAMA,* **320** (2018), 749.
4. H. Daido, Why circadian rhythms are circadian: competitive population dynamics of biological oscillators, *Phys. Rev. Lett.,* **87** (2001), 048101.
5. C. A. Czeisler, J. F. Duffy, T. L. Shanahan, et al., Stability, precision, and near-24-hour period of the human circadian pacemaker, *Science,* **284** (1999), 2177–2181.
6. J. A. Mohawk, C. B. Green and J. S. Takahashi, Central and peripheral circadian clocks in mammals, *Annu. Rev. Neurosci.,* **35** (2012), 445–462.
7. D. K. Welsh, D. E. Logothetis, M. Meister, et al., Individual neurons dissociated from rat suprachiasmatic nucleus express independently phased circadian firing rhythms, *Neuron.,* **14** (1995), 697–706.
8. S. Honma, W. Nakamura, T. Shirakawa, et al., Diversity in the circadian periods of single neurons of the rat suprachiasmatic nucleus depends on nuclear structure and intrinsic period, *Neurosci. Lett.,* **358** (2004), 173–176.
9. S. M. Reppert and D. R. Weaver, Molecular analysis of mammalian circadian rhythms, *Annu. Rev. Physiol.,* **63** (2001), 647–676.

10. E. D. Herzog, S. J. Aton, R. Numano, et al. Temporal precision in the mammalian circadian system: a reliable clock from less reliable neurons, *J. Biol. Rhythms.,* **19** (2004), 35–46.
11. D. M. Berson, Strange vision: ganglion cells as circadian photoreceptors, *Trends Neurosci.,* **26** (2003), 314–320.
12. S. Usui, Y. Takahashi, T. Okazaki, Range of entrainment of rat circadian rhythms to sinusoidal light-intensity cycles, *Am. J. Physiol. Regul. Integr. Comp. Physiol.,* **278** (2000), R1148–1156.
13. U. Abraham, A. E. Granada, P. O. Westermark, et al., Coupling governs entrainment range of circadian clocks, *Mol. Syst. Biol.,* **6** (2010): 438.
14. R. Refinetti, (2006) Circadian Physiology (2nd edn.). Boca Raton, Florida: CRC Press.
15. H. O. de la Iglesia, T. Cambras, W. J. Schwartz, et al., Forced desynchronization of dual circadian oscillators within the rat suprachiasmatic nucleus, *Curr. Biol.,* **14** (2004), 796–800.
16. A. B. Webb, N. Angelo, J. E. Huettner, et al., Intrinsic, nondeterministic circadian rhythm generation in identified mammalian neurons, *Proc. Natl. Acad. Sci. USA,* 106 (2009), 16493–16498.
17. P. O. Westermark, D. K. Welsh., H. Okamura, et al., Quantification of circadian rhythms in single cells, *PLoS Comput. Biol.,* **5** (2009), e1000580.
18. T. Hamada, J. LeSauter, J. M.Venuti, et al., Expression of Period genes: rhythmic and nonrhythmic compartments of the suprachiasmatic nucleus pacemaker, *J. Neurosci.,* **21** (2001), 7742–7750.
19. A. B. Webb, S. R. Taylor, K. A. Thoroughman, et al., Weakly circadian cells improve resynchrony, *PLoS Comput. Biol.,* **8** (2012), e1002787.
20. J. H. Rohling, H. T. vanderLeest, S. Michel, et al., Phase resetting of the mammalian circadian clock relies on a rapid shift of a small population of pacemaker neurons, *PLoS One,* **6** (2011), e25437.
21. H. Dardente, V. J. Poirel, P. Klosen, et al., Per and neuropeptide expression in the rat suprachiasmatic nuclei: compartmentalization and differential cellular induction by light, *Brain Res.,* **958** (2002), 261–271.
22. H. T. vanderLeest, J. H. Rohling, S. Michel, et al., Phase shifting capacity of the circadian pacemaker determined by the SCN neuronal network organization, *PLoS One* **4** (2009), e4976.
23. M. D. Schwartz, C. Wotus, T. Liu, et al., Dissociation of circadian and light inhibition of melatonin release through forced desynchronization in the rat, *Proc. Natl. Acad. Sci. U S A,* **106** (2009), 17540–17545.
24. T. Noguchi, K. Watanabe, A. Ogura, et al., The clock in the dorsal suprachiasmatic nucleus runs faster than that in the ventral, *Eur. J. Neurosci.,* **20** (2004), 3199–3202.
25. S. Yamaguchi, H. Isejima, T. Matsuo, et al., Synchronization of cellular clocks in the suprachiasmatic nucleus, *Science,* **302** (2003), 1408–1412.
26. H. Ohta, S. Yamazaki and D.G.McMahon, Constant light desynchronizes mammalian clock neurons, *Nat. Neurosci.,* **8** (2005), 267–269.
27. S. J. Aton, C. S. Colwell, A. J. Harmar, et al., Vasoactive intestinal polypeptide mediates circadian rhythmicity and synchrony in mammalian clock neurons, *Nat. Neurosci.,* **8** (2005), 476–483.
28. L. P. Morin, SCN organization reconsidered, *J. Biol. Rhythms.,* **22** (2007), 3–13.
29. H. Albus, M. J. Vansteensel, S. Michel, et al., A GABAergic mechanism is necessary for coupling dissociable ventral and dorsal regional oscillators within the circadian clock, *Curr. Biol.,* **15** (2005), 886–893.

30. J. A. Evans, T. L. Leise, O. Castanon-Cervantes, et al., Dynamic interactions mediated by nonredundant signaling mechanisms couple circadian clock neurons, *Neuron.,* **80** (2013), 973–983.
31. S. R. Taylor, T. J. Wang, D. Granados-Fuentes, et al., Resynchronization Dynamics Reveal that the Ventral Entrains the Dorsal Suprachiasmatic Nucleus, *J. Biol. Rhythms.,* **32** (2017), 35–47.
32. J. C. Leloup and A. Goldbeter, Toward a detailed computational model for the mammalian circadian clock, *Proc. Natl. Acad. Sci. U S A,* **100** (2003), 7051–7056.
33. H. Dardente and N. Cermakian, Molecular circadian rhythms in central and peripheral clocks in mammals, *Chronobiol. Int.,* **24** (2007), 195–213.
34. S. Becker-Weimann, J. Wolf, H. Herzel, et al., Modeling feedback loops of the Mammalian circadian oscillator, *Biophys. J.,* **87** (2004), 3023–3034.
35. D. Gonze, S. Bernard, C. Waltermann, et al., Spontaneous synchronization of coupled circadian oscillators, *Biophys. J.,* **89** (2005), 120–129.
36. A. T. Winfree, (2001) The geometry of biological time. New York: Springer-Verlag.
37. S. Bernard, D. Gonze, B. Cajavec, et al., Synchronization-induced rhythmicity of circadian oscillators in the suprachiasmatic nucleus, *PLoS Comput. Biol.,* **3** (2007), e68.
38. J. C. Locke, P. O. Westermark, A. Kramer, et al., Global parameter search reveals design principles of the mammalian circadian clock, *BMC Syst. Biol.,* **2** (2008), 22.
39. T. Hirota and Y. Fukada, Resetting mechanism of central and peripheral circadian clocks in mammals, *Zoolog. Sci.,* **21** (2004), 359–368.
40. C. Liu, D. R. Weaver, S. H. Strogatz, et al., Cellular construction of a circadian clock: period determination in the suprachiasmatic nuclei, *Cell,* **91** (1997), 855–860.
41. B. Ananthasubramaniam, E. D. Herzog and H. Herzel, Timing of neuropeptide coupling determines synchrony and entrainment in the mammalian circadian clock, *PLoS Comput. Biol.,* **10** (2014), e1003565.
42. Z. Lu, K. Klein-Cardena, S. Lee, et al., Resynchronization of circadian oscillators and the east-west asymmetry of jet-lag,. *Chaos*, **26** (2016), 094811.
43. C. Schmal, J. Myung, H. Herzel, et al., A theoretical study on seasonality, *Front. Neurol.,* **6** (2015), 94.
44. C. Vasalou, E. D. Herzog and M. A. Henson, Small-World Network Models of Intercellular Coupling Predict Enhanced Synchronization in the Suprachiasmatic Nucleus, *J. Biol. Rhythms*., **24** (2009), 243–254.
45. C. Vasalou and M. A. Henson, A multicellular model for differential regulation of circadian signals in the core and shell regions of the suprachiasmatic nucleus, *J. Theor. Biol*., **288** (2011), 44–56.
46. C. Bodenstein, M. Gosak, S. Schuster, et al., Modeling the seasonal adaptation of circadian clocks by changes in the network structure of the suprachiasmatic nucleus, *PLoS Comput. Biol.,* **8** (2012), e1002697.
47. H. Kori and A. S. Mikhailov, Entrainment of randomly coupled oscillator networks by a pacemaker, *Phys. Rev. Lett.,* **93** (2004), 254101.
48. H. Kori and A. S. Mikhailov, Strong effects of network architecture in the entrainment of coupled oscillator systems, *Phys. Rev. E. Stat. Nonlin. Soft. Matter. Phys.,* **74** (2006), 066115.
49. S. Varadarajan, M. Tajiri, R. Jain, et al., Connectome of the Suprachiasmatic Nucleus: New Evidence of the Core-Shell Relationship, *eNeuro.,* **5** (2018).

50. L. P. Morin and C. N. Allen, The circadian visual system, 2005, *Brain Res. Rev.,* **51** (2006), 1–60.
51. J. Hannibal, M. Moller, O. P. Ottersen, et al., PACAP and glutamate are co-stored in the retinohypothalamic tract, *J. Comp. Neurol.*, **418** (2000), 147–155.
52. D. A. Golombek, R. E. Rosenstein, Physiology of circadian entrainment, *Physiol. Rev.,* **90** (2010), 1063–1102.
53. C. Gu, A. Ramkisoensing, Z. Liu, et al., The proportion of light-responsive neurons determines the limit cycle properties of the suprachiasmatic nucleus, *J. Biol. Rhythms.*, **29** (2014), 16–27.
54. C. Gu, Z. Liu, W. J. Schwartz, et al, Photic desynchronization of two subgroups of circadian oscillators in a network model of the suprachiasmatic nucleus with dispersed coupling strengths, *PLoS One*, **7** (2012), e36900.
55. C. Gu, H. Yang, J. H. Meijer, et al., Dependence of the entrainment on the ratio of amplitudes between two subgroups in the suprachiasmatic nucleus, *Phys. Rev. E.,* **97** (2018), 062215.
56. J. H. Meijer and W. J. Rietveld, Neurophysiology of the suprachiasmatic circadian pacemaker in rodents, *Physiol. Rev.,* **69** (1989), 671–707.
57. C. Gu, J. Xu, Z. Liu, et al., Entrainment range of nonidentical circadian oscillators by a light-dark cycle, *Phys. Rev. E. Stat. Nonlin Soft. Matter. Phys.*, **88** (2013), 022702.
58. C. Gu and H. Yang, The asymmetry of the entrainment range induced by the difference in intrinsic frequencies between two subgroups within the suprachiasmatic nucleus, *Chaos* **27** (2017), 063115.
59. C. Gu, X. Liang, H. Yang, et al., Heterogeneity induces rhythms of weakly coupled circadian neurons, *Sci. Rep.*, **6** (2016), 21412.
60. C. Gu and H. Yang, Differences in intrinsic amplitudes of neuronal oscillators improve synchronization in the suprachiasmatic nucleus, *Chaos*, **27** (2017), 093108.
61. C. Gu, H. Yang and Z. Ruan, Entrainment range of the suprachiasmatic nucleus affected by the difference in the neuronal amplitudes between the light-sensitive and light-insensitive regions, *Phys. Rev. E.*, **95** (2017), 042409.
62. C. Gu, M. Tang, J. H. Rohling, et al., The effects of non-self-sustained oscillators on the en-trainment ability of the suprachiasmatic nucleus, *Sci. Rep.*, **6** (2016), 37661.
63. C. Gu, H. Yang and J. H. Rohling, Dissociation between two subgroups of the suprachiasmatic nucleus affected by the number of damped oscillated neurons, *Phys. Rev. E.*, **95** (2017), 032302.
64. C. Gu, J. Wang and Z. Liu, Free-running period of neurons in the suprachiasmatic nucleus: Its dependence on the distribution of neuronal coupling strengths, *Phys Rev E Stat Nonlin Soft Matter. Phys.*, **80** (2009), 030904.
65. C. Gu, J. H. Rohling, X. Liang, et al. Impact of dispersed coupling strength on the free running periods of circadian rhythms, *Phys. Rev. E.*, **93** (2016), 032414.
66. C. Gu, M. Tang and H.Yang, The synchronization of neuronal oscillators determined by the directed network structure of the suprachiasmatic nucleus under different photoperiods, *Sci. Rep.*, **6** (2016), 28878.
67. H. T. VanderLeest, T. Houben, S. Michel, et al., Seasonal encoding by the circadian pacemaker of the SCN, *Curr. Biol.*, **17** (2007), 468–473.
68. C. Gu and H. Yang, The circadian rhythm induced by the heterogeneous network structure of the suprachiasmatic nucleus, *Chaos*, **26** (2016), 053112.

69. C. G. Gu, P. Wang and H. J. Yang, Entrainment range affected by the heterogeneity in the amplitude relaxation rate of suprachiasmatic nucleus neurons, *Chin. Phys. B,* **28** (2019), 018701.

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