

An introduction
to the
mathematical
modeling
of the
sleep

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Lesson 3

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What we will learn today?

- The sleep
- Homeostatic and circadian aspects of the sleep
- Derivation of the 2-process model
- REM-nonREM sleep alternation
- Derivation of 2 variants of the McCarley's model

Sleep and literature

- Judeo-Christian tradition: the Bible compares death to sleep more than 50 times; New Testament writers consider that the disciples' inability to remain awake represented a figurative abandonment of Jesus
- In Greek mythology, Hypnos was the god of sleep; Hypnos lived next to his twin brother, Thanatos (death personified) in the underworld
- The "Roman Hypnos" was known as Somnus; the term Insomnia comes from this Roman name (insomnia = no sleep)



Sleep and literature

- William Shakespeare wove themes of sleep: *“To die, to sleep; To sleep: perchance to dream: ay, there's the rub; For in that sleep of death what dreams may come”* (Hamlet)
- Charles Dickens wrote of a specific sleep disorder in “The Pickwick Papers”
- “Baku” are Japanese supernatural beings that devour dreams and nightmares



Sleep research

The importance of sleep research is both in medicine and in mathematical modeling

After the pain, sleep disturbances are the second most frequent indicator of illness

During sleep, human brain goes through several psychophysiological states that are relatively stable

Moreover, many nervous centers are inactive, so brain becomes a less complex system and is a suitable object for mathematical modeling

Nevertheless, sleep is a mystery

Sleep and EEG

The beginning of modern sleep research dates back to the 1930s and is closely connected with the invention of the EEG

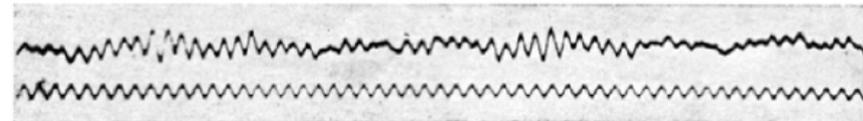
In 1937, Loomis was the first to observe that sleep is not a homogeneous state during the whole night and described different stages of sleep based on EEG

In 1953, Aserinsky and Kleitman observed a special state of sleep - rapid eye movement (REM) sleep -, during which rapid, binocularly symmetrical eye movements occur

They also divided nonREM sleep into 4 stages

Kleitman and Dement specified the cyclic pattern of REM-nonREM sleep

One cycle of REM-nonREM lasts about 90-100 minutes and during the night, 4-5 cycles occur





Studies of sleep regulation rely heavily on recordings of the EEG, which specify the stages of sleep and define their temporal organization

Sleep stages

The main states during the day are wakefulness, REM sleep and nonREM sleep

NonREM sleep is further divided into 4 stages from the lightest Stage 1 to the deepest Stage 4

Stages 3 and 4 are referred to as **slow wave sleep (SWS)**

The frequency of sleep stages alters during the night - in the early hours of sleep SWS dominates, whereas REM sleep occurs more often in the second part of sleep

The portion of REM sleep during night changes with age, in newborn babies REM sleep lasts for 50%, in adults for 20%

Sleep duration Approximately 8h

Sleep latency 10 min

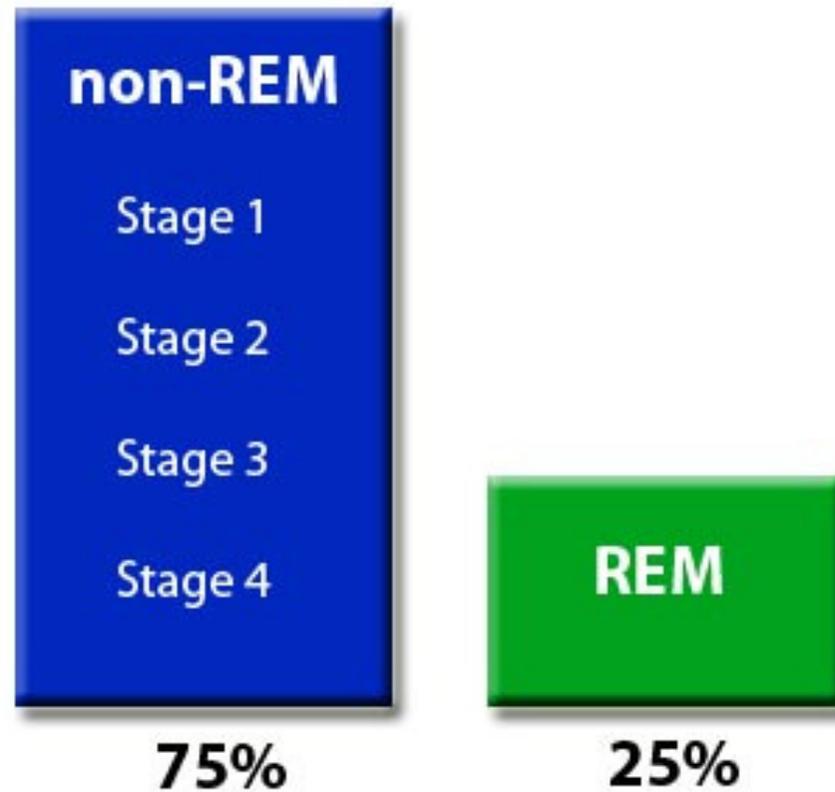
Stage 1 5%

Stage 2 50%

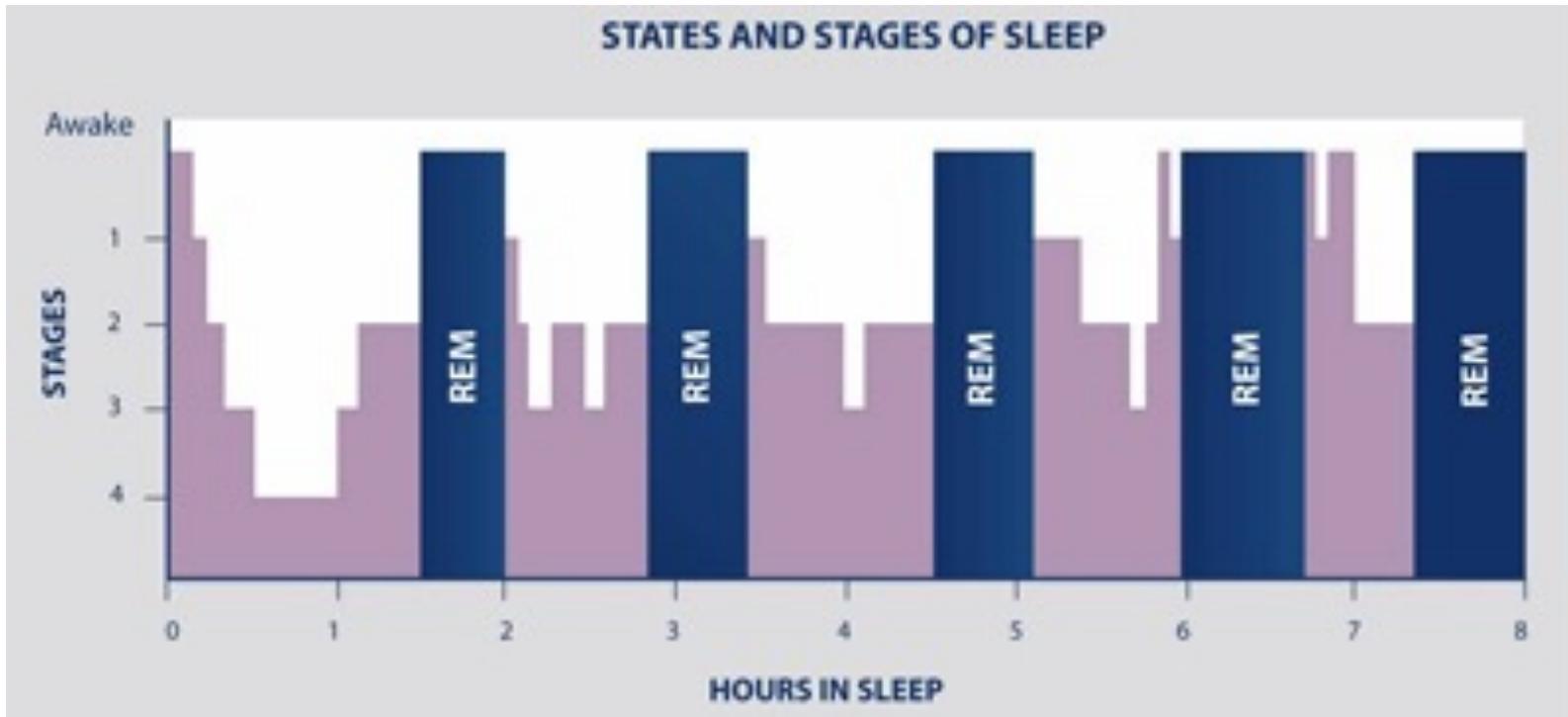
Stages 3 & 4 20%

REM 25%

Two Types of Sleep



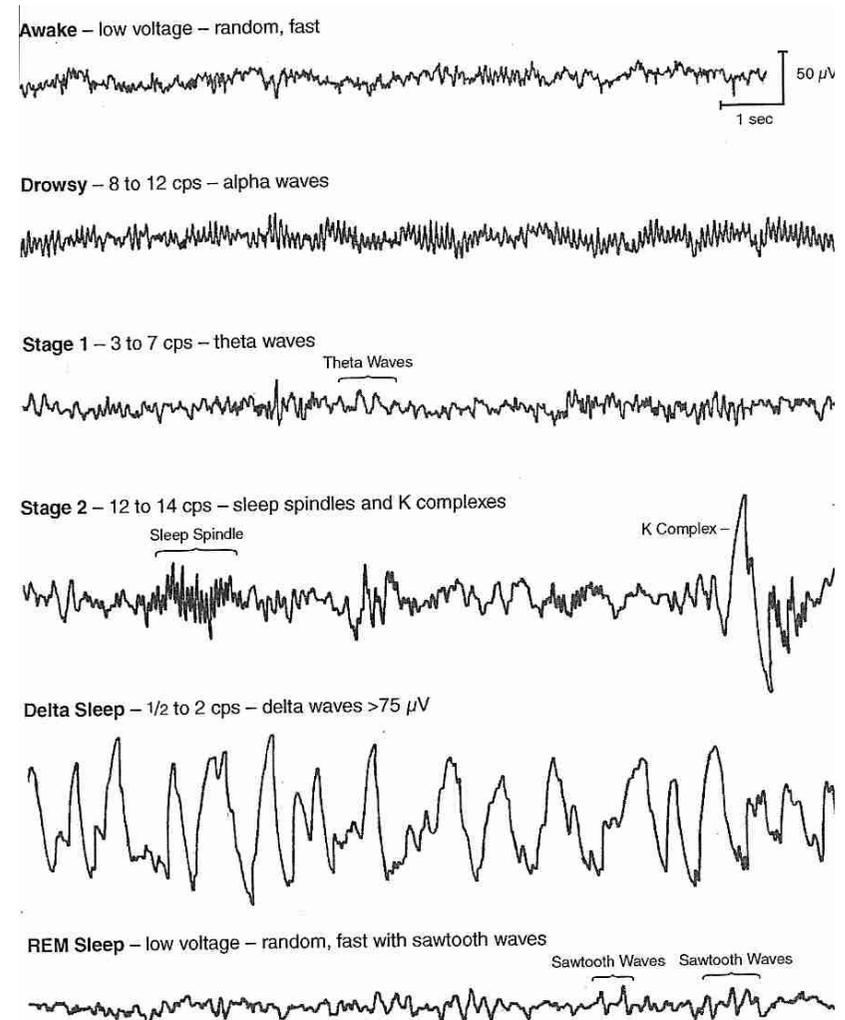
One cycle of nonREM and REM sleep



Sleep architecture: 4 - 5 cycles

EEG waves

- Alpha waves: 8 - 12 / 13 Hz
- Beta waves: 15 / 18 - 30 Hz
- Theta waves: 3,5 / 4 - 7,5 / 8 Hz
- Delta waves: 0,75 / 1 - 3 / 4,5 Hz
- Gamma waves: > 31 Hz



Theta and delta waves

- Normally are seen during sleep
- They are known as slow waves
- Delta waves are seen during deep sleep



Waking

- Adults are typically awake for at least two-thirds of the 24-hour day
- Behavioral cues, including open eyes, movement, and conversation, demonstrate alertness
- As activities wind down, people recline and close their eyes; it is at this time that the brainwaves slow to an alpha rhythm
- **Alpha rhythm is the bridge between wake and sleep**



nonREM sleep

Stage 1 is the typical transition from wakefulness to sleep

It is characterized by a reduction of **alpha** waves, and then by low amplitude mixed EEG frequencies in the **theta** range

It is the lightest stage of sleep; typically accounts for 5 - 10 % or less of the total sleep time in young adults

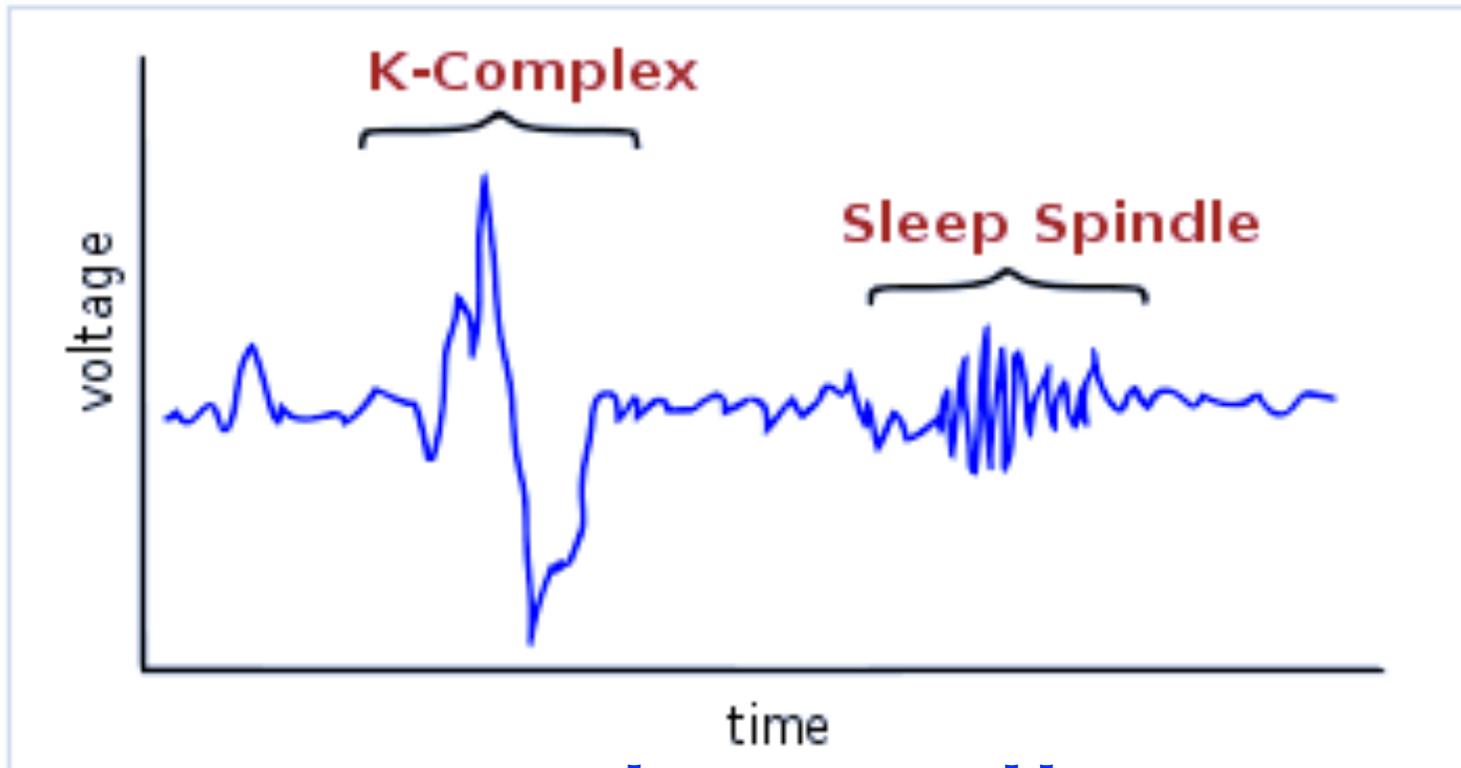
Stage 2 generally comprises the largest percentage of total sleep time in a normal middle aged adult, typically 45 - 55 % of the night

It is characterized by **theta** EEG frequency, but in addition there are two distinct features of nonREM sleep that appear for the first time on the EEG: **sleep spindles** and **K-complexes**

Stage 3 (in the past Stages 3 and 4) is frequently referred to as "**slow wave sleep**" or "deep sleep"

It is characterized by low frequency and high amplitude **delta** waves

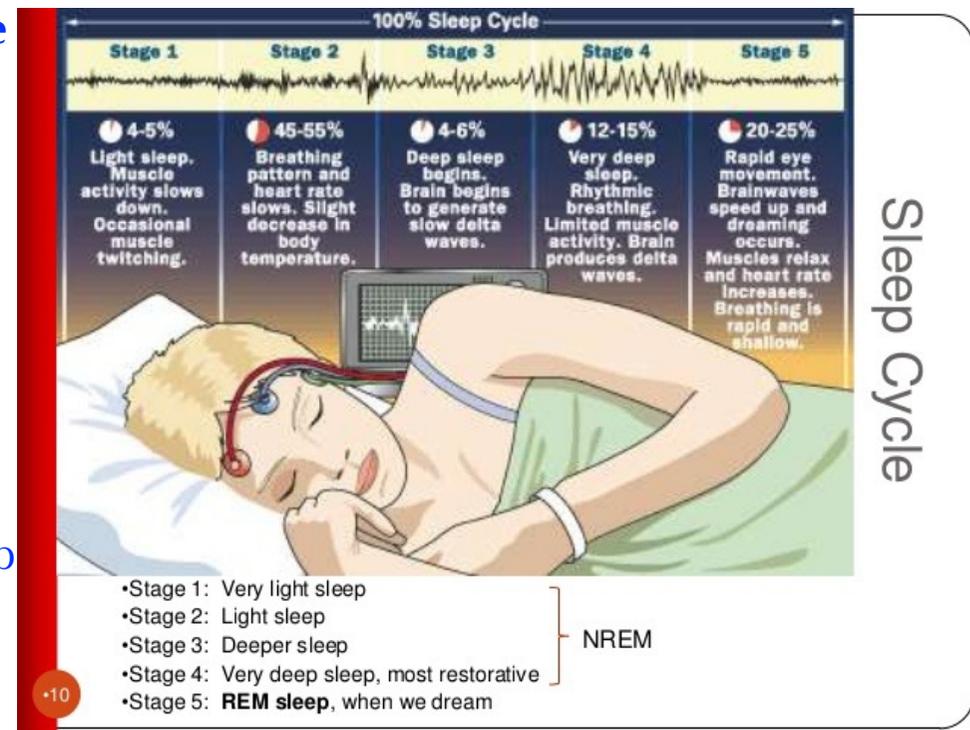
Stage 3 sleep typically accounts for 10 to 20 % of the total sleep time in young to middle age adults and decreases with age



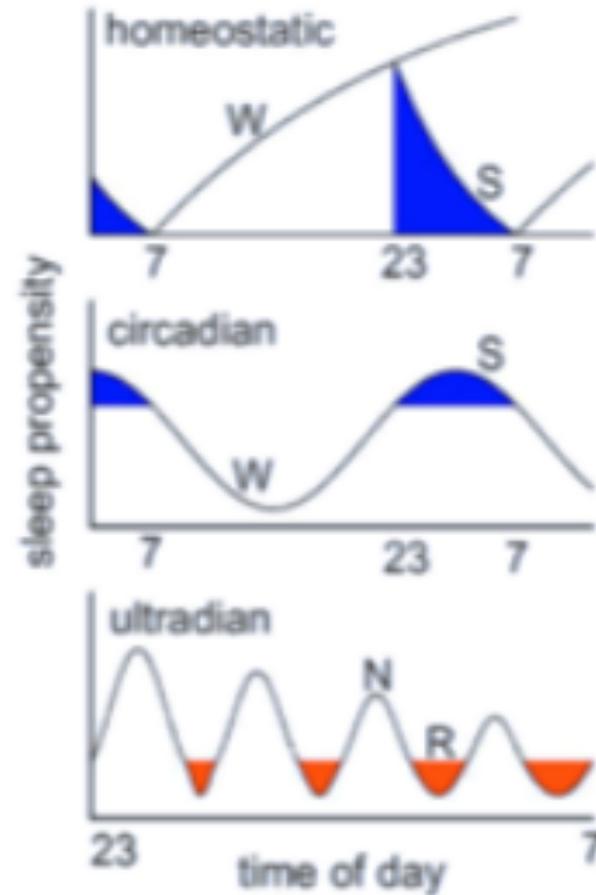
K and spindles

REM sleep

- There are 2 phases of REM sleep: phasic and tonic
- Phasic REM sleep contains bursts of **rapid eye movements**, respiratory variability, and brief electromyographic activity
- More limited motor activity occurs during tonic REM sleep, with few eye movements
- REM sleep has typically been associated with vivid dreaming, based on early studies in which patients were awoken out of REM sleep
- One hypothesis suggests that REM sleep is a time of memory consolidation
- Several sleep disorders may be related to abnormalities in REM sleep



Mathematical models of sleep regulation



Today it is generally accepted that there are 3 processes that regulate sleep:
a homeostatic process, a circadian process and an ultradian process

Homeostatic process

The term **sleep homeostasis** refers to the sleep-wake dependent aspect of sleep regulation, because homeostatic mechanisms counteract deviations from an average reference level of sleep

The homeostatic process takes control of the amount of sleep and wakefulness, so that the homeostasis is reached

It increases the fatigue and sleep propensity during wakefulness and decreases it during sleep

The longer we are active (and, perhaps, the more we are active), the deeper we sleep



Circadian process

Circa: "about" Dies: "day"

Circadian rhythms are physiological and behavioral characteristics that follow a pattern

cycle lasting approximately 24 h

Circadian process reflects the influence of external events which oscillate with circadian rhythm

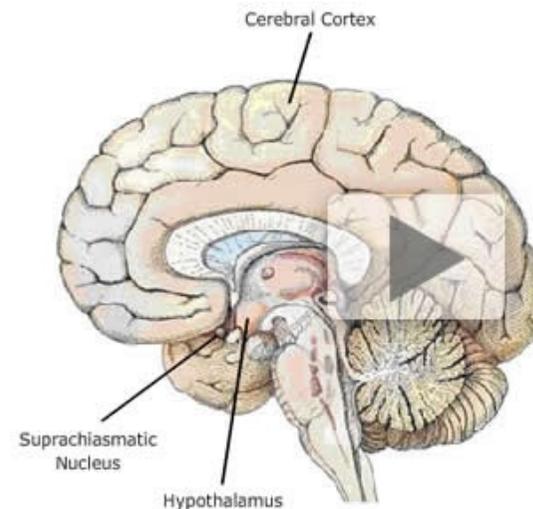
Circadian principle in the sleep represents the alternation of sleep propensity with 24 h rhythm:

the longer we are active, the shorter we sleep



Circadian process

- In humans, the main pacemaker regulating endogenous (internal) circadian rhythms is the **suprachiasmatic nucleus (SCN)**
- This is a small group of cells located in the area of the brain called the **hypothalamus**
- On the contrary, until now, physiological centre of the homeostatic process has not been identified



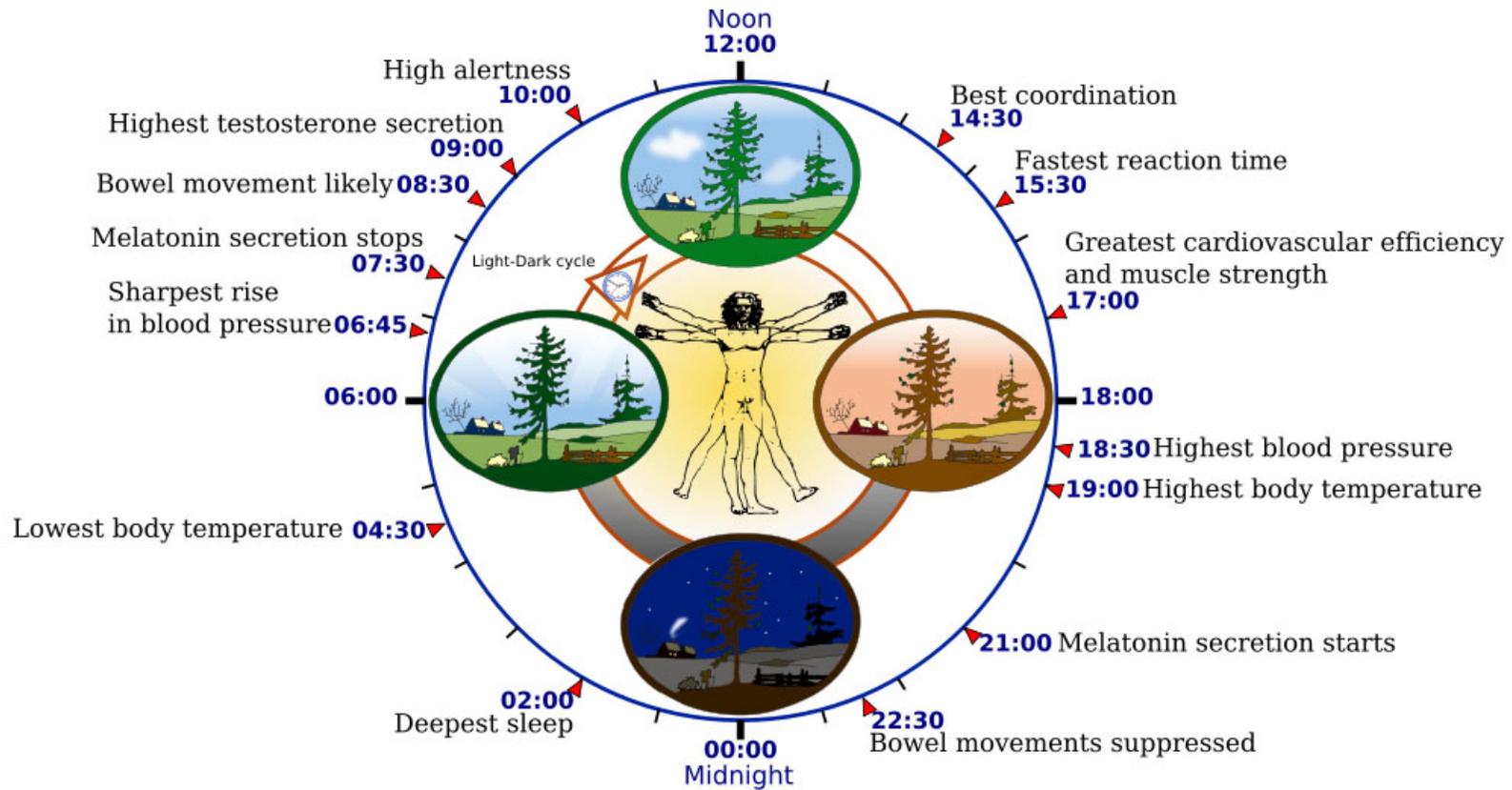
Synchronizes behaviors and regulates timing related to:

Temperature

Sleep-Wake Cycle

Hormone Release

Eating Behavior



Examples of circadian processes

Ultradian process

- Ultradian rhythms: a period or cycle shorter than a day
- milliseconds it takes for a neuron to fire
 - 90 / 100 minutes sleep cycle (REM and nonREM sleep)
 - your attention span in class

On the contrary, infradian rhythms have period longer than a day



The 2-process model of Borbely & Daan

(qualitative model 1982; quantitative model 1984)

This model assumes the interaction of the homeostatic S and circadian C processes

S, representing sleep debt, increases during wakefulness and declines during sleep, within a value-range that oscillates with a periodicity that is normally entrained to day and night by a circadian pacemaker



The process C

- The Authors postulate a first process C, regulated by a circadian pacemaker
- It can be entrained by an external cue, called **zeitgeber**, that influences the timing of this internal clock, by providing a stimulus
- The most common example of zeitgeber is the **light - dark** cycle, via the **retinohypothalamic** tract and the **pineal gland** that releases **melatonin**
- Readiness for nocturnal sleep is initiated by the circadian signal of melatonin release in the evening, which induces distal vasodilatation, enhancing the probability of sleep onset

The process C

- The investigation of circadian factors is difficult under standardized experimental conditions, as a variety of environmental and circadian rhythms occur
- For the analysis of the circadian aspects of the sleep, the association between sleep and body temperature is very important
- Several studies concur that the variations in sleepiness are a mirror image of the body temperature rhythm
- Sleep propensity is highest at the time of the circadian temperature minimum and lowest at the time of the temperature maximum

Outline of the model

- Borbely & Daan introduce a second process S
- S increases during wakefulness and decreases during sleep
- The begin of sleep and wakefulness occur when S is above or below the thresholds H and L , respectively
- The model rests on the assumption that 2 independent processes underlie sleep regulation

Some experimental data on the independence of the 2 processes

In the course of a prolonged sleep deprivation period, subjective alertness showed a prominent circadian rhythm

In studies in which the phase of the circadian process (as indexed by body temperature and plasma melatonin) was shifted by morning bright light, the course of slow waves sleep (which is connected to S) remained unaffected

Furthermore, the homeostatic response to sleep deprivation persists even after circadian rhythmicity had been disrupted or abolished by lesioning the suprachiasmatic nucleus (in animals)

Some experimental data on connection between S, slow waves sleep (SWS) and slow waves activity (SWA)

- With the progression of waking time, the level of sleepiness increases and sleep latency (i.e. the amount of time that it takes to fall asleep) shortens
- **The association between sleep parameters and the duration of prior waking is not linear:** the “slept debt” is only partially compensated by an increase in the duration of recovery sleep and, probably, sleep loss can be balanced by an enhancement of sleep intensity (during nonREM sleep)
- The Authors chose SWS as a candidate for a high-intensity sleep because: i) it predominates in the first part of the sleep; ii) it is enhanced after sleep deprivation iii) if the sleep time is extended and/or naps occur the amount of SWS is reduced
- The **EEG spectral power in the delta band** (0,75 - 4,5 Hz) has been selected as a physiological indicator of the intensity of the sleep process: EEG slow-wave activity - **SWA**

EEG spectral power

"Spectral power" answers the question "which frequencies contain the signal's power?"

Spectral analysis is used to investigate the signal's power in the various frequency bands

It is based on Fourier transform which displays signal in the frequency domain:

$$X_k = \sum_{j=0}^{N-1} x_j e^{2\pi i j k / N} \quad k = 0, \dots, N-1$$

where x_1, \dots, x_N is the measured signal in the time domain, X_k is the amplitude corresponding to the k^{th} frequency and N is the number of values

An example

The spectral power of a particular frequency band is computed as the sum of modulus-square amplitudes belonging to this band

The power in EEG alpha band (8Hz-12Hz)

$$P_{\alpha} = \sum_{k=k_{8Hz}}^{k=k_{12Hz}} |C_k|^2$$

where k_{8Hz} is the lower limit of alpha band and k_{12Hz} is the upper limit of alpha band

And what about EEG delta band?

The qualitative model: the sleep propensity

- Sleep propensity is assumed to be determined by the combined action of the S and C processes
- The top of the picture shows the exponential decline of SWA after a waking period (continuous line) and a prolonged vigil (interrupted line)
- The lower part shows the time course of S obtained by interpolating selected measure values of SWA
- **Sleep propensity corresponds to the difference between S and C (or to the sum between S and - C)**

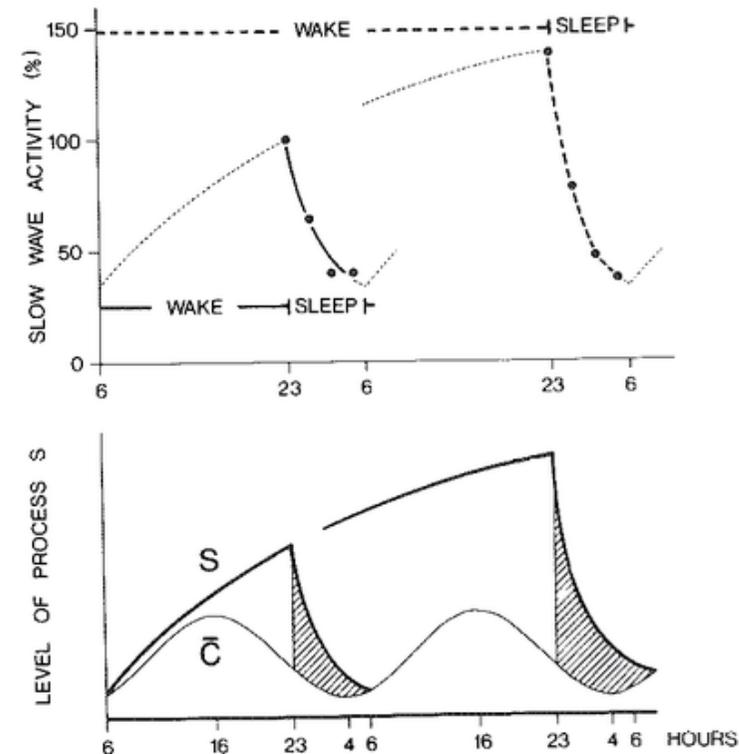


Fig. 4. Timecourse of sleep processes after regular and extended waking periods. *Upper part:* Exponential decline of slow wave activity over four consecutive sleep cycles (value of first cycle = 100%; cf. Fig. 2) for a baseline night (continuous line) and after sleep deprivation (interrupted line). 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)

The qualitative model: the sleep propensity

- The process C is represented by a sine function
- The minimum of the function was set for 16 h and the maximum for 4 h
- In the lower part of the figure, the negative image of C ($-C$) has been plotted; $-C$ can be interpreted as the circadian body temperature (maximum: 16 h and minimum: 4 h)

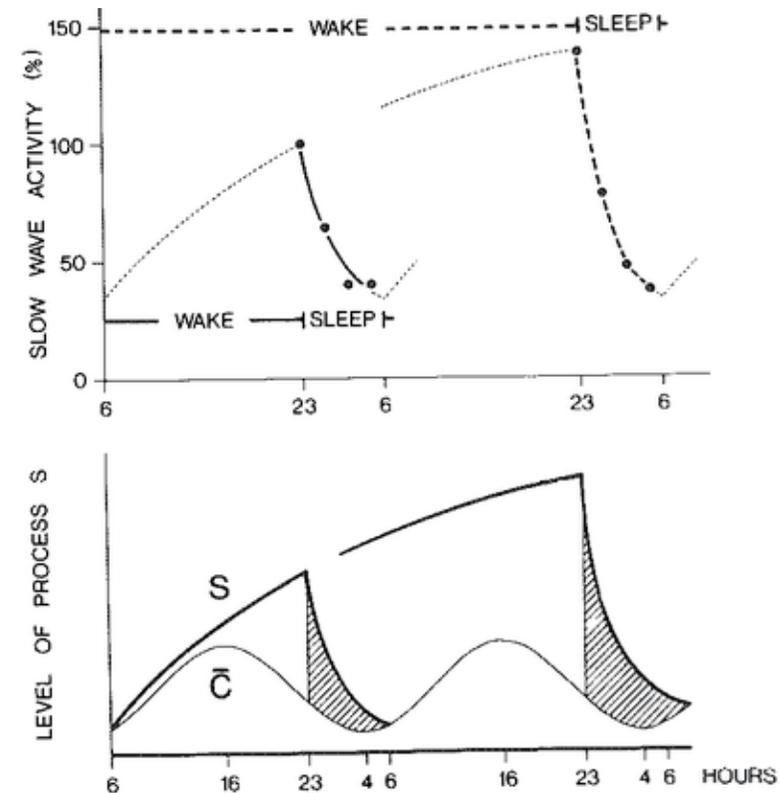
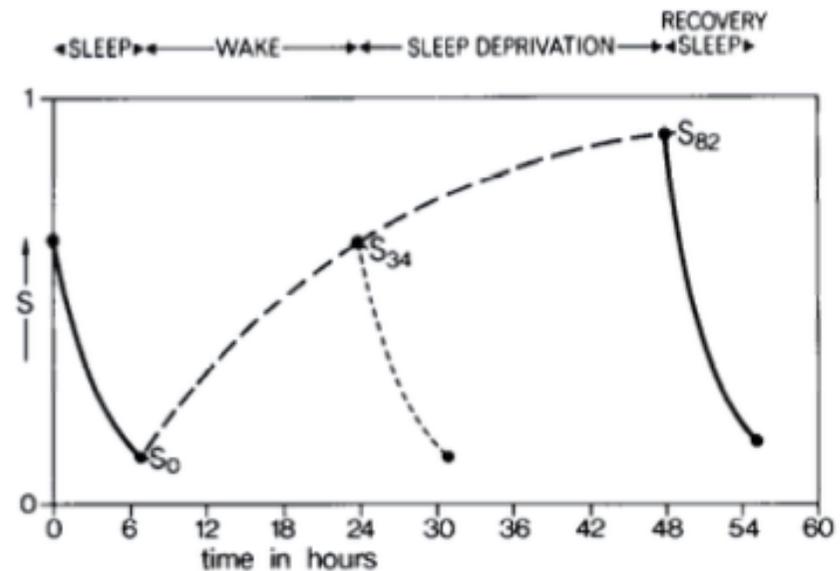


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The qualitative expression of S: during wakefulness

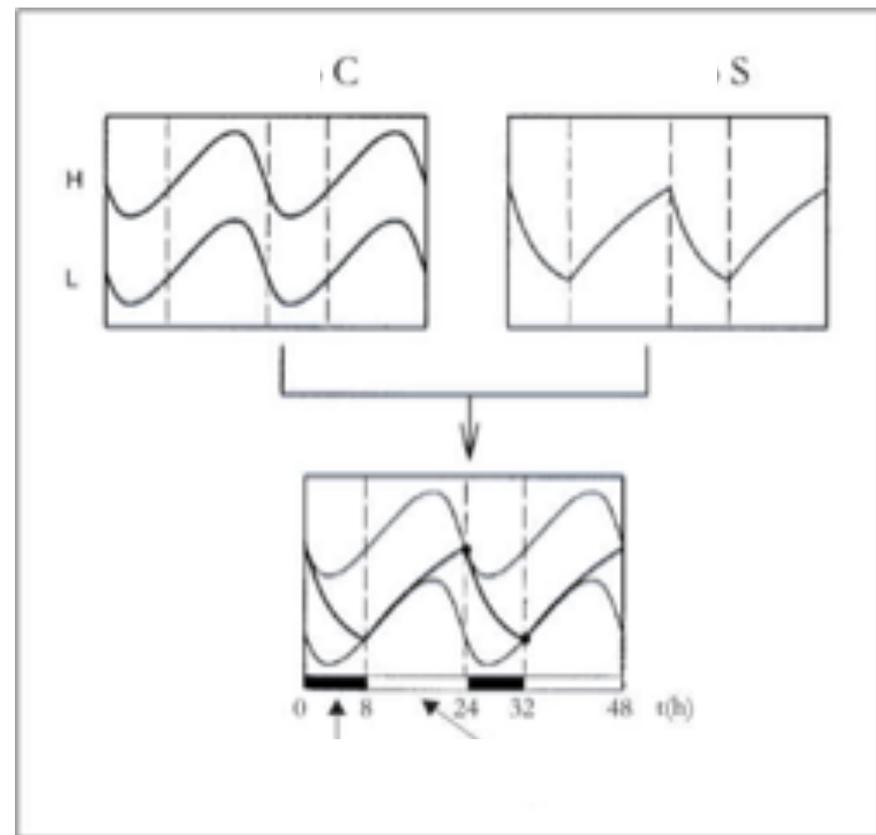
The rate of S buildup has been estimated by interpolating 3 data points:

- EEG SWA at the end of a normal sleep night (S_0 in the picture)
- SWA at the end of a normal waking day (S_{34})
- SWA after 24 h of sleep deprivation (S_{82})

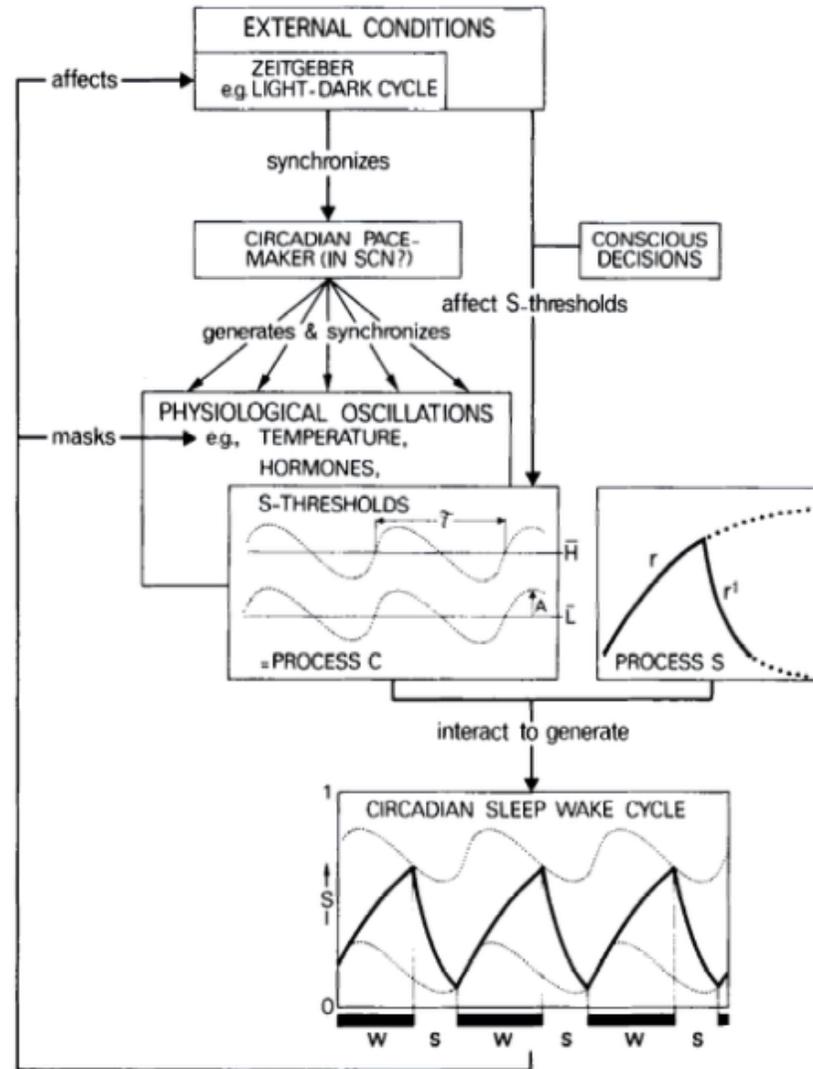


The qualitative model: the begin and the end of the sleep

- In the 2-process model the sleep homeostatic process and the circadian process interact only at discrete (2) events
- S increases monotonically during wakefulness until it reaches H , at which point **sleep is initiated**, and declines monotonically during sleep until it reaches L , when **sleep is terminated**
- The system acts like a **thermostat** (“somnostat”) that switches off at a higher threshold than it switches on
- The H threshold could be influenced by habits, for example naps may decrease H and social stimulations could increase it



INVITED OPINIONS



The 2-process model

The quantitative expression of S: during sleep

S is described by a recursive formulation

S decreases and asymptotically approaches 0 during the sleep

$$S(t = i) = e^{-d/2} * S(t = i - 1)$$

d is the decay factor of S, t the time

From experimental data on healthy subjects, the Authors estimated $d = 0,238$, considering that the decrease of SWA during sleep is essentially exponential:

$$S(t = i) = 0,888 S(t = i - 1)$$

In all simulations, 30-min period has been used as a convenient time unit

The quantitative expression of S: during wakefulness

S increases and approaches an upper asymptote U

$$S(t = i) = U - e^{-r/2} [U - S(t = i - 1)]$$

r is the rise factor of S

For convenience, the Authors assumed $U = 1$

From experimental data $r = 0,055$:

$$S(t = i) = 1 - 0,973 [1 - S(t = i - 1)]$$

Derivation of thresholds

If 7:00 a.m. (S_0) and 11:00 p.m. (S_{32}) represent the average times of spontaneous sleep termination and onset in healthy adults:

$$S(t = i) = 0,888 S(t = i - 1)$$

$$S_0 = S_1 * 0,888^2 = \dots = S_{32} * 0,888^{16} = 0,093$$

(minimum of sleepiness)

$$S(t = i) = 1 - [1 - S(t = i - 1)] * 0,973$$

$$S_{32} = 1 - (1 - S_{31}) * 0,973^{31} = \dots = 1 - (1 - S_0) * 0,973^{32} \\ = 0,622 \text{ (maximum of sleepiness)}$$

The quantitative expression of C

- A amplitude of skewed wave;
t: time; tau: period of C; t₀:
the circadian phase at the
beginning of the simulation

$$C = A \left\{ \begin{array}{l} 0.97 \sin[\omega(t-t_0)] + 0.22 \sin[2\omega(t-t_0)] + 0.07 \sin[3\omega(t-t_0)] \\ + 0.03 \sin[4\omega(t-t_0)] + 0.001 \sin[5\omega(t-t_0)] \end{array} \right\}$$
$$\omega = \frac{2\pi}{\tau}$$

- Core body temperature and
melatonin rhythms are
markers of C

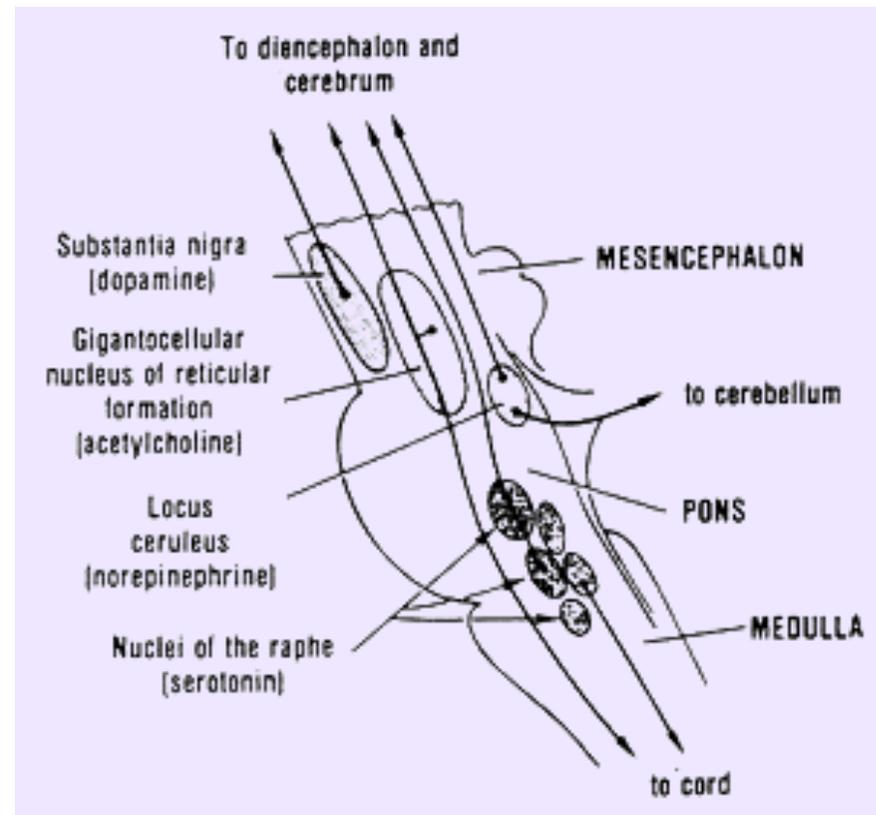
Model weakness

- While SWS is the “high intensity” fraction of nonREM sleep, SWS and REM sleep exhibit opposite trends in the sleep period
- The proportion of REM sleep increases across successive nonREM - REM sleep cycles, a trend that becomes even more apparent if sleep is extended into the morning hours
- This model is not complete, because it does not take into account the cyclic succession of nonREM-REM sleep

- The circadian literature is replete with physical, electronic, and mathematical models and these analyses have proved invaluable for understanding the basic properties of circadian oscillators
- On the contrary, researchers who have attempted to model the mechanisms generating the REM-nonREM cycle are few; in ultradian rhythmicity, functions are far from clear
- Dement and Kleitman's research provides us with evidence of internal infradian and ultradian rhythms which help control cycles within the body, but such research is mostly conducted in a laboratory setting which lacks external validity as results may not generalize to real life settings

The McCarley-Hobson (1975)

McCarley and Hobson proposed a model of REM sleep, and supposed that reciprocal interaction between excitatory and inhibitory neural populations may determine the alternation of nonREM-REM sleep



Experimental observations

MH observed time course of discharge activity in **2** neuronal populations:

- “**REM-on**” neurons in the pontine reticular formation mPRF (in particular pontine giant cell field) that became active in REM sleep and promote this sleep phase;

- “**REM-off**” neurons in the locus coeruleus (LC) and dorsal raphe nucleus (DR) whose discharge activity had a reciprocal time course to the “REM-on” population

“REM-off” cells nearly ceased discharge activity with the advent of REM sleep

What mechanisms might be involved in generation of these non sinusoidal, periodic neuronal activity curves?

The most relevant features of the discharge time course of REM-on neurons, over multiple sleep-waking cycles, are the periodically and non sinusoidal occurring peaks of discharge activity, each of which corresponds to a REM episode

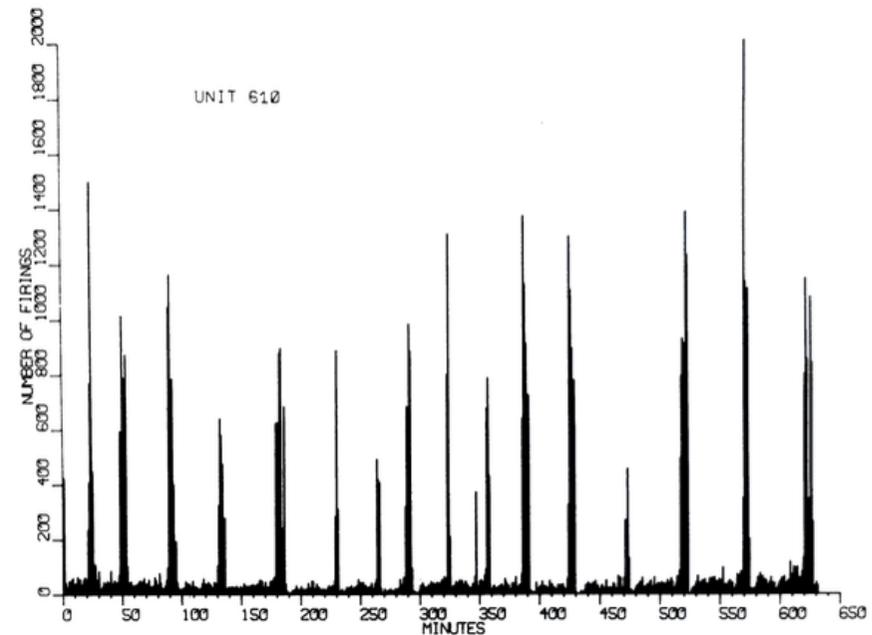


Fig. 1. Discharge activity of FTG neuron 610 recorded over multiple sleep-waking cycles. Each peak corresponds to a desynchronized sleep episode, and a regular trend of discharge activity over a cycle is observable: a peak in desynchronized sleep; a rapid decline at the end of the desynchronized sleep episode; a trough, often associated with waking; a slow rise (in synchronized sleep); and an explosive acceleration at desynchronized sleep onset. Note also the extreme modulation of activity and the periodicity.

What mechanisms might be involved in generation of these non sinusoidal, periodic neuronal activity curves?

- No proof for the time course of REM-on generated by pacemaker neurons involved in control of ultradian rhythmic activity
- McCarley and Hobson hypothesized that the periodic occurrence of REM sleep might be a function of reciprocal interaction between REM-on and REM-off populations

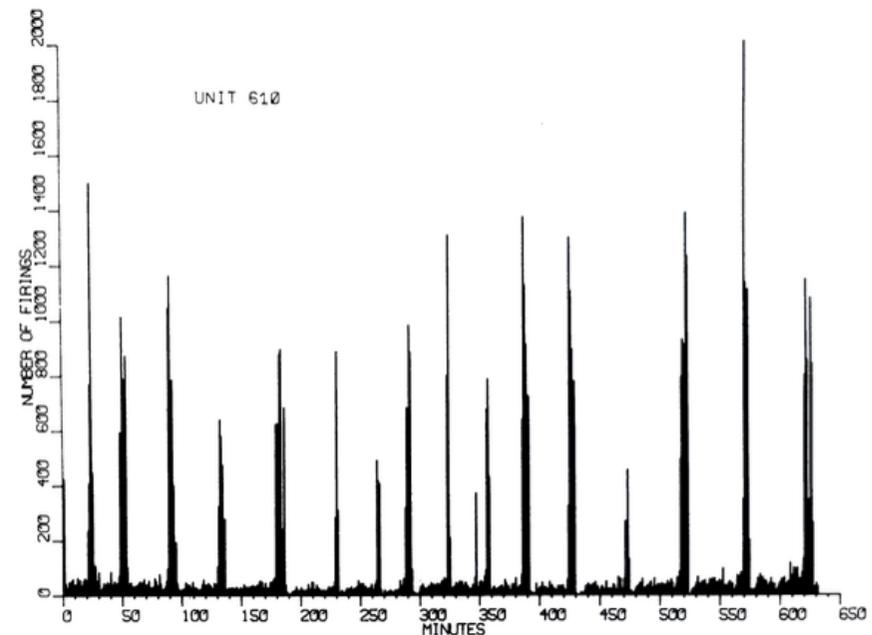
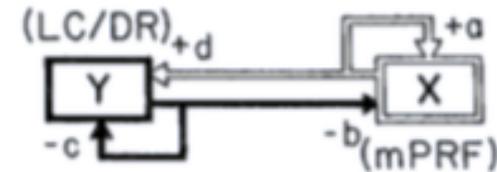


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The reciprocal interaction model

- X represents the population REM-on, excitatory, and medial pontine reticular formation (mPRF) neurons are used as exemplars
- Y is the population REM-off, inhibitory, and locus coeruleus (LC) and dorsal raphe (DR) neurons are used as exemplars
- “-” indicates inhibitory and “+” excitatory connections
- The model describes the influence of REM-on itself (“+ a”) and an excitatory effect of REM-on on REM-off population (“+ d”), probably using acetylcholine as a neurotransmitter
- The Authors proposed the same for REM-off population but with a negative sign because the feedback is inhibitory, respectively “- c” and “- b” terms, i.e there is an inhibitory effect of REM-off on REM-on, probably regulated by the neurotransmitter norepinephrine



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The reciprocal interaction model

- The highly non sinusoidal nature of REM-on activity suggests a nonlinear REM-on / REM-off interaction
- McCarley and Hobson model the nonlinearity effect with the product of activities in the 2 populations
- This is in accord with the physiological hypothesis that the effect of an excitatory (or inhibitory) input to the population will be proportional to the current level of discharge activity

Mathematical formulation

It is a Lotka - Volterra (LV) system, originally proposed as a model for prey - predator interaction:

$$X'(t) = aX - bXY \text{ and}$$

$$Y'(t) = -cY + dXY$$

It is a system of first-order nonlinear differential equations

As **REM-on** neurons excite themselves, they behave as an autonomous self-replicating **prey** population

On the contrary, **REM-off** neurons inhibit the growth in the activity of mPRF neurons while their own activity die off in the absence of mPRF input, so they behave as a **predator** population



LV system

$$X'(t) = aX - bXY \text{ and } Y'(t) = -cY + dXY$$

X and Y represent the firing rate of REM-on and REM-off populations, respectively

$X'(t) = aX \longrightarrow X(t) = e^{at}$, a constant, shows the REM-on response to self-excitation (that increases exponentially)

$X'(t) = -bXY \longrightarrow X(t) = e^{-bYt}$, represents the exponential decay of X activity, with a rate dependent on constant b and Y activity

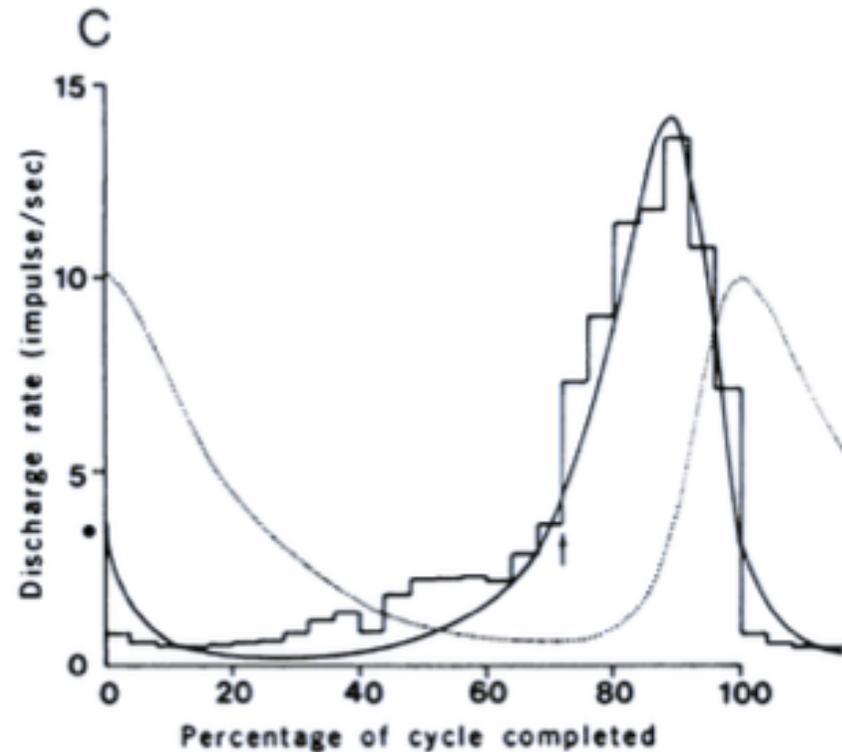
$Y'(t) = -cY \longrightarrow Y(t) = e^{-ct}$, c constant, represents an exponential decay in Y activity

$Y'(t) = dXY \longrightarrow Y(t) = e^{dXt}$, is the exponential growth of Y activity, with a rate dependent on constant d and X activity

The Authors found a good match between theoretical behavior of REM-on neurons and experimental data

The line histogram describes the observed data, while the solid curve the REM-on fit and the dotted line the REM-off fit derived from the model (with $a = 0,55$; $c = 0,27$; $x(0) = 1$; $y(0) = 3$)

The dot in the ordinate scale indicates the equilibrium values for the 2 populations

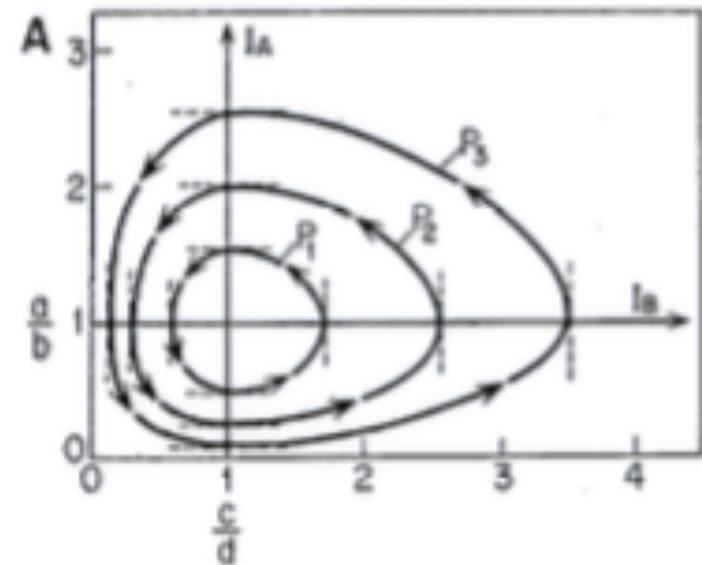


LV system

- The equations have periodic solutions and there is not a simple expression in term of trigonometric functions
- Population equilibrium occurs in the model when neither of the population levels is changing, i.e. when both of the derivatives are equal to 0; so the 2 solutions are $P_0(0, 0)$ and $P^*(c/d, a/b)$
- P_0 represents the extinction of both species, and P^* a fixed point at which both populations sustain their current numbers
- The levels of populations at which this equilibrium is achieved depend on the chosen values of a , b , c and d
- The study of stability of P^* shows that the levels curves are closed orbits surrounding the fixed points: the levels of populations cycle and oscillate around the fixed point

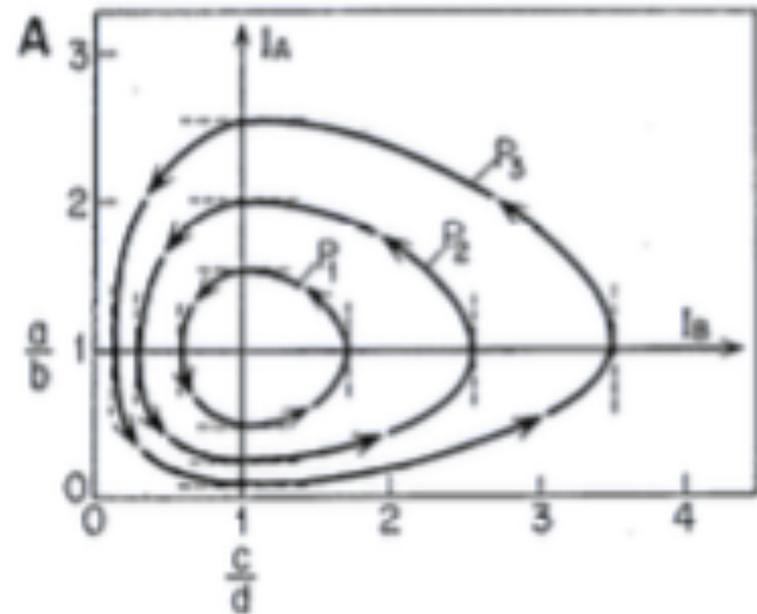
LV system

- LV study is facilitated by plotting the level of activity of X vs. that of Y, at different times; this X - Y phase plan captures the evolution of the X - Y interaction when we start with different combination of population levels (i.e. low X and Y, high X and low Y...)
- The level of X is plotted on the x-axis while the level of Y on the y-axis
- Each point represents a combination of levels of the 2 populations
- Any stable oscillation of X and Y populations is represented as a closed oval orbit (path), with a constant “energy level”



LV system

- In the picture, P_1 , P_2 , and P_3 correspond to separate solutions generated by different initial conditions and with the same values for a , b , c and d
- For each population, there is a (zero) isocline; for example the X isocline is a combination of levels of the 2 populations where X does not increase or decrease
- The isocline equations are $I_A: X = c/d$ and $I_B: Y = a/b$; in the figure being $a = b = 2c = 2d$, the isoclines are located at $X = 1$ and $Y = 1$



Limitations in LV model

The LV system displays “neutral stability”, that is the system’s long-term behavior was determined entirely by its initial conditions

This would imply that, to generate the REM-nonREM cycles, a REM oscillator would have to be set into motion each night with highly reproducible precision and to maintain stability in the face of internal and external influences

LV model produces a cyclic behavior, but the cycles are not stable limit cycles (i.e. not able to assimilate small perturbations and to come back to the original configuration); on the contrary, if perturbed the LV system would origin a different cycle

These conditions are alien to physiological systems

Towards a new version of the model

An additional complications of the “neutral stability” was the difficulty in modeling circadian influences, which would have necessitated postulating the existence of unreasonable phase resetting mechanisms

Furthermore, the LV system does not explain the increases in REM length during the sleep

Finally, there is no limitation on the amplitude of neuronal discharge

The limit cycle or McCarley-Massaquoi model (1986)

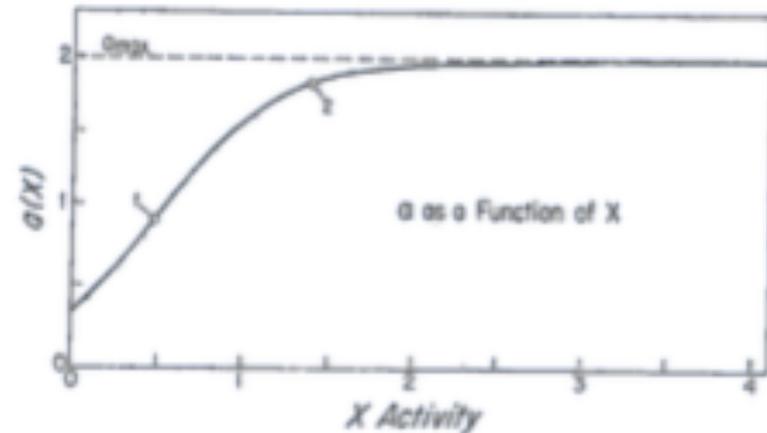
The model is mostly based on physiological data

$$X'(t) = a(X) X S_1(X) - b(X) X Y \text{ and}$$

$$Y'(t) = -cY + d(\text{circ}) X Y S_2(Y)$$

$a(X) = a_{\max} L_1(X)$, where $L_1(X)$ is a sigmoid, i.e. a function defined by $1 / (1 + e^{-t})$

$a(X)$ is the REM-on self-excitation growth function, smaller with smaller X



Limit cycle model

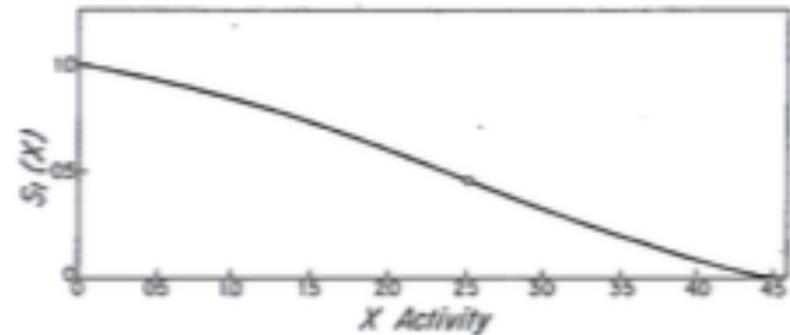
$S_1(X)$ is a sigmoidal saturation function that constrains the growth of REM-on population to finite levels

The slow rate of descent of S_1 reflects the heterogeneity of the X population, i.e. some neurons are limited at relatively low rates and others at relatively high discharges rates

$b(X)$ indicates REM-on dependence on REM-off inhibitory input; that means that it exists a nonzero basal level of REM-on activity that cannot be suppressed by inhibition

$$b(X) = b_{\max} * 1 / (1 + e^{-80(x - 0,11)}),$$

where b_{\max} is set to 2



Limit cycle model

REM-off firing rate is also dependent on the phase of the circadian temperature oscillator

$d(\text{circ})$ indicates the dependence of d of circadian aspects of the sleep:

$$d(\text{circ}) = d + A \sin(\omega t + p_0),$$

where d is the average level (fixed), A the amplitude of the oscillations (fixed), p_0 is the circadian phase in radians at start of simulation, t the time, and ω the frequency of oscillation (period = 24 h)

$d(\text{circ})$ modulates Y and X (if Y is high thus X activity is low) and also turns the REM sleep oscillations on and off

$S_2(Y)$ is a sigmoidal saturation function, limiting the growth of REM-off to finite levels

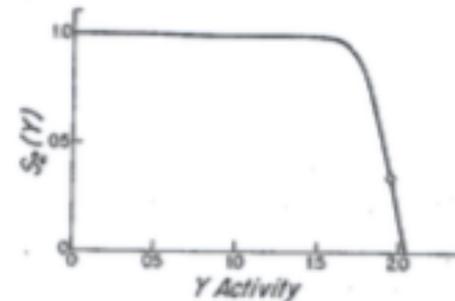
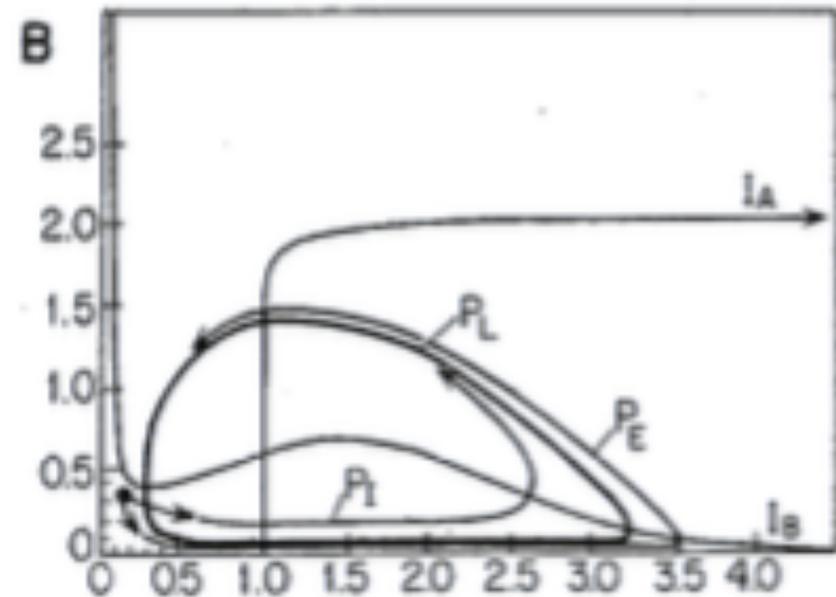


FIG. 17. Shape of logistic curve indicating limitation on locus coeruleus maximal firing rates.

Solutions

- The limit cycle model solutions are families of spirals that converge to a unique oval termed the limit cycle (P_L)
- P_L is approached regardless of whether the initial approach is exterior (P_E) or interior (P_I) (depending on the starting conditions), demonstrating the stability of the oscillatory system



The McCarley's models: 40 years later

The history of the McCarley models encompasses the history of discovery of neurons and neurotransmitters involved in REM sleep



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Control of Sleep and Wakefulness

Ritchie E. Brown, Radhika Basheer, James T. McKenna, Robert E. Strecker, Robert W. McCarley
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Abstract

The Borbely's model: 30 years later

- Brain differentiation: **regional differences in the sleep EEG**; analysis of the parameters of process S have confirmed topographic differences
- Both the increase and decrease of S are slowest in the front - central area
- Such regional differences imply that quantitative SWA predictions are dependent upon which brain area is chosen to estimate the time course of S
- In the Borbely's original model, the homeostatic and the circadian processes interact at discrete events (H and L thresholds); now, scientific evidence suggests a **continuous mutual influence between the 2 processes**

30 years later

- The view of the circadian system has undergone profound changes; the **SCN is now viewed as orchestrating and integrating rhythms** rather than simply generating and driving them
- Now it has been hypothesized **a role for the metabolism** in determining the rest - activity rhythms relative to the SCN
- Furthermore, if sleep does not occur within the appropriate phase of the sleep-awake cycle, by being either too short or too long, the risk of **type 2 diabetes** increases

Some references

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An exercise

Try to find an alternative expression for S