A Mathematical Model of Sleep Regulation

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Why mathematical models?

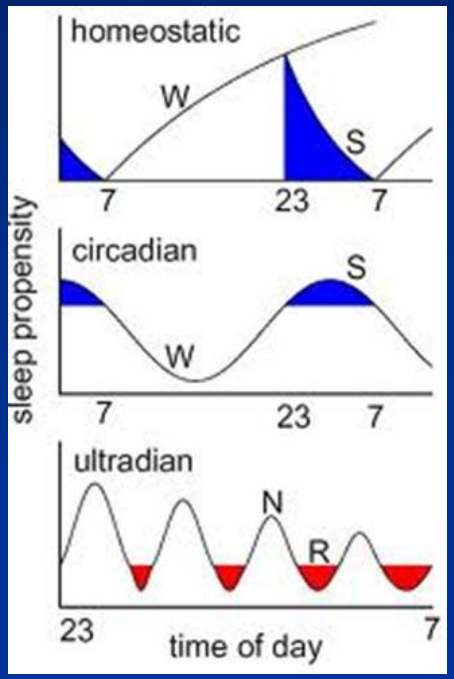
Human beings spend a third of their life in sleep, which along with diet and exercise is vital for good health. Modern life has desynchronized our lives from nature causing disruption of sleep.

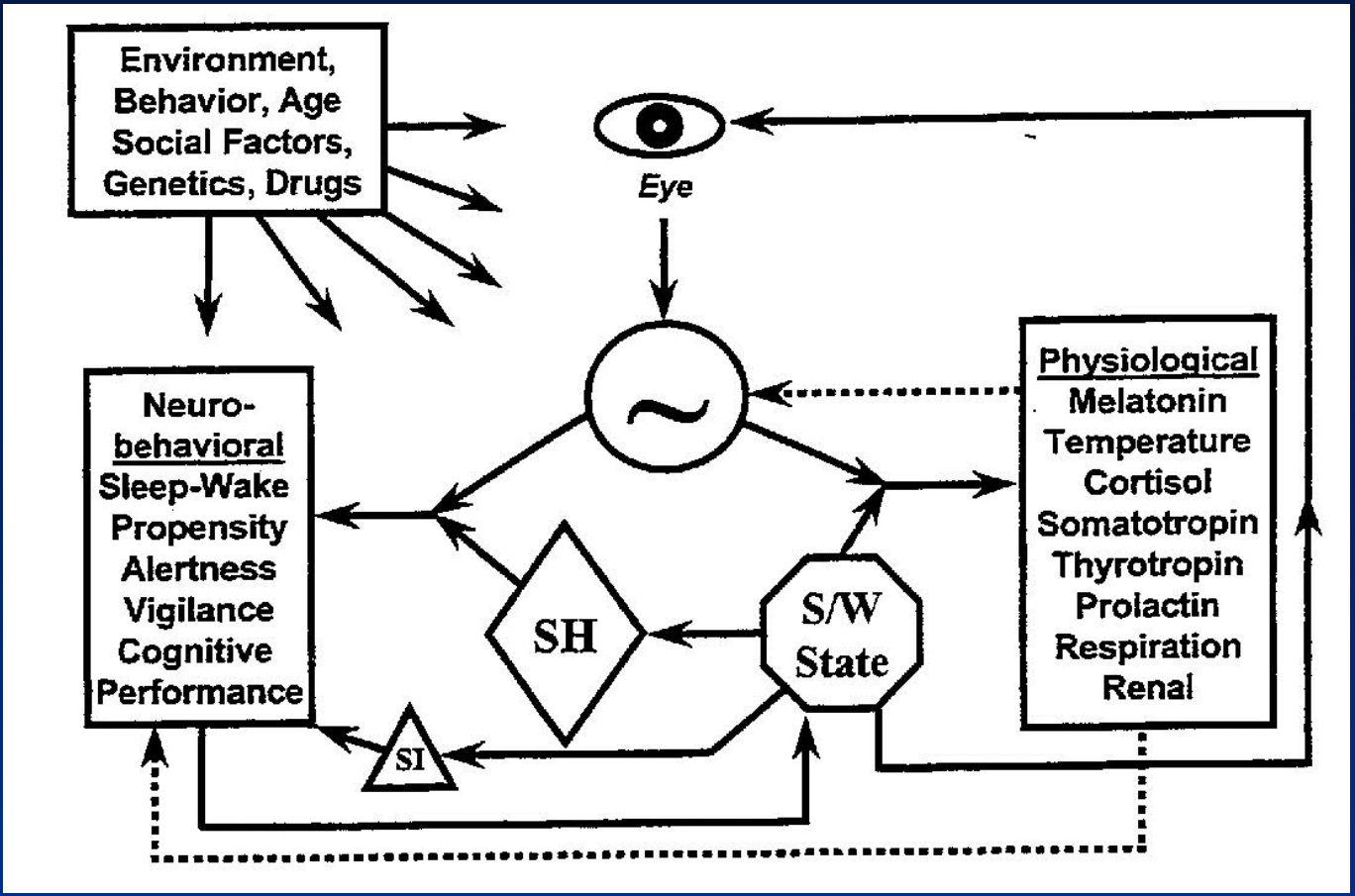
Mathematical models can help provide insight into the mechanisms underlying human sleep patterns and predict consequences of different sleep-wake schedules on behavior, mood and performance.

Sleep Terminology

Humans alternate between waking(W) and Sleep(S) states. Sleep is an active process consisting of alternating Rapid Eye Movement (REM) and non-REM (NREM) sleep. The processes underlying sleep regulation consist of

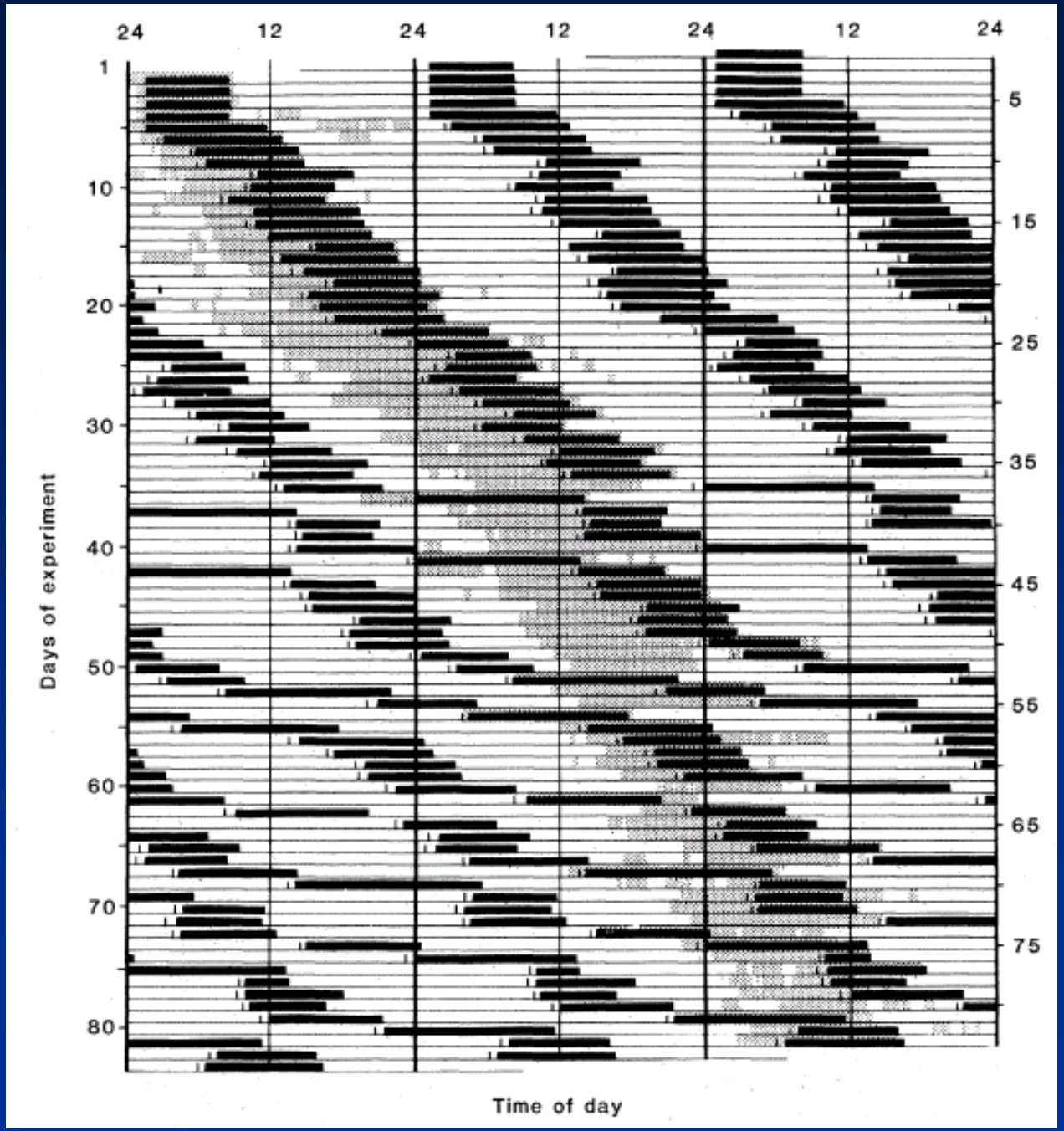
1) **a *homeostatic* process;**
2) **a *circadian* process**
3) **an *ultradian* process**

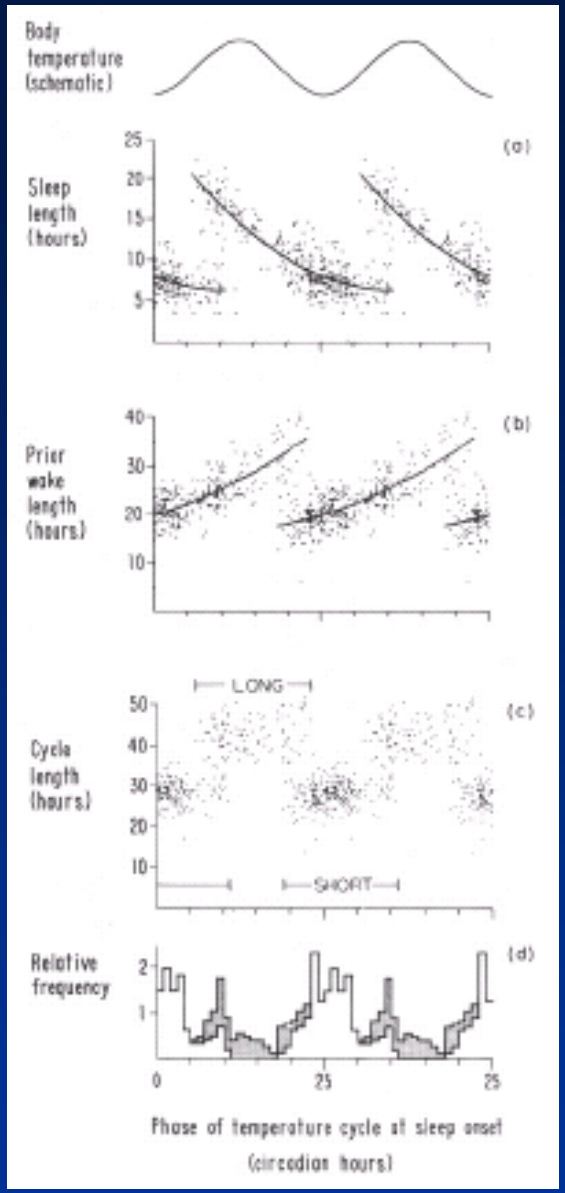




~ = Circadian pacemaker
SH = Sleep Homeostasis
S/W = State Sleep/Wake State
SI = Sleep Inertia

2005 Czeisler et al *Principles and Practice of Sleep Medicine*





Strogatz 1986 (above)
Czeisler 1980 (left)

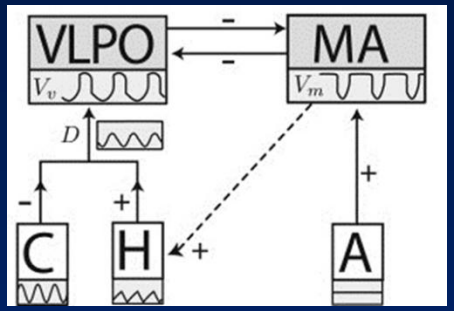
The EEG

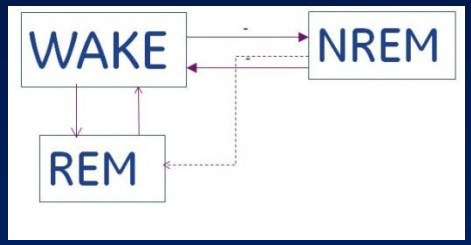
The electroencephalogram (EEG) measures the electrical activity of the neurons of the brain. The EEG taken during sleep state shows an abundance of Slow Wave Activity (SWA) which is an indicator of the homeostatic process. SWA predominates in the first part of sleep and its presence during the night gradually decreases.

Stages of Sleep

Each of the sleep stages (Wake, REM and NREM) are characterized by activation or inhibition of different neural populations in the Ascending Arousal System of the brain.

Neurobiological background





flip-flip switch

Figure 3: Reduced model of Sleep State interactions (Diniz-Behn and Booth, *Siam Journal of Applied Dynam. Systems*, 2011)

During wake state, the Locus Coerulus (LC) and the dorsal raphe (DR) in the brainstem remain active releasing excitatory monoamine (MA) neurotransmitters serotonin, histamine and norephinephrine.

The neurotransmitter GABA is released by the ventrolateral preoptic nucleus (VLPO) in the hypothalamus, sending inhibitory signals to the LC and DR to promote sleep.

Equations governing Sleep

The dynamics of the flip-flop switch (W and N) and the reciprocal interaction(N and R) were modeled by accounting for the interaction of W, N and R states with their respective neurotransmitters E(norEphinephrine), G(GABA) and A(Acetylcholine) using these 3 equations:

$$\tau_W \cdot F'_W = F_{W\infty}(g_{G,W}C_{G\infty}(F_N)+g_{A,W}C_{A\infty}(F_R))-F_W$$

$$\tau_N \cdot F'_N = F_{N\infty}(g_{E,N}C_{E\infty}(F_W))-F_N$$

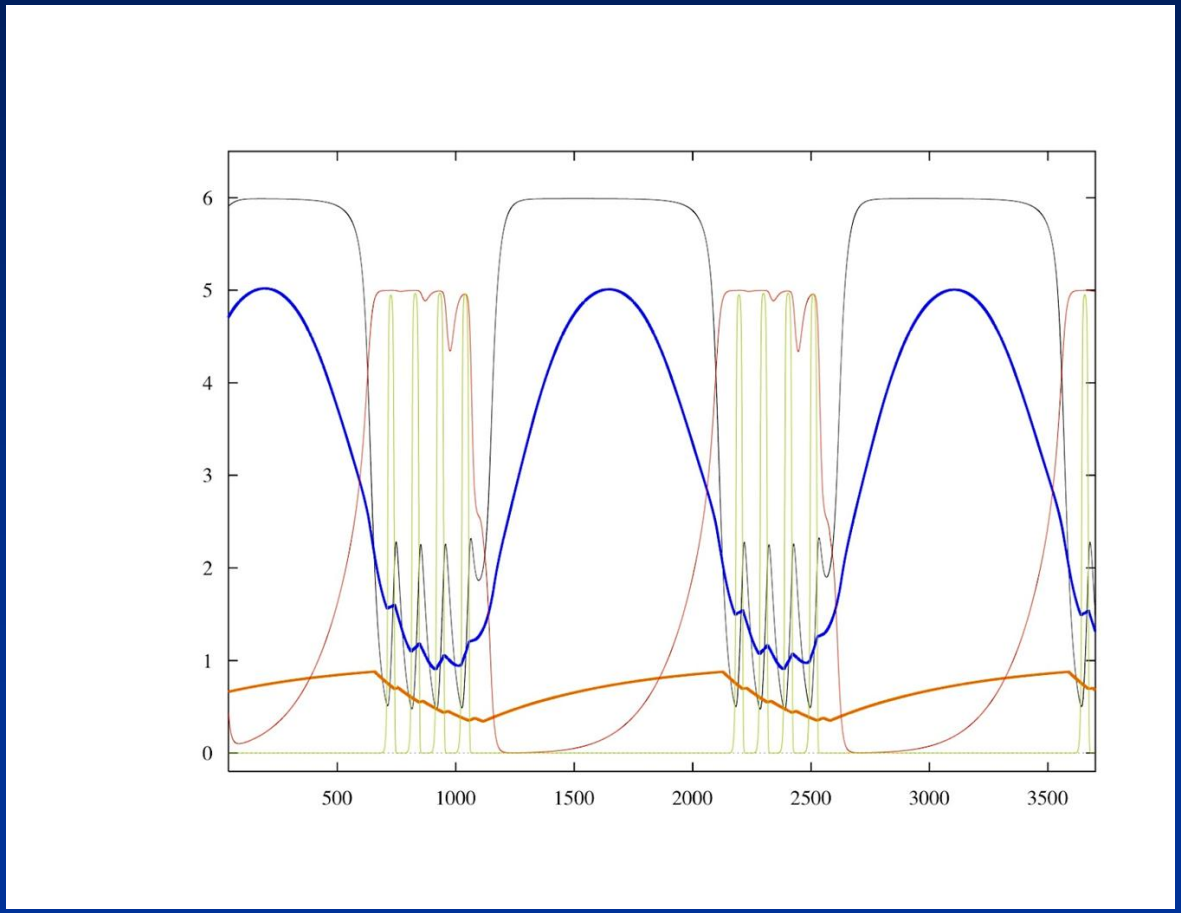
$$\tau_R \cdot F'_R = F_{R\infty}(g_{E,R}C_{E\infty}(F_W)+g_{A,R}C_{A\infty}(F_N))-F_R$$

Output of the model

WAKE = black, NREM = red, REM = green, Sleep homeostasis= orange, Daily circadian output = dark blue.

20 polysomnograms obtained from ASCS were scored in 30-second epochs by a Baylor Sleep Center technologist and imported into MATLAB and statistics calculated.

The mean total sleep time for the 20 recordings (10 male and 10 female) was 7.62 hours. The minimum sleep time was 6.25 hours and the maximum was 10.03 hours. The PSG data was exported in the EDF format and reviewed using Polyman software.



Why we sleep…

- Like body temperature, the body always tries to return sleep to a set-point.
  - Sleep deprivation, followed by compensatory recovery
- Model proposed by Borberly and colleagues describes 2 drives for sleep
  - Circadian
  - Homeostatic

Why we sleep… Homeostasis

- Homeostatic influence results from accumulation of “some substance” during prolonged wakefulness
- VLPO neurons do not accumulate need for sleep; just start firing 2x as fast with sleep onset – so influenced by something else
- During prolonged wakefulness, energy producing brain systems run down and ATP levels deplete, ADP levels accumulate
- Extracellular adenosine levels rise with time

Mathematical Models let us…

- Provide insight into the mechanisms underlying human sleep patterns
- Predict consequences of different sleep-wake schedules on behavior, mood and performance.