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Human sleep and circadian rhythms: a simple model based on two coupled oscillators*

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Abstract. We propose a model of the human circadian system. The sleep–wake and body temperature rhythms are assumed to be driven by a pair of coupled nonlinear oscillators described by phase variables alone. The novel aspect of the model is that its equations may be solved analytically. Computer simulations are used to test the model against sleep–wake data pooled from 15 studies of subjects living for weeks in unscheduled, time-free environments. On these tests the model performs about as well as the existing models, although its mathematical structure is far simpler.

Key words: Sleep — Circadian — Human — Model — Oscillator

1. Introduction

In the first half of this decade, the time seemed ripe for mathematical modeling of the human sleep–wake cycle. Czeisler [8, 9] and Wever [38] had recently summarized the results of years of "free-run" experiments, in which subjects had lived alone for weeks or even months in clockless chambers, eating and sleeping when they pleased, isolated from the external light–dark cycle and the other 24-h periodicities of the outside world. The experimental data revealed some striking and unexpected regularities in the timing of the subjects' spontaneous sleep episodes, leading Winfree [42] to write: "A Rosetta Stone has appeared in our midst . . .".

In this atmosphere of excitement, a number of mathematical models were born [12, 22, 26, 27, 31, 34, 35, 43]. All postulated at least a pair of oscillators in order to explain the phenomenon of "spontaneous internal desynchronization" [1, 8, 38] between the sleep–wake cycle and various autonomic circadian rhythms. During internal desynchronization, a free-running subject unknowingly lives on a "day" which is 30–50 h long, while body temperature and neuroendocrine variables controlled by the circadian pacemaker continue to oscillate with a stable

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period of 24–25 h. This strange phenomenon has no counterpart in ordinary life. In the outside world, the dual oscillator structure of the circadian system is concealed — for those of us on a regular schedule, the circadian and sleep–wake rhythms are typically phase-locked to one another and to the 24-h environment.

It is only during a disruption of our usual schedule, as a result of jet lag or a rotating shift work schedule, that the interplay among the sleep–wake cycle, the circadian cycle and the environment becomes all too apparent. The effects of jet lag, shift work schedules, and insomnia have great clinical and economic importance, affecting millions of people each year [30], and these provide some of the principal motivations for research on human sleep and circadian rhythms.

Since the initial flurry of theoretical work on the sleep–wake cycle, the debates between the proponents of the various models have been lively [24, 28, 39, 42] but little consensus has emerged. There seem to be two obstacles. First, the authors have tested their models against different sets of data, and have expressed doubts about the reliability of the data used by others. In an attempt to remedy this problem, we have recently reanalyzed much of the world literature on internal desynchronization [34, 36], the one phenomenon which all modelers consider to be of prime theoretical importance. The rules of sleep–wake timing extracted from those data will be used often in what follows.

A second obstacle in the way of consensus is that most of the existing models have a nonlinear mathematical structure, rendering analytical work difficult and forcing one to resort to comparing computer simulations against actual experimental records. Even when the match between theory and experiment appears good, one is left wondering — does the accuracy of the fit reveal some essential "correctness" of the model, or could alternative models have done as well?

The purpose of this article is to propose a simple model of the human sleep–wake cycle. It is not intended to be realistic in detail, but only to capture the key features of the experimental phenomena. The novel aspect of the model is that its equations may be solved exactly. The resulting analytical transparency allows us to sort out which of the observed phenomena follow from simple mathematical considerations alone, as distinct from those which require some additional biological explanation.

The remainder of this paper is organized as follows. Section 2 reviews the main findings of free-run experiments. In Sect. 3, we propose and analyze a new model of the human sleep–wake cycle. It is tested against both data and other models in Sect. 4. The discussion in Sect. 5 indicates the limitations of the present study, its relation to earlier work, and directions for future research.

The analysis presented in this paper is drawn from my doctoral thesis, published as [34]. In particular, Sect. 3 and the Appendices are taken essentially verbatim from [34], pp. 157–171. Section 4 is a synopsis of results discussed in [35] and in Chap. 7 of [34].

2. Experimental background

Free-run studies of human subjects began in the 1960's [1, 32] following a decade of vigorous research on circadian rhythms in plants and animals. The free-run

protocol is designed to highlight the endogenous generation of circadian rhythms by shielding the organism from 24-h time cues and environmental cycles. Only after this simplest situation is understood does one try to characterize the influence of the light-dark cycle and other external synchronizers on the circadian system.

Figure 1 shows the sleep-wake record of one of the longest free-run studies ever conducted [33]. In that experiment, Michel Siffre spent six months alone in a cave. His account of that harrowing experience [33] is unforgettable reading, including encounters with bat guano, mice, near-suicidal depression, and an electrical shock delivered through cardiac electrodes that he happened to be wearing during a lightning storm. All in the name of science — Siffre was himself the leader of the research team, as well as the subject.

As shown in Fig. 1, for the first 35 days of the experiment, Siffre lived on a fairly regular 26-h schedule, rising and retiring about two hours later each day. On day 37, he unintentionally skipped his expected bedtime, and stayed up for several extra hours. He then slept and slept. This odd pattern of long wakes and sleeps occurred intermittently for the next month. Spontaneously on day 63 he reverted to the 26-h "day". After 9 more weeks, "wild variations" [33] appeared again on day 130, and continued in a "seemingly random pattern" for 20 days.

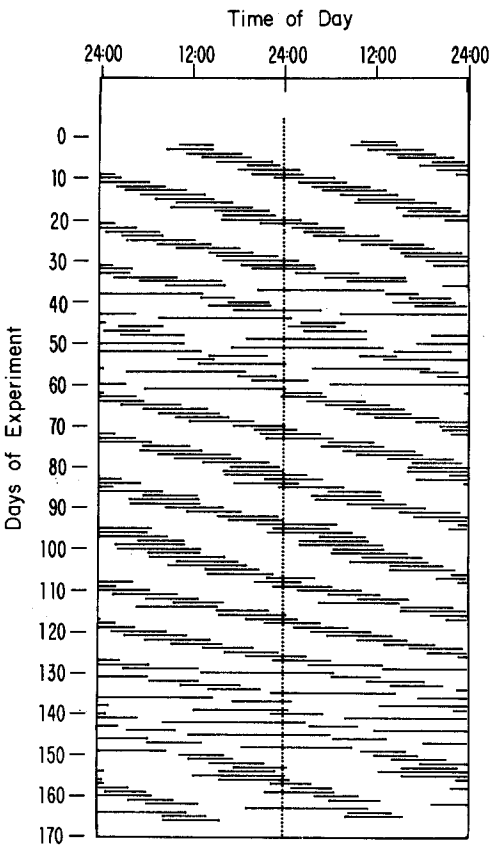

Fig. 1. Sleep-wake record of Siffre's [33] time-isolation study in Midnight Cave, Texas, 1972. *Black bars* represent time when subject was asleep. Each sleep episode is plotted twice: beneath the previous episode and also to the right of it. This "double raster-plot" emphasizes the continuity in the data across the artifactual edge at 24:00 h. Internal desynchronization occurs spontaneously after day 37 and again after day 130 (see text)

These again gave way (day 150) to a 26-h day, which persisted until the end of the experiment.

The means for decoding records such as Fig. 1 have been furnished by Czeisler [8, 9] and Wever [38]. They and their colleagues have conducted free-run experiments in settings far more hospitable than Siffre's cave — their experiments take place in soundproofed, windowless apartments. The subjects in Czeisler's studies have their rectal temperature recorded continuously. Tiny samples of blood are drawn frequently through an indwelling catheter and monitored for hormone levels, and the subjects' brain waves are recorded while they sleep.

Czeisler's work [8, 9] demonstrates that the circadian cycle, most prominently marked by the body temperature rhythm, is the key to deciphering the timing of sleep-wake patterns in free-run. For example, the minimum of the temperature cycle has been shown to coincide with a time of minimum alertness and a maximum tendency to fall asleep [9]. Free-running subjects usually go to bed when their temperature cycle reaches its trough — in this case, the sleep-wake and temperature rhythms remain "internally synchronized" even though external synchronization to the 24-h clock has been lost. In Fig. 1, the first 35 days correspond to a state of internal synchronization.

Even when the sleep-wake cycle spontaneously desynchronizes from the circadian temperature cycle, there is still an ongoing circadian modulation of sleep. To emphasize this modulation, the records of four of Czeisler's [8] desynchronized subjects have been replotted on a circadian basis (Fig. 2). Each record is plotted modulo the period of the subject's circadian temperature cycle, with phase 0 defined as the mid-trough of the subject's average temperature cycle. Thus points on the same vertical line correspond to the same phase of the circadian cycle.

It now becomes apparent that there are regularities which are consistent across internally desynchronized subjects: (1) Long sleep episodes begin near high temperature, and shorter sleep episodes begin near the temperature trough. (2) Almost all awakenings occur on the rising limb of the temperature cycle, and practically none occurs in the quarter-cycle before the temperature minimum. (3) Many sleep episodes begin at one of two peak phases in the circadian cycle — near the temperature trough, or just before the temperature maximum. There are also two zones (stippled bands) in which the subjects rarely fall asleep.

These and other regularities were found [34] to be present throughout the world literature on internally desynchronized subjects. Four such regularities are shown in Fig. 3, which contains data pooled from 15 desynchronized subjects [36]. Notice that the durations of sleep, prior wakefulness, and the wake-sleep cycle are all highly dependent on the phase of the circadian cycle at bedtime. For example, when bedtime occurs near the phase of maximum temperature, the preceding wake episode (Fig. 3b) and the subsequent sleep episode (Fig. 3a) both tend to be long, and hence they sum to a long wake-sleep cycle length (Fig. 3c). Other interesting features of Figs. 3a-c are the steep vertical sections of data, representing phases at which sleep or wake durations are discontinuous or even double-valued [15, 36, 43].

In the next section, we show that a simple model can illuminate these empirical relationships. In particular, the relation between sleep length and circadian phase of sleep onset (Fig. 3a) is discussed as a test case in Sect. 3.5.

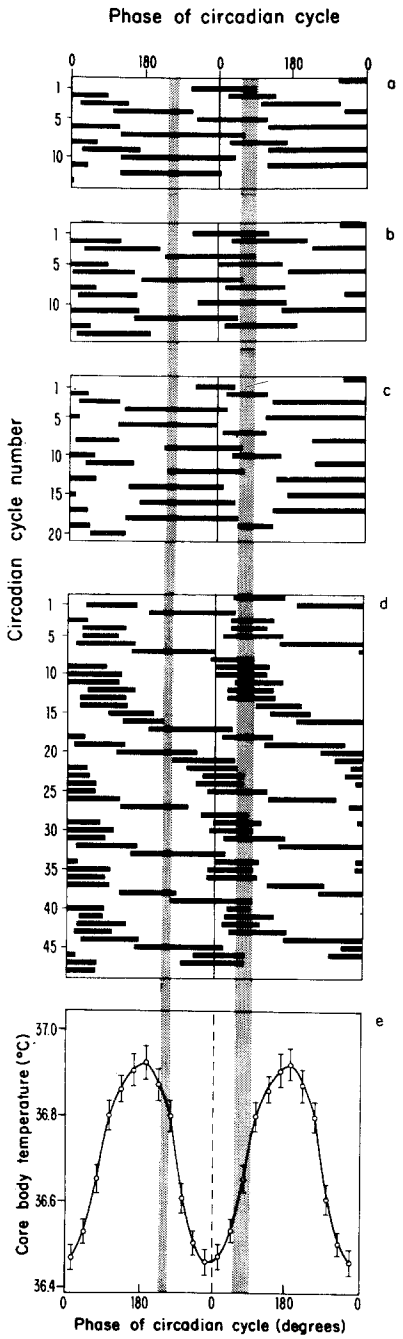

Fig. 2 a–d. Double raster plots of four of Czeisler's [8] internally desynchronized subjects. As in Fig. 1, *black bars* represent sleep. Rasters are normalized with respect to period and phase of each subject's average temperature rhythm, to show relation of sleep timing and duration relative to circadian temperature cycle. *Stippled bands* show zones where subjects rarely fall asleep. **e** Average waveform of body temperature (mean ± standard error) for the four subjects of **a–d**

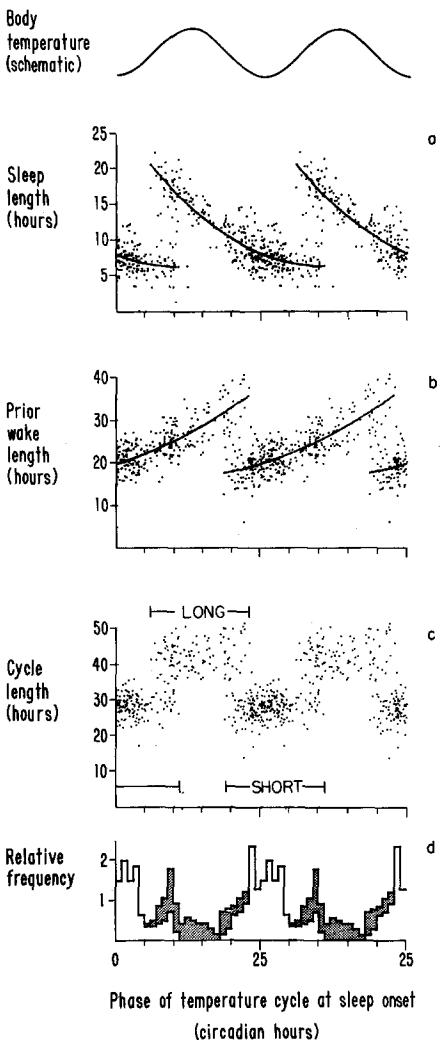

Fig. 3 a–d. The phase of the circadian temperature cycle at bedtime is related to: **a** the length of the subsequent sleep episode; **b** the length of the preceding wake episode and **c** the combined wake-sleep cycle length. **d** Sleep onsets are distributed bimodally in the circadian cycle. A frequency of 1 corresponds to the mean across all phases. The *shaded* and *open parts* of the histogram correspond to the LONG and SHORT cycles in **c**, respectively. Here and henceforth, period of average temperature cycle is divided into 25 "circadian hours". $N = 359$ sleep episodes, pooled from 15 subjects listed in [36] (Reprinted from [36], with permission)

3. PHASE model

3.1. Introduction

We now propose one of the simplest possible differential equation models of the human circadian system. It is based on two pacemakers, one manifested by the circadian rhythm of body temperature and the other by the sleep-wake cycle. The pacemakers are assumed to be coupled in such a way that each accelerates or slows the other, depending only on their mutual phase relation. Because this model ignores such variables as amplitude and considers only phase, it will be called the PHASE model.

The mathematical simplicity of our model stems from the assumptions that its constituent oscillators have circular state spaces and that they interact through phase differences only. This convenient mathematical structure has been exploited

by modelers of various physiological oscillations. To mention just a few examples, phase models have been proposed in the context of circadian activity rhythm splitting in rodents [13, 21, 25], flashing rhythms of fireflies [17], frequency plateaus in the intestine [16], and swimming rhythms controlled by central pattern generators in fish [7, 23]. The model presented here extends this approach to human sleep and circadian rhythms.

3.2. Model structure

The structure of the PHASE model is summarized in Fig. 4. The phases of the two oscillators are denoted θ_1, θ_2. Although the phases are real numbers, we often regard them as points on the circle of unit circumference. The governing equations are

$$\dot{\theta}_1 = \omega_1 - C_1 \cos 2\pi(\theta_2 - \theta_1) \tag{1a}$$

$$\dot{\theta}_2 = \omega_2 + C_2 \cos 2\pi(\theta_1 - \theta_2) \tag{1b}$$

where

ω_1, ω_2 are intrinsic frequencies

and

C_1, C_2 are coupling strengths.

The overdot signifies time differentiation. All the parameters are taken to be non-negative. The chosen form of the coupling is such that the first oscillator slows down and the second speeds up when they are in phase. This property is suggested by the observed modulations of sleep-wake cycle lengths (e.g. Fig. 2d) as the activity and temperature rhythms cross through each other during internal desynchronization.

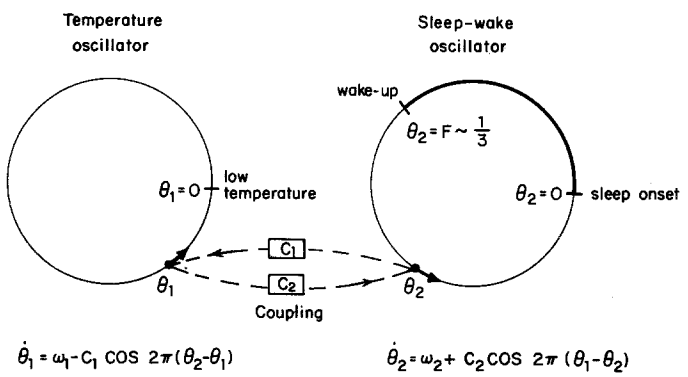

Fig. 4. Structure of the PHASE model. Sleep-wake and temperature rhythms are controlled by different "phase-only" oscillators, but these oscillators are coupled. Low temperature occurs when $\theta_1 = 0$ and sleep occurs when $0 \leq \theta_2 \leq F$, where F is a parameter controlling the sleep fraction. Note that all phases are regarded as real numbers (mod 1)

We adopt the conventions that oscillator # 1 drives the circadian temperature rhythm and oscillator # 2 drives the sleep-wake cycle. Sleep is defined to occupy some fraction F of the θ_2 circle:

$$\begin{aligned} \theta_2 &= 0 \quad \text{at sleep onset} \\ \theta_2 &= F \quad \text{at wake-up.} \end{aligned} \tag{2}$$

Here $0 \leq F \leq 1$, and typically $F \sim 1/3$, since people sleep about a third of the time. Since sleep onset during internal synchrony occurs near low temperature [8, 38], we take $\theta_1 = 0$ as circadian phase 0, the minimum of the endogenous temperature cycle.

3.3. Synchrony

To study the synchronization and desynchronization of the constituent oscillators, consider the phase difference

$$\psi = \theta_1 - \theta_2. \tag{3}$$

Subtracting the equations in (1) we see

$$\dot{\psi} = \Omega - C \cos 2\pi\psi \tag{4}$$

where

$$\Omega = \omega_1 - \omega_2 \tag{5a}$$

$$C = C_1 + C_2 > 0. \tag{5b}$$

Here Ω is the difference of the intrinsic frequencies of the two oscillators and C is the total coupling in the system.

Synchrony is enforced when the total coupling C is larger than the magnitude $|\Omega|$ of the frequency difference, so that $\dot{\psi} = 0$ has a solution. Otherwise the phase-difference ψ continues to grow as one oscillator periodically overtakes the other. This desynchronized case will be considered in Sect. 3.4. For now consider the synchronized case, i.e., assume

$$k = \left| \frac{C}{\Omega} \right| > 1. \tag{6}$$

Then the internally synchronized phase relation ψ^* is obtained by solving (4) for $\dot{\psi} = 0$:

$$\psi^* = \pm \frac{1}{2\pi} \cos^{-1}\left(\frac{\Omega}{C}\right). \tag{7}$$

These are two solutions implicit in (7); the stable one is that for which $d\dot{\psi}/d\psi < 0$. Here the range of $\cos^{-1}$ is taken as $[0, \pi]$, so

$$\psi^* = (-1/2\pi) \cos^{-1}(\Omega/C) \tag{8}$$

is the stable solution.

Using (7) we can also find the "compromise" frequency ω^* adopted by the synchronized system. During internal synchrony (1) becomes

$$\dot{\theta}_1 = \omega_1 - C_1\left(\frac{\Omega}{C}\right) \tag{9a}$$

$$\dot{\theta}_2 = \omega_2 + C_2\left(\frac{\Omega}{C}\right). \tag{9b}$$

Since $\dot{\theta}_1 = \dot{\theta}_2 = \omega^*$ during synchrony, either of these two expressions simplifies to

$$\omega^* = \frac{C_1\omega_2 + C_2\omega_1}{C_1 + C_2}. \tag{10}$$

This frequency differs from the intrinsic frequencies ω_1 and ω_2 by amounts $\Delta\omega_1$ and $\Delta\omega_2$:

$$\Delta\omega_1 = \omega^* - \omega_1 = -C_1\Omega/C \tag{11a}$$

and

$$\Delta\omega_2 = \omega^* - \omega_2 = C_2\Omega/C. \tag{11b}$$

Note that during synchrony the oscillators' frequencies are shifted from their intrinsic values in proportion to the coupling strengths:

$$\left|\frac{\Delta\omega_1}{\Delta\omega_2}\right| = \left|\frac{C_1}{C_2}\right|. \tag{12}$$

Estimates of the absolute magnitudes of the parameters C_1, C_2, for human subjects are obtained in Appendix A.

3.4. Desynchrony

Equation (4) corresponds to desynchrony when $k<1$, i.e. when $C<|\Omega|$. The phase difference ψ between the oscillators always increases, sometimes slowly and sometimes rapidly, exhibiting what circadian biologists call "internal relative coordination" [8, 38]. The oscillators periodically move through a full cycle of mutual phase relations, with a "beat" frequency β, obtained as follows. From (4) the time required for ψ to change from 0 to 1 is $1/\beta$, given by

$$\begin{aligned} 1/\beta &= \int_0^{1/\beta} dt = \int_0^1 \frac{d\psi}{\Omega - C\cos 2\pi\psi} \\ &= (\Omega^2 - C^2)^{-1/2}. \end{aligned} \tag{13}$$

(For a derivation of the beat frequency, see Appendix B.) Hence the beat frequency β satisfies

$$\begin{aligned} \beta &= (\Omega^2 - C^2)^{1/2} \\ &= \Omega\left(1 - \frac{C^2}{\Omega^2}\right)^{-1/2}. \end{aligned} \tag{14}$$

Two special cases:

(i) For $C = 0$, the beat frequency reduces to $\beta = \Omega = \omega_1 - \omega_2$, the noninteractive beat frequency.

(ii) As $C \to |\Omega|$, $\beta \to 0$ according to a square root dependence (14). Thus the tendency to synchronize grows rapidly as C approaches the critical coupling.

An analytically convenient special case of the model is that in which $C_1 = 0$, i.e. there is no feedback onto the circadian pacemaker. As discussed in Appendix A this is a reasonable first approximation, and it will be assumed in what follows.

Let the arbitrary zero of time be chosen such that $\theta_1(0) = 0$. Then scaling time such that

$$\omega_1 = 1 \tag{15}$$

we obtain

$$\theta_1(t) = t. \tag{16}$$

As shown in Appendix B, Eq. (4) may be solved exactly to yield a complicated (but monotonic and hence invertible) function $\psi(t)$. Rather than writing this function explicitly here, it will be referred to simply as $\psi(t)$.

Having solved for $\theta_1(t)$ and $\psi(t)$, we obtain $\theta_2(t)$:

$$\begin{aligned} \theta_2(t) &= \theta_1(t) - \psi(t) \\ &= t - \psi(t). \end{aligned} \tag{17}$$

3.5. Model prediction of an empirical relationship

It would be pleasant if the model's predictions of various empirical relations could be extracted *explicitly* from the solutions to the model equations. Unfortunately, only *implicit* solutions are possible. For example, consider the model's prediction of the dependence of the duration ρ of the sleep episode on the phase ϕ_s of the circadian temperature cycle at sleep onset. As discussed briefly in Sect. 2 (Fig. 3a) the experimental finding is that sleep episodes beginning near the temperature trough tend to be short (~7 h), while those beginning near the temperature maximum are long (~15 h). The robustness of this $\phi_s : \rho$ relationship came as a surprise, and has been discussed extensively in the literature [9, 15, 22, 36, 41-44]. Many theoreticians have used it as a benchmark to test their models [11, 12, 22, 26, 35, 43]. Hence it is of interest to derive the form of the $\phi_s : \rho$ relationship predicted by the PHASE model.

According to the conventions established in (2), sleep duration ρ is given by the time required for θ_2 to move from 0 to F. The circadian phase ϕ_s of sleep onset is given by θ_1 when $\theta_2 = 0$. To calculate the $\phi_s : \rho$ relationship it is most convenient to choose a new origin of time, with $t = 0$ at sleep onset, i.e.

$$\theta_2(0) = 0 \tag{18a}$$

$$\theta_1(0) = \phi_s \tag{18b}$$

$$\psi(0) = \theta_1(0) - \theta_2(0) = \phi_s. \tag{18c}$$

Now to find the time at which wake-up occurs, we seek ρ such that

$$\theta_2(\rho) = F \tag{19a}$$

$$\theta_1(\rho) = \phi_s + \rho \tag{19b}$$

$$\psi(\rho) = \phi_s + \rho - F. \tag{19c}$$

Together (18c) and (19c) constitute an implicit set of equations for ρ, as a function of ϕ_s and F. Because of the trigonometric form of ψ (see Eqs. (B14), (B15) of Appendix B), the solution for ρ requires graphical or numerical techniques.

One such graphical method is indicated in Fig. 5. As shown in Sect. 3.4 and Appendix B, the governing equations, with $C_1 = 0$, may be integrated exactly to yield the curves $\theta_2(t)$ and $\psi(t)$. Initial conditions were $\theta_1(0) = \theta_2(0) = 0$, and the integration continued until all mutual phase relations ψ between 0 and 1 had been attained. Thus all possible circadian phases of sleep onset are attained, since $\phi_s = \psi$ when $\theta_2 = 0$. To find $\rho(\phi_s)$, we follow a multi-step procedure (Fig. 5):

(i) Choose ϕ_s, the phase of sleep onset.

(ii) Find t_s such that $\psi(t_s) = \phi_s$. This is always possible since ψ is invertible.

(iii) Regarding t_s as the time of sleep onset, find (the first) t_w such that $\theta_2(t_w) = \theta_2(t_s) + F$.

(iv) Thus t_w represents the time of wake-up and so $\rho = t_w - t_s$. As Fig. 5b reveals, long sleeps arise when the phase of mid-sleep falls near the inflection point of $\theta_2(t)$. Thus the longest sleeps are predicted to begin in the first half of the circadian cycle (Fig. 5c), as observed in real data (Fig. 3a). Figure 5c also mimics the sheared sinusoidal shape of the observed $\phi_s : \rho$ relation (Fig. 3a).

The steps of the graphical construction can be summarized in terms of ψ^{-1} and θ_2^{-1}, the inverse functions to $\psi(t)$ and $\theta_2(t)$, respectively. (We have not yet shown that θ_2 is invertible — see Appendix B for the conditions under which it

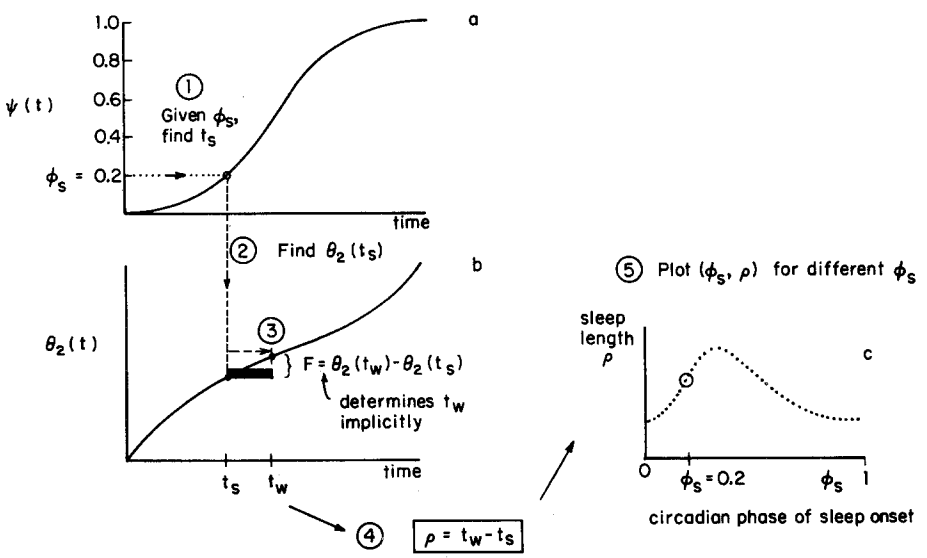

Fig. 5 a–c. Graphical construction of $\phi_s : \rho$ relationship in PHASE model. The method is illustrated for $\phi_s = 0.2 \sim 5$ h after the temperature minimum. **a** The time t_s corresponding to $\phi_s = 0.2$ is located on the $\psi(t)$ curve. **b** The phases $\theta_2(t_s)$ and $\theta_2(t_s) + F$ are obtained. They represent the beginning and end of sleep. Wake-up occurs at $t = t_w$; hence sleep length $\rho = t_w - t_s$. **c** The point (ϕ_s, ρ) is plotted, for a sequence of different ϕ_s values. Compare Fig. 3a

is.) For notational simplicity, let

$$g = \psi^{-1} \quad \text{and} \quad h = \theta_2^{-1}. \tag{20}$$

From step (ii) above,

$$g(\phi_s) = t_s. \tag{21}$$

From step (iii),

$$t_w = h(\theta_2(t_s) + F) = h(\theta_2(g(\phi_s)) + F). \tag{22}$$

Thus

$$\rho(\phi_s) = h(\theta_2(g(\phi_s)) + F) - g(\phi_s). \tag{23}$$

Equation (23) is the first instance of an exact expression for the $\phi_s : \rho$ relation derived from a mathematical model of the sleep-wake cycle.

4. Testing the PHASE model against data and other models

4.1. Strategy

In this section the PHASE model is tested against experimental data on the timing and duration of sleep episodes recorded during internally desynchronized free-run (see Sect. 2). To gain perspective on the model's performance, we compare its predictions to those of the two leading models [12, 26], both of which are more sophisticated than the PHASE model. For the sake of further comparison, we also include the predictions of a fourth model, which is even simpler than the PHASE model.

Other authors have not attempted this sort of comparative analysis, but we believe it yields certain important insights not otherwise available. For example, both Kronauer et al. [26] and Daan et al. [12] claim that their models provide a good fit to the data (Fig. 3a) relating sleep duration to circadian phase of sleep onset [9, 36, 44]. The problem is that we have no way of knowing *a priori* whether that test is a discriminating one — perhaps many other models could do as well. A comparative analysis allows us to distinguish mild tests from stringent ones, and provides a rational basis for the evaluation of models.

Because such a comparative analysis of models of the sleep-wake cycle is presented in detail elsewhere [34, 35], only a brief discussion is offered here. It begins with a review of the other models and then tests them against data on the duration of sleep, the timing of wake-up, and the timing of sleep onset.

4.2. Other models of internal desynchronization

The model of Kronauer et al. [26, 27] postulates that the human circadian system is dominated by two mutually coupled, weakly nonlinear van der Pol oscillators,

x and y. The circadian pacemaker (x) strongly influences the sleep-wake rhythm generator (y), and receives feedback from it which is small but significant. Desynchronization between x and y occurs as a result of an assumed spontaneous lengthening of the intrinsic period of y. The main difference between this model and the PHASE model is that the van der Pol oscillators x and y have more degrees of freedom (amplitudes as well as phases) and consequently richer dynamical behavior (for example, the possibility of "phase-trapping", in which x and y have the same average period but periodically varying phase-difference).

The model of Daan, Beersma, and Borbély [2, 3, 11, 12] contains a circadian pacemaker (C) which corresponds to oscillator # 1 of the PHASE model and the x-oscillator of Kronauer's model. It is the treatment of the sleep-wake oscillator (S) which distinguishes the model of Daan et al. from other models. Process S is an integrate-and-fire or relaxation oscillator — S builds up during wakefulness until it strikes a threshold which triggers sleep onset. Then S declines until it strikes a wake-up threshold, and the cycle repeats. Both thresholds are modulated by the circadian oscillator C and subjected to some random jitter in their mean levels. Desynchronization between C and S occurs as a result of an assumed weakening of the circadian modulation of the thresholds.

The final model of internal desynchronization to be considered here is called BEATS [34, 35] because it models desynchronization as a beat phenomenon between two sine waves. These sinusoids represent the outputs of two circadian oscillators of different frequencies, and they are added in different proportions to yield the activity-rest rhythm (A) and the circadian temperature rhythm (T). This simple model was suggested by Wever ([38], p. 229) as a pedagogical example to demonstrate that many phenomena observed in desynchronization do not require dynamical coupling of the two oscillators, but merely an output summation. Whereas Wever [38] assumed that sleep occurs when A falls below some level A_0, we assume that sleep occurs in a certain wedge of $(A, \dot{A})$, phase space [34, 35].

For brevity, the models shall henceforth be called PHASE, KRONAUER, DAAN, and BEATS. We also consider a slightly MODIFIED DAAN model involving a change in a parameter value. The ranges of all parameters used in the computer simulations presented here have been reported in [34, 35].

We now summarize the method by which the models were tested (see [34] for further description.) Five simulations of 50 sleep-wake cycles each were run for all the models, except the DAAN model, for which six simulations of 45 cycles were performed. Each of the simulations explored a different degree of internal desynchronization. The circadian period was fixed at 25 h, but sleep-wake cycle periods were chosen in the range 29–41 h. The intrinsic period of the sleep-wake cycle was always fixed within a simulation, but varied across simulations. In the DAAN and MODIFIED DAAN model, the same effect was produced by altering the mean level of the sleep-wake thresholds. Moreover, in the BEATS and PHASE models, the coupling from the circadian oscillator to the sleep-wake oscillator decreased linearly throughout the simulation, to allow a more general view of the behavior of these simple models.

The resulting simulations were then pooled and compared to experimental data, as discussed next.

4.3. *Duration of sleep*

Figure 6 shows the $\phi_s : \rho$ relationships (Sect. 3.5) predicted by the models as well as the observed data pooled from 15 desynchronized subjects (Fig. 3a and [34–36]). The quadratic arc which was fit to the data has been replotted in each panel to aid comparison between theory and experiment.

All the models are able to simulate the general shape of the $\phi_s : \rho$ relationship. Yet only MODIFIED DAAN produces anything like a quantitative fit — DAAN is too short at all phases, KRONAUER is too long. BEATS predicts that for sleeps beginning during the temperature trough, sleep length ρ is nearly independent of phase ϕ_s, instead of decreasing as in the observed data. PHASE predicts that the $\phi_s : \rho$ relation is most variable near the temperature maximum and tightest near the trough, whereas the data show the opposite trend.

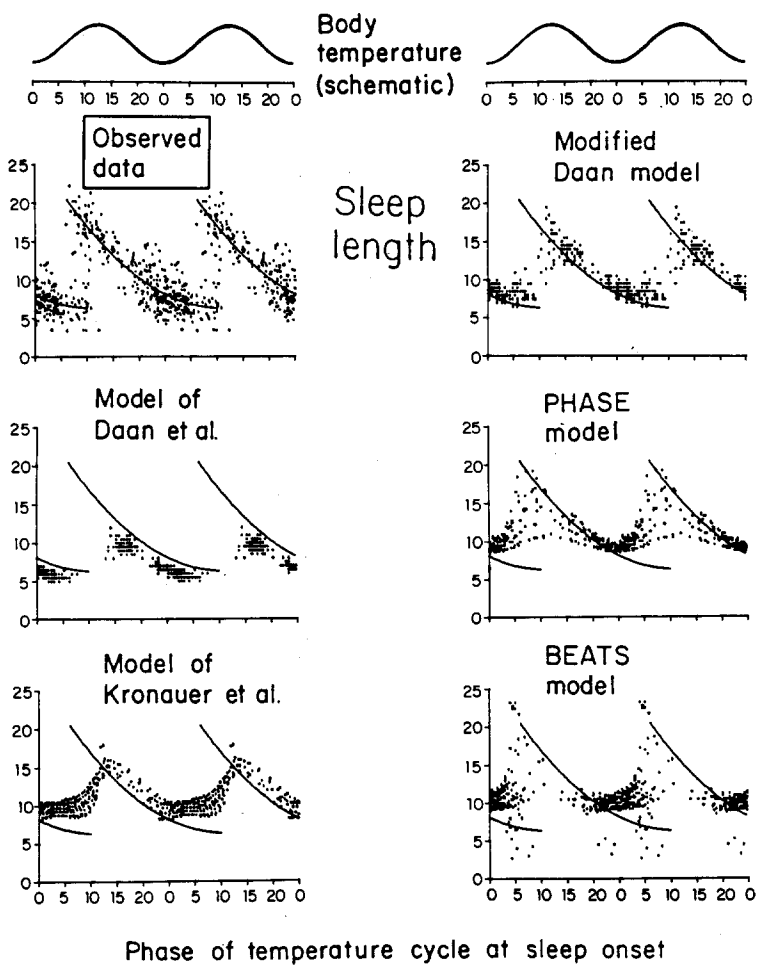

Fig. 6. Observed data and model predictions of $\phi_s : \rho$ relationships. A quadratic arc was fit to the data by the method of least squares, as in Fig. 3a, and then reproduced in each panel for easier comparison between theory and experiment

4.4. *Timing of wake-up*

Winfree [41–43] has emphasized the existence of a zone in the circadian cycle when spontaneous wake-up is "forbidden". It occurs just before the temperature minimum and is about 6 h wide (Fig. 7). About 85% of all awakenings occur on the rising limb of the circadian cycle [9, 34], which thus seems to signal the ringing of the body's internal alarm clock.

This regularity is well simulated by the simple models PHASE and BEATS, and also by MODIFIED DAAN. However, note that DAAN produces an unrealistic bimodal distribution, while KRONAUER generates a peak frequency of only 1.5 times the mean across all phases, which is too low.

4.5. *Timing of sleep onset*

The frequency distribution of sleep onsets in the circadian cycle is bimodal (Fig. 3d), with one peak near the temperature trough and a second peak about 9 h later. In the ordinary 24-h world, the phase of this second peak would coincide with the time of afternoon napping [34], suggesting that the siesta common in many cultures is at least in part biologically based [4, 37].

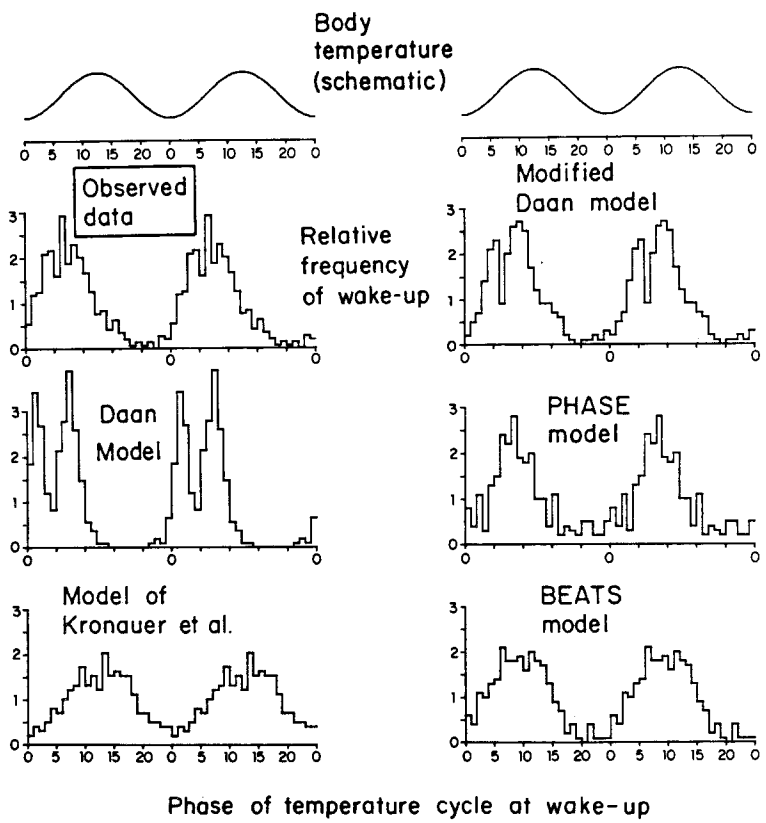

Fig. 7. Observed data and model predictions of distribution of spontaneous awakenings, relative to circadian temperature cycle. A frequency of 1 corresponds to the mean across all phases

The bimodal distribution of sleep onsets poses a stringent test of models (Fig. 8). PHASE, BEATS, and KRONAUER incorrectly predict a unimodal distribution, a deficiency which stems from the lack of a significant second harmonic component in these models. DAAN and MODIFIED DAAN generate bimodal distributions but with the nap peak incorrectly phased after the temperature maximum instead of before it, as in the observed data.

4.6. Summary

The PHASE model captures the qualitative features of the observed timing and duration of sleep. It correctly predicts the shape of the $\phi_s : \rho$ relation (Fig. 6), the unimodality of the wake-up distribution (Fig. 7), and the tendency for sleep episodes to begin near the temperature trough (Fig. 8). In these respects it performs about as well as DAAN [11, 12] and KRONAUER [26, 27], the two leading models of the human circadian system.

However, none of these models achieves quantitative accuracy when tested against sleep duration data (Fig. 6) or the bimodal distribution of sleep onsets (Fig. 8). On the whole, the MODIFIED DAAN model [12, 34, 35] appears to be

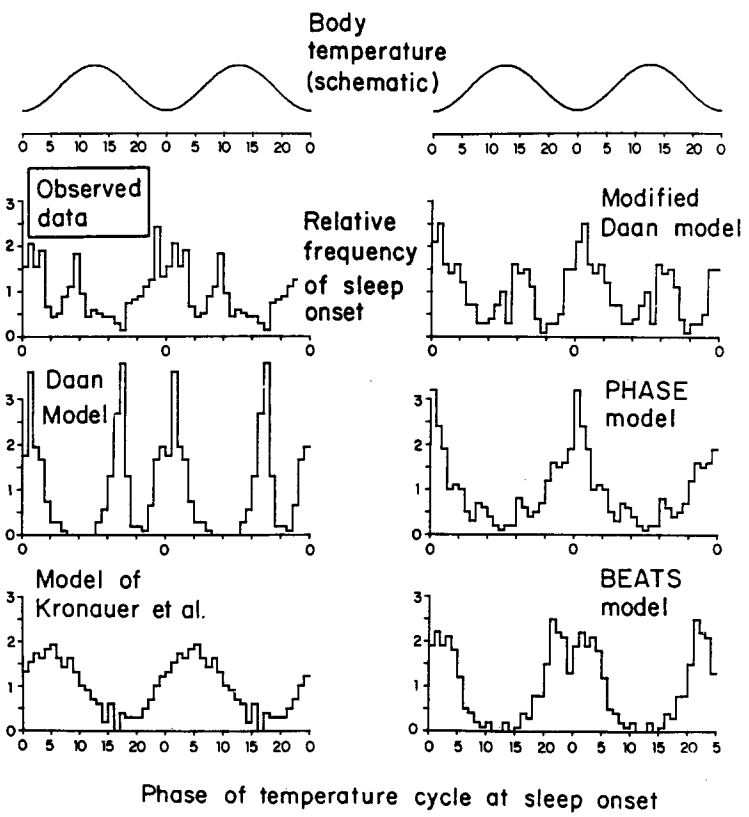

Fig. 8. Observed and predicted distributions of sleep onsets in the circadian cycle. A frequency of 1 corresponds to the mean across all phases. Compare Fig. 3d

the most accurate model of the sleep-wake cycle during internal desynchronization.

5. Discussion

We have shown that a simple model of the human sleep-wake cycle can account for a variety of phenomena observed in temporal isolation experiments. The model proposed here is the first analytically tractable model of the human circadian system, yet its performance is comparable to that of more elaborate models proposed by others [12, 22, 26, 40].

However there are a number of limitations in the present study. First, we have concentrated on the *autonomous* sleep-wake dynamics revealed in free-run experiments. While this is a necessary first step, one would ultimately like to address the *entrainment* of the human circadian system by external synchronizers, and its disruption during jet lag or rotating shift work schedules. Gander and colleagues [18–20] have made some impressive attempts in this direction, including simulations of Wever's [38] entrainment experiments. Beersma et al. [2] have recently begun to incorporate entrainment phenomena in their model. The PHASE model proposed here (Section 3) could be modified easily to include external forcing. On the other hand, it may be somewhat premature to theorize about external forcing of the human circadian system because of a lack of hard data. The phase-shifting effects of sleep, meals, light, social cues, etc. have yet to be quantified. Only recently has it been shown that bright light can reset the human circadian pacemaker [10], and that case study does not support extensive generalization as yet.

A second limitation of our approach is its phenomenological character. The model parameters do not correspond in any obvious way to anatomical, neural, or pharmacological entities. It is also unclear how to relate the human circadian system to that of other organisms including mammals. These problems are rectified somewhat in the neural models of Enright [14] and Carpenter and Grossberg [5, 6], but at the expense of mathematical complexity.

Finally, the model proposed here treats sleep as a homogeneous state. It ignores the fascinating questions surrounding the various stages of sleep: rapid eye-movement (REM) sleep, in which dreams occur; slow-wave sleep, the deepest stage which in pathological cases is associated with bedwetting, sleepwalking, and night terrors; and the lighter stages of non-REM sleep, which mediate the transitions between dreaming, deep sleep, and wakefulness. These sleep stages oscillate in a 90-min cycle, and the interaction of this REM/non-REM cycle with the circadian cycle [3, 29] represents one of the most exciting open problems of theoretical sleep research.

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Appendix A: Parameter estimates for human subjects

The earlier Eqs. (7-11) may be used to estimate the coupling strengths C_1, C_2 for typical human subjects. When internal synchrony is lost, the period of the sleep-wake cycle lengthens by much

more than that of the temperature cycle shortens [8, 34, 38]. Hence we expect

$$C_1 \ll C_2. \tag{A1}$$

Since $\Omega = C$ at the onset of desynchrony, and $C = C_1 + C_2 \sim C_2$, the frequency difference Ω provides an estimate of C_2:

$$C_2 \sim \text{frequency difference } \Omega \text{ observed at onset of desynchrony.} \tag{A2}$$

Choosing units where $\omega_1 = 1$, a typical value of Ω would be

$$\Omega \sim 1/6 \cong 0.16 \ (\sim 6 \text{ day beat period}). \tag{A3}$$

Hence,

$$C_2 \sim 0.16. \tag{A4}$$

From (11), (A1), and (A3),

$$\Delta\omega_2 \sim 0.16. \tag{A5}$$

To obtain C_1, we recall Wever's [38] result that after desynchrony, the temperature cycle shortens by ~ 0.7 h. For a synchronized period of 25.5 h, this corresponds to

$$\omega^* = 24.8/25.5 \cong 0.97. \tag{A6}$$

Since

$$\begin{aligned} \Delta\omega_1 &= \omega^* - \omega_1 \\ &\sim 0.97 - 1.0 \\ &\sim -0.03 \end{aligned} \tag{A7}$$

we find from (11) that

$$\begin{aligned} C_1 &= |C_2 \Delta\omega_1 / \Delta\omega_2| \\ &\sim 0.03. \end{aligned} \tag{A8}$$

$$|C_1/C_2| \sim |0.03/0.16| \sim 1/5. \tag{A9}$$

Appendix B: Exact solution for θ_1 and θ_2

We consider the system

$$\begin{aligned} \dot{\theta}_1 &= 1 \\ \dot{\theta}_2 &= \omega + C \cos 2\pi(\theta_1 - \theta_2). \end{aligned} \tag{B1}$$

This system subsumes Eq. (1) of Sect. 3.2, for the case $C_1 = 0$. Time is scaled so that $\omega_1 = 1$; then ω_2 becomes ω and C_2 becomes C in this new notation.

Let

$$\psi = \theta_1 - \theta_2. \tag{B2}$$

Then

$$\dot{\psi} = 1 - \omega - C \cos 2\pi\psi \tag{B3}$$

$$= \Omega - C \cos 2\pi\psi \tag{B4}$$

where

$$\Omega = 1 - \omega. \tag{B5}$$

Rescale time again: Set

$$T = \Omega t \tag{B6}$$

and let

$$\psi' = d\psi/dT. \tag{B7}$$

Then

$$\psi' = 1 - k\cos 2\pi\psi \tag{B8}$$

where

$$k = C/\Omega. \tag{B9}$$

Here k represents a dimensionless coupling constant; desynchrony occurs when

$$k < 1. \tag{B10}$$

Equation (B8) can be solved by separation of variables, followed by integration. Using the substitution

$$x = \tan \pi\psi \tag{B11}$$

we obtain

$$T + \text{constant} = \int \frac{d\psi}{1 - k\cos 2\pi\psi} = \left(\frac{1}{\pi(1+k)b}\right) \arctan(x/b) \tag{B12}$$

where

$$b^2 = (1-k)/(1+k). \tag{B13}$$

Equation (B12) may be solved for x and then for ψ to yield

$$\psi(t) = (1/\pi) \arctan u(t) \tag{B14}$$

where

$$u(t) = b\tan(\pi\beta t + C_0) \tag{B15}$$

$$\beta = \Omega(1-k^2)^{1/2} \text{ is the beat frequency} \tag{B16}$$

$$C_0 = \arctan((1/b)\tan \pi\psi_0) \tag{B17}$$

$$\psi_0 = \psi(t=0) \text{ is the initial condition} \tag{B18}$$

$$b^2 = (1-k)/(1+k) \tag{B19}$$

$$k = C/(1-\omega) \text{ is the dimensionless coupling.} \tag{B20}$$

The Eqs. (B14)-(B20) solve the equation given by (B3) for the desynchronized case assumed in (B10). Then θ_1 and θ_2 are easily solved for, as shown in Eqs. (16), (17) of Sect. 3.4.

Monotonicity of $\theta_2(t)$

Around the discussion of Fig. 5, it was stated that $\theta_2(t)$ is a monotonic function of t, for certain reasonable choices of parameters. All that is required in fact is $C < |\Omega|$ (the condition characterizing desynchrony) and $\omega_2 > 1/2$ (activity rhythm period is less than ~50 h). The monotonicity of θ_2 is established as follows:

$$\begin{aligned}
&\omega_2 > 1/2 \Rightarrow \omega_2 > 1 - \omega_2 \\
&\Rightarrow \omega_2 > \Omega \quad \text{(from (15) and (5a))} \\
&\Rightarrow \omega_2 + \Omega\cos 2\pi\psi > 0 \quad \text{for all } \psi \\
&\Rightarrow \omega_2 + C_2\cos 2\pi\psi > 0, \quad \text{since } C_2 \leqslant C \leqslant |\Omega| \\
&\Rightarrow \dot{\theta}_2 > 0 \quad \text{(from (1))} \\
&\Rightarrow \theta_2(t) \quad \text{is monotone in } t, \text{ as required.}
\end{aligned}$$

As a corollary, the function $\rho(\phi_s)$ is continuous; the graphical argument of Fig. 5b shows that discontinuities in ρ arise only at points where $\dot{\theta}_2(t_w) = 0$. Hence in the PHASE model, desynchrony with a discontinuous $\phi_s : \rho$ relation is impossible until τ_2 exceeds bicircadian lengths.

The continuity of $\rho(\phi_s)$ may be a drawback of the model if, as is suggested in [15, 34, 36, 43], the experimental data contain a genuine discontinuity at $\phi_s \sim 9$ (Fig. 3a) and not merely a steep section.

References

1. Aschoff, J.: Circadian rhythms in man. Science **148**, 1427–1432 (1965)
2. Beersma, D. G. M., Daan, S., Dijk, D. J.: Sleep intensity and timing: A model for their circadian control. Lect. Math. Life Sci. **19**, 39–62. Providence: American Mathematical Society (1987)
3. Borbély, A. A.: A two process model of sleep regulation. Human Neurobiol. **1**, 195–204 (1982)
4. Broughton, R.: Biorhythmic variations in consciousness and psychological functions. Can. Psychol. Rev. **16**, 217–239 (1975)
5. Carpenter, G. A., Grossberg, S.: A neural theory of circadian rhythms: The gated pacemaker. Biol. Cybern. **48**, 35–59 (1983)
6. Carpenter, G. A., Grossberg, S.: A neural theory of circadian rhythms: Aschoff's rule in diurnal and nocturnal mammals. Am. J. Physiol. **247**, R1067–R1082 (1984)
7. Cohen, A. H., Holmes, P. J., Rand, R. H.: The nature of the coupling between segmental oscillators of the lamprey spinal generator for locomotion: A mathematical model. J. Math. Biol. **13**, 345–369 (1982)
8. Czeisler, C. A.: Human circadian physiology: Internal organization of temperature, sleep-wake and neuroendocrine rhythms monitored in an environment free of time-cues. Ph.D. thesis, Stanford University, Stanford, CA (1978)
9. Czeisler, C. A., Weitzman, E. D., Moore-Ede, M. C., Zimmerman, J. C., Knauer, R. S.: Human sleep: Its duration and organization depend on its circadian phase. Science **210**, 1264–1267 (1980)
10. Czeisler, C. A., Allan, J. S., Strogatz, S. H., Ronda, J. M., Sánchez, R., Ríos, C. D., Freitag, W. O., Richardson, G. S., Kronauer, R. E.: Bright light resets the human circadian pacemaker independent of the timing of the sleep-wake cycle. Science **233**, 667–671 (1986)
11. Daan, S., Beersma, D.: Circadian gating of human sleep-wake cycles. In: Moore-Ede, M. C., Czeisler, C. A (eds.) Mathematical models of the circadian sleep-wake cycle, pp. 129–158. New York: Raven Press 1984
12. Daan, S., Beersma, D. G. M., Borbély, A. A.: Timing of human sleep: Recovery process gated by a circadian pacemaker. Am. J. Physiol. **246**, R161–R178 (1984)
13. Daan, S., Berde, C.: Two coupled oscillators: Simulations of the circadian pacemaker in mammalian activity rhythms. J. Theor. Biol. **70**, 297–313 (1978)
14. Enright, J. T.: The timing of sleep and wakefulness. Studies in Brain Function **3**. Berlin, Heidelberg, New York: Springer 1980
15. Enright, J. T.: Sleep duration for human subjects during internal desynchronization. In: Moore-Ede, M. C., Czeisler, C. A. (eds.) Mathematical models of the circadian sleep-wake cycle, pp. 201–205. New York: Raven Press 1984
16. Ermentrout, G. B., Kopell, N.: Frequency plateaus in a chain of weakly coupled oscillators, I. SIAM J. Math. Anal. **15**, 215–237 (1984)
17. Ermentrout, G. B., Rinzel, J.: Beyond a pacemaker's entrainment limit: Phase walk-through. Am. J. Physiol. **246**, R102–R106 (1984)
18. Gander, P. H., Kronauer, R. E., Czeisler, C. A., Moore-Ede, M. C.: Simulating the action of zeitgebers on a coupled two-oscillator model of the human circadian system. Am. J. Physiol. **247**, R418–R426 (1984)
19. Gander, P. H., Kronauer, R. E., Czeisler, C. A., Moore-Ede, M. C. Modeling the action of zeitgebers on the human circadian system: Comparisons of simulations and data. Am. J. Physiol. **247**, R427–R444 (1984)
20. Gander, P. H., Kronauer, R. E., Graeber, R. C.: Phase shifting two coupled circadian pacemakers: Implications for jet lag. Am. J. Physiol. **249**, R704–R719 (1985)
21. Hoppensteadt, F. C., Keener, J. P.: Phase locking of biological clocks. J. Math. Biol. **15**, 339–349 (1982)

22. Kawato, M., Fujita, K., Suzuki, R., Winfree, A. T.: 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)
23. Kopell, N., Ermentrout, G. B.: Symmetry and phaselocking in chains of weakly coupled oscillators. Comm. on Pure and Appl. Math. **39**, 623-660 (1986)
24. Kronauer, R. E.: Reply to R. A. Wever. Am. J. Physiol. **242**, R22-R24 (1982)
25. Kronauer, R. E.: Temporal subdivision of the circadian cycle. Lect. Math. Life Sci. **19**, 63-120. Providence: American Mathematical Society 1987
26. Kronauer, R. E., Czeisler, C. A., Pilato, S. F., Moore-Ede, M. C., Weitzman, E. D.: Mathematical model of the human circadian system with two interacting oscillators. Am. J. Physiol. **242**, R3-R17 (1982)
27. Kronauer, R. E., Czeisler, C. A., Pilato, S. F., Moore-Ede, M. C., Weitzman, E. D.: Mathematical representation of the human circadian system: Two interacting oscillators which affect sleep. In: Chase, M. H., Weitzman, E. D. (eds.) Sleep disorders: basic and clinical research, pp. 173-194. New York: Spectrum 1983
28. Kronauer, R. E., Gander, P. H.: Commentary on the article of Daan et al. Am. J. Physiol. **246**, R178-R182 (1984)
29. McCarley, R. W., Massaquoi, S. G.: A limit cycle mathematical model of the REM sleep oscillator system. Am. J. Physiol. **251**, R1011-R1029 (1986)
30. Moore-Ede, M. C., Czeisler, C. A., Richardson, G. S.: Circadian timekeeping in health and disease 2. Clinical implications of circadian rhythmicity. New England J. Med. **309**, 530-536 (1983)
31. Moore-Ede, M. C., Czeisler, C. A. (eds.): Mathematical models of the circadian sleep-wake cycle. New York: Raven Press 1984
32. Siffre, M.: Beyond time (ed. and transl. H. Briffault) New York: McGraw-Hill 1964
33. Siffre, M.: Six months alone in a cave. National Geographic **147**(3), 426-435 (1975)
34. Strogatz, S. H.: The mathematical structure of the human sleep-wake cycle. Lect. Notes Biomath. **69**. Berlin, Heidelberg, New York: Springer 1986
35. Strogatz, S. H.: A comparative analysis of models of the human sleep-wake cycle. Lect. Math. Life Sci. **19**, 1-38. Providence: American Mathematical Society 1987
36. Strogatz, S. H., Kronauer, R. E., Czeisler, C. A.: Circadian regulation dominates homeostatic control of sleep length and prior wake length in humans. Sleep **9**, 353-364 (1986)
37. Webb, W. B.: Sleep and naps. Spec. Sci. Tech. **1**, 313-318 (1978)
38. Wever, R.: The circadian system of man. Berlin, Heidelberg, New York: Springer 1979
39. Wever, R.: Commentary on the mathematical model of the human circadian system by Kronauer et al. Am. J. Physiol. **242**, R17-R21 (1982)
40. Wever, R. A.: Toward a mathematical model of circadian rhythmicity. In: Moore-Ede, M. C., Czeisler, C. A. (eds.) Mathematical models of the circadian sleep-wake cycle, pp. 17-79. New York: Raven Press 1984
41. Winfree, A. T.: Human body clocks and the timing of sleep. Nature **297**, 23-27 (1982)
42. Winfree, A. T.: The tides of human consciousness: Descriptions and questions. Am. J. Physiol. **242**, R163-R166 (1982)
43. Winfree, A. T.: Impact of a circadian clock on the timing of human sleep. Am. J. Physiol. **245**, R497-R504 (1983)
44. Zulley, J., Wever, R., Aschoff, J.: The dependence of onset and duration of sleep on the circadian rhythm of rectal temperature. Pflügers Arch. **391**, 314-318 (1981)

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