Cell. Mol. Life Sci. 64 (2007) 1236 – 1243
1420-682X/07/101236-8
DOI 10.1007/s00018-007-6534-z

Cellular and Molecular Life Sciences

Mathematical models of regulatory mechanisms of sleep-wake rhythms

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Online First 15 March 2007

Abstract. Studies of regulatory mechanisms of sleep-wake rhythms have benefited greatly from mathematical modeling. There are two major frameworks of modeling: one integrates homeostatic and circadian regulations and the other consists of multiple interacting oscillators. In this article, model constructions based on these respective frameworks and their characteristics are reviewed. The two-process model and the multioscillator model are explained in detail. An appropriate mathematical abstraction is also shown to provide a viewpoint unifying the model structures, which might seem to be distinct. Recently acquired knowledge of neural regulatory mechanisms of sleep-wake rhythm has prompted modeling at the neural network level. Such a detailed model is also reviewed, and could be used to explore a possible neural mechanism underlying a pathological state of sleep-wake rhythm.

Keywords. Two-process model, homeostasis, multioscillator, photic entrainment, nonphotic entrainment, feedback, circle map, flip-flop.

Introduction

Study of the regulatory mechanisms of sleep-wake rhythms using mathematical modeling has led to at least three different model structures. Alertness and cognitive performance are modeled in an empirical way [1, 2], while mathematical abstractions are used to explain underlying physiological mechanisms [3–6]. When detailed physiological mechanisms are studied, models at the neural or molecular level are used [7–9].

In spite of the variety in these models, the two-process model is still one of the most widely accepted models, 20 or more years since it was developed [10, 11]. It integrates the two processes of homeostatic and circadian regulation of sleep-wake rhythm in a simple and elegant way, schematized in Figure 1a. Recent models generally share the same framework of the two-process model, although the interaction between the homeostatic and circadian regulations (homeostasis-rhythm interaction) are differently expressed [2, 11, 12]. Borbély and his colleagues have been attempting to extend the applicability of the two-process model by including a process of vigilance state and REM (rapid-eye-movement sleep)-NREM (non-REM sleep) ultradian rhythm whose period is much shorter than 24 h [13, 14]. Although it is appeling, the framework of homeostasis-rhythm interaction is not necessarily applicable for all aspects of sleep-wake rhythm. Circadian rhythms often behave like a multi-oscillator system, which leads another trend in modeling [3–6, 15]. This multioscillator framework is schematized in Figure 1b (see also the following sections).

In this article, model constructions based on these respective frameworks and their characteristics are reviewed comparatively. In addition, mathematical abstraction is shown to provide a viewpoint unifying the model structures which might seem otherwise to be distinct from each other. Recently acquired knowledge of the neural regulatory mechanisms of sleep-wake rhythm has prompted a shift in modeling to a neural network level. Such a detailed model is also

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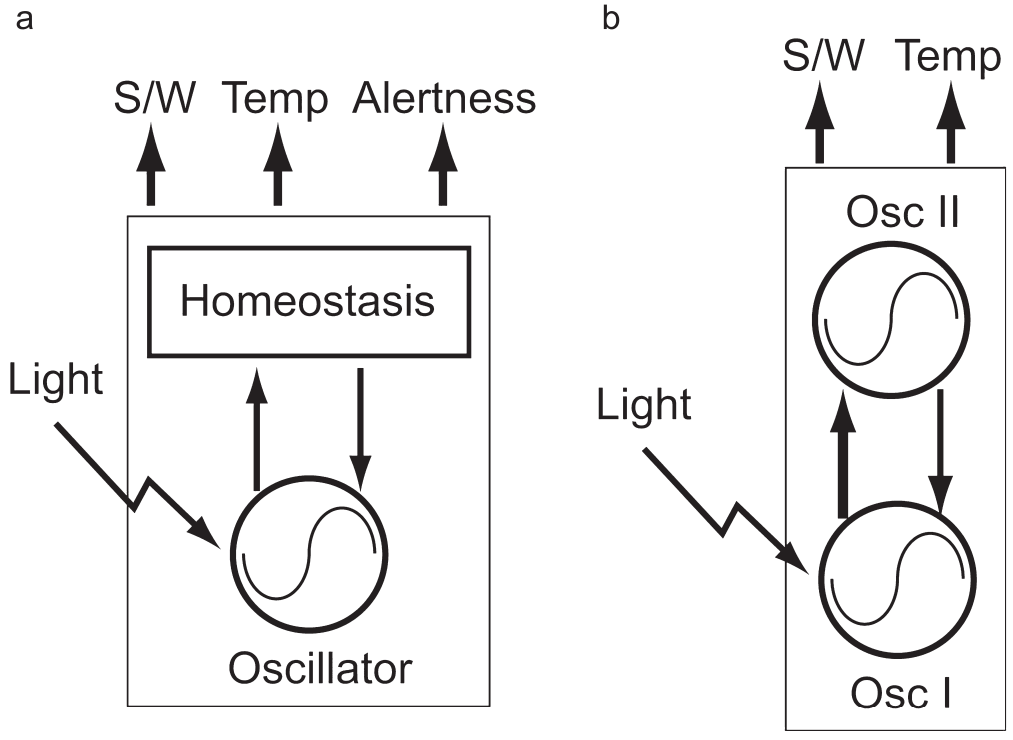

Figure 1. Major frameworks for modeling sleep-wake rhythms. S/W and Temp denote sleep-wake and temperature rhythms, respectively. (**a**) Two-process framework integrating homeostatic and circadian regulations. (**b**) Multioscillator framework consists of interacting multiple oscillators, where line thickness indicates strength of coupling. For more detail explanation, see the text.

reviewed, which could serve for exploring a possible neural mechanism underlying pathological states of sleep-wake rhythm.

Models based on interactions between homeostatic and circadian regulations of sleep-wake rhythm

Homeostatic regulation of sleep-wake rhythm can be intuitively understood, because it is usually experienced that sleep deficit is compensated by a deeper and/or longer recovery sleep. This intuition is well embodied in the two-process model [10, 11], which consists of periodic C processes and an exponentially rising-decaying S process. The C process works as a reflecting boundary against the S process: the S process rebounds when it reaches the C process. Because many reviews of the two-process model have already been written by Borbély and his colleagues (e.g., [16]), here we summarize aspects of the model not typically covered elsewhere. The two-process model was developed based on the empirical data obtained under short-term sleep deprivation [11]. Namely, the S process represents a buildup of slow-wave electroencephalographic activity (SWA) during wake, and its decay during sleep. The shape of the C process is determined by a level of SWA and sleep-onset/wake-onset timing [10,11]. The two-process model provides an intuitively tractable structure that enables researchers to test their ideas by manipulating the parameters and model operations: changing the gap between C processes (short and long sleeper), skipping the reflection of S process at the intersection of two processes (sleep deprivation and shift work), reducing buildup of the S process (napping), and so on [16]. For 20 or more years since the development of the two-process model, its simplicity and utility have led to its extensive acceptance as a symbolic conceptualization of the integration of homeostatic and circadian regulation.

One possible modeling framework of homeostatic regulation is negative feedback control. According to the physiological finding that thermoregulation and sleep control may be integrated in the preoptic/anterior hypothalamic area [17], a thermoregulatory model of sleep control was developed. In this context, the mathematical model consists of two circadian oscillators and two negative feedback loops for thermoregulation, one of which is mediated by sleep-wake rhythm [18, 19]. This model has variables mimicking 'sleepiness' in addition to sleep-wake patterns, the hypothalamic temperature, and a set point of thermoregulation. This model can predict behavior of sleepiness and temperature under various

situations, such as sleep deprivation and shift work [18,19]. A possible physiological origin of biphasic sleepiness was explored in light of this model structure [20]. This is another mathematical modeling of the interactions between homeostatic and circadian regulations of sleep-wake rhythm.

Prediction of alertness and cognitive performance under various environments is a major target of modeling [1, 2, 12]. Most of the models generally share the framework of the two-process model, although the interactions between the homeostatic and circadian regulations are differently expressed. In addition, another component such as sleep inertia (transitional state of lowered arousal occurring immediately after awakening) can be included as in a three-process model [2, 21]. The distinct structure in these models is nonlinear mutual interaction between homeostatic and circadian regulation, in contrast with the unidirectional effect of the C process on the S process in the original two-process model. The nonlinear interactions were added to reflect results from the forced desynchronization protocol, which attempts to separately evaluate the homeostatic and circadian regulation of a wide variety of physiological and cognitive variables [22–24]. Borbély and his colleagues have been extending the structure of the two-process model by including circadian and ultradian REM-NREM oscillators in a composite form [13], or by implementing a REM-NREM regulatory mechanism [25]. Daytime vigilance can also be simulated by the extended model [14, 33].

Variations of the two-process model have extended the applicability of the original model. However, what the simple structure of the original two-process model implies is worth revisiting. In the context of nonlinear physics, an oscillator structured like the two-process model is called a relaxation oscillator, and is used for investigating the dynamics of externally forced oscillators [26, 27]. In this sense, the S process is only a part of the nonlinear oscillator, although sleep physiologists interpret it as a generally separate, homeostatic regulatory process. This may sound paradoxical, but can be understood from the fact that the two-process model has a 'circle map'. Figure 2a shows that two phase maps, $f_w : \phi_w \mapsto \phi_s$ and $f_s : \phi_s \mapsto \phi_w$, can be defined for the two-process model [28]. Combining the maps gives $\phi_s^{n+1} = F_s^{(1)}(\phi_s^n) = f_w(f_s(\phi_s))$. $F_s^{(1)}$ determines the dynamics of the sleep-onset phase $\phi_s^n \in [0, 1]$, where n denotes the cycle number. By reversing the combining order, a similar map is obtained for the wake-onset phase ϕ_w^n. $F_s^{(1)}$ is called a circle map and is a mathematical tool for characterizing a nonlinear oscillator [28]. Figure 2b shows how $F_s^{(1)}$ depends on the gap of the C process. Characteristically, there is a discontinuous jump in $F_s^{(1)}$, which underlies the unique properties of the two-process model [28]. As such a complex nonlinear oscillator the two-process model can easily accommodate a wide variety of behaviors in sleep-wake rhythms. Actually, the different types of internal desynchronization can be understood as bifurcations of the dynamics of the two-process model [28, 29].

The beauty of the two-process model may be in its simple and abstract structure, with no redundancy. However, practical applications of mathematical models require that they predict various physiological and cognitive variables, rather than the abstract behavior of sleep-wake rhythms. The functional extensions of the two-process model increase practicality, but at the cost of its sophisticated structure as a nonlinear oscillator.

Models based on interacting multiple oscillators

Discovery of the dissociation between temperature/melatonin and sleep-wake rhythms (internal desynchronization) in a situation without any time cues such as light and feeding (free-run) prompted development of multioscillator models [3, 4, 15, 30]. As shown in Figure 1b, the fundamental framework of a multi-oscillator model is two mutually interacting oscillators: one drives temperature and melatonin rhythms (tentatively called Osc I), generally reflecting the actions of the suprachiasmatic nucleus (SCN), and the other controls sleep-wake rhythm (tentatively called Osc II), which is often represented by plural oscillators [5,15]. In addition, Osc I is photoresponsive and exerts a stronger effect on Osc II than the opposite direction. This organization is assumed because of the robustness of Osc I relative to Osc II. These models simulate the behavior of circadian rhythms in a free-run situation that includes the internal desynchronization and the non-monotonic relationship between the sleep-onset phase and corresponding sleep length [31].

The physiological reality of the multioscillator framework and the homeostasis-rhythm interaction framework has been disputed [32]. Currently, prediction of alertness and cognitive performance prefers the latter framework. However, it is argued how homeostatic and circadian regulations interact with each other [2, 33]. It should be noted that the rigid experimental and theoretical separations between homeostatic and circadian regulations are difficult to perform, because a stable limit cycle, which is a general model of circadian oscillator, is characterized by an ability to

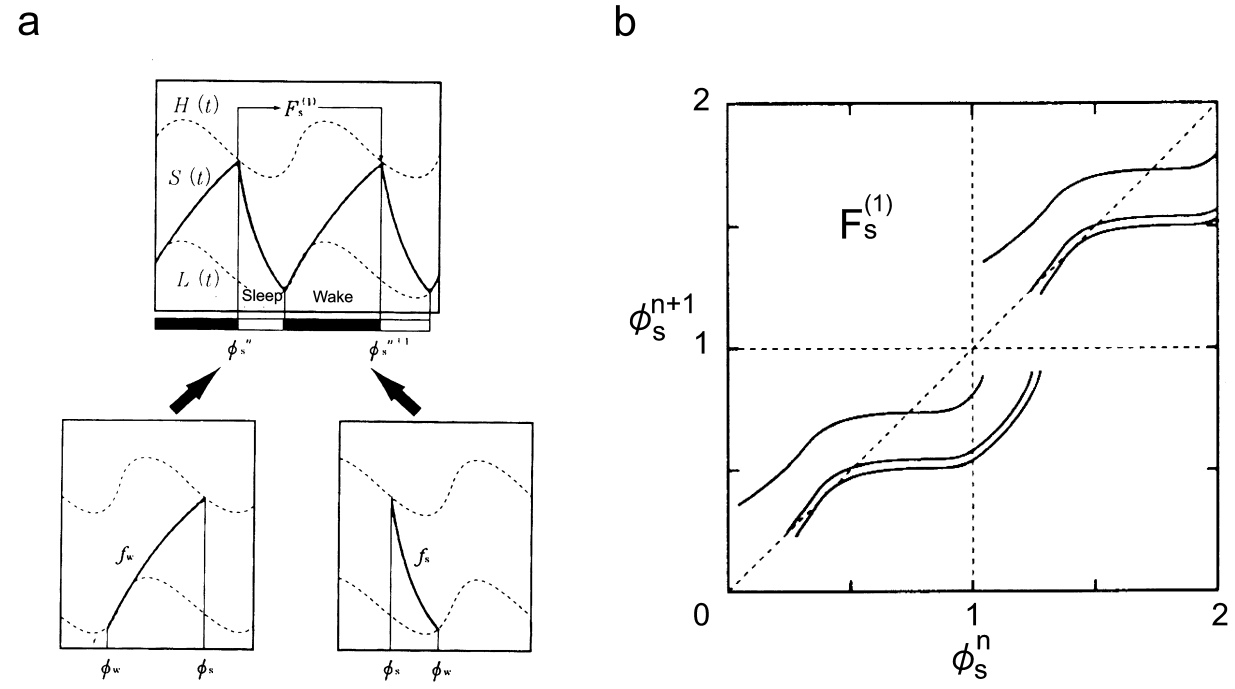

Figure 2. Circle maps of models based on different frameworks (adapted from [28]). (**a**) Construction of a circle map of the two-process model. (**b**) Circle maps of the two-process model for varied gaps between C processes (0.610, 0.450, 0.415; from top to bottom).

restore its oscillatory orbit against external perturbations just like homeostasis.

In the multioscillator framework, a physiological origin of Osc II has not yet been identified, in contrast to Osc I (which represents the SCN). This fact may weaken its physiological reality. Honma and his colleagues have tried to map Osc II onto a physiological process or structure, and to clarify its dynamics [34]. In their experiment, the rest-activity cycle (schedule) of a subject was advanced by 8 h relative to spontaneous sleep-wake rhythm under free-run conditions, and the re-entrainment of the melatonin rhythm was traced after release from the schedule. It took several days for the sleep-wake rhythm to be re-entrained to the melatonin rhythm after an 8-day advanced schedule. In contrast, after a 4-day schedule, the sleep-wake rhythm immediately caught up with the melatonin rhythm in most subjects. These results suggest that the sleep-wake rhythm is underlain by an oscillator (presumably Osc II) which could be entrained by the rest-activity schedule (i.e. a nonphotic entrainment). The nonphotic entrainment of Osc II was found to take 4 days or longer, implying that there is a critical period for the entrainment of Osc II. In other words, an adaptive feedback mechanism from the rest-activity cycle to the circadian oscillators is suggested to exist. There is physiological evidence supporting such adaptive feedback mechanisms [35–38]. Existence of feedback leads to the multi-oscillator model, which consists of Osc I, II, and SW (Figure 3). Osc SW is an overt sleep-wake rhythm which is replaced by the rest-activity cycle during a forced schedule. In a steady state, the unidirectional coupling Osc I→Osc II→Osc SW dominates model dynamics. In order to implement adaptive feedback mechanisms, the coupling strength between oscillators is designed to change depending on the correlation between Osc I/II and SW. Thanks to this adaptive mechanism, the rest-activity cycle comes to exert stronger effects on Osc I and II, and Osc I dominates Osc SW instead of Osc II, when the rest-activity cycle is forced to deviate from the mutually entrained phase position with Osc I and II. As shown in Figure 4, this model faithfully reproduces the behavior of sleep-wake and melatonin rhythms observed in the experiment [5, 34]. In addition, the behavior of circadian rhythms in transmeridian flights can also be simulated [6]. Figure 5 shows that the departure time differentiates the resulting re-entrainment processes of melatonin (Osc I) and sleep-wake (Osc II) rhythms in eastward flights over an 11-h time difference. The environmental circadian cycles phase-advance in an eastward flight. Departure at 7am causes the phase delay of Osc I and the phase advance of Osc II (antidromic re-entrainment by partition [39]). In contrast, when departing at 11am, both oscillators phase-advance (orthodromic reentrainment [39]). Note that the photic and nonphotic entrainment mechanisms should interact with each other in a transmeridian flight. Such an interaction could hap-

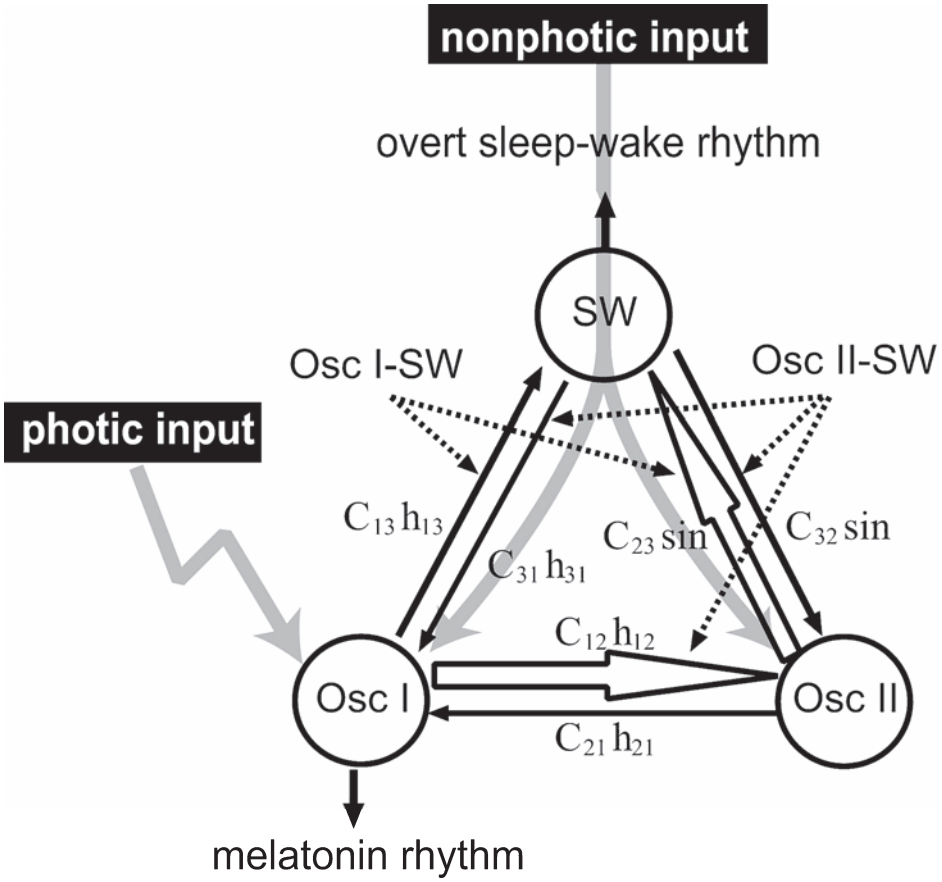

Figure 3. Multioscillator model with feedback from the rest-activity cycle to circadian oscillators [5,6]. $C_{ij}(i,j=1,2,3;i\neq j)$ denotes coupling strength, and h_{ij} and *sin* denote functions of the phase angle between oscillators. A dotted arrow indicates which correlation modulates which coupling strength.

pen in shift work as well. Therefore, a model which allows various entrainments is essential to predict the behavior of circadian rhythms in real-world environments; the multioscillator model with its adaptive feedback mechanism meets these requirements.

Physiology-based model of sleep-wake rhythm

Most of the aforementioned models have abstract structures in which the details of mechanisms at the neural and molecular level are not explicitly represented. Their applicability in understanding the mechanisms underlying the pathological states of sleep-wake rhythm is therefore confined to the behavioral level. Thus, a microscopic level model of sleep-wake rhythm is needed.

The reciprocal interaction model which McCarley and Hobson [40] proposed initiated modeling studies of ultradian rhythm of REM/NREM alternation. Their model is based on the concept that a prey-predator-like interaction between cholinergic and monoaminergic neurons in the brainstem induces the ultradian rhythm, and their later work extended the prey-predator model to the limit cycle model [7, 41]. Their model was then included in the composite model based on the two-process model [25]. Physiological knowledge of the neural mechanisms regulating sleep-wake rhythm has been advanced by recent findings concerning sleep/wake-related preoptic/anterior hypothalamic and perifornical (orexin-containing)/posterior hypothalamic neurons. This new knowledge has prompted sleep researchers to update the prey-predator framework. A 'flip-flop' model was recently proposed for state switching between NREM and wake [42, 43], where the flip-flop is a metaphor of mechanism that each of possible two states is alternatively activated. However, it remains unclear what mechanism flips the flip-flop and how the flip-flop mechanism regulates REM. Tamakawa et al. [9] proposed a mathematical model of the mechanisms orchestrating a neural system 'quartet' of sleep and wake composed of: 1) the sleep-active preoptic/anterior hypothalamic neurons (N-R group); 2) the wake-active hypothalamic and brainstem neurons exhibiting the highest rate of discharge during wake

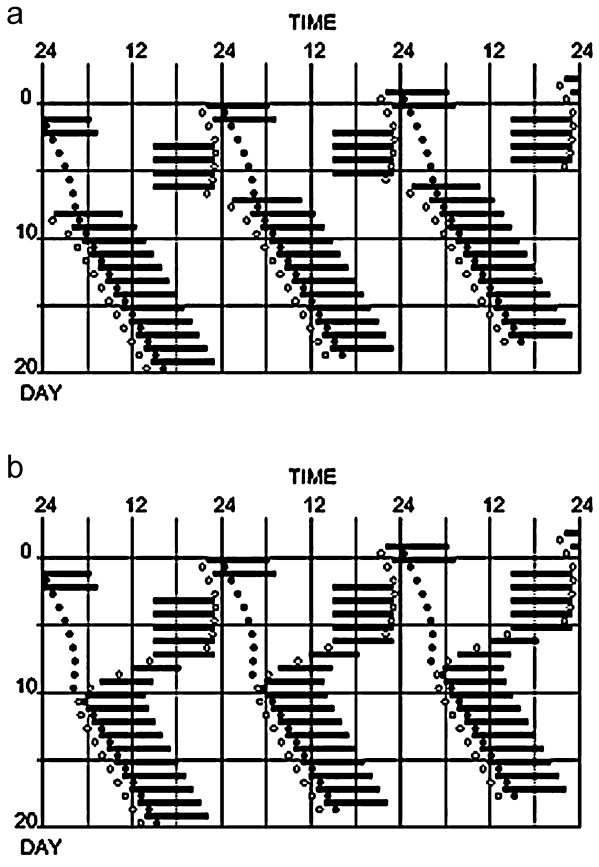

Figure 4. Behavior of circadian rhythms after release from the forced 8-h-advanced rest-activity cycle (adapted from [27]. (**a**) Four-day schedule. (**b**) Five-day schedule. Black bar denotes rest (sleep) period. ● and ○ denote $\theta_1 = 0$(phase of Osc I; melatonin peak phase) and $\theta_2 = 0$(phase of Osc II), respectively.

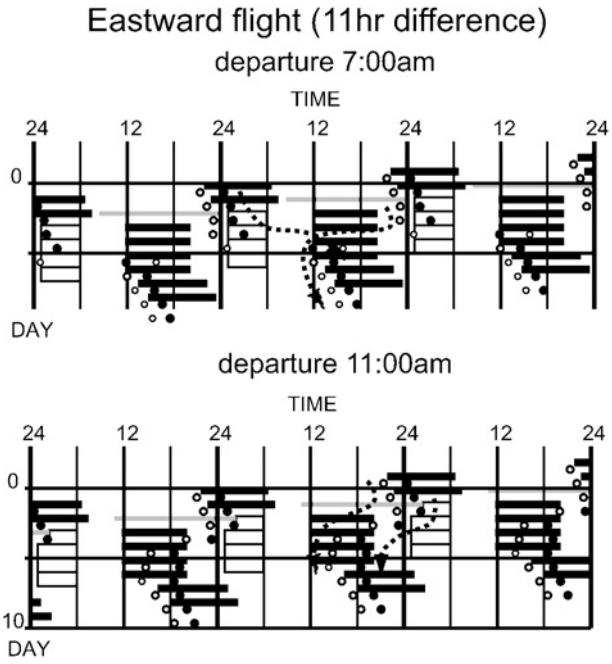

Figure 5. Simulation result of eastward transmeridian flight over 11-h difference [6]. Blank and gray bars denote a light period and a flight, respectively. A dotted line indicates the re-entrainment process of each oscillator. The other notations follow those in Figure 4.

and the lowest rate of discharge during REM (WA group); 3) the brainstem neurons exhibiting the highest rate of discharge during REM (REM group); and 4) the basal forebrain, hypothalamic, and brainstem neurons exhibiting a higher rate of discharge during both wake and REM than during NREM (W-R group). The model configuration is shown in Figure 6. This can be considered a 'multi-flip-flop' model in which a flip occurs by accumulation and dissipation of sleep-promoting substances (SPSs) underlying homeostatic regulation of sleep and wake. The model reproduces the actual sleep-wake patterns of rats, in addition to sleep-related neuronal activities across state transitions. Human sleep-wake rhythm can also be simulated by manipulating only a few model parameters. Narcolepsy, a well-known disorder of the sleep-wake mechanism, is understood as a dysfunction of orexin (hypocretin) receptors [44, 45]. Genetically orexin-deficient mice exhibit an increased proportion of REM during the dark period, but their organization of sleep and wake was unchanged during the light period [46, 47]; this result is predicted by excluding the perifornical orexin neuron from the multi-flip-flop model [9]. The simulation shows that the proportion of REM during the active (dark) period is increased without changing the organization of sleep and wake during the inactive (light) period. In spite of the success of the multi-flip-flop model in simulating a wide variety of sleep phenomena, how the dysfunction is linked to the pathological state of sleep-wake rhythm at a molecular level remains unknown. However, this model could yet provide the framework for exploring possible mechanisms underlying pathological states of sleep-wake rhythm.

Future prospects

A recent objective of modeling sleep-wake rhythm is to predict alertness and cognitive performance rather than focusing on the behavior of circadian rhythms. Although these models have provided a close fit to the time course of alertness and cognitive performance observed experimentally, still to be modeled are age dependence and/or the pathological alternation of the phase relationships between sleep-wake and temperature rhythms, and between temperature rhythm and clock time [38]. Feedback from the rest-activity cycle to the oscillators is thought to exist, but models have yet to

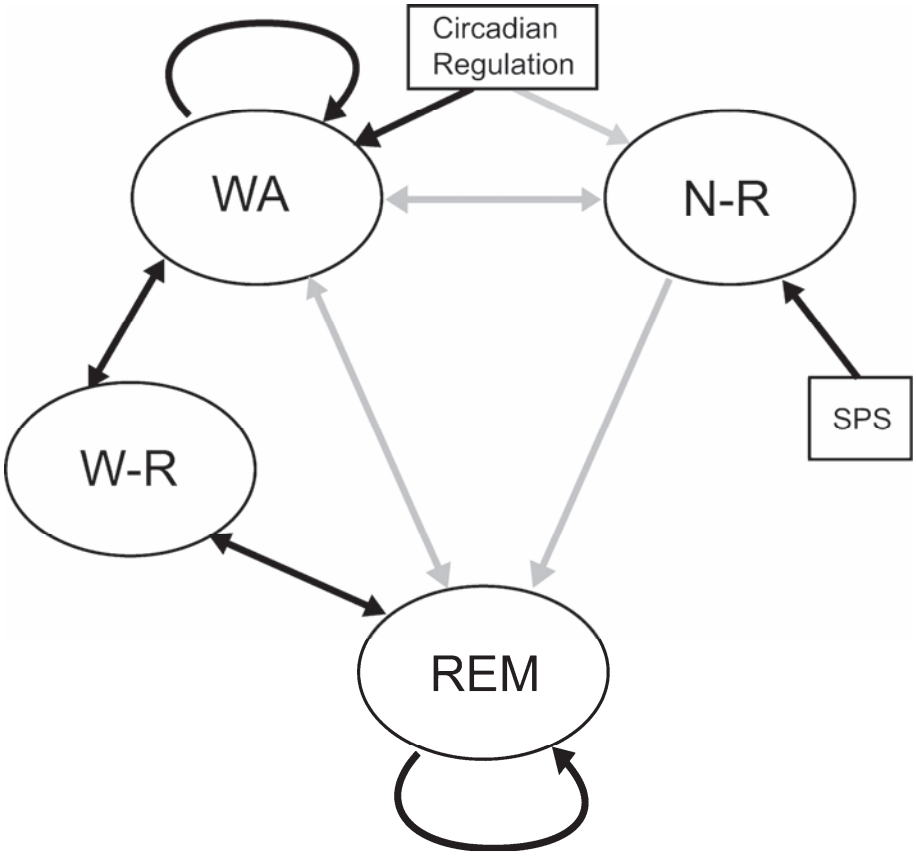

Figure 6. Schematic representation of the model composed of the quartet of neuron groups, WA, N-R, REM, and W-R under the controls of circadian component and sleep-promoting substances (SPSs) [9]. Criteria of the grouping are described in the text. Black and gray arrows indicate excitatory and inhibitory effects, respectively. Note that the model is constructed roughly by the mutual inhibitions between the neural groups and the auto-excitation in each group.

incorporate such components [38]. These aspects of internal and external entrainment could easily be understood in the framework of the multioscillator model [48]. On the other hand, a detailed model is required to link the findings at the molecular as well as the neural level to disorders of sleep-wake rhythm. A neural network model is shown to successfully simulate the sleep-wake rhythm of genetically orexin-deficient animals [9]; however it does not model alertness and cognitive performance. Therefore, mathematical models will continue to play key roles in study and conceptualization from molecular to behavioral levels of sleep-wake regulation. A comprehensive model is essential for integrating hierarchical regulatory mechanisms of sleep-wake rhythm [49].

Acknowledgments. This work was supported in part by the 'Academic Frontiers' Project for Private Universities (the Kansei Fukushi Research Center of Tohoku Fukushi University), a matching fund subsidy from the Ministry of Education, Culture, Sports, Science and Technology of Japan (2004–2008).

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