A MATHEMATICAL MODEL OF SLEEP REGULATION

Overview

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.

Terminology

Humans alternate between waking(W) and Sleep(S) states. Sleep is itself 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 responsible for the rise of sleep propensity during waking and its dissipation during sleep; 2) a *circadian* process independent of prior sleep and waking, and 3) an *ultradian* process occurring within the sleep episode and representing the alternation every 90 minutes of NREM (N) and REM or R sleep.

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.

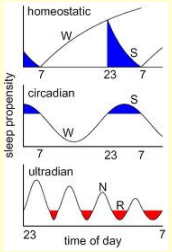


Figure 1: Three processes underlying sleep regulation*

*Acherman and Borbely: Mathematical models of sleep regulation. *Frontiers In Bioscience, 2003*

Hypothesis and Project Plan

The hypothesis being tested is that a physiologically based mathematical model would fit to EEG data obtained from sleeping humans. The project goal was to develop a simplified model of sleep regulation which would account for the three main drivers of the human sleep: the circadian rhythm, the homeostatic drive and the ultradian alternation.

EEG data would be obtained and used for calibrating the model. The mathematical model could be used to test predictions.

Neurobiological Background

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. 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.

The three sleep stages exhibit fairly regular cycling throughout the night. The 24-hour circadian oscillation (C) between sleep and wake is regulated by the suprachiasmatic nucleus (SCN) in the hypothalamus. Fluctuation of SCN firing activity corresponds to cycling of light and dark, with greater activity in the light period. The homeostatic (H) factor also drives the sleep/wake switch and is hypothesized to be due to the accumulation of a somagen (adenosine). Phillips and Robinson proposed a sleep-wake "flip-flop" with mutual inhibition between the VLPO and MA neurons which did not account for the ultradian rhythm. In 2011, Diniz-Behn and Booth proposed a simplified network with a flip-flop switch between WAKE and NREM, and a reciprocal interaction to create REM/NREM oscillation thus accounting for all three processes.

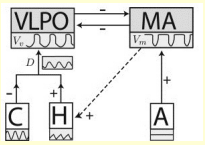


Figure 2: Normal Sleep-Wake Flip-Flop (Phillips and Robinson, *Journal of Biological Rhythms, 2007*)

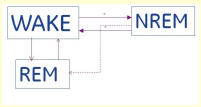


Figure 3: Reduced model of Sleep State Interactions (Diniz-Behn and Booth, *Siam Journal of Applied Dyna.n. Systems*, 2011)

Methods

The mathematical model was implemented in MATLAB. All-night polysomnographic (PSG) records (including EEG) with no identifying information other than gender was obtained from American Sleep and Cardiopulmonary Services (ASCS) in Houston and scored by a registered sleep technologist of the Baylor College of Medicine before the data was imported into MATLAB for data reduction.

Math Model and Analysis

The simplified three neural-population model allowed for better analysis of sleep dynamics. 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). If F_i corresponds to the state i with time scale τ_W promoted by the corresponding neurotransmitter, then:

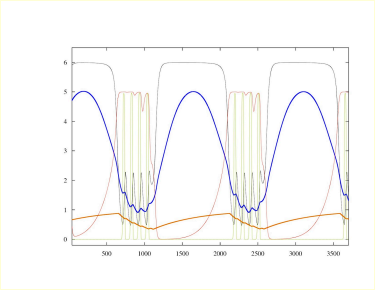
$$\tau_W \cdot F'_W = F_{W\infty}(g_{G,W}C_{G\infty}(F_N)+g_{A,W}C_{A\infty}(F_R))-F_W$$
$$\tau_N \cdot F'_N = F_{N\infty}(g_{E,N}C_{E\infty}(F_W))-F_N$$
$$\tau_R \cdot F'_R = F_{R\infty}(g_{E,R}C_{E\infty}(F_W)+g_{A,R}C_{A\infty}(F_N))-F_R$$

The Diniz Behn & Booth model was adjusted to fit an average human sleep pattern of 16 hours of Wake followed by 8 hours of Sleep. 4 REM periods were fit into the 8 hours of sleep with an approximate length of 20 minutes. The values of connection parameters between neural populations were calculated to be:

$g_{A,W}=1$, $g_{G,W}=-1.68$, $g_{A,R}=1.6$, $g_{G,R}=-1.3$ and $g_{G,N}=-0.1$

20 polysonograms 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. The following is a output of the model where WAKE is black, NREM is red, REM is green, sleep homeostat is orange, and the daily circadian output from the SCN is dark blue.



Results

A model incorporating features of both the Phillips-Robinson and Diniz Behn-Booth models was calibrated to represent physiologically feasible values of the 24-hour circadian rhythm.

The reduced model showed the expected interaction between wake, NREM and REM and the sleep homeostat. The average durations of the REM bouts was calculated. The number of REM periods ranged from two to six with a mean of 3.9. The duration for each successive REM period increased for first four episodes, while the final episode was reduced.

The mean number of REM periods of 3.9 is less than the average of 4-6 reported by Carskadon and Dement but that could be explained by the small data set. The calculations showed that nearly 20% of the night was spent in REM sleep which is on the lower end of the 20-25% reported by Carskadon and Dement.

Future Research

The next step is to obtain more PSG data sets and extend and expand the mathematical model.

The development of physiologically based models of brain dynamics can create the foundation which could help in the treatment of shift work, jet lag and deviant chronotypes. Extending the model to handle multi-time scale data will be considered.

Techniques developed in complexity science can provide additional tools like computer modeling, wavelet transforms, dynamical systems and bifurcation analysis.

Another area of study is the application of non-linear time series analysis to EEGs to determine the dimensional complexity and spectral properties.

Conclusions & Discussion

The sleeping brain is a complex dynamical system Whose EEG oscillations span multiple scales of time ranging from the order of seconds to hours to days. The future challenge is to develop a unified model which spans the different time scales.