The Second International Symposium on Optimization and Systems Biology (OSB'08)
Lijiang, China, October 31– November 3, 2008

Analysis of the Special Structure of the Suprachiasmatic Nucleus

Ying Li[1] Jian-Bao Zhang[2]

[1]College of Information Technology, Shanghai Ocean University, Shanghai 201303, China
[2]School of Science, Hangzhou Dianzi University, Hangzhou 310018, China

Abstract In mammals, the suprachiasmatic nucleus (SCN) of the hypothalamus is considered as the master circadian pacemaker. In this paper, we analyze the special structure of SCN from mathematical viewpoint in an analytical way. We show how the special structure of the SCN is exploited in synchronization in an analytical way, i.e., why the ventrolateral (VL) part has fewer but compactly connected neurons, while dorsomedial (DM) part has more but sparsely connected neurons.

Keywords Circadian rhythm; Suprachiasmatic nucleus; Synchronizability.

1 Introduction

Circadian rhythms are observed in the physiology and behavior of mammals and other higher organisms. In mammals, the circadian rhythms are controlled by a pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus [1, 2]. The SCN is composed of 20000 neurons arranged in a symmetric bilateral structure, including astrocytes and multiple neuropeptidergic classes of neurons. It has been shown that isolated single neurons are able to produce circadian oscillations, with periods ranging from 20 to 28 hours [3, 4]. The free-running periods of isolated neurons indicate that a coupling mechanism is operating among the neurons. The key is that the circadian oscillator must maintain synchrony with environmental cycles to drive behavioral, physiological and metabolic outputs at the appropriate time of day.

There are many outside factors that affect the entrainment of circadian rhythms, such as daily environmental cycles of light, temperature, food, social interactions and so on. Light is generally considered to be the strongest and most pervasive factor. In nature conditions, the circadian clock is subject to alternation of days and nights and in response to this cycling environment, phase-locks to the LD cycle, enabling the body to follow a 24-h rhythm. What's more, there are also intrinsic factors that affect the entrainment of circadian rhythms, such as the coupling among neurons, the special structure of SCN and so on.

It is well known that the SCN is anatomically organized into a dorsomedial (DM) "shell" and a ventrolateral (VL) "core" [5] according to the neuropeptides expressed by the cells in these areas. The DM shell of the SCN can be defined by cells containing arginvasopressin polypeptides (AVP), while the VL core of the SCN can be defined by cells

containing vasoactive intestinal polypeptide (VIP), substance P, and gastrin-releasing peptide [2, 6]. Most SCN inputs (from the retina, raphe, and intergeniculate leaflet) are segregated to the ventral part of the nucleus. Only a subset of SCN cells is directly retinorecipient [7, 8]; photoresponsiveness is observed in about 20% to 33% of SCN cells in the ventral part of the nucleus [9, 10, 11]. VIP is an intrinsic SCN factor implicated in acute activation and electrical synchronization of SCN neurons [12, 13] and coordination of behavioral rhythms [14]. AVP neurons occupy a large part of the SCN to produce an integrated output. AVP is synthesized and secreted by the SCN in a circadian pattern. AVP has an important excitatory role by activating V1a receptors [15] to increase the amplitude of firing rates in the SCN during subjective day [16, 17]. That is to say, the cells in VL core of the SCN receive photic signals from the retina and then relay them to the nonretinorecipient cells in DM shell. Ref. [18] and [19] gave the process of the circadian rhythm's generation which include three courses, i.e., information afferent inputs, oscillation, and information efferent outputs. The signal of LD cycle from outside firstly reaches the VIP neurons in the VL part. Then the neurons in the VL part are synchronized with the same period as that of the LD cycle owing to their compact couplings and the effect of the LD cycle. At last, VIP neurons transform the synchronous information to the AVP neurons in the DM part.

Based on the special structure of SCN, many studies have been carried out[20, 21, 22, 23]. But there are not any analysis about the special structure of SCN which are subdivided into two parts. That is to say why the VL part has fewer neurons which are compactly arranged and the DM part has more neurons which are sparsely arranged. In this paper, we mainly analyze the SCN's structure from mathematical viewpoint. One major effect for coupling of the neurons in the VL part is to increase their synchronizability. On the other hand, comparing with the number of DM parts, the number of the neurons in the VL part is generally small, which guarantees that the overall biological network is still kept to be sparse.

2 Analysis for the special structure of SCN

From last section, we know that the VL part has fewer neurons which are compactly connected, while the DM part has more neurons which are sparsely connected. Now we give the theoretical explanation from mathematical viewpoint.

For the DM part, Yamaguchi and his co-workers [25] showed that the DM cells are not synchronized when this area is disconnected from the rest of the SCN. This observation suggests that ventrolateral (VL) cells synchronize the oscillations and that the internal coupling between DM cells may be negligible. It also explains why the neurons in the DM part are connected sparsely.

For the VL part, we will explain why the neurons are arranged compactly from mathematical viewpoint. Neurons and their contacts form a network. The numbers of their contacts can be regarded as the number of links in the network. We mainly prove that the more edges a network with oscillators has, the more easily it achieves synchronization. That is to say adding links to a network can generally improve the ability to synchronization, which explains from theoretical viewpoint why the neurons in the VL part are compactly connected.

Without loss of generality, consider the following general network with identical os-

cillators,

$$\dot{x}_i = f(x_i) + c\sum_{i=1}^{N} a_{ij}x_j,\ i = 1,2,\ldots N, \tag{1}$$

where the coupling matrix $A = (a_{ij}) \in R^{N\times N}$ represents the coupling configuration of the entire network. Assume that A is a symmetric and irreducible matrix, which means that the network is connected in the sense of having no isolated clusters. Then zero is the largest eigenvalue of matrix A with multiplicity 1, and all other eigenvalues $0 > \lambda_2 \geq \cdots \geq \lambda_N$ are strictly negative. The coupled network (1) is said to achieve (asymptotical) synchronization if the synchronization manifold S of Eq.(1) satisfies

$$S = \{(x_1(t), x_2(t), \ldots, x_N(t))\big|x_1(t) = x_2(t) = \cdots = x_N(t) = s(t)\}, \tag{2}$$

where $s(t)$ can be an equilibrium point, a periodic orbit or even a chaotic attractor, satisfying $\dot{s}(t) = f(s(t))$. Then one obtained the conclusion as follows.

Lemma 1. [26] Consider the network (1) with identical nodes. If

$$c > \frac{h_{max}}{|\lambda_2|},$$

where $h_{max} > 0$ is the maximum Lyapunov exponent of the individual system $\dot{s}(t) = f(s(t))$, then the synchronization manifold is exponentially stable.

From the above result, one knows that $|\lambda_2|$ describes the synchronizability of the network (1). Particularly, the increase of $|\lambda_2|$ can reduce the requirement of the coupling strength for synchronization i.e., increase the synchronizability of network (1). In the following, we prove that the more edges a network with oscillators has, the more easily it achieves synchronization. Specially, we study the variation of synchronizability of network (1) if some edges are added. We define another symmetric diffusion matrix $\bar{A} = (\bar{a}_{ij}) \in R^{N\times N}$, denoting the edges added to the network, where $\bar{a}_{ij} \neq 0$ implies that one edge weighted $\bar{a}_{ij}$ is added to network (1) between the ith node and the jth node. The coupling matrix of the new network can be written as $A + \bar{A}$. From the Lemma 2, one knows that $\lambda_2(A) \geq \lambda_2(A + \bar{A})$. Considering all the eigenvalues of A is non-positive, one obtains $|\lambda_2(A)| \leq |\lambda_2(A + \bar{A})|$, which implies that the synchronizability of network (1) is improved after some edges are added to it.

Lemma 2. [27]*Suppose that A, and B are Hermitian matrices with eigenvalues*

$$\lambda_1(A) \leq \lambda_2(A) \leq \cdots \leq \lambda_n(A),$$

$$\lambda_1(B) \leq \lambda_2(B) \leq \cdots \leq \lambda_n(B).$$

Then the eigenvalues of matrix $A + B$, $\lambda_1(A + B) \leq \lambda_2(A + B) \leq \cdots \leq \lambda_n(A + B)$, *satisfy*

$$\left.\begin{array}{l} \lambda_i(A) + \lambda_1(B) \\ \lambda_{i-1}(A) + \lambda_2(B) \\ \cdots \\ \lambda_1(A) + \lambda_i(B) \end{array}\right\} \leq \lambda_i(A + B) \leq \left\{\begin{array}{l} \lambda_i(A) + \lambda_n(B) \\ \lambda_{i+1}(A) + \lambda_{n-1}(B) \\ \cdots \\ \lambda_n(A) + \lambda_i(B) \end{array}\right.$$

On one hand, a biological network is generally sparse with scale-free property. For a biological network with N nodes, generally the number of the links is about $O(N)$. In the special network of the SCN composed by the oscillators in the VL and the DM parts, the number of nodes is $N_1 + N_2$, where N_1 and N_2 are numbers of neurons in VL and DM part respectively. Therefore, the edges of the whole network is expected to be about $O(N_1+N_2)$. On the other hand, in the subnetwork of oscillators in the VL part, the number of edges is about $O(N_1^2)$ because of the global coupling, and the number of the DM part is zero because of uncoupling among oscillators. That is to say $O(N_1 + N_2) \sim O(N_1^2)$, which requires $N_1 \ll N_2$, i.e., it means that there are fewer neurons in the VL part from the theoretical analysis, which are also consistent with biological evidences.

Based on the functional and structural heterogeneity of the SCN cells and regions mentioned above, we propose a scheme to describe the process of the circadian rhythm's generation in SCN as shown in Figure 1. In the VL part, the neurons are globally coupled with each other and the information of daily LD cycle is introduced. In contrast, the neurons are not coupled in the DM part, but receive the input from the VL neuronal projections without feedback, consistent with dense anatomical projections from ventral to dorsal SCN and sparse reciprocal projections [24].

The signal of LD cycle from outside firstly reaches the VIP neurons in the VL part. The neurons in the VL part are synchronized with the same period of as that of the LD cycle owing to their compact coupling and the effect of the LD cycle owing to their compact couplings and the effect of the LD cycle. At last, VIP neurons transform the synchronous information to the AVP neurons in the DM part to produce an integrated output.

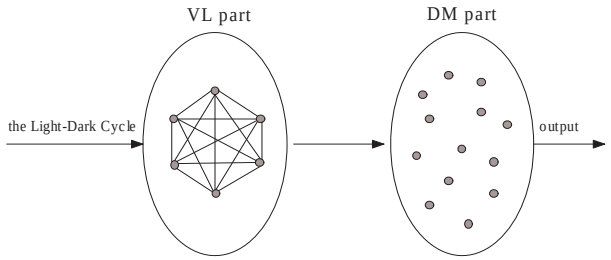

Figure 1: Scheme of the process of the circadian rhythm's generation in SCN

3 Conclusion and discussion

Circadian rhythm mediated by SCN is an important phenomenon in mammals, and many theoretical and experimental works have been carried out to understand its mechanism. The special structure of SCN is one of the important factors affecting circadian rhythm of mammals. In this paper, we analyze the heterogeneous structure of SCN from mathematical viewpoint. From the theoretical analysis in this article, we obtained the following conclusions:

One major effect for coupling of the neurons in the VL part is to increase their synchronizability. Accordingly, with the dense coupling, every neuron in the VL part is able

to easily achieve circadian rhythm entrained by the 24h LD cycle. On the other hand, comparing with the number of DM parts, the number of the neurons in the VL part is generally small. As a result, the overall biological network is still kept to be sparse. In particular, the results and analytical framework proposed here may provide insight to better understand the SCN structure, and may also have implication for applications, such as designing interventions to treat circadian disorder. Based on the special heterogeneous structure of SCN, the analytical study of the synchronization mechanism of Circadian Rhythms in the Suprachiasmatic Nucleus has been carried out in our another paper[28].

Acknowledges

This research is supported by the NNSF of China (Grant: 10672093). We express special thanks. The authors would like to thank Prof. Zengrong Liu for helpful discussions and suggestions.

References

[1] Reppert, S. and Weaver, D.: 'Coordination of circadian timing in mammals', *Nature*, 2002, **418**, pp. 935-941

[2] Moore, R., Speh, J. and Leak, R.: 'Suprachiasmatic nucleus organizarion', *Cell Tissue Res.*, 2002, **309**, pp. 89-98

[3] Welsh, D., Logothetis, D., Meister, M. and Reppert, S.: 'Individual neurons dissociated from rat suprachiasmatic nucleus express independently phased circadian firing rhythms', *Neuron*, 1995, **14**, pp. 697-706

[4] Honma, S., Nakamura, W., Shirakawa, T. and Honma, K.: 'Diversity in the circadian periods of single neurons of the rat suprachiasmatic nucleus on nuclear structure and intrinsic period', *Neurosci. Lett.*, 2004, **358**, pp. 173-176

[5] Moore, R.: 'Entrainment pathways and the functional organization of the circadian system', *Prog. Brain Res.*, 1996, **111**, pp. 103-119

[6] Kalamatianos, T., Kallo, I., Piggins, H. and Coen, C.: 'Expression of VIP and/or PACAP receptor mRNA in peptide synthesizing cells within the suprachiasmatic nucleus of the rat and in its efferent target sites', *J. Comp. Neurol.*, 2004, **475**, pp. 19-35

[7] Meijer, J. and Schwartz, W.: 'In search of the pathways for light-induced pacemaker resetting in the suprachiasmatic nucleus', *J. Biol. Rhy.*, 2003, **18**, pp. 235-249

[8] Morin, L. and Allen, C.: 'The circadian visual system, 2005', *Brain Res. Rev.*, 2006, **51**, pp. 1-60

[9] Shearman, L., Zylka, M., Weaver, D., Kolakowski, L., and Reppert, S.: 'Two period homologs: circadian expression and photic regulation in the suprachiasmatic nuclei', *Neuron*, 1997, **19**, pp. 1261-1269

[10] Shigeyoshi, Y., Taguchi, K., Yamamoto, S., Takekida, S., Yan, L., Tei, H., Moriya, T., Shibata, S., Loros, J., Dunlap, J. and Okamura, H.: 'Light-induced resetting of a mammalian circadian clock is associated with rapid induction of the mPer1 transcript', *Cell*, 1997, **91**, pp. 1043-1053

[11] Albrecht, U., Sun, Z., Eichele, G. and Lee, C.: 'A differential response of two putative mammalian circadian regulators, mper1 and mper2, to light', *Cell*, 1997, **91**, pp. 1055-1064

[12] Cutler, D., Haraura, M., Reed, H., Shen, S., Sheward, W. Morrison, C., Marston, H., Harmar, A. and Piggins, H.: 'The mouse VPAC2 receptor confers suprachiasmatic nuclei cellular rhythmicity and responsiveness to vasoactive intestinal polypeptide in vitro', *Eur. J. Neurosci.*, 2003, **17**, pp. 197-204

[13] Aton, S., Colwell, C., Harmar, A., Waschek, J. and Herzog, E.: 'Vasoactive intestinal polypeptide mediates circadian rhythmicity and synchrony in mammalian clock neurons', *Nat. Neurosci.*, 2005, **8**, pp. 476-483

[14] Harmar, A., Marston, H., Shen, S., Spratt, C., West, K., Sheward, W., Morrison, C., Dorin, J., Piggins, H., Reubi, J., Kelly, J., Maywood, E. and Hastings, M.: 'The VPAC(2) receptor is essential for circadian function in the mouse suprachiasmatic nuclei', *Cell*, 2002, **109**, pp. 497-508

[15] Ingram, C., Ciobanu, R., Coculescu, I., Tanasescu, R., Coculescu, M. and Mihai, R.: 'Vasopressin neurotransmission and the control of circadian rhythms in the suprachiasmatic nucleus', *Prog. Brain Res.*, 1998, **119**, pp. 351-364

[16] Mihai, R., Juss, T. and Ingram, C.: 'Suppression of suprachiasmatic nucleus neuron activity with a vasopressin receptor antagonist: possible role for endogenous vasopressin in circadian activity cycles in vitro', *Neurosci. Lett.*, 1994, **179**, pp. 95-99

[17] Mihai, R., Coculescu, M., Wakerley, J. and Ingram, C.: 'The effects of [Arg8] vasopressin and [Arg8] vasotocin on the firing rate of suprachiasmatic neurons in vitro', *Neuroscience*, 1994, **62**, pp. 783-792

[18] Eskin, A.: 'Circadian system of the Aplysia eye: properties of the pacemaker and mechanisms of its entrainment', *Fed Proc.*, 1979, **38(12)**, pp.2573-9

[19] He, G. and Sun, S.: 'Structure and role of suprachiasmatic nucleus in the circadian rhythem', *Process of Anatomical Science*, 2000, **6(2)**, pp. 97-101(in Chinese)

[20] Antle, M., Foley, D., Foley, N. and Silver, R.: 'Gates and oscillators: a network model of the brain clock', *J. Bio. Rhy.*, 2003, **18(4)**, pp. 339-350

[21] Antle, M., Foley, N., Foley, D. and Silver, R.: 'Gates and oscillators II: zeitgebers and the network model of the brain clock', *J. Bio. Rhy.*, 2007, **22(1)**, pp. 14-25

[22] To, T., Henson, M., Herzog, E. and Doyle III, F.: 'A molecular model for intercellular synchronization in the mammalian circadian clock', *Biophys. J.*, 2007, **92**, pp. 3792-3803

[23] Antle, M. and Silver, R.: 'Orchestrating time: arrangements the brain circadian clock', *Trends in Neurosci.*, 2005, **28(3)**, pp. 145-151

[24] Abrahamson, E. and Moore, R.: 'Suprachiasmatic nucleus in the mouse:retinal innervation,intrinsic organization and efferent proje ctions', *Brain Res.*, 2001, **916**, pp. 172-191

[25] Yamaguchi, S., Isejima, H., Matsuo, T., Okura, R., Yagita, K., Kobayashi, M. and Okamura, H.: 'Synchronization of cellular clocks in the suprachiasmatic nucleus', *Science*, 2003, **302**, pp. 1408-1412

[26] Li, X. and Chen, G.: 'Synchronization and desynchronization of complex dynamical networks: An engineering viewpoint', *IEEE Trans Circuits Syst I*, 2003, **50(11)**, pp. 1381-1390

[27] Zhang, X.: 'Matrix Analysis and Applications', (Springer, 2004)

[28] Li Y., Liu, Z. and Zhang, J.: 'Synchronization Mechanisms of Circadian Rhythms in the Suprachiasmatic Nucleus', *IET Systems Biology*, Revised.