

Chapter 2

Dynamic NREM Sleep Regulation Models

Abstract In this chapter we provide an overview about those NREM sleep regulation models which take into consideration the effects of external and internal input factors apparently unrelated to the core sleep regulatory mechanisms but deeply influencing their dynamism. McCarley and Massaquoi (J Sleep Res 1(2):132–137, 1992) have begun to incorporate the influence of external noise according to the observations showing frequent brief nonbehavioral EEG and polygraphic “awakenings” in sleep. Lo et al. (Proc Natl Acad Sci USA 101(50): 17545–17558, 2004) studying brief sleep-wake transitions were able to show that these events can be commonly observed across different species with different sleep patterns. The universality of the distributions of short wake episodes strikingly contrasts the species-specific distributions of sleep bouts. Lo concludes that this relationship reveals a universal regulatory mechanism shaping the dynamism of sleep. Behn et al. (J Neurophysiol 97(6):3828–3840, 2007) created a model of sleep-wake network composed of coupled relaxation oscillation equations. This model could be considered as a crucial one in trying to explain the dual nature of sleep-regulation: gross sleep-wake regulatory mechanisms depending on the already described neural circuitry of the flip-flop switch and fine structure shaped by short bouts of wakefulness. We have hypothesized a parallel regulation of sleep in our model (Halász et al. J Sleep Res 13(1):1–23, 2004). Tonic processes were hypothesized to involve mainly intracerebral, slow, and chemical influences, while the phasic ones extracerebral, fast, and neuronal-synaptic ones tailoring the interaction of the reciprocal antagonistic influence between the sleep and arousal centers depicted in the flip-flop model of Saper et al. (Trends Neurosci. 24(12):726–731, 2001). The specificity of our model relied in the differential analysis of the descending and ascending slopes of the sleep cycles, which are usually undifferentiated in current models of sleep regulation.

Keywords Sleep regulation • Sleep-wake transition • Sleep micro-structure Power-law behavior • Coupled relaxation oscillators • Phasic regulation • Arousals in sleep Ascending slope • Descending slope

Previous models of sleep-wake behavior were based on network dynamics of neuronal systems assumed to having control over behavioral states (McCarley and Hobson 1975; Borbély 1982; Daan et al 1984). External input factors, according to the open system characteristics, were initially not taken into consideration. Later, Mc Carley has begun to incorporate the influence of external noise (McCarley and Massaquoi 1992) according to the observations showing frequent brief nonbehavioral EEG and polygraphic “awakenings” in sleep (Schieber et al. 1971; Halász 1982, 1993). These brief awakening-like phasic events were often discounted as “noise,” and they have been only recently recognized as essential element of sleep architecture (Dijk and Kronauer 1999; Halász et al. 2004; Lo et al. 2004).

This combined approach: attributing significance not only to the network properties of wake- and sleep-promoting systems but also to external input aspects driving phasic events in the system has obtained strong support from studies using mathematical models for characterizing network dynamics behind sleep-wake behavior of experimental animals.

Lo et al. (2004) studying brief sleep-wake transitions were able to show that these events can be commonly observed across different species having different sleep patterns. They hypothesized that these brief awakenings from sleep may reflect aspects of endogenous sleep control mechanism. Analyzing sleep recordings from mice, rats, cats, and humans, they found that durations of the episodes during sleep exhibit a scale-free power-law behavior with an exponent ($\alpha=2.2$) that remains the same for all investigated species. In contrast, sleep episode duration follows a species-specific exponential distribution, depending on body mass and metabolic rate. These findings indicate that brief awakenings from sleep are controlled by species-independent mechanisms in the sleep-wake neural networks. Lo et al. (2004) hypothesize that these could be determined by structural characteristics of the neural networks, the nature of the fluctuations around the sleep-wake transitional threshold, or other neurophysiologic features independent of species-specific body size. Furthermore, it is possible that internal and external inputs may excite wake-promoting neurons, leading to brief awakenings with power-law characteristics remaining the same across species. This dual, wake- and sleep-dependent regulation of the process resembles the dynamism known as self-organized criticality, determining recurring neural avalanches in the brain, emerging from quiet states. In coherence with this assumption, the size and duration of neural excitations in cortical networks were shown to follow power-law behavior, while quiet episodes follow a metabolic-rate-dependent timescale. In other words, the gross measures of sleep-regulation (sleep homeostasis and the ultradian cycles) follow the well-known rules of sleep regulation guided by the flip-flop circuitry, while on the finer timescale, this processes are shaped and scored by an alternative regulatory mechanism which is species independent finding its roots in some network properties, hitherto unrevealed by Lo et al. (2004).

Behn et al. (2007) created a model of sleep-wake network composed of coupled relaxation oscillation equations. This model could be considered as a crucial one in trying to explain the dual nature of sleep-regulation: gross sleep-wake regulatory mechanisms depending on the already described neural circuitry of the flip-flop

switch and fine structure shaped by short bouts of wakefulness. The model is based on physiological data and can be considered as a further development of the concepts described by Lo et al. (2004). Mathematical analysis of the deterministic model provided insight into the dynamics underlying state transitions and predicted mechanisms for each transition time. With addition of noise, the stimulated sleep-wake behavior generated by the model reproduced many qualitative and quantitative features of mouse sleep-wake behavior. They wrote: "In contrast to the expected behavior of a pure flip-flop switch, this activity does not necessarily exhibit transition of the network from sleep to sustained wake: instead, switching between states depends on the strength of the impulse. If the pulse sufficiently depresses activity in sleep, the network will show transition from sleep to wake; otherwise the activity in wake self – terminates with falling phase of the oscillation and sleep bout continues." The strength of the pulse inhibition from wake to sleep during a brief awakening is terminated by a variable describing homeostatic NREM sleep drive. In general, depending on the strength of inhibition from sleep to wake or the reverse, the effect of stimulation could be influenced by the state dominance of sleep- or wake-promoting forces on the descending or ascending slopes of the cycles, as we describe later.

The Behn paper emphasizes that their model predicts conditions determining concurrent activity in wake and sleep-active neuronal populations. This is specifically the case when awakening impulses arrive in a state of high homeostatic drive, and no sustained transition to wake state occurs. Transcending the all-or-nothing type approach of the original flip-flop model, without denying its basic tenets and strengths, is the major advantage of this model. However, neither the Lo et al. (2004) nor the Behn et al. (2007) paper considers the difference between the descending and ascending slopes of the sleep cycles which seems to be a crucial one in sleep regulation.

We have hypothesized a parallel regulation of sleep in our model (Halász et al. 2004). Tonic processes were hypothesized to involve mainly intracerebral, slow, and chemical influences, while the phasic ones extracerebral, fast, and neuronal-synaptic ones tailoring the interaction of the reciprocal antagonistic influence between the sleep and arousal centers depicted in the flip-flop model (Saper et al. 2001, 2010). This parallel working mode of the tonic and phasic processes provides the flexibility of sleep maintaining at the same time the core features of endogenously determined, species-specific sleep structure. The specificity of our model relied in the differential analysis of the descending and ascending slopes of the sleep cycles, which are usually undifferentiated in current models of sleep regulation (Fig. 2.1). In our opinion, this is a particularly important issue in the dynamics of ultradian sleep cycles. Examples are the differential distribution of the microstructural elements, as well as the differences in cardiocerebral coupling along the descending and ascending slopes. Taking into consideration the striking sleep-microstructural differences between these slopes, we suggested that the descending slope is characterized by an increasing influence of the sleep system exerting inhibition over the wake system, while the opposite trends were attributed to the ascending slopes. The dynamism of these influences determine the sensorial inputs from the

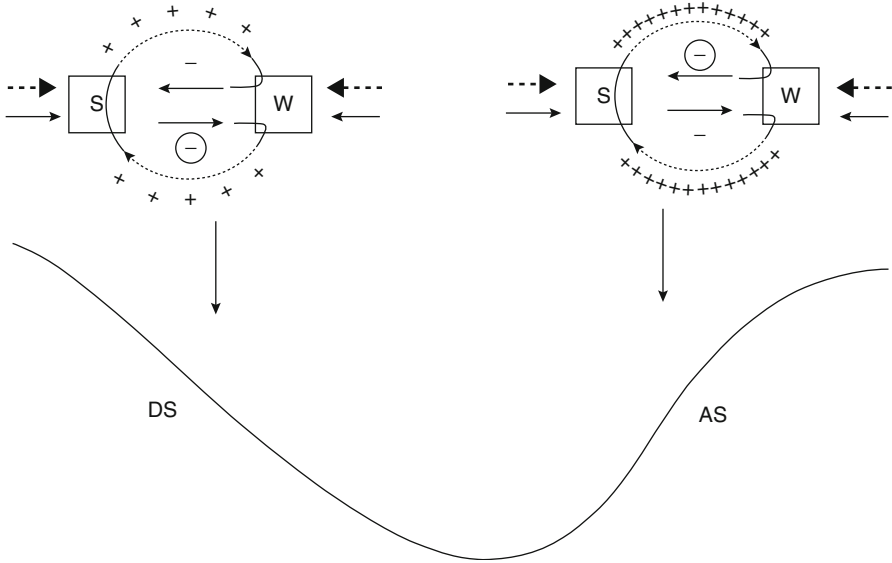


Fig 2.1 Assumed tonic and phasic interaction between sleep (S)- and wake (W)-promoting neuronal assemblies during the descending (DS) and ascending (AS) slopes of sleep cycles. *Arrows* (with positive and negative signs) between the S and W boxes indicate reciprocal antagonistic relationship between sleep- and wake-promoting neuronal groups. Descending slope is characterized by dominance of sleep promotion, while ascending slope by wake promotion. When sleep promoting forces are overwhelming (on the descending slope), the external and internal sensorial input (*thick interrupted arrow*) is rare, and the elicited responses appear in sleep like (K-complexes, slow waves) form. Contrasting on the ascending slope, the inhibition of the wake-promotion neurons decrease, and the sensorial input is able to elicit more frequent arousal like responses. *Continuous arrows* indicate the endogenous chemical influences, *intererupted arrows* the external sensorial influences.

internal and external environment to evoke mild and infrequent arousals in the descending slopes of the sleep cycles, while during the ascending slopes, a higher frequency and intensity of arousals is facilitated by the increasing influence of the wake system. The arousals contribute to the sleep regulatory process by fuelling the dynamics of the sleep cycles potentially resulting in sleep facilitation during the descending slope and awakening in the ascending one (Halász et al. 2004). The sleep-promoting effects of sensory stimulation (Bohlin 1971; Oswald 1960; Webb and Agnew 1979) as well as the deepening of sleep during the descending slopes of its cycles in presence of sensory stimulation (Hirshkowitz 2002) were reported but remained largely unexplained and unmodeled in the literature. Although innovative and integrative, our arousal model did not directly address the issue of sleep homeostasis, which is crucial in understanding the nature of sleep. Some sorts of micro-arousals or reactive sleep EEG elements are composed by the slow EEG waves known to be the physiological basis of sleep homeostasis. Thus, the question arises whether these reactive slow elements contribute to the process of sleep homeostasis

or are some different processes resembling but not contributing to it? In other words, what is the relationship between sleep homeostasis and the microstructure of sleep?

In the following chapters of this book, we will base our reasoning on observations about the microstructural dynamics of NREM sleep and experimental data on the functional characteristics of wake- and sleep-promoting subcortical networks.

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