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Review

Physiologically-based modeling of sleep–wake regulatory networks

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ABSTRACT

Mathematical modeling has played a significant role in building our understanding of sleep–wake and circadian behavior. Over the past 40 years, phenomenological models, including the two-process model and oscillator models, helped frame experimental results and guide progress in understanding the interaction of homeostatic and circadian influences on sleep and understanding the generation of rapid eye movement sleep cycling. Recent advances in the clarification of the neural anatomy and physiology involved in the regulation of sleep and circadian rhythms have motivated the development of more detailed and physiologically-based mathematical models that extend the approach introduced by the classical reciprocal-interaction model. Using mathematical formalisms developed in the field of computational neuroscience to model neuronal population activity, these models investigate the dynamics of proposed conceptual models of sleep–wake regulatory networks with a focus on generating appropriate sleep and wake state transition patterns as well as simulating disease states and experimental protocols. In this review, we discuss several recent physiologically-based mathematical models of sleep–wake regulatory networks. We identify common features among these models in their network structures, model dynamics and approaches for model validation. We describe how the model analysis technique of fast–slow decomposition, which exploits the naturally occurring multiple timescales of sleep–wake behavior, can be applied to understand model dynamics in these networks. Our purpose in identifying commonalities among these models is to propel understanding of both the mathematical models and their underlying conceptual models, and focus directions for future experimental and theoretical work.

1. Introduction

The field of sleep research has a strong history of using mathematical models to frame understanding of sleep–wake cycling and circadian rhythms. As we all experience on a daily basis, these cycles are governed by the inevitable drive for sleep after periods of wakefulness and the circadian (∼24 h) rhythm propagated by the brain's suprachiasmatic nucleus (SCN). Within a sleep episode, additional rhythms occur in the transitions between rapid eye movement (REM) sleep and non-REM (NREM) or slow wave sleep with a period of approximately 90 min. These cyclic phenomena motivated the development of the classical mathematical models for sleep–wake regulation which include the two-process model for the timing of sleep based on the interaction of the homeostatic sleep drive and the circadian rhythm [1,2], coupled oscillator models for the same interactions [3,4] and the reciprocal interaction model for REM sleep cycling [5,6]. Although generally phenomenological in nature, each of these mathematical models had a significant impact on the field by formalizing conceptual models to guide experimental investigations and providing a context for interpreting experimental data.

Recent experimental results have clarified more of the anatomy and physiology underlying sleep–wake control. Most notably, identification of numerous brainstem and hypothalamic neuronal populations that have wake or sleep-promoting effects and elucidation of neurotransmitter-mediated interactions among these populations has led to the formulation of a putative regulatory network for the control of sleep and wake transitions. While experiments have established clear roles for some populations in such a network, such as the wake-promoting locus coeruleus (LC) and dorsal raphe (DR), the role of other populations, such as those involved in the regulation of REM sleep, are less clear. As described in more detail below, the classical reciprocal interaction hypothesis for REM sleep has been challenged by recent results implicating a role for mutually inhibitory interactions among neuronal populations with REM-promoting and REM-suppressing effects. However, consensus regarding the exact architecture of an inhibition-based REM regulatory network has not been reached,

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and competing models for REM sleep regulation are vigorously debated.

Motivated by these recent results, mathematical models with a stronger physiological basis have been developed to provide quantitative underpinnings for the classical and more recent conceptual models of a sleep regulatory network [7–12]. Using a range of mathematical formalisms developed in the field of computational neuroscience to model neuronal population activity, these models investigate the dynamics of proposed conceptual models of sleep–wake regulatory networks with a focus on generating realistic sleep and wake state transition patterns and appropriate responses to simulated disease states and experimental protocols. To introduce these models, sample output from two recent sleep–wake network models is shown in Fig. 1. In Fig. 1A, the network model [13] simulates stereotypical human sleep where the hypnogram in the top trace summarizes the transitions in simulated behavioral state (wake, NREM sleep or REM sleep) dictated by the transitions in activity of the associated state-promoting neuronal populations shown in the lower traces (average firing rate (in Hz) of wake-promoting (f_W), NREM sleep-promoting (f_S) and REM sleep-promoting (f_R) neuronal populations). The model includes a homeostatic sleep drive variable (H), similar to Process S of the two-process model, that increases during wake and decreases during sleep to promote transitions between these two states. Additionally, the network accounts for the influence of the circadian rhythm on sleep–wake behavior by including input from the SCN (f_{SCN}) that varies on a 24 h time scale. In Fig. 1B, the sleep–wake network model [11,14] simulates typical rat sleep, as shown in the experimentally recorded hypnogram of rat sleep–wake behavior during the day (top trace). The highly variable nature of rat sleep is accounted for by including noise sources in the model. Below we discuss the anatomy and physiology that these and other recent sleep–wake network models are based on (Section 2) and the mathematical formalisms used to construct them (Section 4).

These recent physiological network models can play an important role in the scientific investigation of neuronal sleep–wake regulatory mechanisms because experimental investigations are uniquely limited by the fact that the outcome measurement, namely sleep–wake behavior, only exists in the intact animal. Key characteristics of the sleep or waking state have not been observed in reduced experimental preparations, such as brain slice, in situ preparation or culture of disassociated cells, which could permit close study of the time-varying activity of neuronal interactions. Thus, the experimental techniques available to probe neuronal regulatory mechanisms are limited to those that can be conducted in vivo without disrupting sleep, or post-mortem studies that can identify anatomy but not dynamic interactions. Physiologically-based mathematical models can bridge the gaps left by these limitations in experimental studies. In particular, numerous experimental groups have proposed schematics of conceptual network models and provided hypothetical descriptions of how network interactions could drive behavioral state transitions. However, these static conceptual models are not able to replicate time dynamics of transitions between sleep–wake states or to determine dynamic interactions inherent to network structure. Construction and analysis of mathematical models of these proposed networks can identify the dynamic interactions of constituent populations and neurotransmitters, and provide quantitative understanding of how network dynamics generate the temporal architecture of sleep–wake behavior. This architecture includes the timing, duration, and patterning of wake, NREM sleep, and REM sleep. Model analysis can identify limitations of different proposed network structures in accounting for various characteristics of sleep–wake regulation and can generate predictions suggesting

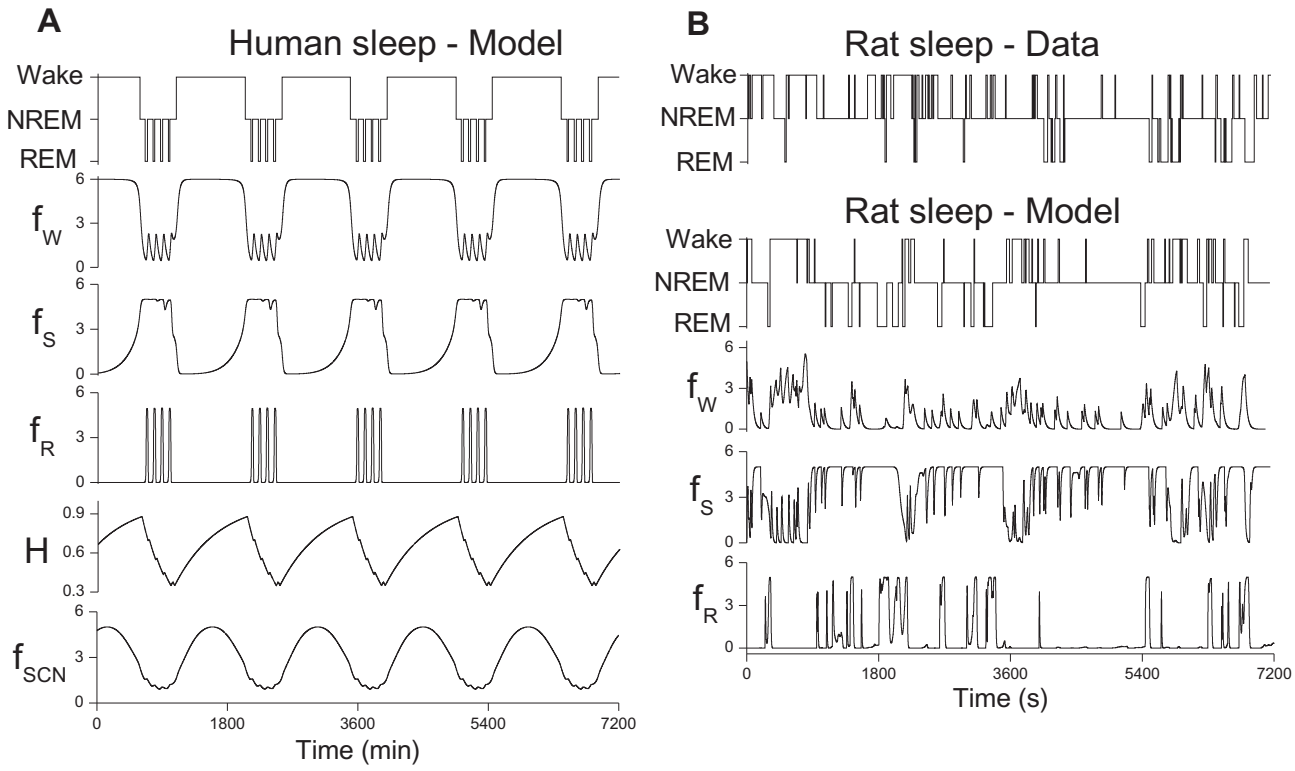

Fig. 1. Output of sleep–wake regulatory network models simulating stereotypical human sleep–wake behavior (A, [13]) and simulating typical rat sleep–wake behavior during the day (B, [11,14]) as shown in experimentally recorded rat behavior (B, top trace). Hypnograms (A, top trace; B, top two traces) summarize behavioral state changes over time and, in model outputs, are determined by the changes in average firing rates (in Hz) of wake-promoting (A, B: f_W), NREM sleep-promoting (A, B: f_S) and REM sleep-promoting (A, B: f_R) neuronal populations. A: the network model included influences of the homeostatic sleep drive (H) and the circadian rhythm propagated by the suprachiasmatic nucleus (f_{SCN}). B: to replicate the high variability of rat sleep, noise sources were included in the model. (rat sleep–wake behavioral data provided by George A. Mashour, University of Michigan).