A Thermoregulatory Model of Sleep Control

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Abstract We hypothesize that non-rapid-eye-movement sleep (NREM) is controlled by thermoregulatory mechanisms of the preoptic/anterior hypothalamus. Circadian and homeostatic thermoregulatory processes may be integrated in this brain area. To investigate this hypothesis, we have developed a mathematical model of qualitative features of human sleep-waking behavior based on a thermoregulatory feedback control mechanism, with modulation by two circadian oscillators, one a temperature rhythm, the other modulating sleepiness. Homeostatic features of the sleep rhythm are generated by integration of a heat load associated with waking. Simulations under entrained conditions show that the model closely mimicks typical features of human sleep rhythms, including a biphasic daily pattern of sleepiness and sleep-onsets and awakenings fixed in a descending phase and an ascending phase of the temperature rhythm, respectively. Sleep duration is strongly controlled by the phase difference between the two oscillators with the same period; these could represent two phase-differentiated expressions of a single oscillator. In addition, the simulation of sleep deprivation provides a natural interpretation of the experimentally observed phenomena, which shows that the homeostatic and the oscillatory aspects of the human circadian system is successfully integrated in our model. The promising results obtained suggest that the control of sleep-wake rhythm could be understood within the framework of the thermoregulation.

Key words: hypnogenic warm sensitive neurons, human circadian rhythm, heat loss, heat load, thermoregulatory model of sleep.

The experimental analysis of sleep processes has been aided by the development of quantitative models of human sleep-wake rhythms. These include a

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self-sustained dual oscillator model [1] and an empirical model based on the interaction of a homeostatic process and an oscillator [2]. Both models include a circadian oscillator. In this paper, we present the initial description of a model which shares features of the previous models, but which is also based on current neurophysiological and physiological concepts of sleep regulation. Evidence suggesting that thermoregulatory mechanisms provide primary control of non-rapid-eye-movement sleep (NREM) and that such mechanisms could also account for homeostatic aspects of sleep are summarized below. On the basis of this evidence, we have developed a model in which a sleep-inducing (hypnogenic) homeostatic thermoregulatory process interacts with circadian rhythmic thermoregulatory processes to control sleep-wake rhythms.

In modelling the sleep control system, we hypothesize that NREM is involved in thermoregulatory feedback mechanisms. That is, (i) accumulated heat loads augment NREM, and (ii) NREM evokes heat loss processes which decrease the heat loads. Evidence to support this hypothesis includes the following points. Firstly, aspect (i) of NREM is described. An increased waking temperature, or "heat load," appears to be the common element of experimental manipulations, other than sleep deprivation, which increase the amount or intensity of NREM. Thus, afternoon or evening hot bath immersion increases subsequent stage 3-4 sleep in humans [3, 4]. The increase in stage 3-4 sleep after intense exercise was found to be dependent upon body heating and could be eliminated by fan cooling during the exercise [5]. Increases in stage 3-4 sleep in humans reflect increases in the intensity of sleep [6]. Heat loads also increase total subsequent NREM in rats [7].

Aspect (ii) of NREM could be understood from the following observations. Brain and body temperatures fall during sleep [8]; these falls are regulated and are superimposed on the circadian temperature rhythm [9]. They are also independent of the activity changes at sleep-onset [10]. Hypnogenesis integrates cerebral, behavioral, hormonal, and autonomic effector elements to induce heat loss and reduce heat production [11]. NREM is characterized by nearly complete behavioral suppression and greatly reduced cerebral metabolic rate [12]. These basic features of NREM can be interpreted as thermoeffector mechanisms, facilitating a temperature drop by reducing heat production. Therefore, since heat loads increase the intensity or duration of NREM and sleep provides cooling, this defines a homeostatic system [13].

Neural control mechanisms of NREM are strongly modulated by thermoregulatory mechanisms. The following neurophysiological findings suggest possible mechanisms mediating heat loads to the NREM control system. The best documented NREM neuroregulatory brain region includes the medial preoptic-anterior hypothalamic area (POAH) and adjacent basal forebrain. This is the only brain area for which studies using chronic lesions, localized electrical, chemical, and thermal stimulation, and neuronal unit recordings all support a hypnogenic function [14]. The POAH is also a major thermosensitive and thermoregulatory site in mammals [15], and available evidence shows that the hypnogenic and thermo-

regulatory functions of this area are closely integrated. Like other heat loss responses, NREM has been elicited by localized POAH warming [16] and has been tonically increased by “clamping” the POAH temperature at an elevated level [17]. In the latter study, the total sleep time was found to be linearly related to the difference between hypothalamic temperature (T_{hypo}) and a “set point” (T_{set}) for increased heat production. NREM can be elicited and sustained by POAH warming, and we have also reported the “sleep active” neurons in this area which had very low discharge rates in waking, but increased discharge just prior to and during NREM [18, 19]. Since this site is well-known to contain a high proportion of warm-sensitive neurons, it is naturally hypothesized that there are some warm-sensitive neurons which additionally take part in sleep regulation (HWSNs: hypnogenic warm-sensitive neurons). Although direct evidence for the existence of HWSNs has not yet been found, suggestive findings have been obtained as follows (see also [20]). POAH warm-sensitive neurons exhibit dynamic changes in local temperature sensitivity related to the sleep-wake rhythm [21]. Thermosensitivity is also modulated by circadian rhythms [21].

We develop the thermoregulatory model of sleep based on the above behavioral and neurophysiological observations concerning the close relationship between thermoregulation and sleep control. We incorporate the thermoregulatory feedback loops mediated by the “heat memory,” heat load and loss processes associated with sleep-wake cycles, which are modulated by two circadian oscillators. In our model, the HWSNs are assumed to integrate thermoregulation and sleep control. The model is applied to simulate the typical dynamical features of sleep-wake cycles and body temperature, including their tight phase relationship, biphasic daily pattern of sleepiness, and their behavior under long- and short-term sleep deprivation. Through these simulations, the reality of our hypothesis on which the model structure is based is examined.

Our thermoregulatory model of sleep applies to NREM. Like other quantitative models, our current model does not provide separate consideration of REM. However, REM sleep has well-documented thermoregulatory properties that differ from those of NREM [11], and we believe that these can ultimately be included in our model.

MODEL DESIGN

We hypothesize that the homeostatic regulation of sleep is a form of long-term thermoregulation; relative heat loads associated with waking are compensated by cooling that is evoked by sleep. This suggests that our model should include a mechanism that encodes storage or “memory” for heat loads which could facilitate subsequent sleep. We have incorporated a memory process in our model by integrating the waking heat load as defined by the elevation of body temperature above the set point.

Figure 1 depicts the model configuration. The model consists of two blocks:

Fig. 1. Model configuration.

one is for thermoregulation, the other regulating sleep propensity and sleep-wake cycles. The well-known circadian thermoregulatory rhythm block is under the control of the circadian oscillator X ; the sleep timing block is under the control of the circadian oscillator Y . The thermoregulatory block receives the masking process associated with sleep-wake cycles, and provides an error signal of temperature regulation: $T_{hypo} - T_{set}$ and "heat memory" which is given by integrating the error signal. This block represents the postulated mechanisms producing hypothalamic temperature and regulating a set point. The timing block receives the error signal and the heat memory from the former block, and feeds the masking process related to sleep-wake cycles back to the thermoregulatory block. This block generates sleepiness and sleep-wake cycles. The hypnogenic warm-sensitive neurons (HWSNs) collectively generate the sleepiness which times sleep- and wake-onsets. In the model, there exist a global feedback loop connecting these two blocks, and a local feedback loop in the thermoregulatory block for regulating the set point through the integrated error signal, i.e., the heat memory. Detailed explanations on the mathematical structure of the model are given in the next two subsections.

1. Thermoregulatory block. The temperature of the hypothalamus T_{hypo} is regarded as an observable temperature, and is defined as follows.

$$T_{\text{hypo}}(t) = g(\sigma) * (T_{\text{set}}(t) + T_m(t)), \quad (1)$$

where $T_{\text{set}}(t)$ and $T_m(t)$ indicate the set point of the temperature [15], and the masking effect responsible for a heat load during wake and a heat loss by NREM, respectively. $x(t) * y(t)$ indicates the convolution between $x(t)$ and $y(t)$. $g(\sigma)$ is a unified impulse response function for systemic thermal responses to the set point regulation and the masking process. The hypothalamic temperature is assumed to result from the superposition of both responses. These responses presumably involve many physiological processes such as vasomotor activities and metabolism. Characteristics of these systemic responses may depend also on the heat capacity of the whole body, which could be related to body mass and size. Therefore, their response dynamics are expected to be very complex. Here, g is assumed to be a 2nd order linear system, i.e., the dynamics of $T_{\text{hypo}}(t)$ is described by

$$\frac{d^2 T_{\text{hypo}}(t)}{dt^2} + 2\zeta\omega_n \frac{dT_{\text{hypo}}(t)}{dt} + \omega_n^2 T_{\text{hypo}}(t) = T_{\text{set}}(t) + T_m(t), \quad (2)$$

where ζ is the damping factor and ω_n is the intrinsic frequency.

The set point $T_{\text{set}}(t)$ is expected to be subject to circadian regulation [22]. Therefore, it is defined as follows.

$$T_{\text{set}}(t) = x(t) - c_h h(t), \quad c_h > 0, \quad (3)$$

where $x(t)$ denotes the circadian X oscillator, $h(t)$ the heat memory, and c_h determines the feedback gain of $h(t)$ to the set point regulation. The X oscillator represents the body temperature expression of the primary circadian clock, where we have borrowed the X , Y terminology of Kronauer *et al.* [1] because of the similarity in the intuitive meaning of these variables in their model and ours. $h(t)$ is assumed to contribute negatively to the set point regulation. This could account for the down-regulation of the core temperature during sleep deprivation [23] (see SIMULATION RESULTS), where the heat load is supposed to be accumulated monotonically in the memory. $x(t)$ is an oscillator defined by a sinusoidal function.

$$x(t) = a_x \sin(\omega_x t/k + \theta_x), \quad k = 24/2\pi, \quad a_x > 0. \quad (4)$$

The period of $x(t)$ is 24 h in the present simulations, i.e., $\omega_x = 1$. θ_x is a constant.

The heat memory $h(t)$ is given as the following integration of the deviation of the hypothalamic temperature from the set point.

$$h(t) = \int_{-\infty}^t (T_{\text{hypo}}(t') - T_{\text{set}}(t')) dt'. \quad (5)$$

It rises when T_{hypo} is above T_{set} , and decays when below T_{set} . The error signal, $T_{\text{hypo}}(t) - T_{\text{set}}(t)$, is expected to be produced mainly by the delay in the systemic thermal response and the masking process. Among them, since characteristics of

the systemic response are invariant, the masking process dynamically contributes to constructing $h(t)$. In this sense, the heat memory represents the total history of heat load and loss during the past sleep-wake cycles, which realizes the homeostatic regulation of sleep.

2. *Timing block.* The sleepiness controlled by the Y oscillator in the model is given by

$$\begin{aligned} \text{Sleepiness} &= [\text{sensitivity}] \times [\text{sigmoidal function}] \\ &= [(y(t) + c_w h(t)) + c_g] \times \frac{1}{1 + \exp(-(T_{\text{hypo}}(t) - T_{\text{set}}(t))/c_i)}, \\ c_w, c_i, c_g &> 0, \end{aligned} \quad (6)$$

Normally, c_g is set well above the amplitude of $(y(t) + c_w h(t))$, which means the response magnitude of HWSNs takes a positive value. The second term in Eq. (6) shows that the error signal of the temperature regulation is transformed sigmoidally into sleepiness. The sigmoidal function is natural as a saturating strength-response curve of a sensory neuron [24]. c_w denotes the contribution ratio of $h(t)$ to the sensitivity of HWSNs, and c_i determines the slope of the sigmoidal function. Warm (or cold) sensitive neurons in the hypothalamus are thought to encode the difference $T_{\text{hypo}}(t) - T_{\text{set}}(t)$ [15], which coincides with our definition of the response properties of HWSNs in Eq. (6).

The oscillator Y is defined as a sinusoidal function.

$$\begin{aligned} y(t) &= a_y \sin(\omega_y t/k + \theta_y), \\ a_y &> 0. \end{aligned} \quad (7)$$

Under the entrained conditions about which we are concerned in this paper, $\omega_x = \omega_y = 1$ and the constant phase difference $\phi = \theta_y - \theta_x$ are naturally assumed except as noted. Dynamic interactions between X and Y are neglected.

To determine sleep-onset and wake-onset times, two thresholds are introduced in a similar manner to Daan *et al.* [2]. A sleep-onset is regarded as the moment when the sleepiness crosses the sleep threshold r_s upward, and a wake-onset is when the sleepiness crosses the wake threshold r_w downward ($r_s > r_w$). Accordingly, the sleepiness defined here controls the initiation of sleep (wake), not its depth. In this sense, the process of sleepiness could correspond to the results of MSLT (Multiple Sleep Latency Test) [25].

The masking effect is generally regarded as a component which masks the net circadian process such as a temperature rhythm. Here, we are confined to thermal effects: a heat load during wake and a heat loss during sleep (see the introduction). The masking effect $T_m(t)$ is approximated by a low-pass filtered rectangular alternating process associated with sleep-wake cycles as follows.

$$\begin{aligned} T_m(t) &= \begin{cases} (A_w + A_s)(1 - \exp(-(t - t_w)/\tau)) - A_s, & \text{during wake} \\ (A_w + A_s) \exp(-(t - t_s)/\tau) - A_s, & \text{during sleep} \end{cases} \\ A_w, A_s &> 0, \end{aligned} \quad (8)$$

where t_w and t_s denote the times of the latest wake and sleep onsets, respectively. τ is the time constant. By this low-pass filtering, the masking effect rises or decays to its limiting value, A_w or $-A_s$, gradually, which is included to implement realistic time courses of heat load and loss processes. The magnitude of a heat loss could be related to the depth of sleep which is possibly regulated by the homeostatic process. Therefore, A_s is naturally expected to be modified by $h(t)$ (indicated by the dashed line with an arrow in Fig. 1). The homeostatic regulation of the sleep depth is explicitly included in the simulations of sleep deprivation, where the following masking amplitude A_s' is used during sleep instead of the constant one.

$$A_s' = (A_w + A_s) \times \left(\rho_s + \frac{\Delta \bar{\rho}_s}{1 + \exp[-h(t_{\text{onset}})]} \right), \quad (9)$$

where $\rho_s = A_s / (A_w + A_s)$, and $\Delta \bar{\rho}_s$ is the positive fraction, and t_{onset} denotes the moment of sleep-onset. That is, the heat loss during sleep, which corresponds to the depth of sleep, depends on the magnitude of $h(t)$ at the sleep onset. In this paper, however, we are essentially confined to the steady state behavior of the model. Therefore, A_w and A_s are regarded as constants unless otherwise stated.

The above is the fundamental structure of our model. In the simulations of a persistent sleep deprivation, a sigmoidal saturating function is applied (Fig. 3A). Such a function set upper and lower limits of temperature variation and is approximately linear in the temperature range between both limits. These limits are naturally expected from the relatively narrow temperature range observed in most mammals.

SIMULATION RESULTS

1. Model behavior in steady state

Figure 2 shows typical time courses of model variables, i.e., T_{set} , T_{hypo} , the sleepiness, the masking process which simultaneously indicates the sleep-wake cycle, the heat memory ($h(t)$), $T_{\text{hypo}} - T_{\text{set}}$, the sensitivity of HWSNs ($y(t) + c_w h(t)$), and X and Y oscillators, where the wake duration is 16 h and the sleep is 8 h. Each of these variables takes a dimensionless and relative value in our model. If one needs an absolute value, the corresponding absolute value can be easily obtained by multiplying the relative value by an appropriate factor without changing the model operation. Besides, the "0" levels for the temperature rhythms, the heat memory, and X and Y oscillators indicate their mean levels. The parameter values used here are listed in Table 1. The numerical integration is done by following the 4th order Runge-Cutta method with a time step of 0.05 [h]. All simulations in this study are performed for at least 20 circadian cycles except for initial transient cycles to confirm a stable oscillation. A few cycles extracted from the simulated stable cycles are shown in this paper. The issue concerning model stability and model dynamics dependent on model parameters will be discussed in a companion paper [26]. The period of a sleep-wake cycle is fixed at 24 h in all simulations.

Fig. 2. Typical dynamical features of model variables. T_{hypo} , temperature of hypothalamus; T_{set} , set point of temperature; Slnss, sleepiness; S/W Mask, sleep-wake masking process; Heat Mem, heat memory; $T_{\text{hypo}} - T_{\text{set}}$, input to HWSNs; Sens: HWSN, sensitivity of HWSNs; X Osc., X oscillator; Y Osc., Y oscillator. These abbreviated notations are used through the following figures. Used parameter set is listed in Table 1. Vertical thick bars indicate calibrations for 5 (2.5 in S/W Mask.). Horizontal ticks indicate level 0. These also apply to Figs. 3, 5, and 7.

Table 1. Used parameter set.

Parameter	Value
ζ	0.8
ω_n	$2\pi/5.5$ [rad/h]
a_x	2.0
a_y	3.0
$A_m (=A_w + A_s)$	2.5
$\rho_s (=A_s/A_m)$	0.635
c_h	0.06
c_w	0.15
c_i	0.5
r_s	3.0
r_w	0.3
c_g	5.5
τ	1.5 [h]
ϕ	6.2 [h]
ω_x, ω_y	1.0

The dynamical features of the model behavior in a steady state are summarized as follows.

(1) A biphasic distribution of sleepiness is observed: one near the peak and the other on the lower descending limb of the temperature rhythm, which closely mimics the biphasic circadian pattern of the nap sleep latency [25, 27]. Between these higher NREM propensity zones, there are periods of low sleep propensity which correspond to the experimentally observed so-called wake-maintenance zones [28].

(2) Sleep-onset occurs in the descending phase of the temperature rhythm, and wake-onset occurs in the trough phase of the temperature rhythm.

(3) T_{set} is higher than T_{hypo} during the rising period of the temperature rhythm, and T_{set} is lower than T_{hypo} during the descending period. T_{set} and T_{hypo} intersect in their troughs and acrophases. This is the predicted behavior of the model based on the feedback control system.

(4) Note that the temperature begins to fall well before sleep-onset, as seen in human subjects.

(5) The sleepiness, the output of HWSNs, continues to increase after sleep-onset, but declines rapidly at the end of sleep to a low point at the time of morning awakening. The sleepiness is controlled by the interaction among the temperature error signal ($T_{\text{hypo}} - T_{\text{set}}$), the heat memory, and the Y oscillator. In the model, the sensitivity of HWSNs begins to rise before sleep-onset and continues to rise during sleep, but falls during most of the waking period.

2. Sleep deprivation

In the externally entrained steady state, rhythmic aspects of a sleep-waking system are pronounced compared with a homeostatic process. Sleep deprivation possibly enhances the contribution of the homeostatic regulatory process so that the interaction between the rhythmicity and the homeostatic process is expected to appear distinctly. Here, simulations of sleep deprivation are carried out to see how the homeostatic mechanism works and interacts with the rhythmicity in our model. In Fig. 3A, the simulation result for persistent sleep deprivation is shown. During the deprivation, T_{hypo} and T_{set} monotonically decrease as they oscillate with decreasing amplitudes. The sleepiness and $h(t)$ rise monotonically. T_{hypo} is above T_{set} because of the maintained waking state. These simulation results successfully reproduce the experimentally observed decrease in the mean temperature during sleep deprivation (e.g., [23]). The modelistic interpretation for this phenomenon is given in DISCUSSION.

Concerning short-term sleep deprivation, Åkerstedt and Gillberg [29] discovered the interesting relationship between the deprivation time and the duration of recovery sleep. There is a discontinuity in the duration of recovery sleep for the deprivation of around 14 h. Simulation results of the short-term sleep deprivation well mimic this relationship, as in Fig. 4. Furthermore, the model predicts the duration of second recovery sleep for varied deprivation times. Although no

Fig. 3. Simulations of sleep deprivation. A: the persistent sleep deprivation. B: 4 h sleep deprivation. C: 16 h sleep deprivation. D: 20 h sleep deprivation. Horizontal thick bars above traces indicate sleep periods. This also applies to Figs. 5 and 7. The vertical lines with arrowheads indicate the normal sleep-onset times.

available data are known for the second recovery sleep, this result deserves to be studied experimentally. Figure 3B, C, and D show the time courses of model variables responsible for the short-term sleep deprivations, 4, 16, and 20 h, respectively. For 4 h of deprivation, the wake-onset occurs in the trough phase of the temperature despite the late sleep initiation. For 16 h, the waking state is prolonged beyond the next normal wake-onset phase, and the wake-onset is postponed to the next trough phase of temperature. It is also worth noting that the model shows a napping for 20 h or longer deprivation time after the first recovery sleep (the plots

Fig. 4. Relationship between sleep deprivation time and duration of recovery sleep. After the 1st recovery sleep with *, the model exhibits a nap.

with * in Fig. 4): the sleepiness rises beyond the sleep threshold in the daytime. This seems quite natural for human behavior, which suggests the reality of the model.

The discontinuous jump of the recovery sleep length could be attributed to the fact that the wake-onset is fixed around the trough of the temperature. That is, the duration of the recovery sleep is supposed to be the time between the sleep-onset and the nearest coming trough. Therefore, under the deprivation of around 14 h, the postponed sleep-onset possibly exceeds the critical moment of awakening, so that the wake-onset drastically jumps to the next trough of the temperature rhythm.

In the simulation of short-term sleep deprivation, the masking amplitude during sleep is determined by Eq. (9) which implements the homeostatic regulation of the sleep depth. Parameters $\Delta\bar{\rho}_s$ and $A_w + A_s$ are 0.25 and 0.625, respectively; the other parameter values are the same as in Table 1.

3. Model behavior for varied phase differences between X and Y oscillators

From the physiological point of view, it is very intriguing how the model behavior depends on the phase difference ϕ between X and Y . Actually, this phase difference under entrainment is expected to result from interactions among X , Y , and zeitgebers. Although the dynamical interactions between those oscillators are not explicitly included in our current model, ϕ -dependency of the model behavior is essential information for applying the model to various situations such as free running and jet lag.

Figure 5 shows how dynamical features of model variables are modified by varied phase advances ϕ (Y oscillator to X). Plots are made synchronously at the moment of wake-onset. Each wake-onset is relatively fixed to the trough phase of the temperature rhythm. This is known from the fact that, compared with the temperature rhythms, there exists large variation in the phase of the HWSNs sensitivity which is dominantly controlled by the Y oscillator. In contrast, the

Fig. 5. Model dynamics for varied phase advances from Y to X oscillator. A: the dynamical features of model variables for $\phi = 4.8, 9.6, 14.4,$ and 19.2 [h], where $(\rho_s; A_s/(A_w + A_s), d_s; \text{sleep duration}) = (0.71, 6.1), (0.48, 12.1), (0.29, 17.4),$ and $(0.17, 19.5)$, respectively. Arrows in this figure indicate the order of traces responsible for the sequence of parameter values listed above. The short arrow in the heat load traces indicates the trace for $\phi = 19.2$ [h]. B: sleep duration as a function of ϕ .

sleep-onset is shifted in parallel with ϕ . Consequently, the more the phase of the Y oscillator advances to the phase of X, the longer the sleep duration d_s becomes. This relationship is illustrated in Fig. 5B. Interestingly, there is discontinuity in the relationship: the sleep duration jumps abruptly when ϕ crosses the boundary around 0.

As presented in the companion paper, most of the model parameters studied change sleep durations and wake-onset times to some extent, but do not remarkably alter the consistent phase relations between sleep-onsets and temperature rhythms: sleep-onsets are fixed in the descending limb of the temperature rhythm. Therefore, sleep-onsets are shown to be strongly coupled with the Y oscillator. In this point, ϕ is distinct from the other parameters in controlling sleep-onset times.

In this simulation, the proportion between A_w and A_s is also modified appropriately in order to realize stable sleep-wake patterns, keeping the total masking amplitude $A_w + A_s$ constant.

4. Internal desynchronization

As shown above, there is the critical phase difference (around $\phi = 0$), which produces the discontinuous change in sleep duration from the long to the short. This suggests that our model can be used to produce the phenomena seen under internally desynchronized conditions [30]. We may anticipate that a critical aspect

Fig. 6. Double plotted sleep-wake cycles simulated for internal desynchronization. Used parameters are $\omega_x=1.0$, $\omega_y=0.92$, $k=25/2\pi$, $\rho_s=0.5$. Others are the same as in Table 1. Horizontal bars indicate sleep.

of entrainment will be the maintenance of certain phase relationships between the two oscillators. If we assume that the phase relationship between the X and Y oscillators changes after release from zeitgebers, turbulent sleep-wake patterns would be generated in our model. To determine whether such is actually the case, the preliminary simulation of the internal desynchronization is performed, where there is no interaction between two oscillators with angular frequencies $\omega_x=1$, $\omega_y=0.92$, and $k=25/2\pi$. This condition might be responsible for an extreme case of internal desynchronization where the mutual interaction between oscillators is supposed to be weakened. The resultant sleep-wake cycles in Fig. 6 seem to mimic actual desynchronized sleep-wake patterns [30], which is explained as follows. Since the phase relationship between X and Y oscillators fluctuates in a cyclic manner due to the difference in their intrinsic frequencies, drastic changes in sleep duration could occur every time the critical phase difference is crossed. As a matter of fact, we have to incorporate a process of entrainment in our model to complete this type of simulation.

5. Polyphasic sleep-waking rhythm

Figure 7 depicts the simulation of a polyphasic sleep-wake pattern like that seen in rodents, which is achieved by reducing the distance between thresholds for sleep- and wake-onsets, following the approach of Daan *et al.* [2]. In this simulation, the time constant τ in Eq. (8) and the damping factor ζ in Eq. (2) are also reduced in addition to lowering the threshold r_s . The simulation results show

Fig. 7. Simulation of polyphasic sleep-wake pattern with the parameters: $\zeta=0.2$, $r_s=1.0$, and $\tau=1.0$.

that the appropriate circadian-modulated polyphasic pattern is realized here. This is done without reference to light-dark cycle. Such behavior of the brain temperature closely associated with polyphasic sleep-waking patterns is commonly observed in rodents (e.g., [31]).

DISCUSSION

We have developed a quantitative model of sleep control which can generate appropriate features of human sleep-wake patterns, including a suitable phase relationship between the sleep-wake cycle and the temperature rhythm and the biphasic pattern of sleepiness. We have produced a complex model with many parameters. However, some of these are required by our choice of a feedback control model, and the obligatory parameters associated with such an approach. In the companion paper, the parameter dependency and the stability condition of the model operation are studied based on the linear system theory and the simulations.

Because of the physiological basis of our model, our simulations suggest which mechanisms could underlie the features of human sleep-wake rhythm within the framework of the model structure. Some of them are summarized below.

- (1) Wake-onsets occur at the minima in sleepiness which reflect those in $T_{\text{hypo}} - T_{\text{set}}$, i.e., the input to the HWSNs.
- (2) The Y circadian oscillator strongly modulates the overall distribution of sleepiness and the onset of sleep (see Fig. 4).
- (3) The afternoon peak in the biphasic distribution of sleepiness coincides with the ascending phase of $T_{\text{hypo}} - T_{\text{set}}$ and the descending phase of the HWSNs sensitivity.
- (4) The duration of sleep depends on the phase difference between X and Y .
- (5) The nocturnal peak in sleepiness is associated with the peak of $T_{\text{hypo}} - T_{\text{set}}$ and the ascending phase of the HWSNs sensitivity.
- (6) Persistent sleep deprivation decreases the mean level of the temperature

rhythm. The duration of recovery sleep exhibits the discontinuous jump for the deprivation of around 14 h. The sleep durations in the second recovery night for varied deprivation times are predicted.

Several important features of the model behavior summarized above were not considered in model development and are, therefore, "predictions" of the model.

In developing this model, we adjusted several parameters to produce the appropriate model behavior. For example, we chose suitable parameters for the $X-Y$ phase difference, the amplitude of masking effect, the sensitivity of HWSNs, and the systemic thermal response characteristics. Among the typical features, sleep and wake durations are strictly fitted to 8 [h] and 16 [h], respectively, chiefly by controlling ρ_s , r_s , and ϕ . For the other features such as the biphasic daily pattern of sleepiness and the characteristic phase relationship between the temperature and the sleep-wake rhythms, we evaluated the fitness of the model behavior to the actual observation by sight inspection. This is because qualitative fitting is thought to be enough for understanding the modelistic mechanism underlying the typical features of human circadian systems. In fact, parameter fitting has been done based on the knowledge concerning the parameter dependency of model behavior described in the companion paper.

In our model, sleepiness is an important variable generated collectively by HWSNs which are hypothesized to mediate between a thermoregulatory process and a sleep-wake timing system. The population sensitivity of HWSNs is considered to be modified by the heat memory, and additionally assumed to be regulated by the Y circadian oscillator. As described in the introduction, POAH warm-sensitive neurons exhibit dynamic changes in thermosensitivity related to the sleep-wake rhythm [21]. Although we do not have any direct evidence that the heat memory could modify their thermosensitivity, there are supporting findings as follows. Morairty *et al.* [7] observed, following whole body heating, a long-lasting relative hypothermia associated with, but outlasting the increase in NREM in rats. This suggests that the heat memory produced by whole body heating enhances the heat loss mechanisms mediated by warm-sensitive neurons. On the other hand, prostaglandin D₂, known to be a sleep-promoting substance, was shown to exert its excitatory effect on the activities of sleep-related neurons in POAH [20]. Provided that such a substance underlies the heat memory, the memory might be able to control the sensitivity of HWSNs. Therefore, the above assumption concerning the sensitivity regulation of HWSNs could be regarded as a natural one.

To reproduce the intriguing phenomena of human circadian rhythms, many mathematical models have recently been developed: coupled nonlinear oscillators [1, 32, 33], and the combination of the oscillatory thresholds (C process) and the relaxation process (S process) [2, 34]. Among them, the kinetics of the interaction between the sleep-wake and the temperature rhythms were emphasized in the former group, and the homeostatic properties in the latter. However, those models could not explain the mechanisms underlying the daily distribution of sleepiness [25, 27]. In addition, since those models had simplified mathematical structures,

the direct physiological interpretation of the model variables are difficult. In this regard, our model has the prominent structure based on the physiological findings.

Our model includes two circadian oscillators which are essential to provide the biphasic sleep propensity, and to account for the different circadian courses of temperature and sleepiness. In contrast with Kronauer *et al.* [1], we distinguish the oscillators themselves from overt rhythmic phenomena, which might make their biological entities abstract. However, this appears to be a realistic organization of circadian systems. Since our oscillators have the same period, this could be understood as reflecting the output of a single pacemaker, with two phase-differentiated expressions, analogous to the relationship between the temperature rhythm and ACTH secretion [35]. Nevertheless, the critical variable was the phase relationship between the two oscillators. In our simulations, the $X-Y$ phase difference, 6.2 h, was chosen to produce a suitable sleep duration within the structure of our model. Since completing this work, we have discovered that Lavie [36] derived a very similar phase difference, 7.4 h, on the basis of studies of the midafternoon-nocturnal sleep "gate" time difference in entrained subjects studied in a 20-min sleep/wake cycle paradigm. Thus, the phase difference we assumed for entrained conditions agrees with physiological data, although, in our model, the exact positions of afternoon and nocturnal sleep-onsets would also be modulated by other parameters.

As mentioned above, during long-term sleep deprivation, the mean body temperature is observed to decrease gradually as the deprivation progresses. However, this behavior of the temperature seems paradoxical, because, intuitively, the masking effect during the prolonged waking state ought to increase the mean temperature. Our model presents an intriguing interpretation on the underlying mechanism of this paradoxical phenomenon as follows. During sleep deprivation, the feedback loops within the thermoregulatory block are highly activated by the accumulation of heat load in the memory, while the other loop mediated by the timing block is not available because of sleep deprivation. As a consequence, the rising $h(t)$ is negatively fed back to the set point regulation so that T_{set} is lowered gradually during the deprivation.

In simulating the internally desynchronized behavior, we have proposed a scenario whereby the weakened interaction between oscillators results in an unstable phase relationship between them, which could produce the turbulent sleep-wake patterns because of the existence of the critical phase relationship. Although the model structure is different, a similar idea was proposed in Strogatz's model [33]: ϕ has a stable equilibrium point under synchronized conditions, and it changes temporarily under desynchronized situations. In Kronauer's and Kawato's models, the difference in the oscillator periods was assumed to increase gradually after release from zeitgebers. On the other hand, the amplitude of C process is assumed to be reduced gradually during free running periods in Daan's model. These three types of assumptions are all designed to realize a weakening of the coupling between oscillators under free running situations. From the structure of our model, another

factor could be involved in the desynchronization, which is a fluctuation in the masking effect (heat load during wake and loss during sleep). Since this fluctuation could cause fluctuation in the heat memory, dynamical interplay between the homeostatic process (heat memory) and the rhythmicity (X and Y oscillators) could underlie the internal desynchronization. Although this type of fluctuation is not incorporated in our model, it appears to be an intriguing story concerning the internal desynchronization. However, further study is required to evaluate each hypothesis.

In the introduction, we summarized evidence that circadian, neural, and physiological control of NREM was closely linked to thermoregulation. The thermoregulatory model provides a natural method to integrate circadian and homeostatic processes at both behavioral and neurophysiological levels, as both are regulated by overlapping medial POAH structures. Further, the thermoregulatory model of NREM is also consistent with several functional concepts of sleep, including energy conservation, participation in immune defense processes, control of circadian aspect of the ecological niche, or protection against sustained high waking temperatures. That is, each of these "functions," as they are expressed through sleep, depends neuromechanistically on co-regulation of temperature and sleep [37]. We believe that the strength of our model is the potential to relate mathematical parameters to physiology. In the development of this initial version of our model, we made several assumptions about the nature of the control system regulating sleep. The model may benefit from some modifications when it is extended to additional species or used to simulate more complex aspects of human sleep. However, such modifications would not be arbitrary, but may be related to knowledge about thermoregulatory phenomena in each experiment. Thus, we must predict that changes in "set points" produced by experimental manipulations of energy balance or immune factors would be related to specific changes in sleep parameters. Evaluation of such predictions in the context of our model could eventually help identify both thermoregulatory and non-thermoregulatory aspects of sleep regulation.

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REFERENCES

1. Kronauer RE, Czeisler CA, Pilato SF, Moore-Ede MC, and Weitzman ED : Mathematical model of the human circadian system with two interacting oscillators. *Am J Physiol* **242**: R3–R17, 1982
2. Daan S, Beersma DG, and Borbély AA: Timing of human sleep recovery process gated by a circadian pacemaker. *Am J Physiol* **246**: R161–R178, 1984

3. Bunnell DE, Agnew JA, Horvath SM, Jopson L, and Wills M: Passive body heating and sleep: Influence of proximity to sleep. *Sleep* **11**: 210–219, 1988
4. Horne JA and Reid AJ: Night-time sleep EEG changes following body heating in a warm bath. *Electroencephalogr Clin Neurophysiol* **60**: 154–157, 1985
5. Horne JA and Moore VJ: Sleep EEG effects of exercise with and without additional body cooling. *Electroencephalogr Clin Neurophysiol* **60**: 33–38, 1985
6. Borbély AA, Baumann F, Brandeis D, Strauch I, and Lehmann D: Sleep deprivation: Effects on sleep stages and EEG power density in man. *Electroencephalogr Clin Neurophysiol* **51**: 483–493, 1981
7. Morairty S, Szymusiak R, Thomson D, and McGinty D: Selective increases in non-rapid eye movement sleep following whole body heating in rats. *Brain Res* **617**: 10–16, 1993
8. Obal F Jr: Thermoregulation during sleep. *Exp Brain Res (Suppl)* **8**: 157–172, 1984
9. Mills JN, Minors DS, and Waterhouse JM: The effect of sleep upon human circadian rhythms. *Chronobiologia* **5**: 14–27, 1978
10. Gillberg M and Åkerstedt T: Body temperature and sleep at different times of day. *Sleep* **5**: 378–388, 1982
11. Parmeggiani PL: Temperature regulation during sleep: A study in homeostasis. *In*: *Physiology in Sleep*, ed. Orem J and Barnes CD, Academic Press, New York, pp 97–143, 1980
12. Kennedy C, Gillin JC, Mendelson W, Suda S, Ito M, Nakamura RK, Storch FI, and Petigrew K: Local cerebral glucose utilization in non-rapid eye movement sleep. *Nature* **297**: 325–327, 1982
13. McGinty D and Szymusiak R: The basal forebrain and slow wave sleep: Mechanistic and functional aspects. *In*: *Slow Wave Sleep: Physiological, Pathophysiological and Functional Aspects*, ed. Wauquier A, Dugovic C, and Radulovacki M, Raven Press, New York, pp 61–74, 1989
14. McGinty D and Szymusiak R: Keeping cool: A hypothesis about the mechanisms and functions of slow wave sleep. *Trends Neurosci* **13**: 480–487, 1990
15. Boulant JA: Hypothalamic control of thermoregulation: neurophysiological basis. *In*: *Handbook of Hypothalamus*, ed. Morgane PJ and Panksepp J, Dekker, New York, Vol. 3A, pp 1–82, 1980
16. Roberts WW, Bergquist EH, and Robinson TCL: Thermoregulatory and sleep-like relaxation induced by local warming of the preoptic area in opossum. *J Comp Physiol Psychol* **67**: 182–188, 1969
17. Sakaguchi S, Glotzbach SF, and Heller HC: Influence of hypothalamic and ambient temperatures on sleep in kangaroo rats. *Am J Physiol* **237**: R80–R88, 1979
18. Szymusiak R and McGinty D: Sleep-related neuronal discharge in the basal forebrain of cats. *Brain Res* **370**: 82–92, 1986
19. Szymusiak R and McGinty D: Sleep-waking discharge of basal forebrain projection neurons in cats. *Brain Res Bull* **22**: 423–430, 1989
20. Koyama Y and Hayaishi O: Modulation by prostaglandins of activity of sleep-related neurons in the preoptic/anterior hypothalamic areas in rats. *Brain Res Bull* **33**: 367–372, 1994
21. Glotzbach SF and Heller HC: Thermoregulation. *In*: *Principles and Practice of Sleep Medicine*, ed. Kryger MH, Thomas R, and Dement WC, WB Saunders Company, Philadelphia, pp 300–309, 1989

22. Cabanac M, Hildebrandt G, Massonnet B, and Strempel H: A study of the nycthemeral cycle of behavioural temperature regulation in man. *J Physiol (Lond)* **257**: 275–291, 1976
23. Froberg JE: Twenty-four-hour patterns in human performance, subjective and physiological variables and differences between morning and evening active subjects. *Biol Psychol* **5**: 119–134, 1977
24. Schmidt RF: *Fundamentals of Sensory Physiology*, Springer Verlag, Berlin, 1978
25. Richardson GS, Carkadon MA, Orav EJ, and Dement WC: Circadian variation in sleep tendency in elderly and young adult subjects. *Sleep* **5**: S82–S94, 1982
26. Nakao M, McGinty D, Szymusiak R, and Yamamoto M: Dynamical features of thermoregulatory model of sleep control. *Jpn J Physiol* **45**: 311–326, 1995
27. Lavie P and Scherson A: Ultrashort sleep-waking schedule. I. Evidence of ultradian rhythmicity in “sleepability.” *Electroencephalogr Clin Neurophysiol* **57**: 35–42, 1981
28. Strogatz SH, Kronauer RE, and Czeisler CA: Circadian regulation dominates homeostatic control of sleep length and prior wake length in humans. *Sleep* **9**: 353–364, 1986
29. Åkerstedt T and Gillberg M: The circadian variation of experimentally displaced sleep. *Sleep* **4**: 159–169, 1981
30. Zulley J, Wever R, and Aschoff J: The dependence of onset and duration of sleep on the circadian rhythm of rectal temperature. *Pflügers Arch* **391**: 314–318, 1981
31. Franken P, Tobler I, and Borbély AA: Sleep and waking have a major effect on the 24-h rhythm of cortical temperature in the rat. *J Biol Rhythms* **7**: 341–352, 1992
32. Kawato M, Fujita K, Suzuki R, and Winfree AT: A three oscillator model of the human circadian system controlling the core temperature rhythm and the sleep-wake cycle. *J Theor Biol* **98**: 369–392, 1982
33. Strogatz SH: Human sleep and circadian rhythms: A simple model based on two coupled oscillators. *J Math Biol* **25**: 327–347, 1987
34. Borbély AA: A two-process model of sleep regulation. I. Physiological basis and outline. *Human Neurobiol* **1**: 195–204, 1982
35. Moore-Ede MC, Sulzman FM, and Fuller CA: *The Clocks That Time Us*, Harvard University Press, Cambridge, pp 134–135, 1982
36. Lavie P: Ultrashort sleep-waking schedule: III. Gates and “forbidden zones” for sleep. *Electroencephalogr Clin Neurophysiol* **63**: 414–425, 1986
37. Berger RJ: Slow wave sleep, shallow torpor, and hibernation: Homologous states of diminished metabolism and body temperature. *Biol Psychol* **19**: 305–326, 1984