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# A Two Process Model of Sleep Regulation

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**Summary.** Two processes play a dominant role in sleep regulation: a sleep-dependent process (Process S) and a sleep-independent circadian process (Process C). The timecourse of Process S was derived from the spectral analysis of slow wave activity in the human EEG. Its level shows an exponential decline during sleep and an increase during waking. The level of Process S at sleep onset is therefore a function of prior waking time. Process C is reflected by the rhythmic variation of sleep propeusity during prolonged sleep deprivation, and is assumed to be controlled by a circadian oscillator. In the model, sleep propensity and the duration of sleep are determined by the combined action of the two processes. The model is able to simulate the variations of sleep duration as a function of sleep onset time. Since the amount of REM sleep is little influenced by prior sleep or waking and shows a marked circadian rhythmicity, it is assumed to reflect largely the level of Process C. The cyclic alternation of nonREM and REM sleep is assumed to result from a reciprocal interaction between the two sleep states. In contrast to previous models, only a single circadian oscillator is required to account for the sleep-wake cycle and the sleep organization under entrained and non-entrained schedules. The model also encompasses sleep regulation in animals and may provide indications as to the phylogenetic origin of sleep.

**Key words:** Sleep regulation – Model – Circadian rhythm – Slow wave sleep – Sleep/wake cycle

In this article a model of sleep regulation is presented which is based on experimental studies. The first two sections are devoted to a review of the relevant literature. The model itself and some of its implications are described and discussed in sections III and IV.

## I. Sleep-dependent Aspects of Sleep Regulation

### *Slow Wave Sleep and Sleep Intensity*

With the progression of waking time, the level of sleepiness increases and sleep latency shortens (e.g. Fröberg et al. 1975; Carskadon and Dement 1981). However, the relationship between sleep parameters and the duration of prior waking is not linear. For example, the "sleep debt" incurred during a prolonged vigil is only to a small part compensated by an increase in the duration of recovery sleep. This was dramatically shown in an experiment in which a subject stayed awake for 264 h and then slept only for 14.4 h (Gulevich et al. 1966). In a similar observation reported earlier, a 90-h sleep deprivation period was followed by only 10 h of sleep (Blake and Gerard 1937). The question therefore arises whether sleep loss can be compensated by an enhancement of "sleep intensity". What are the characteristics of a putative intensity parameter of sleep? As a presumably monotonic function of the antecedent waking period, this parameter would be expected to have a high value immediately after sleep onset, and decline progressively with ongoing sleep. Moreover, following an extended waking period, the initial value of sleep intensity should be increased.

Slow wave sleep (SWS; stages 3 and 4 of nonREM sleep) appears to be a good candidate for a high-intensity sleep stage. It predominates in the first part of sleep (Dement and Kleitman 1957; Williams et al. 1964b; Webb 1971) and is enhanced after sleep deprivation (Berger and Oswald 1962; Williams et al. 1964a; Webb and Agnew 1971; Moses et al. 1975a; Nakazawa et al. 1978; Borbély et al. 1981a). Conversely, if sleep time in the previous night is extended or if day-time napping is allowed to occur, the amount of SWS is reduced (Karacan et al. 1970b; Feinberg et al. 1980).

If SWS is indeed a high-intensity sleep stage, it should be a "deeper" form of sleep. Therefore a high arousal threshold would be expected to prevail in this stage. Experimental data support this prediction. As early as 1937 Loomis and coworkers noted that as the sleeper approaches SWS, sleep is less easily disrupted by external stimuli. More recent studies have confirmed that the thresholds for EEG changes elicited by pain or acoustic stimuli were higher in SWS than in stage 2 (Williams et al. 1964a; Goodenough et al. 1965). However, the thresholds of behavioral and vasomotor responses showed a less clear relationship to sleep stages (Williams et al. 1964a).

Sleep stages are insufficient for investigating sleep intensity in more detail. They are generally defined by criteria such as the prevalence of high-amplitude slow waves (stages 3 and 4) or the occurrence of phasic events (e.g. spindles and K-complexes for stage 2; rapid eye movements for REM sleep) (Rechtschaffen and Kales 1968). Their acceptance and widespread use creates the impression that sleep stages constitute genuine physiological stages. All-night spectral analysis of the sleep EEG revealed, however, that the nonREM stages 1–4 represent a crude and rather arbitrary subdivision of a con-

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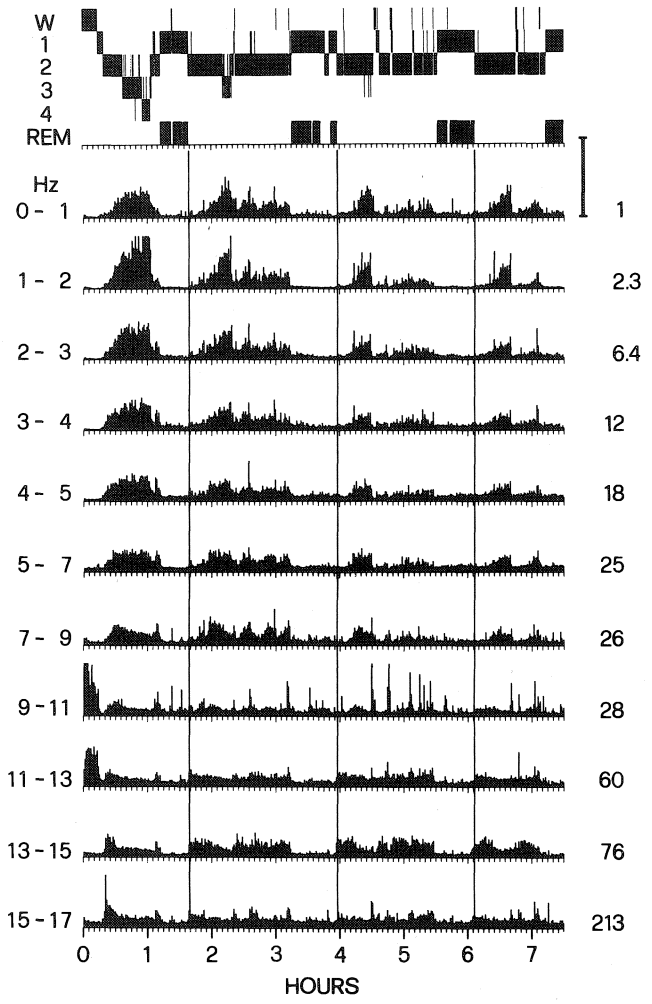


**Fig. 1.** Sleep states and EEG power density plots of a human baseline night. Sleep states (top) are plotted for 30-s epochs (W: waking; 1–4: nonREM sleep stages; REM: REM sleep) (note that REM sleep epochs are also plotted as stage 1 sleep). Power density of the various frequency bands is plotted for 1-min segments. The lower limits of the frequency bands are 0.25 Hz higher than indicated on the left. The calibration mark at the right of the top frequency band corresponds to 200 $(\mu V)^2/0.25$ Hz for scale factor 1. The other scale factors indicated on the right represent relative values which were chosen to make the area of the plots equal. The nonREM–REM sleep cycles are delimited by vertical lines (unpublished data from Borbély et al. 1981a)

EEG power density in the low frequency bands and its decreasing trend throughout the sleep period were also observed for individual sleep stages (SWS, stage 2, REM sleep). The latter observation is in accordance with the decrease of the arousal threshold in the course of sleep, which occurred independently of sleep stages (Shapiro et al. 1963; Rechtschaffen et al. 1966).

In an effort to quantify the trends in the sleep EEG, the integrated power density values (range 0.75–25.0 Hz) were calculated for the successive nonREM–REM cycles, standardized with respect to the first cycle (100%), and plotted on a logarithmic scale at the cycle midpoint times (Fig. 2).

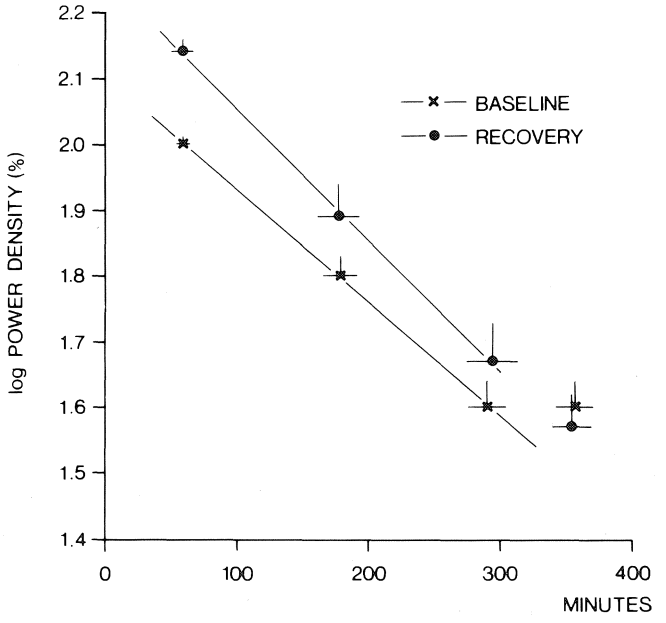


**Fig. 2.** EEG power density of total sleep plotted for the first four nonREM–REM sleep cycles of the baseline night and the first recovery night after 40.5 h of sleep deprivation. The integrated values plotted at cycle midpoint time represent means with standard errors. For each subject (n = 8) the integrated power density between 0.75 and 25.0 Hz in the first cycle of the baselines nights (mean of two nights) was defined as 100%. The relative power density is plotted on a logarithmic scale, and the regression lines were computed for the first three cycles (modified from Borbély et al. 1981a)

tinuous process. This is particularly obvious for the gradual increase of slow wave activity after sleep onset, a change that is inadequately mirrored by the sleep stages (Fig. 1). Similarly, while the attenuation of slow wave peaks over successive sleep cycles is clearly evident from the spectral plots, it is incompletely represented by the sleep stage pattern. Moreover, trends *within* individual sleep stages are not taken into account by the conventional sleep scoring procedure. For example, stage 2, the sleep stage occupying the largest portion of sleep, is not a homogeneous state, but shows a decline of slow wave activity by 50% from nonREM–REM cycles 1 to 3 (Borbély et al. 1981a).

Effects of sleep deprivation have been clarified by the spectral analysis of the sleep EEG. An extended waking period of 40.5 h caused a massive increase of slow wave activity during recovery sleep. The enhancement of the Since most of the spectral power density is contained in the low frequency bands, the integrated values correspond largely to slow wave activity. As shown in Fig. 2 the changes across the first three sleep cycles can be described by an exponential function, since the logarithmic values fit closely a linear regression line. In the night after sleep deprivation, the initial value is significantly higher than the corresponding baseline value ($p < 0.01$), while the slope of the regression line does not differ significantly from control.

In conclusion, the data support the hypothesis that the EEG power density in the low frequency range is an indicator of a progressively declining sleep process whose initial level is determined by the duration of prior waking. EEG slow wave activity may therefore represent an intensity parameter of the sleep process.

*Regulation of REM Sleep and nonREM Sleep*

Up to this point only aspects relating to nonREM sleep have been considered. The following paragraphs will focus upon differences in regulation between nonREM and REM sleep.

While SWS, the proposed "high intensity" fraction of nonREM sleep, can be readily related to prior waking, it is more difficult to establish such a relationship for REM sleep. The proportion of REM sleep increases across successive nonREM–REM sleep cycles (Feinberg 1974), a trend that becomes even more apparent if sleep is extended into the morning hours (Webb et al. 1966; Verdone 1968). The fact that SWS and REM sleep exhibit opposite trends in the sleep period suggests either that the two states are antagonistically coupled or that they are controlled by separate regulatory mechanisms. The latter possibility is supported by sleep deprivation experiments, which indicate that sleep loss has a differential effect on the two sleep states. Thus an extended waking period of approximately 40 h increased the amount of SWS, while REM sleep was not affected (Nakazawa et al. 1978; Borbély et al. 1981a). The greater sensitivity of SWS to sleep loss is also evident in partial sleep deprivation experiments in which REM sleep was reduced while the amount of SWS was maintained or even increased (Dement and Greenberg 1966; Jones and Oswald 1968; Webb and Friel 1970; Hartmann et al. 1971; Johnson and MacLeod 1973; Webb and Agnew 1974a). Finally, as a converse approach to sleep deprivation studies, sleep regulation can be also investigated by generating "sleep satiety". An extension of sleep time in the morning or extra daytime sleep reduced the amount of SWS in the subsequent night, whereas REM sleep was little influenced (Whitehead et al. 1969; Karacan et al. 1970a, b; Feinberg et al. 1980). Therefore, in these experiments also, REM sleep proved to be more resistant to manipulations of sleep time than SWS.

*Selective sleep deprivation* experiments constitute probably the most direct approach to explore the specific regulatory characteristics of the substates of sleep. Dement (1960, 1965) discovered that selective REM sleep deprivation for a few nights is followed by a REM sleep rebound. Subsequent experiments demonstrated that the selective denial of stage 4 also gives rise to a stage 4 rebound (Agnew et al. 1964, 1967; Moses et al. 1975a).

A selective deprivation is usually achieved by awakening the subject at the first sign of REM sleep or by administering a stimulus at the onset of stage 4 and thus inducing a shift to another nonREM sleep stage. The examination of the number and distribution of stimulations during deprivation nights provides additional information on the regulatory properties of a sleep state. To prevent REM sleep for several consecutive nights, the number of stimulations per nights had to be progressively increased (Dement 1960, 1965; Kales et al. 1964; Sampson 1965; Agnew et al. 1967). This contrasts with the stimulation pattern required to prevent stage 4, which either increased initially (nights 1–4) and then levelled off (nights 4–7) (Agnew et al. 1967), or showed no increasing trend at all (Moses et al. 1975a).

Finally, clear differences in the *timecourse of rebound* have been found. Thus, while the increase of SWS was typically confined to the first recovery night (Agnew et al. 1967), REM sleep remained elevated during several nights (Dement 1960, 1965; Dement et al. 1966; Agnew et al. 1967; Moses et al. 1975a). Similar observations were made in studies in which total sleep deprivation was maintained for several days. In these experiments, the rebound of SWS showed a maximum in the first recovery night (Williams et al. 1964a; Moses et al. 1975a), whereas REM sleep rebound was most prominent in the second night and persisted during subsequent nights (Berger and Oswald 1962; Williams et al. 1964a; Dement 1965; Gulevich et al. 1966; Agnew et al. 1967; Kales et al. 1970; see also Benoit et al. 1980). A long-lasting REM sleep rebound is known to occur following a drug-induced suppression of REM sleep in man (Oswald 1969) and after REM sleep deprivation by non-pharmacological means in animals (Dement 1969).

On the basis of the deprivation studies sleep may appear to be essentially a dual process in which SWS and REM sleep can be independently manipulated. However, based on the arguments presented above, the nonREM sleep stages 2, 3, and 4 may represent sections along a continuous slow wave intensity gradient. Consequently, it can be expected that the selective deprivation of stage 4 is partly compensated by the increase of slow wave activity in stage 2, the sleep stage substituting primarily for SWS (Agnew et al. 1967). This prediction is supported by the observation that two nights of total sleep deprivation that were followed by two nights of selective stage 4 deprivation, gave rise to less stage 4 rebound than two nights of total sleep deprivation alone (Moses et al. 1975a). It is likely that the slow wave sleep deficit in the former schedule was partly compensated by an increase of slow wave activity in other sleep stages.

The situation is different for REM sleep for which a wake-time dependent intensity parameter has not been specified. In the all-night spectral plots of the sleep EEG, REM sleep episodes are characterized by low power density values in the low frequency bands and in the spindle range (11–15 Hz) (Fig. 1), which exhibit no consistent trend across the sleep period (Borbély et al. 1981a). The density of rapid eye movements in REM sleep is equally an unlikely candidate for a wake-time-dependent intensity parameter, since it exhibits an increasing trend during sleep (Aserinsky 1969; Feinberg et al. 1980) and is little affected by REM sleep deprivation (Antonioli et al. 1981; see Borbély and Wirz-Justice 1982 for further discussion). However, there is some evidence for a possible functional relationship between REM sleep and stage 1. Disregarding the phasic events, REM sleep, stage 1, and initial stage 2 have in common the low level of EEG slow wave activity. The similar EEG pattern as well as the observation that stage 1 showed a massive increase during REM sleep deprivation nights (but not in stage 4 deprivation nights) (Moses et al. 1975a; see also Agnew et al. 1967) may point to a common underlying process.

*Interdependence of REM Sleep and nonREM Sleep*

The evidence for separate regulatory mechanisms of REM sleep and nonREM sleep should not obscure the strong interdependence of these sleep states. This is evident from their orderly succession, which gives rise to the regular nonREM–REM sleep cycles. The length of the sleep cycles exhibits a consistent curvilinear trend across the night with little variance within age groups (Feinberg and Floyd 1979). While they have been considered as the indicator of a "basic rest activity cycle" (BRAC) (Kleitman 1963), it is more likely that sleep cycles represent a sleep-dependent rhythm (Moses

et al. 1975b, 1977, 1978) whose period length is sensitive to intrinsic sleep factors (e.g. the proportion of SWS within a sleep cycle; Brezinova 1974). The observation that the sequence of stimuli required to prevent REM sleep episodes shows a cyclic recurrence (Lehmann et al. 1976; and own unpublished data) indicates that the occurrence of REM sleep is not a prerequisite for sleep cycles.

*In summary,* fundamental differences are apparent in the regulation of SWS and REM sleep. While even minor deviations from the regular level of SWS cause an immediate, short-lasting compensatory response, only a severe deficit in REM sleep results in a rebound which is often delayed and prolonged. However, a model of sleep regulation is not complete without taking into account the cyclic succession of nonREM and REM sleep as a major invariant feature of the sleep process.

## II. Sleep-independent, Circadian Aspects of Sleep Regulation

Sleep propensity is not only a function of waking time. This was clearly demonstrated in a 72-h sleep deprivation experiment in which the fatigue ratings showed a marked circadian rhythm throughout the experiment (Åkerstedt and Fröberg 1977) (Fig. 3). This persistence of rhythmic variations in sleepiness was recognized in early studies (e.g. Patrick and Gilbert 1896) and has been confirmed repeatedly (e.g. Murray et al. 1958). The prominent effect of circadian factors on sleep parameters was impressively demonstrated in a recent study where sleep duration first decreased below its regular level, and then increased well beyond the baseline, as the time of sleep onset was successively delayed by 4-h intervals (Åkerstedt and Gillberg 1981). The data of this study will be analyzed in the following section in the context of the model (Fig. 5).

The investigation of circadian factors is difficult under regular experimental conditions in which a variety of environmental and social influences act as synchronizers of circadian rhythms. Experiments conducted in the absence of time cues have therefore been of paramount importance. Aschoff and Wever (1962) were the first to record in man circadian rhythms of rest-activity and other variables. In subsequent studies, non-entrained (i.e. free-running) circadian rhythms were also documented for the polygraphically recorded sleep-wake cycle (Jouvet et al. 1974; Webb and Agnew 1974b).

For the analysis of the circadian facet of sleep regulation the relationship of sleep and *body temperature* is very important. As was pointed out in early reports (Kleitman 1933) and reviewed more recently (Colquhoun 1971), the variations of vigilance are closely related to the 24-h rhythm of body temperature. Several studies concur that the variations in sleepiness are a mirror image of the body temperature rhythm (Murray et al. 1958; Åkerstedt and Fröberg 1977; Moses et al. 1978). As experimental subjects proceed from the entrained to a non-entrained (free-running) schedule, the phase-relationship between the rhythms of sleep and body temperature changes. While in a 24-h environment sleep onset occurs typically on the descending limb of the temperature cycle, it coincides closely with the temperature minimum in the absence of time-cues (Aschoff et al. 1967; Czeisler et al. 1980a; Zulley et al. 1981). However, in the course of a prolonged non-entrained schedule, more dramatic changes may occur. The rhythms of sleep and body temperature may develop different periodicities, a condition that has been designated as "internal desynchronization" (see Wever 1979). While the rhythm of body temperature usually exhibits a period close to 25 h, the rhythm of sleep can assume a much larger range of values (Wever 1979; Fig. 37). However, despite the apparent independence of the two rhythms, a preferred phase-relationship still persists. Thus sleep propensity is highest at the time of the circadian temperature minimum, and lowest at the time of the maximum (Czeisler 1978; Zulley 1979, 1980; Czeisler et al. 1980a, b; Zulley and Wever 1982; Zulley et al. 1981). Also sleep duration exhibits a specific phase relationship to body temperature (Czeisler et al. 1980a; Zulley et al. 1981).

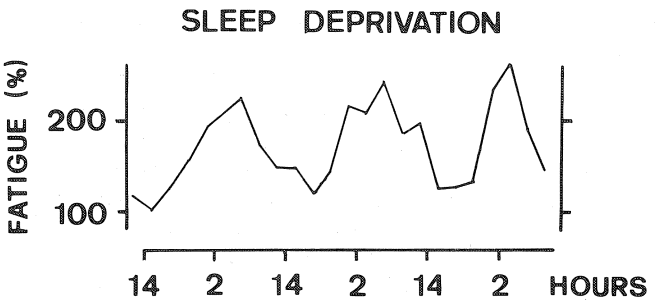


**Fig. 3.** Fatigue self-ratings obtained at 3-h intervals during a 72-h sleep deprivation period. Mean values (N = 15). (modified from Åkerstedt and Fröberg 1977)

*Sleep organization* shows typical alterations in the absence of time-cues. Thus while under entrained schedules the amount of REM sleep increases across the sleep period, no such rise or even a decreasing trend is seen under non-entrained conditions (Weitzman et al. 1980; Zulley and Schulz 1980). Moreover, when time-cues are not present, the first REM sleep episode is prolonged and REM sleep latency shortened. In contrast to REM sleep, the pattern of SWS remains largely unchanged (Zulley 1979; Weitzman et al. 1980). The only peculiar feature that was occasionally observed for very long sleep periods, consisted in a second SWS peak 12–18 h after sleep onset (Webb 1978; Weitzman et al. 1979).

*REM sleep* exhibits a prominent circadian rhythm even under regular entrained schedules and, in addition, shows a close association to body temperature. Nap studies have shown that more REM sleep occurs early in the day than during later daytime hours (Maron et al. 1964; Webb et al. 1966; Webb and Agnew 1967). This decreasing trend of REM sleep propensity was even present after a night without sleep (Endo et al. 1981). The coincidence of maximum REM sleep with minimum body temperature was observed in studies where subjects underwent a 60 min sleep/160 min wake schedule for 40 h (Moses et al. 1975b, 1978) or a 120 min sleep/60 min wake schedule for 10 days (Weitzman et al. 1974; Czeisler et al. 1980b). The inverse relationship between REM sleep propensity and body temperature persisted in non-entrained, internally desynchronized subjects in whom the highest percentage of REM sleep relative to total sleep, the longest average REM sleep episode, and the shortest REM sleep latency all coincided closely with the circadian temperature minimum (Czeisler et al. 1980b). These results led the

authors to postulate that the circadian REM sleep propensity rhythm reflects the activity of a self-sustained circadian oscillator to which also the body temperature rhythm is closely coupled (Czeisler et al. 1980a). In the following section arguments will be presented to the effect that both physiological processes are controlled by a single circadian oscillator.

## III. Outline of the Model

The model rests on the assumption that two separate processes underlie sleep regulation. One process is itself a function of sleep and waking, whereas the other process is controlled by a circadian oscillator. Sleep propensity is assumed to be determined by the combined action of the two processes which are illustrated in Fig. 4. The upper part of the figure shows the exponential decline of slow wave activity during a sleep period following upon a regular waking period (continuous line) and a prolonged vigil (interrupted line; cf. Fig. 2). The thin interrupted lines interpolate the values between two consecutive sleep periods and represent the rising level of SWS propensity with the progression of waking. Note that the time constant for the rising part of the process is longer than for the declining part. The lower section of the figure shows the timecourse of *Process S* which is derived from the measured values of slow wave activity during sleep and from the interpolated slow wave propensity during waking. In the model, Process S is regarded as the major sleep-dependent component of total sleep propensity. The latter is assumed to be the combined result of Process S and of a circadian sleep process (Process C). The level of *Process C* corresponds therefore to the circadian component of sleep propensity. It is assumed to be controlled by a circadian oscillator which is unaffected by the occurrence of waking and sleep. The phase-position of Process C has been derived from the rhythm in vigilance during prolonged sleep deprivation (Fig. 3). The minimum of the sine function representing Process C was set for 1600 hours, the maximum for 0400 hours. To better visualize the combined effect of the two processes, the negative function (mirror image) of Process C (designated $\overline{C}$) has been plotted in Fig. 4. Total sleep propensity, which corresponds to the summation of S and C, is therefore represented by the difference between S and $\overline{C}$. Curve $\overline{C}$ may be considered as reflecting the circadian variation of the "sleep threshold" which is highest when circadian sleep propensity is lowest (i.e. in the afternoon). Curve $\overline{C}$ also corresponds to the circadian body temperature rhythm which is inversely related to sleep propensity (see section II.). The widening gap between the two curves in the evening hours of a regular waking period shows the increase in total sleep propensity. After sleep onset at 2300 hours the difference between the curves (hatched area) decreases until it reaches zero at the time of awakening. If the wake period is extended 24 h beyond its regular duration, the separation of the curves continues to increase. However, due to the rising limb of $\overline{C}$, the difference between the curves decreases during the first part of the day before increasing again in the evening hours. After sleep deprivation, sleep propensity and the level of slow wave activity are higher than after a regular waking period. However, due to the exponential decline of Process S, sleep duration is not much prolonged.

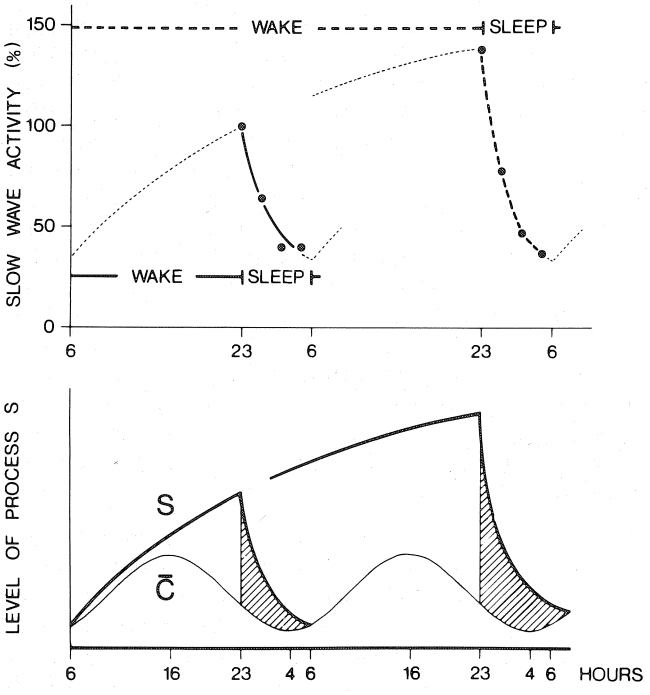


**Fig. 4.** Timecourse of sleep processes after regular and extended waking periods. *Upper part:* Exponential decline of slow wave activity over four consecutive sleep cycles (value of first cycle = 100%; cf. Fig. 2) for a baseline night (continuous line) and after sleep deprivation (interrupted line). The exponential increase of slow wave sleep propensity during waking time is indicated by the dotted curve. *Lower part:* Timecourse of Process S and the negative function of Process C (curve C)

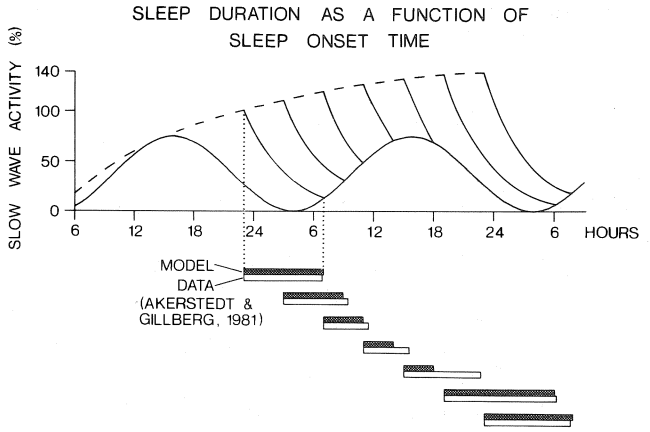


**Fig. 5.** Sleep duration as a function of sleep onset time. Simulation of the experimental data of Åkerstedt and Gillberg (1981). Black bars indicate sleep durations computed from the model, white bars indicate the experimental data

### *Simulation of Data*

Fig. 5 shows that the model can account for the variations of sleep duration as a function of sleep onset time. As in the previous figure, sleep duration is assumed to correspond to the time interval between sleep onset and the intersection of curves S and $\overline{C}$. The seven sleep periods illustrated in Fig. 5 result from the successive delays of sleep onset by 4-h intervals. The figure represents a simulation of data obtained by Åkerstedt and Gillberg (1981). While the timecourse of curve S

was based on slow wave activity in analogy to Fig. 4, the amplitude of the circadian rhythm (curve $\bar{C}$) has been defined arbitrarily. The black horizontal bars below the curves represent the sleep duration computed from the model, the white bars the measured values. As sleep onset time is delayed from the habitual hour (2300 hours) by 4–12 h, sleep duration shortens. However, further delays (by 16–24 h) cause a marked prolongation of the sleep period, which in one case (sleep onset at 1900 hours) greatly exceeds the baseline level. There is a close correspondence between the model and the data for the first three and the last two values. The sleep period showing the largest mismatch between simulated and actual data (sleep onset at 1500 hours) is defined in the model by the intersection of the two curves at a narrow angle. A minor phase-adjustment or a skewing of the sine curve (suggested by Daan and Beersma 1982) leads to a closer correspondence with the data. The data of Åkerstedt and Gillberg (1981) have been simulated in a quantitative study by Daan and Beersma (1982).

*NonREM–REM Sleep Cycle*

So far, Process S has been represented by a continuously declining exponential function, which did not take into account the cyclic alternation of nonREM and REM sleep periods (see Fig. 1). The model was therefore extended to include also this salient feature of sleep. In Fig. 6 REM sleep propensity (R) is represented by a horizontal interrupted line during waking and by the black areas during sleep. The constant level of R during the regular sleep-wake cycle indicates that in contrast to Process S, REM sleep propensity is not influenced by sleep or waking. Consequently, REM sleep propensity is defined by the difference between R and $\bar{C}$, and corresponds to the circadian component of total sleep propensity (Process C).

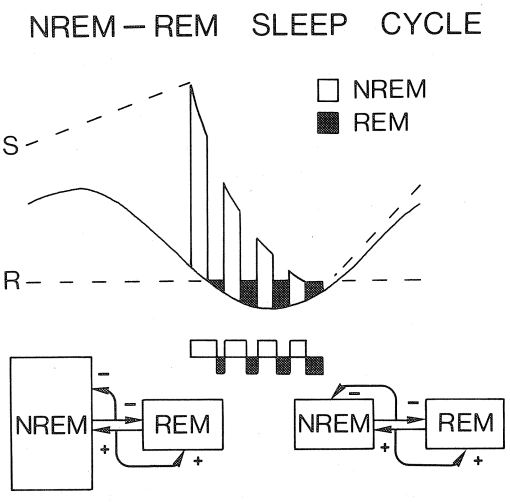


**Fig. 6.** Diagramatic representation of the extended model which includes the nonREM–REM sleep cycle. In the upper part S and R are plotted relative to $\bar{C}$. The rectangles below the curve show the decreasing duration of nonREM sleep periods (white) and the increasing duration of REM sleep periods during sleep. The bottom diagrams illustrate the reciprocal interaction of a nonREM and a REM sleep controlling process (see text)

The nonREM–REM sleep cycles are represented by the succession of white and black areas. The upper boundary of the white areas is defined by the exponentially declining Process S, the upper boundary of the black areas by the constant level of R, while the lower boundary of all areas is delimited by curve $\bar{C}$. The white and black rectangles below the curve indicate the duration of nonREM and REM sleep periods in successive cycles. In the model, the ratio of nonREM/REM sleep is assumed to be determined by the ratio of their respective propensities. Thus while at sleep onset the propensity for nonREM sleep ($S-\bar{C}$) is high and for REM sleep ($R-\bar{C}$) low, the propensities are practically equal at the end of the sleep period. As a consequence, the first REM sleep period represents only a small fraction of the sleep cycle, while the fourth period occupies 50% of the cycle.

The two bottom diagrams in Fig. 6 show the mechanism that is proposed to account for the cyclic alternation of nonREM and REM sleep. This part of the model is based on the reciprocal interaction model of McCarley and Hobson (1974), which they used to simulate the dynamic relationship between REM-sleep–enhancing and REM-sleep–inhibiting neuronal populations. The authors presented evidence that large neurons situated in medial brainstem nuclei are most active during REM sleep while smaller neurons in lateral brainstem nuclei have their activity peak in nonREM sleep. Moreover, the large neurons exert an excitatory action on the small neurons which in turn inhibit the former ones. Finally, each neuronal population receives a feedback from its own collaterals which exert a self-excitatory and a self-inhibitory influence, respectively. The interaction between the two populations and the resulting oscillatory process can be described by two sets of differential equations of the Lotka-Volterra type. In the present model, the cyclic alternation of nonREM and REM sleep are assumed to result from an analogous reciprocal interaction between two processes representing nonREM ($S-\bar{C}$) and REM sleep propensity ($R-\bar{C}$). However, in contrast to the neuronal model, the two processes are not constant throughout the sleep period: While the former process predominates at sleep onset (indicated by the large nonREM box in the bottom left diagram), the two processes become more similar with the progression of sleep (boxes of equal size at bottom right). Thus REM sleep is inhibited by its counterpart during the major fraction of the first sleep cycle, but only during one half of the last cycle. It should be noted that the progressive increase in the REM sleep fraction is a consequence of both the circadian rhythm ($R-\bar{C}$ is largest in the later part of the sleep period) and the declining inhibition by Process S.

It must be mentioned that the present extended version of the model needs further elaboration to include a sleep-dependent component of REM sleep regulation. On the basis of the discussion in the first section of this paper, it would be necessary to introduce a threshold for R below which a regulatory response is elicited (cf. Borbély and Neuhaus 1979). Thus a distinct Process R may have to be introduced whose time constant is much longer than for Process S. However, at this point the data relating to REM sleep regulation in man are still not consistent enough (e.g. the unexplained absence of REM sleep rebound after three nights of selective deprivation; Cartwright et al. 1967 and own unpublished data) to provide a reliable basis for such a model.

*Non-entrained Schedules*

The model in its present version is intended to describe sleep regulation under entrained conditions. However, it should be noted that the typical changes in the REM sleep pattern under non-entrained schedules can also be accounted for. Since under such conditions subjects go to bed near the temperature minimum and not on the descending limb of the temperature rhythm (see section II.), it can be assumed that sleep onset time exhibits a corresponding phase-shift with respect to Process C. Yet if sleep begins at the peak of Process C (the minimum of curve $\overline{C}$), the circadian REM sleep propensity ($R-\overline{C}$) is at its maximum already at sleep onset, counteracting more strongly thereby the influence of Process S than under entrained conditions. The short REM sleep latency, the prolonged first REM sleep period, and the flat distribution of REM sleep across the sleep period are all logical consequences of such an altered balance.

Daan and Beersma (1982) have also developed a circadian gating model of human sleep regulation, which in its basic aspects corresponds to the present model. They focused their work on the sleep-wake pattern in the absence of time cues. In addition to Process C (whose negative function is regarded in the present model as a sleep termination threshold; see Fig. 5), these authors proposed another circadian process determining the time of sleep onset. The parallel variations of these processes representing the thresholds of sleep onset and sleep termination, are considered to be controlled by a single circadian oscillator. In their computer simulation, a process analogous to Process S was made to oscillate between the two circadian thresholds whose interval, amplitude and period was varied. The reduction of the amplitude resulted in the transition from a circadian to a circabidian pattern, a change that has been observed in free-running subjects (e.g. Czeisler 1978; Wever 1979). Moreover, by adding "noise" to the circadian thresholds, the typical irregularly occurring phase-jumps of internal desynchronization could be simulated.

In summary the model, which assumes a single circadian oscillator, can well account for various typical alterations of the sleep-wake pattern under free-running schedules, changes that so far have been explained on the basis of two or more circadian oscillators (Wever 1979; Kronauer et al. 1982).

*Comparison to Other Models*

Kronauer et al. (1982) have proposed a two-oscillator model where REM sleep and body temperature are both controlled by a stable circadian oscillator, whereas the sleep-wake cycle is determined by another, more labile circadian oscillator. Wever (1979) postulated the existence of several circadian oscillators with different "oscillatory strength". Since Process S represents a relaxation oscillator which may show a gradual transition to a circadian oscillator of the Van der Pol type, the present model and the one proposed by Kronauer et al. (1982) are on a formal level not fundamentally different. However, the physiological implications are basically different, since the present model does not need to postulate two distinct circadian pacemakers, one controlling body temperature, REM sleep and cortisol rhythms, the other the sleep-wake cycle (see More-Ede et al. 1980). In particular, the rather tenuous assumption of the two-oscillator model that REM sleep, a major substate of sleep, should be controlled by a different circadian oscillator than the sleep-wake cycle itself, is not necessary. In the present model, REM sleep propensity is a reflection of the circadian component of total sleep propensity (Process C) which is inversely related to the body temperature rhythm. Another difference between the models derives from the fact that the rising and falling parts of a relaxation oscillation (Process S) can be directly related to the physiological processes of waking and sleep, respectively, whereas such a dichotomy is not evident for a process controlled by a circadian oscillator of the Van der Pol type.

A final consideration relates to the influence of external Zeitgebers. Kronauer et al. (1982) postulated that Zeitgebers act directly on the weak circadian oscillator (controlling the sleep-wake cycle) which in turn influences the strong oscillator. In the present model it is reasonable to assume that it is Process S which is most readily affected by external influences. In analogy to Kronauer's hypothesis it is tempting to consider the possibility that the entrainment of the circadian component of the sleep-wake cycle (Process C) is mediated by Process S. Such a proposition is supported by the observation that in a split-sleep schedule, a 4-h "anchor-sleep" period recurring at 24-h intervals can synchronize the body temperature rhythm (Minors and Waterhouse 1981, p. 32; see also Eastman 1980). This would imply that the sleep-dependent component of sleep regulation can affect the circadian oscillator as an internal Zeitgeber.

## IV. Some Implications of the Model

*Animal Sleep*

The physiological basis of the two-process model is not limited to human sleep regulation, but includes also sleep in animals. Since various implications relating to animal experiments have been already published (Borbély 1980a, b, 1981, 1982; Borbély et al. 1982), only a few selected aspects will be discussed.

In animals as in man the amount of slow wave activity in sleep is a function of prior waking. In the rat, for example, the slow wave fraction of nonREM sleep declines gradually during the daily light phase, the animal's sleep period, and increases in the dark phase when the rat is mostly awake and active (Borbély and Neuhaus 1979). The REM sleep fraction of total sleep exhibits an opposite trend: It increases in the course of the light phase, a tendency that is again similar to the rising trend of REM sleep in human sleep (Borbély 1980a). Moreover, the decrement of slow wave activity during the sleep period of the rat can be described by an exponential function whose initial value is determined by the duration of prior waking (Borbély et al. in preparation). The importance of a circadian component in sleep regulation was clearly shown by experiments in which a conflict was created between the sleep-dependent and the circadian component of sleep propensity (Borbély and Neuhaus 1979). Thus when a 24-h sleep deprivation period was made to terminate at dark onset, the beginning of the rat's circadian waking period, the rebound of SWS occurred in two stages: A first peak was present in the initial part of the dark period as an immediate response to sleep deprivation, while a second peak was situated in the first light hours, the rat's circadian

rest period. These results have been qualitatively simulated in a previous version of the model (Borbély 1982). Subsequent experiments indicated that the sleep-dependent and the circadian component of sleep regulation in the rat are based on separate physiological mechanisms. Thus neither the phase-relation nor the period of the free-running rest-activity rhythm of rats maintained in constant darkness was affected by a sleep deprivation period of 24 h (Borbély et al. 1982 and unpublished data). Conversely, animals in which lesions of the suprachiasmatic nuclei had disrupted the circadian rest-activity rhythm still exhibited the usual rebound in SWS and REM sleep following sleep deprivation (Borbély et al. 1982; Tobler et al. in preparation). This experiment demonstrated that an intact circadian rhythm is not a prerequisite for the sleep-dependent component of sleep regulation.

*Neurochemical Correlates*

In the present model the timecourse of Process S has been based on the changes of EEG slow wave activity, an electrophysiological parameter. Recent developments indicate the possibility of defining also neurochemical correlates of this process. There is evidence that a sleep-promoting factor accumulates during sleep deprivation in the brain of experimental animals (Fencl et al. 1971; Pappenheimer et al. 1975; Krueger et al. 1978; Nagasaki et al. 1974, 1980; Uchizono et al. 1978; see Borbély and Tobler 1980, for a short review). When the sleep factor was administered to rabbits, it induced the same type of EEG slow wave activity during sleep as sleep deprivation (Pappenheimer et al. 1975). The sleep factor has been also isolated from human urine (Krueger et al. 1980) and appears to be a muramyl peptide (Krueger et al. 1982). It is therefore possible that a specific neurochemical process may correspond to Process S of the present model.

*Evolutionary Implications*

As has been mentioned, the variations of the circadian component of sleep propensity (Process C) appear to be a mirror image of the body temperature rhythm. Under free-running schedules, body temperature assumes a periodicity that deviates only slightly from 25 h (Wever 1979; Fig. 37). The secretion of cortisol is another parameter exhibiting a prominent and stable circadian rhythm (Weitzman et al. 1979, 1981). It may be more than a coincidence that processes controlling vigilance, metabolism, and stress are all under the tight control of a circadian oscillator. Viewed from the evolutionary perspective, a "pre-programmed" reduction of metabolism coupled with an inhibition of spontaneous motor activity during specific parts of the day-night cycle may have enhanced the chances of survival. The presence of a circadian rest-activity rhythm in a wide variety of organisms which do not exhibit the electrographic features of mammalian sleep, suggest the possibility that the circadian rest-phase may represent a phylogenetic precursor of sleep. In the course of evolution, the advantage of confining the rest-phase to a predetermined part of the daily cycle may have been offset by the lack of a flexible behavioral response to unexpected external challenges during this period. Sleep as a more "need-dependent" process may have conferred added flexibility to a too rigidly programmed circadian rest-phase. In the framework of these arguments, REM sleep, a sleep state that is controlled to a large extent by a circadian oscillator, could be considered as a more "primitive" type of sleep. As has been mentioned, its sleep-dependent aspect of regulation is rather "sloppy", since variations of the amount of REM sleep within a relatively broad range (corresponding to the facultative REM sleep quota of Parmeggiani and Rabini 1970) do not give rise to a regulatory response (see also Borbély and Neuhaus 1979). It may have been the evolution of SWS which supplied a truly "need-dependent" component to sleep regulation, since it is sensitively regulated in response to prior sleep or waking and shows practically no circadian variation. Moreover, since slow wave activity presumably constitutes an intensity dimension of nonREM sleep, its regulation does not require adjustments in sleep time. This represents an important difference to REM sleep regulation where a large deficit has to be repaid in the hard currency of time. The cyclic alternation of nonREM and REM sleep periods may be an optimal solution for activation of the two types of sleep processes whose simultaneous occurrence seems to be precluded on neurophysiological ground.

In *summary,* the present model provides a link between the circadian rest-activity rhythm, an ubiquitous feature in living organisms, and sleep, a process that has been specified only in vertebrates. It is proposed that mammalian sleep is the combined result of a circadian and a sleep-dependent process. The circadian component of sleep appears to be closely related to the circadian rhythms of metabolic and endocrine processes. Circadian rhythms may have been of adaptive significance on an evolutionary scale. "Need-fulfillment" can be advanced as an explanatory construct to account for the sleep-dependent component of sleep regulation. Nevertheless, the specification of the "need" in terms of physiological and neurochemical processes remains an open problem and continues to constitute a major challenge in sleep research.

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