Entrainment of the suprachiasmatic nucleus network by a light-dark cycle

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The synchronization of biological activity with the alternation of day and night (circadian rhythm) is performed in the brain by a group of neurons, constituting the suprachiasmatic nucleus (SCN). The SCN is divided into two subgroups of oscillating cells: the ventrolateral (VL) neurons, which are exposed to light (photic signal), and the dorsomedial (DM) neurons, which are coupled to the VL cells. When the coupling between these neurons is strong enough, the system synchronizes with the photic period. Upon increasing the cell coupling, the entrainment of the DM cells has been recently shown to occur via a very sharp (jumping) transition when the period of the photic input is larger than the intrinsic period of the cells. Here, we characterize this transition with a simple realistic model. We show that two bifurcations possibly lead to the disappearance of the endogenous mode. Using a mean-field model, we show that the jumping transition results from a supercritical Hopf-like bifurcation. This finding implies that both the period and strength of the stimulating photic signal, and the relative fraction of cells in the VL and DM compartments, are crucial in determining the synchronization of the system.

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I. INTRODUCTION

The circadian rhythm in the brain results from the activity of neurons, which are spontaneously oscillating with an endogenous period close to the 24-h cycle, and which, under the influence of light (photic signal), synchronize with the alternation of day and night. In mammals, the primary circadian clock is the suprachiasmatic nucleus (SCN), which is located in the hypothalamus and receives information about illumination through the eyes. It is composed of a large network of $\sim 2 \times 10^4$ coupled neurons. This assembly of cells can be divided into two subgroups: the ventrolateral (VL) and the dorsomedial (DM) subgroups. The VL neurons are exposed to photic input from the retina and entrain the DM neurons. While the two subgroups of neurons are functionally different, a coherent, periodic output results from their coupling [1–11].

In the absence of the daily light-darkness cycle, the free-running period varies from species to species in the range 20–28 h [1–3,6–8]. This implies that the proper response of the system to the 24-h period results from a dynamic process of synchronization. In this respect, it has been noticed that when exposed for several weeks to a constant light, the SCN of rodents (hamsters) exhibits a phase-splitting behavior, with two sets of neurons oscillating out of phase [12–17]. It has been recently shown that both the coupling strength and its distribution can influence the diversity of the free-running period and the phase-splitting [10,11]. Lastly, the desynchronization of the circadian oscillations between VL and DM subgroups has been observed when the external light-dark cycle has a period very different from the 24 h circadian period [18–22]. When the period of the light-dark cycle is shorter than 24 h, such as 22 h (11 h of light alternating with 11 h of darkness), the VL subgroup is entrained by the light and oscillates with a period equal to the external cycle (22 h), whereas the DM subgroup is not entrained and oscillates with its free-running period around 24 h, as observed experimentally in rats [19,23]. In the opposite case, in which the period of the light-dark cycle is longer than 24 h, such as 26 h (13 h of light alternating with 13 h of darkness), numerical simulations [22] predict that the VL subgroup is entrained by the light but the DM subgroup has a period smaller than 24 h. By gradually increasing numerically the number of neurons in the VL subgroup, the period of the DM subgroup is observed to decrease. Theoretically, the entrainment phenomenon has been analyzed in terms of frequency locking in the case of a homogeneous VL population [24]. In the case of a heterogeneous population with both DM and VL neurons, one of the intriguing observations of [22] is the existence of a threshold for the ratio between the number of neurons in the VL and DM. When the ratio reaches a critical value, the period of the DM subgroup jumps to the external light-dark cycle. We focus here on this jumping transition phenomenon, which provides new insight into the entrainment of photic input in SCN, i.e., the appearance of rhythm.

To investigate the mechanism of the jumping transition in the SCN, we use a model with a mean-field coupling and characterize both the period and amplitude in each subgroup. We find that as the fraction of VL neurons is increased, the period of the DM subgroup decreases and so does its amplitude. Based on this finding, we study a single oscillator with both constant light and monochromatic light. We find that this model shows the very same behavior as the DM subgroup, including the disappearance of amplitude via a Hopf-like bifurcation, which explains the jumping transition. The main implication concerning the generation and synchronization of rhythm in the SCN network is that both the period and strength of the stimulating photic signal, and the relative fraction of cells in the VL and DM compartments, are crucial in determining the synchronization of the system.

II. A JUMPING TRANSITION IN THE GOODWIN MODEL

A typical model to simulate circadian rhythms in SCN cells is the Goodwin oscillator with three variables, describing a

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negative transcription-translation feedback loop [25]. Several elaborations of this model have been proposed [1,3,6–8]. For example, [1,3,6–8] considered a globally coupled system, via neurotransmitter concentration. Important aspects of the functionality of the SCN strongly depend on this global coupling, as stressed by Locke *et al*. [4]. We consider here the mean-field Goodwin oscillator presented by Gonze *et al*. [3], which can be represented as follows:

$$\begin{aligned}
\dot{x}_i &= \frac{\alpha_1}{1+(z_i/k_1)^4} - \frac{\alpha_2 x_i}{k_2+x_i} + \frac{\alpha_c g F}{k_c+gF} + L_i,\\
\dot{y}_i &= k_3 x_i - \frac{\alpha_4 y_i}{k_4+y_i},\\
\dot{z}_i &= k_5 y_i - \frac{\alpha_6 z_i}{k_6+z_i},\\
\dot{V}_i &= k_7 x_i - \frac{\alpha_8 V_i}{k_8+V_i}, \quad i = 1,2,\ldots,N,\\
F &= \frac{1}{N}\sum_{i=1}^{N} V_i.
\end{aligned} \tag{1}$$

The variables x_i, y_i, and z_i are the concentrations of the clock gene mRNA, the clock protein, and the inhibitor of protein expression, respectively [3]. V is the concentration of neuropeptide induced by the activation of the clock gene and can synchronize clock cells. The three-variable model obtained with x_i, y_i, and z_i constitutes a negative feedback loop in the clock cell i. g measures the strength of the mean-field coupling F, and L denotes the external light input. Following Ref. [4], we take other parameters as $\alpha_1 = 0.7$ nM/h, $k_1 = 1.0$ nM, $n = 4.0$, $\alpha_2 = 0.35$ nM/h, $k_2 = 1.0$ nM, $k_3 = 0.7$/h, $\alpha_4 = 0.35$ nM/h, $k_4 = 1.0$ nM, $k_5 = 0.7$/h, $\alpha_6 = 0.35$ nM/h, $k_6 = 1.0$/h, $k_7 = 0.35$/h, $\alpha_8 = 1.0$ nM/h, $k_8 = 1.0$ nM, $\alpha_c = 0.4$ nM/h, and $k_c = 1.0$ nM. We renormalize the time by a factor 1.26 to have a free-running period of 24 h, and we use $g = 0.5$.

Our model of the SCN network is composed of N oscillators, all obeying Eq. (1) and coupled together via the mean field F. The observation of Ref. [22] that the variability of the coupling constant g in the model does not affect qualitatively the transition suggests that taking a fixed value of g is a sensible approximation to investigate the entrainment of DM by VL neurons. This assumption, however, prevents the model from explaining phenomena such as phase-splitting, which possibly rests on the variability of the properties of the system [10,26]. The assembly of neurons is divided into two subgroups. The oscillators in the VL subgroup receive photic input $L_i = L(t)$, while oscillators in the DM subgroup do not receive any light (hence $L_i = 0$). The fraction of VL neurons in the SCN network is denoted p, so the system consists of pN VL neurons and $(1-p)N$ DM neurons. We study the entrainment of the system by an alternation of day and light, with a period of 26 h, with a photic input $L(t)$ chosen to be on for 13 h: $L(t) = K$ during the day period, and off for 13 h: $L(t) = 0$ during the period of darkness. We checked the behaviors of $\{x_i\}$ in Eq. (1) and found that the DM oscillators are completely synchronized with one another. We observed that this was the case for any value of p. We define the period of a subgroup (VL or DM) as the period of the average V variable in the subgroup. After a long transient, all the oscillators in each sub-population become synchronized. Their frequencies were determined numerically by computing the Fourier spectrum. Figure 1 shows how the period of the subgroups evolves with p, which is an important factor for the entrainment of the period of photic input [22]. As p is increased from 0, Figure 1 shows that the period of VL is quickly frequency-locked to the external period (26 h) in a 1:1 relation for a small value of p [24], whereas the period of DM decreases with increasing p until a critical value $p_c \approx 0.41$ is reached. At the value $p = p_c$, we observe a transition, characterized by a sharp discontinuity in the period of the DM neurons, which jumps from $\approx$20.8 h to the external light period 26 h. At values of $p \geqslant p_c$, the DM neurons are entrained at the external period, 26 h. We have observed the jumping transition at different values of the coupling constant g, and also by varying g at a fixed value of p. What is the mechanism describing this jumping transition? To gain some insight, we measured the amplitude of the oscillations of DM oscillators.

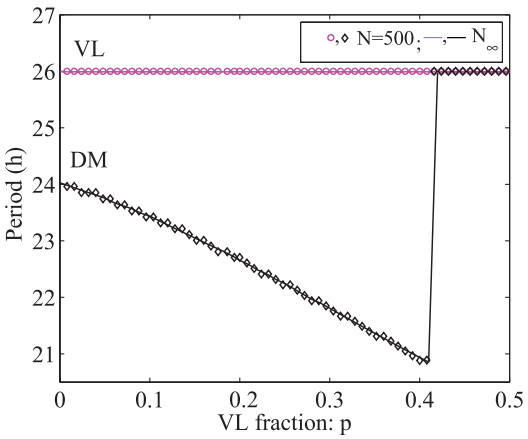

FIG. 1. (Color online) Evolution of the period of the VL (diamond ◇) and DM (circle ○) subgroups in a system with a fraction p of VL neurons. The VL neurons are exposed to a 26-h cycle of light of intensity $K = 0.02$. The system is evolved from random initial conditions. Symbols represent a system of $N = 500$ neurons, and continuous lines represent a two-neuron system (labeled N_∞).

Because of the mean-field structure of the coupling between neurons, together with the observation that neurons from a given subgroup are perfectly synchronized in this subgroup for any value of p [22], all oscillators from a subgroup can be treated as a single oscillator. It is therefore sufficient to study a two-neurons system, composed of one VL neuron receiving external light $L(t) \neq 0$ and one DM neuron insensitive to light, both being coupled by the mean field $F = pV_{\mathrm{VL}} + (1-p)V_{\mathrm{DM}}$. Although this approach can potentially lead to incorrect results close to the transition, due to the divergence of the relaxation time, we explicitly checked that this is not the case for reasonable integration times (500 h). Figure 1 shows that the jumping transition occurs for the same value of p in the two-neuron system as in a large-N system.

Considering that the mean-field term F is the only coupling between VL and DM neurons, and because we are willing to study the effect of the fraction p of cells in the two subgroups, we study the dependence on p of V_{VL} and V_{DM}. To this end, we decomposed for each subgroup the variable V into three parts: the stationary value $\langle V \rangle$, the oscillating components

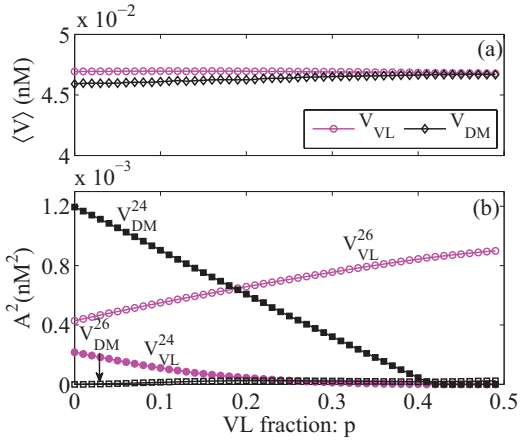

FIG. 2. (Color online) Evolution with p of the V variable in a two-neuron system. (a) Stationary component $\langle V\rangle$ for the VL (circle ○) and DM populations (diamond ⋄). (b) Square amplitude of the two main oscillating modes of VL and DM populations. The forcing mode has a period of 26 h, while the free-running mode has a period ranging from 24 h down to 20.8 h, according to Fig. 1.

V^{26} corresponding to a period of exactly 26 h, i.e., the forcing period, and V^{24} corresponding to the branch that starts at 24 h (free-running mode) and diminishes down to 20.8 h at the transition for the DM population. The amplitudes of V^{26} and V^{24} are measured by integrating the power spectrum density under the corresponding peaks. We observe in Fig. 2 that the constant part of the variable V does not depend much on p, and that it is approximately the same, up to at most a 2% variation, for both the VL and the DM neuron. Therefore, we can consider $\langle F\rangle$ as a constant. The amplitude $V^{26}_{\rm VL}$ of the mode at period 26 h increases for the VL neurons due to the increase of the ratio of VL neurons in the system. For DM neurons, $V^{26}_{\rm DM}$ also increases with p but remains very small. In contrast, the $V^{24}_{\rm VL}$ mode in the VL neuron has a decreasing amplitude with p, while the amplitude of the free-running mode of the DM neuron starts, at $p = 0$, at a much larger value and vanishes close to $p = p_c$ as $\propto(p - p_c)^{1/2}$ [the squared amplitude is plotted in Fig. 2(b)]. This indicates a bifurcation from a dynamics involving two incommensurate frequencies toward periodic motion as $V^{24}_{\rm VL}$ goes to 0, known as a Neimark-Sacker bifurcation [27]. The observed disappearance of the amplitude of the endogenous mode as $\propto(p - p_c)^{1/2}$ close to the transition is very reminiscent of a Hopf bifurcation. For this reason, we denote this transition here as a "Hopf-like" bifurcation. From the definition of F and the values of $V_{\rm VL}$ and $V_{\rm DM}$ in Fig. 2(a), we note that the mean value of F is always positive and large. In fact, the amplitude of the oscillating part is small, so F remains strictly positive at all times. This is to be contrasted with the photic input L, which is zero for half a period.

The main effect of the mean field is to transfer the information about the external forcing from the VL population to the DM population. As p is increased, the mean field contains more information about the VL population and the transfer to the DM population is more efficient. This leads to the disappearance of the free-running mode in the DM subgroup via a Hopf-like bifurcation. In the next section, we explore the transition by studying the effect of the external forcing on a single Goodwin oscillator.

III. SINGLE NEURON ANALYSIS

To understand the entrainment of a given subgroup by the photic signal, it is useful to consider first the simplified case of a single neuron, subject to a periodic photic forcing $L(t) = L_0 + L_1 \sin(\omega t)$, with $2\pi/\omega = 26$ h. In general, the behavior of neurons of either category (VL or DM) is determined by a balance between the coupling with the mean field $F = V$ and the external forcing. For this reason, we investigate the dependence of the dynamics on the parameters, g (the strength of the coupling); L_0 (the amplitude of the constant forcing); and L_1 (the amplitude of a periodic monochromatic forcing) with a period 26 h. We will then use our knowledge of this system of isolated neurons to describe the behavior of VL and DM populations in network. To this end, we represent the excitatory signal $L(t)$ in Eq. (1) by merging together the external light and the contribution from the mean field.

A. VL population

We first study a single VL neuron at a fixed value of the coupling, $g = 0.5$ (Fig. 3). Over a wide range of values of L_0

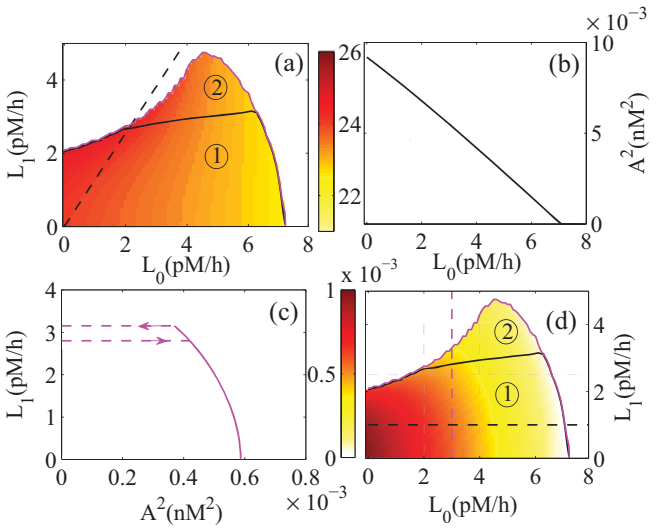

FIG. 3. (Color online) Period and square amplitude of the oscillation of a single neuron model. (a) Period as a function of (L_0, L_1) for fixed $g = 0.5$. White color corresponds here to the forcing period 26 h (the neuron is entrained by the external light). Dashed line represents the situation in which the system is subject to a periodic on-off light. The solid line delimits two subregions for the endogenous mode: below the solid line, region ①, the endogenous oscillation is the only solution, whereas above the solid line, region ②, there is bistability and both the endogenous solution and the entrained solution can be observed depending on initial conditions. (b) Supercritical Hopf-like bifurcation occurs when reducing L_0 for fixed $L_1 = 1$ pM/h. (c) Subcriticality is revealed by a hysteresis and bistability in the squared amplitude when increasing L_1 for fixed $L_0 = 3$ pM/h. (d) Squared amplitude of the free-running mode in the (L_0, L_1) plane for $g = 0.5$. Dashed lines in (d) give the location of the cuts plotted in (b) and (c).

and L_1, the system is observed to oscillate. Figure 3(a) shows the dependence of the period of oscillations on L_0 and L_1. For either large L_0 or large L_1, the VL neuron is entrained by the external light, while it keeps its free-running period for smaller values of L_0 and L_1.

Figure 3(d) shows the dependence of the squared amplitude of the oscillation. We observe that an increase of the constant part of the forcing (parameter L_0), for fixed periodic monochromatic forcing (constant L_1), leads to the vanishing of the amplitude of the free-running mode, while its period decreases (from 24 h down to about 21 h). More precisely, the squared amplitude vanishes linearly when increasing L_0, see Fig. 3(b), provided L_1 is not too large [transition in region 1; see Fig. 3(a)]. This demonstrates that the transition from a nonoscillatory to an oscillatory state, when L_0 decreases, happens through a supercritical Hopf-like bifurcation. In contrast, an increase of the amplitude of the forcing at the period 26 h (parameter L_1) at fixed value of L_0 leads to the abrupt disappearance of the free-running mode [see Fig. 3(c)], at least when L_0 is not too large. The fact that the oscillating solution ceases to exist, while the amplitude of the oscillation is nonzero, suggests a subcritical bifurcation.

This can be used to describe qualitatively the behavior of the VL population in the complete SCN model, where external forcing is chosen as an alternation of darkness ($L = 0$) for 13 h followed by light ($L = K$ for 13 h), which can be decomposed in Fourier series. The constant term is equal to $L_0 = K/2$ and the first harmonic, with period 26 h, has an amplitude $L_1 = 4L_0/\pi$ [dashed line in Fig. 3(a)]. The higher harmonics have a frequency which is too high to trigger a significant response. In more technical terms, the frequencies corresponding to the harmonics of frequency $n \times 2\pi/T$, with $T = 26$ h, are very far from the resonance tongue of the Goodwin oscillator [24,28] as soon as $n > 1$.

Qualitatively, we expect VL neurons in a network to behave as a single neuron receiving a photic signal $L(t)$, in addition to a contribution from the mean field. In the simulation above, it was found that $\langle F \rangle$ is independent of p [see Fig. 2(a)]. As a result, as p is increased, the VL subgroup behaves like a one-neuron system with constant L_0. In contrast, V_{DM}^{26} is negligible compared to V_{VL}^{26}, which increases with the fraction p [see Fig. 2(b)], so the mean field F will contain a mode at a period of 26 h, which will grow like pV_{VL}^{26} when p is increased. This suggests that the VL subgroup behaves like a one-neuron system with increasing L_1 when p increases. According to Fig. 3(d), for fixed L_0 and increasing L_1, we expect the bifurcation to the 26 h state to be subcritical. This corresponds to the transition of the VL population observed at $p = 0$ in Fig. 1, which occurs for larger values of p if the light intensity K is smaller [22].

B. DM population

We now turn to the main object of this article, the DM subgroup, and show quantitatively that the jumping transition to the external forcing frequency is a supercritical Hopf bifurcation.

The DM oscillators are not directly forced by the 26 h periodic light, but indirectly via the mean field F. From the simulations reported previously, see Fig. 2, we find that $gF \simeq$

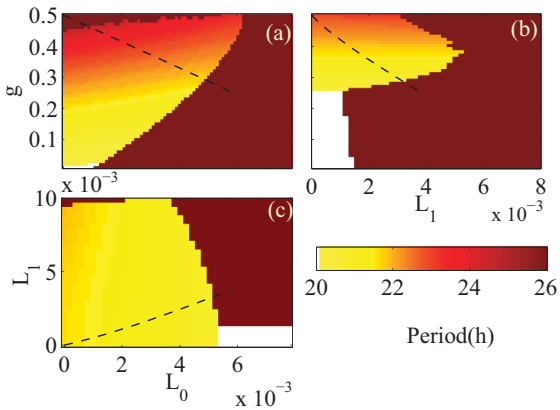

FIG. 4. (Color online) Period of a single neuron as a function of (a) (L_0, g) for fixed $L_1 = 0.0032$, (b) (L_1, g) for fixed $L_0 = 0.0048$, and (c) (L_0, L_1) for fixed $g = 0.295$. Dashed lines are projections of the trajectory of the system for increasing p. White regions correspond to a nonoscillating neuron.

3×10^{-2} nM is always much smaller than $k_c = 1.0$ nM, so the coupling term can be linearized and rewritten by introducing an effective external light:

$$\frac{\alpha_c g F}{k_c + gF} \simeq \frac{\alpha_c g}{k_c} F = \frac{\alpha_c g'}{k_c} V_{\mathrm{DM}} + L_0 + L_1 \sin(\omega t), \quad (2)$$

with an effective coupling $g' = (1 - p)g$, and an external light $L(t)$ proportional to $pV_{\mathrm{VL}}(t)$, with temporal average $L_0 = \alpha_c g p \langle V_{\mathrm{VL}} \rangle / k_c$ and amplitude $L_1 = \alpha_c g p V_{\mathrm{VL}}^{26} / k_c$. Figure 4 presents the dynamical behavior of a single neuron as the three parameters are varied. In this phase space, the trajectory $(g'(p), L_0(p), L_1(p))$ of the complete SCN system obtained by increasing p is deduced from the analytical expressions of the effective parameters by using $\langle V_{\mathrm{VL}} \rangle$ and V_{VL}^{26} from Fig. 2. The projections of this trajectory are plotted as dashed lines in Fig. 4. We observe that the transition of the one-neuron system is a supercritical Hopf-like bifurcation, exactly like the one in Fig. 3(b) for fixed g. This bifurcation occurs for an effective coupling $g' = 0.295$, from which we deduce $p_c = 0.41$, in perfect agreement with the values observed in the complete SCN network (Fig. 1). The period of the free-running mode at the transition (20.8 h) is also the same in this one-neuron analysis as that in the complete SCN network.

IV. DISCUSSIONS AND CONCLUSIONS

We have described the entrainment of both the VL neurons and the DM neurons by a simple model of a single neuron forced by an external light $L(t)$. This forcing is a key element in the description of the Goodwin oscillator. The mean-field coupling between subpopulations blurs the distinction between VL and DM oscillators, which allows us to treat the DM neurons as VL neurons under specific light, and it shows that the DM neurons synchronize with the external light, although they are not directly coupled to it.

We documented that the sharp transition from the endogenous period of the DM population to the external period of the forcing corresponds to a supercritical Hopf-like bifurcation for the endogenous mode. For a ratio p larger than the critical value p_c, there are no more oscillations at a period different

from the forcing period (26 h). Nevertheless, both populations of neurons oscillate and sustain the external period. The DM population then follows exclusively the mean field F, which only contains the 26h mode, while the VL population follows the external forcing. So, in terms of the ratio p, we can predict that the amplitude of the DM oscillations for $p > p_c$ does not vanish but is roughly proportional to the mean field F, i.e., to p itself, as observed in Fig. 5(d) of Ref. [22].

In conclusion, we have isolated two possible transitions to explain the entrainment of the VL and DM populations by an external light under mean-field coupling. The jumping transition of the DM subgroup depicted in Fig. 1 occurs via a supercritical Hopf bifurcation, while the VL neurons are getting entrained via a subcritical bifurcation. A study of codimension-2 points would be of interest in further studies of SCN networks.

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