Mathematical Model of Network Dynamics Governing Mouse Sleep–Wake Behavior

Cecilia G. Diniz Behn, Emery N. Brown, Thomas E. Scammell, and Nancy J. Kopell

INTRODUCTION

In the 1970s McCarley and Hobson (1975) introduced a dynamic model in which alternations between rapid eye movement (REM) sleep and non-REM (NREM) sleep were described by a “predator–prey”-like system composed of inhibitory NREM-active populations and excitatory REM-active populations. Since this early model, much physiologic and genetic work has improved our understanding of the neurophysiology involved in the control of sleep–wake behavior. In particular, mutually inhibitory sleep- and wake-active neuronal populations in the brain stem and hypothalamus are implicated in the production of sleep and wake (see review in Saper et al. 2005). Saper and colleagues (2001) proposed a conceptual model in which this mutual inhibition acts like a flip-flop switch and governs the dynamics of sleep–wake transitions; however, formal modeling of behavioral state control has not yet integrated this new information.

When addressing the control of wake and sleep at the neuronal level, properties of neuronal firing and the resulting structure of sleep–wake behavior must be considered on a fine scale. This structure can be characterized by the number, duration, and organization of bouts of each state in addition to the total percentage of time spent in each state. In contrast to the single consolidated nighttime sleep period typically experienced by adult humans, adult mice exhibit polyphasic sleep–wake behavior (Fig. 1). In addition, many species, including mice and humans, normally experience brief awakenings from sleep as well as sustained bouts of wakefulness associated with feeding and locomotor behavior. In the past, brief awakenings were often discounted as “noise,” but they are now recognized as an essential element of sleep architecture (Dijk and Kronauer 1999; Halasz et al. 2004; Lo et al. 2002, 2004).

Statistical analyses of the distributions of sleep and wake bout durations in multiple species established that sleep bout durations follow an exponential distribution and wake bout durations obey a “power law with a tail” distribution (Blumberg et al. 2005; Lo et al. 2002, 2004). The distinction between wake bout durations for which the power law holds and those bout durations in the “tail” region defines an emergent, species-dependent threshold separating brief and sustained wake bouts; this threshold is about 2 min in mice. Furthermore, this distinction suggests that different mechanisms underlie brief and sustained wake bouts (Halasz et al. 2004; Lo et al. 2004).

To examine the dynamics inherent to this circuitry, we developed a deterministic model based on interactions among wake-, sleep-, and REM-active populations. By considering sleep–wake behavior in the context of neuronal population activity, we incorporate tenets derived from previous modeling of neuronal populations and sleep–wake behavior (Borbely 1982; McCarley and Hobson 1975; McCarley and Massaquoi 1986; Tobler et al. 1992; Wilson and Cowan 1972) while targeting the role of network dynamics in behavioral state control. This model provides a novel framework for exploring dynamical principles that underlie normal and pathologic sleep–wake physiology.

METHODS

Summary of relevant physiology

Although much of the physiology of sleep–wake control is similar across mammalian species, the dynamics of interaction may vary. Therefore we restrict our attention to the mouse sleep–wake
The neuronal populations included in our definition of this network are the locus coeruleus (LC), tuberomammillary nucleus (TMN), dorsal raphe (DR), extended ventrolateral preoptic nucleus (eVLPO), ventrolateral preoptic cluster (VLPO), laterodorsal tegmental nucleus (LDT), and pedunculopontine tegmental nucleus (PPT). Each of these neuronal populations, summarized in Table 1, demonstrates state-dependent firing profiles; causal relationships between the activity of a given population and a particular behavioral state were previously established through extensive experimentation with site-specific lesions and neurotransmitter agonists and antagonists (Saper et al. 2005).

We classify each physiologic neuronal population based on the state (wake, sleep, or REM sleep) in which the population demonstrates a high level of activity and we associate the physiologic population with an abstract wake-, sleep-, and REM sleep-promoting population in the model. We use the designations sleep- and REM-active (rather than NREM- and REM-active) because VLPO neurons exhibit high levels of activity during both NREM and REM sleep (Szymusiak et al. 1998). We do not include neuronal (sub-)populations that are equally active in wake and sleep (either NREM or REM sleep). For example, the LDT includes a subpopulation of neurons that is active mainly during REM sleep and another subpopulation of neurons that is active during both wake and REM sleep (Datta and Siwek 2002); in the theoretical context of the reduced network, we consider the LDT to be REM-active only and we allow the purely wake-active populations to subsume the role of wake-active LDT neurons.

LC, DR, and TMN are associated with the modeled wake-promoting population. The LC and DR are monoaminergic neuronal nuclei located in the brain stem that have long been associated with promoting vigilance and maintaining muscle tone (Aston-Jones and Bloom 1981; Hobson et al. 1975; McGinty and Harper 1976; Wu et al. 2003). The TMN is a wake-promoting hypothalamic nucleus that represents the sole source of histamine in the brain (Sherin et al. 1998; Takahashi et al. 2006). Although orexin neurons are wake-active (Lee et al. 2005; Mileykovskiy et al. 2004) other aspects of their firing profiles and properties differ from the LC, DR, and TMN (Eggermann et al. 2003; Li et al. 2002). Therefore we model the effects of orexin signaling during wakefulness by state-dependently increasing the strength of inhibition from the wake- to the sleep-active populations.

The GABAergic/galaninergic VLPO and eVLPO (Chou et al. 2002; Lu et al. 2000; Sherin et al. 1998) are associated with the modeled sleep-promoting population. Although the distinction between the VLPO cluster and eVLPO is not unanimously recognized, Saper, Lu, and colleagues previously reported anatomic and functional differences between the two: anatomic differences are based on cell density and efferent projections, whereas functional differences suggest that activity (as measured by the expression of fos) in the VLPO core is highly correlated with NREM sleep and activity in the eVLPO is highly correlated with REM sleep (Lu et al. 2000, 2002).

Cholinergic signaling from neurons in LDT/PPT has been directly linked to REM sleep in multiple experiments (Datta and Siwek 1997; Siegel 2005; Steriade et al. 1990; Thakkar et al. 1998). Subpopulations in the LDT/PPT that are mainly active during REM sleep are associated with the modeled REM-promoting population. Although we do not include a separate population of GABAergic REM-active neurons in our model, we include a mechanism for increasing the strength of (GABAergic) inhibition to the wake-active populations immediately preceding and during each REM bout. We attribute this increased inhibition to activation of the eVLPO, but other GABAergic populations (Lu et al. 2006; Maloney et al. 1999) could be responsible.

Because we are focusing on the dynamics of network interactions, the changes in state-dependent activity within these populations are important. Experimental data suggest that transitions in neuronal firing rates are slower than the changes in the electroencephalogram (EEG). For example, in LC neurons, the mean firing rate decreases over the 100 s preceding NREM sleep; the transition from low firing rates during NREM sleep to essentially silent behavior during REM sleep occurs gradually; and firing rates jump quickly at the onset of (or a few seconds before) wakefulness (Aston-Jones and Bloom 1981; Hobson et al. 1975). Transition periods have been considered in other populations in the sleep–wake network [DR (Lydic et al. 1983), TMN (Takahashi et al. 2006), VLPO (Szymusiak et al. 1998), LDT/PPT (Steriade et al. 1990)], but complete time course data have not been reported. Because each of the abstract wake-, sleep-, and REM sleep-promoting populations in the current model combines the features of several physiologic neuronal populations, our model does not reproduce firing rate or time course data. Instead, our model describes heuristic activity levels ranging between 0 and 1 and

<table>
<thead>
<tr>
<th>Active State</th>
<th>Neuronal Population</th>
<th>Neurotransmitters</th>
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</thead>
<tbody>
<tr>
<td>Wake</td>
<td>Dorsal raphe (DR)</td>
<td>Serotonin</td>
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<tr>
<td></td>
<td>Locus coeruleus (LC)</td>
<td>Noradrenaline</td>
</tr>
<tr>
<td></td>
<td>Tuberomammillary nucleus (TMN)</td>
<td>Histamine</td>
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<tr>
<td>Sleep</td>
<td>Ventrolateral preoptic cluster (VLPO)</td>
<td>GABA/Galanin</td>
</tr>
<tr>
<td></td>
<td>Extended ventrolateral preoptic nucleus (eVLPO)</td>
<td>GABA/Galanin</td>
</tr>
<tr>
<td>REM sleep only</td>
<td>Laterodorsal tegmental nucleus (LDT)</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td></td>
<td>Pedunculopontine tegmental nucleus (PPT)</td>
<td>Acetylcholine</td>
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</tbody>
</table>

FIG. 1. Experimentally observed alternations between wake (W), sleep (S), and rapid eye movement (REM) sleep (R) in a behaving mouse. If brief awakenings are omitted (A), the polyphasic sleep–wake structure is evident. Including brief awakenings (B) illustrates the qualitative differences between brief and sustained awakenings.

TABLE 1. Neuronal populations considered in our model

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transitions between levels of high and low activity are fast, similar to the changes observed in the EEG.

Model formulation

From the physiology reviewed earlier, we extracted a reduced network of three coupled wake-, sleep-, and REM-active neuronal populations (denoted W, S, and R, respectively) as shown in Fig. 2. Individual neurons in these populations demonstrate spontaneous firing (Moriarity et al. 2004; Sakai and Crochet 2000; Steriade et al. 1990; Taddese and Bean 2002; Williams et al. 1984); because the populations tend to exhibit cohesive activity, this suggests spontaneous activity of the population as a whole. In addition, cyclic attributes of brief awakenings and REM bouts were previously reported (Endo et al. 1998; Halasz et al. 2004). Based on these oscillatory and excitable properties, a heuristic level of activity of each population in the reduced network is modeled by relaxation oscillator equations (Morris and Lecar 1981; see appendix for details).

Each population has associated vj and uj variables: vj describes the activity of population j and uj is a recovery variable. Coupling between populations is based on experimentally determined anatomic connections. The variables ts and tu are associated with coupling and are subsequently described in more detail. Homeostatic sleep drives are modeled by scaling variables that modulate coupling effects over time. The variable h is associated with homeostatic NREM drive; the variables eV and r = rf + rs are associated with homeostatic REM drive.

For population j = W, S, and R, the variables vj and uj are governed by relaxation oscillator equations

\[
\frac{dv_j}{dt} = f(v_j, u_j)
\]

\[
\frac{du_j}{dt} = e g(v_j, u_j)
\]

where 0 < e \ll 1; the full model equations are presented in the appendix. Population-dependent parameters (Table A1 in the appendix) determine slightly different intrinsic properties for W, S, and R. The “smallness” of e quantifies the order of magnitude separating rates of change in vj and uj and introduces two timescales: t and et. This permits the model to describe activity on multiple timescales: as previously described, population activity levels change quickly between states and slowly within states.

From the class of relaxation oscillator equations, the Morris–Lecar equations were selected for their geometric properties rather than their biophysical interpretation; the equations have been rescaled to describe heuristic activity levels ranging between 0 and 1. In particular, the shape of the nullclines associated with these equations is important to our analysis. Typically, nullclines separate regions of the v–u-phase plane in which v and u are increasing or decreasing and give insight into the qualitative behavior of solutions of the system of equations. Taking all other variables to be fixed, nullclines Nv and Nu describe the values of v and u for which the equations dvj/dt and duj/dt are zero

\[N_v = \{v, u | dv/dt = 0\}\]

\[N_u = \{v, u | du/dt = 0\}\]

In the associated v–u-phase plane, Nv has a standard cubic shape, whereas Nu is sigmoidal.

Nullclines of this form may assume three possible distinct relative configurations (Fig. 3). It is known from standard stability theory (Guckenheimer and Holmes 1983) that under these conditions, the trajectory associated with network behavior will remain close to the point p at which Nv and Nu intersect if p is on the left or right branch of Nv; if p is on the middle branch of Nu, the trajectory will oscillate around p. Thus the location of p specifies default behavior of the associated population and varies with behavioral state:

- p on left branch of Nv: trajectory near p and (v, u) coordinates of p correspond to low values of v; therefore this nullcline configuration corresponds to low firing activity throughout the population.
- p on middle branch of Nv: trajectory oscillates around p with v taking on high and low values; therefore this nullcline configuration corresponds to an oscillation between high and low firing activity throughout the population.
- p on right branch of Nv: trajectory near p and (v, u) coordinates of p correspond to high values of v; therefore this nullcline configuration corresponds to high firing activity throughout the population.

We assume that each population is tonically active in the absence of coupling (p on right branch); coupling effects give rise to the other nullcline configurations and this geometry underlies the fundamental dynamics of the network.

Connectivity of the model network

As previously mentioned, connectivity of the reduced network in Fig. 2 is based on anatomical connectivity of the neuronal populations of the sleep–wake network. For example, the experimentally identified GABAergic projection from VLPO to TMN (Sherin et al. 1998) is represented as an inhibitory connection from S to W in the reduced network. Population-specific coupling effects, denoted by cj, are introduced into the model equations through the dvj/dt equations as follows

\[
\frac{dv_j}{dt} = f(v_j, u_j) + c_j
\]

where

\[c_i = - g_v(t) - g_u(t)(1 - h) + g_w(t_0) + n_i\]

\[c_v = \begin{cases} - g_v(t) - g_u(t)(\alpha_v - \alpha_c) - g_w(t) + n_v & \text{during NREM sleep} \\ - g_v(t) + n_v & \text{otherwise} \end{cases}\]

\[c_u = \begin{cases} - g_v(t) - g_w(t) + n_k & \text{during sleep} \\ - g_u(t) + n_k & \text{during wake} \end{cases}\]

Here h, r, and eV are scaling variables to be described below; nV, nR, and nR are noise terms; and g_v, g_u, and g_w are constant parameters. The
term \(-g_{aw}(\alpha_{aw} - \alpha_{bc})\) reflects the self-inhibition present in the wake-promoting populations (McCarley and Hobson 1975) and contributes to their gradual shift from low activity during NREM sleep to silence during REM sleep.

The saturating functions \(g_{aw}(t_{aw})\) and \(g_{aw}(t_{aw})\) describe the activation of inhibition as a function of time elapsed since the onset of the wake \((t_{aw})\) or sleep \((t_{aw})\) bout, respectively. These functions describe the mutual inhibition between \(W\) and \(S\) as well as the inhibition of \(R\) by both \(W\) and \(S\). The form of these functions enforces the state dependency of coupling effects: activation of the function is initiated by a high level of activity in the presynaptic population because neuronal activity drives neurotransmitter release. The time course of activation of these saturating functions captures the hypothesized time course of population recruitment; this effect is absent from the relaxation oscillation equations themselves. The saturating function \(g_{ox}(t_{ov})\) describes the activation of orexinergic effects as a function of time elapsed since the onset of the wake bout. The exact form of these equations is given in the Appendix.

Coupling terms determine the state-dependent nullcline configurations of each population. During NREM sleep, the initial inhibition from \(S\) to \(W\) causes the nullclines associated with \(W\) to assume an oscillatory (rather than inactive) configuration. This is consistent with the spontaneous (intrinsic) activity exhibited by these populations (Taddese and Bean 2002; Williams et al. 1984). All other coupling terms impose an inactive configuration on the nullclines associated with the postsynaptic population. Our choice of parameters is based on achieving this state-dependent geometry.

The behavioral state of the network is classified by the heuristic activity level of \(W\), \(S\), and \(R\). If \(v_{aw}\) or \(v_{aw}\) exceeds the “activity threshold” defining the onset of population activity, then the network is assumed to be in wake or REM sleep, respectively. The network enters NREM sleep when \(v_{aw}\) increases below the activity threshold and \(v_{aw}\) and \(v_{aw}\) do not. By imposing additional conditions for NREM sleep, we eliminate ambiguity in scoring simulated behavioral states. For the simulation results we report, 0.5 is taken to be the “activity threshold”; however, because onset and offset of activity in these populations are fast, there is minimal dependence on the choice of threshold separating active and inactive states.

**Homeostatic sleep drives and scaling variables**

Initiation and consolidation of human sleep has been modeled as the interaction of circadian and homeostatic drives known as process C and process S, respectively (Borbely 1982). Circadian drive influences behavior according to time of day, whereas homeostatic sleep drives help maintain fixed daily amounts of NREM and REM sleep by promoting sleep in proportion to preceding waking behavior. The two-process model has been adapted to other mammals (Tobler et al. 1992), including those with polyphasic sleep–wake behavior, by identifying species-specific time courses for homeostatic sleep drive and modifying effects of circadian drive.

Because sleep–wake behavior persists in the absence of a functional circadian pacemaker, we make the simplifying assumption that circadian drives constitute a modulation, rather than an intrinsic dynamic element, of behavioral state control. Therefore in the present study, we restrict our focus to network dynamics driven by homeostatic effects.

Selective sleep-deprivation protocols suggest the existence of separate homeostatic sleep drives for NREM and REM sleep. Agents of REM sleep homeostasis remain unknown, but several factors have been proposed to mediate NREM homeostatic drive (Porkka-Heiskanen et al. 2000; Strecker et al. 2000). The best studied of these is adenosine. Adenosine concentrations rise during both spontaneous waking and waking during sleep deprivation; during sleep these concentrations fall in several brain regions including the preoptic area of the hypothalamus (Porkka-Heiskanen et al. 2000). High adenosine levels reduce the frequency of inhibitory postsynaptic potentials (IPSPs) on VLPO neurons (Chamberlin et al. 2003; Morairty et al. 2004), thus providing a mechanism for the production of sleep. Adenosine may also act through other mechanisms (Scammell et al. 2001), particularly in basal forebrain (Porkka-Heiskanen et al. 1997; Strecker et al. 2000), and much remains to be learned about sleep-promoting factors in general.

Based on our current understanding of adenosine, we model homeostatic sleep drive with a variable \(h\) that rises during wakefulness, falls during sleep, and scales the strength of inhibition from \(W\) to \(S\). Such a mechanism is also consistent with adenosine acting in the basal forebrain (Porkka-Heiskanen et al. 1997). The behavior of \(h\) is effectively described by

\[
\frac{dh}{dt} = \begin{cases} 
(1 - h) + n_h & \text{during wakefulness} \\
\frac{-h}{n_h} + n_h & \text{during sleep}
\end{cases}
\]

where \(\tau_{bw}\) and \(\tau_{bh}\) are time constants controlling the growth and decay of \(h\) during wake and sleep, respectively; and \(n_h\) is a noise term. To obtain the appropriate reduction in inhibition from \(W\) to \(S\), \(g_{aw}(t_{aw})\) is multiplied by \((1 - h)\) in \(v_{aw}\); thus the strength of inhibition from \(W\) to \(S\) varies inversely with \(h\).

In the absence of an identified agent of REM homeostasis, our implementation of homeostatic REM drive is based on phenomenological observations pertaining to REM sleep (Benington 2002; Endo et al. 1997, 1998; Franken 2002; Le Bon et al. 2002; McCarley and Hobson 1975). Experiments suggest that the occurrence of REM sleep is associated with both excitation (or disinhibition) of REM-active populations and a gating mechanism involving a reduction of activity in wake-active populations (Franken 2002; McCarley and Hobson 1975). Therefore the initiation of REM sleep in our model depends on a REM-promoting force \(r\) and a scaling variable \(e_r\), that increases the strength of \(r\) when \(W\) is inactive. Based on a model proposed by Franken (2002), the variable \(r\) is composed of two processes, \(r_f\) and \(r_s\), acting on different timescales: \(r = r_f + r_s\). The fast process, denoted \(r_f\) in our model, is involved in timing REM sleep within a sleep bout and is governed by

\[
\frac{dr_f}{dt} = \begin{cases} 
(r_e - r_f) & \text{during NREM sleep} \\
r_f & \text{otherwise}
\end{cases}
\]

where \(r_e\) and \(\tau_e\) are parameters describing the maximal value and time constant of \(r_f\), respectively; \(r_f\) is reset to zero by the occurrence of a REM bout.
The slow process, denoted \( r_s \) in our model, regulates the daily amount of REM sleep and is governed by the equation

\[
\frac{dr_s}{dt} = \begin{cases} 
-\frac{1}{r_s} & \text{during REM sleep} \\
\frac{1}{r_s} & \text{otherwise}
\end{cases}
\]

where parameters \( r_s^{\text{up}} \) and \( r_s^{\text{down}} \) control the rate of growth and decay of \( r_s \).

The gating mechanism involving reduced activity in wake-active populations is modeled with the variable \( e_{V} \); this variable scales both inhibition to \( W \) and excitation to \( R \) (refer to definition of \( c_w \) and \( c_R \)). Our implementation of an \( e_V \)-scaled excitation to \( R \) is based on observations that eVLPO fos expression is correlated with REM sleep (Lu et al. 2002) and represents disinhibition of \( R \) through indirect pathways: eVLPO neurons inhibit monoaminergic populations represented by \( W \) and other populations (e.g., GABAergic neurons in ventrolateral periaqueductal gray matter) that inhibit LDT/PPT (Lu et al. 2002). The variable \( e_V \) is governed by the equation

\[
\frac{de_v}{dt} = \begin{cases} 
(1 - e_v) / \tau_v & \text{when } W \text{ is inactive} \\
0 & \text{otherwise}
\end{cases}
\]

where \( \tau_{e_v} \) is a parameter controlling the rate of growth of \( e_v \); the occurrence of a REM bout resets \( e_v \) to 0.

**Numerical implementation**

The resulting model consists of 12 differential equations and 40 parameters. To reproduce the "noisiness" inherent in any biological system, we introduced stochastic terms into four of the differential equations in our system: \( dh/dt \) and \( dv/dt \) for \( j = W, S, \) and \( R \). The stochastic terms were normally distributed with mean 0 and variance 0.25, 1, 1, and 20, respectively; at each time step, new values were generated for the stochastic terms and the differential equations were modified accordingly.

All simulations were run on a Linux workstation using the ordinary differential equation (ODE) solver XPPAUT (developed by GB Ermentrout and available at ftp://ftp.math.pitt.edu/pub/software). A Runge–Kutta integration method with step size 0.01 (min) was used for all simulations. Simulation output was analyzed using code written in MATLAB (The MathWorks, Natick, MA).

**RESULTS**

In the absence of noise, our deterministic model network gave rise to a stereotypical sequence of behavior: a sustained wake bout and an extended sleep bout composed of two sleep cycles (alternating between NREM and REM sleep) and four brief awakenings (Fig. 4). The geometry of the system permitted analysis of this solution to identify the dynamic mechanisms underlying state transitions and it suggested separate mechanisms for brief and sustained wake bouts. This approach also allowed us to formally evaluate model sensitivity to parameters. With the addition of noise, our parameter regime generated simulated behavior consistent with experimentally observed mouse sleep–wake behavior.

**Model geometry and predictions**

To better understand dynamic principles of the network and mechanisms of transitions between states, we analyzed the mathematical structure of the network equations in the absence of noise. Complete mathematical details are beyond the scope of this paper, although the METHODS section provides an overview of our approach. By exploiting both the separation of timescales within the network equations and the state-dependent relevance of variables, we were able to reduce the dimension of the system in a state- and population-dependent manner. Through this reduction, we identified a sequence of low-dimensional systems that approximated the behavior of the full system and provided a structured framework for understanding mechanisms of state transitions and parameter dependency in our model.

**Mechanisms for state transitions**

Each low-dimensional system includes the population variables \( (v_j, u_j) \) associated with one of the wake-, sleep-, or REM-active populations. Thus within these systems we could examine network dynamics in terms of nullclines associated with population variables. This analysis resulted in the following predicted mechanisms for each state transition.

The transition from wake to (NREM) sleep is initiated by the homeostatic NREM sleep drive, described by the variable \( h \). During wakefulness \( h \) increases and the strength of inhibition from \( W \) to \( S \) varies inversely with \( h \). When the strength of inhibition is no longer sufficient to prevent the onset of activity in \( S \), the "flip-flop" switch flips: activation of \( S \) initiates inhibition from \( S \) to \( W \) and transitions the network from sustained wake to sleep (Fig. 5). In the coupled oscillator literature, this mechanism is known as "intrinsic escape" (Skinner et al. 1994; Wang and Rinzel 1992).

Recall that the onset of inhibition from \( S \) to \( W \) results in an oscillatory configuration of \( W \) nullclines. Thus in contrast to the inactivity observed in \( S \) when it is inhibited by \( W \), activity in \( W \) alternates between high and low levels in an intrinsic relaxation oscillation. We consider the short intervals of high activity in \( W \) to describe brief awakenings; therefore the model suggests that the occurrence of brief awakenings is linked to intrinsic excitability of the wake-active populations. This is consistent with the theory that regular periods of arousal during sleep act as a safety measure to offset the vulnerability of decreased sensory perception during sleep (Halasz et al. 2004).
As the sleep bout progresses, short-term homeostatic REM pressure increases the strength of inhibition to $W$ and the excitation to $R$. When inhibition to $W$ is sufficiently strong, the $W$ nullclines move to an inactive configuration and oscillation in $W$ activity ceases. The complete cessation of activity in $W$ results in further disinhibition of $R$; if homeostatic REM sleep drive is sufficiently strong, a REM bout occurs.

In our model, a REM bout corresponds to a single excursion (of relaxation oscillation-type) in $R$; thus the form and duration of the REM bout result from intrinsic properties of REM-active populations. A combination of excitation and disinhibition permits the intrinsic escape of $R$; however, the activation of $R$ completely discharges short-term REM pressure and reduces long-term REM pressure: the resulting drop in total REM pressure reverses both the excitation to $R$ and the disinhibition of $W$. Thus $R$ returns to relative inactivity after its excursion and the REM bout activates $W$: depending on the state of the network, this may generate a post-REM brief awakening or a full transition to sustained wake.

The transition from NREM sleep to wake involves a more subtle mechanism than those associated with other state transitions. As previously described, brief episodes of activity in $W$ result in pulses of inhibition from $W$ to $S$. In contrast to the expected behavior of a pure flip-flop switch, this activity does not necessarily transition the network from sleep to sustained wake; instead, switching between states depends on the strength of this pulse. If the pulse sufficiently depresses activity in $S$, the network will transition from sleep to wake; otherwise, the activity in $W$ self-terminates with the falling phase of the oscillation and the sleep bout continues. These possibilities are illustrated in Fig. 6.

The strength of the pulse of inhibition from $W$ to $S$ during a brief awakening is determined by the variable $h$ describing homeostatic NREM sleep drive. As $h$ recovers over the course of the sleep bout, the strength of these pulses increases; thus the value of $h$ during the brief awakening determines whether the network will switch to sustained wake or remain in sleep. Thus the transition from NREM sleep to sustained wake requires both sufficient recovery in $h$ and the initiation of a brief awakening. This suggests a significant role for intrinsic excitability in the reversibility of sleep.
Model sensitivity to parameters

Our model parameters fall into three categories based on the variables they modify: parameters associated with intrinsic properties of W, S, or R; parameters involved in coupling effects; and parameters associated with homeostatic sleep drives. Parameters and their typical values are listed in Tables A1 and A2 of the Appendix.

Mathematical understanding of state transitions in the model provides insights into the role of each parameter in network dynamics. Thus rather than attempting to explore model robustness in a high-dimensional parameter space, we evaluate the effects of parameter variation using our analysis of the model dynamics.

As long as the geometry of the equations is preserved, parameter changes have relatively minor effects on network behavior. Changes to the first category of parameters alter the shape of the nullclines associated with each population; nullcline shape (both cubic and sigmoidal), and thus model behavior, is very robust to minor changes in these parameters. The second and third categories of parameters determine state-dependent nullcline configurations and intrastate changes to these configurations. Minor variation of these parameters does not significantly alter network dynamics; however, if parameter variation results in a significant change in the number of brief awakenings observed in a stereotypical sequence of behavior, quantitative measures of sleep–wake behavior will be affected.

For example, the number of brief awakenings in simulated sleep–wake behavior varies inversely with the maximal strength of inhibition from S to W ($g_{S\text{max}}$); network behavior is less sensitive to changes in the maximal strength of inhibition from W to S ($g_{W\text{max}}$). If $g_{S\text{max}}$ is increased or decreased by >2 or 3%, altered sleep–wake behavior will be reflected by changes in a range of measures: distributions of wake and NREM bout durations (fewer brief awakenings result in a consolidation of NREM bouts), the number and mean durations of wake and NREM bouts, and percentage of time spent in each state. If the increase in $g_{S\text{max}}$ is sufficient (>10% of baseline value) to eliminate all brief awakenings, then the network loses its transition mechanism from sleep to sustained wake and exhibits constant sleep.

Similarly, changing the rate of activation of inhibition from W to S ($r_{W\text{hyp}}$) affects the number of brief awakenings in each stereotypical sequence of behavior. If activation is instantaneous or the rate is increased by >40% of its baseline value, brief awakenings (with concurrent activity in W and S) are eliminated and the network rapidly oscillates between wake and NREM sleep. If the rate is decreased, additional brief awakenings occur. Network behavior is not sensitive to changes in the rate of activation from S to W ($r_{S\text{hyp}}$).

Most of the parameters associated with homeostatic sleep drives (suggestively denoted $\tau$) are time constants describing the evolution of variables that scale coupling strengths in the network. Based on the mechanisms of transitions previously discussed, we expect all transitions, with the exception of the transition from the extended sleep bout to the sustained wake bout, to depend smoothly on these parameters. Simulation results support this conclusion: numbers of all bout types and mean durations of sustained wake and NREM bouts vary with parameters associated with coupling and homeostatic sleep drives.

The exception in smooth dependency arises because, in the absence of noise, the transition from sleep to sustained wake depends on activation of W in the form of a brief awakening. This brief awakening may be intrinsic or may occur following REM sleep; however, transitions to sustained wake are most often caused by post-REM brief awakenings (in both simulated and experimental data). Therefore the duration of extended sleep bouts tends to change in (discrete) units of sleep cycles rather than continuously with varying parameters.

Simulated mouse sleep–wake behavior

With the addition of noise, our model circuitry reproduces experimentally observed sleep–wake behavior including proportions of wake, NREM sleep, and REM sleep; number and duration of bouts; and realistic sleep architecture as measured by transition probabilities. Figure 7 summarizes 2 h of simulated mouse behavior and can be qualitatively compared with Fig. 1. In Figs. 8 and 9, we compare the simulated sleep–wake behavior described by our model with previously published experimental data from eight male C57BL/6J mice (Mochizuki et al. 2004); a discussion of methods used to collect these data is described in the original paper. Simulated behavior was generated with eight runs of the model under a single set of parameters with different initial conditions and random noise.

Daily percentages of wake, NREM sleep, and REM sleep

Our model reproduces experimentally observed daily (24-h) percentages of time spent in wake, NREM sleep, and REM sleep (Fig. 8A). By considering percentages of time spent in each behavioral state over 24 h, we mitigate circadian dependency to reveal underlying homeostatic equilibria. The model produces slightly less REM sleep than is observed experimentally; the source of this difference is a discrepancy in the duration, rather than the raw number, of REM bouts between

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**Fig. 7.** Simulated mouse sleep–wake behavior from the model demonstrates both the polyphasic nature of mouse sleep–wake behavior (A) and the qualitative differences between brief and sustained wake bouts (B). Note the similarities to Fig. 1.
the model and the experimental data. The close agreement between our model results and experimental data for daily percentages of wake, NREM sleep, and REM sleep suggests that the time constants of homeostatic drives in the model are tuned to biophysically reasonable values.

**Number and duration of bouts**

Because mouse sleep–wake behavior is polyphasic, daily amounts of wake, NREM sleep, and REM sleep are composed of many bouts of varying lengths. Scoring behavior in 10-s epochs, Mochizuki and colleagues identified mean numbers and durations for bouts of each behavioral type. As described in the INTRODUCTION, we will consider brief and sustained wake bouts separately.

The mean durations (Fig. 8B) and average numbers (Fig. 8C) of bouts of each behavioral type show good agreement between the model and the experimental data, although the model has fewer brief wake bouts than the experimental data. The discrepancy between the simulated and experimental mean durations of sustained wake bouts probably occurs because our model lacks circadian effects that promote very long wake bouts. Mean bout durations for the other behavioral states show close agreement.

Because bout durations are nonnormally distributed (Lo et al. 2004), we compare the distributions of simulated and experimentally observed bout lengths (Fig. 9). The model captures the relative frequency of each type of wake bout. We measure durations in minutes instead of seconds because very extended wake bout durations occur during the dark period. The slightly lower number of brief (0- to 2-min) wake bouts in model data could be explained by the absence of brief awakenings triggered by uncontrolled environmental factors (occasional noise, vibration, etc.).

There was good qualitative agreement between the model and experimental data in the distribution of NREM bout durations: bouts of NREM sleep were most likely to be <2 min in duration and nearly all bouts of NREM sleep fell in the range from 0 to 8 min in duration. There was a lower incidence of NREM bouts of 2- to 4-min duration and a higher incidence of NREM bouts of 4- to 8-min duration in the model compared with the experimental data; additional noise in the model, particularly random external stimuli, may fracture some of these longer bouts into bouts of shorter duration.

Most REM bouts fall in the first two bins (0 – 40 and 40 – 80 s) in both the model output and the experimental data. The absence in model output of longer REM bouts observed in the experimental data accounts for the discrepancy between the percentage of REM sleep in the simulated and experimental data. This clustering of REM bout durations occurs because REM bouts are modeled as a single excursion of the variable \( v_R \); thus the duration of the excursion is controlled robustly by intrinsic properties of the equations governing \( v_R \) and \( u_R \).

**Organization of sleep–wake behavior**

To quantify the organization of sleep–wake behavior, we computed probabilities of transitioning from one behavioral state to another (given that a state transition occurred). Stereotyped sleep–wake patterns that emerge are often conserved across species: some transitions (e.g., wake → REM sleep) are never seen in normal behavior and can be considered “inappropriate,” whereas others (e.g., NREM sleep → REM sleep) are common. Transition probabilities for simulated and experimental data (Fig. 8D) show similar structure; no inappropriate state transitions are produced by the model.

In addition to specific transitions from one state to another, stereotypical sequences of behavior are observed experimen-
DISCUSSION

We have shown that a network of three coupled relaxation oscillators with variable connectivity can be used to simulate qualitative and quantitative features of mouse sleep–wake behavior including brief and sustained bouts of wake, NREM sleep, and REM sleep. Our model demonstrates fundamental network dynamics generated by the circuitry underlying behavioral state control and we predict mechanisms for each state transition based on formal analysis of our model equations. Because our model development was based on experimentally established physiology, our model has many implications for understanding sleep–wake behavior.

A major feature of our model is its ability to describe the fine architecture of sleep–wake behavior and, in particular, the incidence of brief awakenings. Brief awakenings are an important indicator of sleep quality and abnormal numbers and durations of brief awakenings have been associated with insomnia (Anderson et al. 2005), sleep apnea (Loredo et al. 1999), and compromised histamine H1 receptor signaling (Huang et al. 2006). Although some brief awakenings occur in response to short, random sensory stimuli from uncontrolled environmental factors, the high incidence of brief awakenings throughout sleep suggests that environmental factors are not exclusively responsible.

Previous sleep modeling approaches did not address the occurrence of brief awakenings in sleep–wake behavior. In classical two-process models (Borbely 1982; Tobler et al. 1992), the durations of wake and sleep bouts were governed by the time constants of homeostatic sleep drive and circadian phase; because the durations of brief awakenings cannot be linked logically to sleep homeostasis, they could not occur in this framework. The Chou (2003) stochastic firing rate model of the sleep–wake switch included brief awakenings but used a modeling approach that could not shed light on the dynamic mechanisms associated with the simulated behavior.

Tamakawa and colleagues (2006) recently proposed a model of rat sleep–wake behavior based on the physiology of sleep–wake circuitry. Using formal neuron models of ten neuronal populations, including those described in our model, they produced simulated rat sleep–wake behavior that matched experimentally determined mean durations of wake and sleep bouts. Based on the observation that simulated activity in the ten populations is essentially identical within state-dependent groups corresponding to wake, NREM sleep, REM sleep, and both wake and REM sleep, this is described as a “quartet model.” As previously mentioned, we found it unnecessary to include a population with high levels of activity during wake and REM sleep. Both the quartet model and our model include two different homeostatic sleep drives: their SS1 variable is similar to our h variable, although it acts directly on the VLPO population; their SS2 variable increases during wake and REM sleep and modulates the population representing NREM sleep-active GABAergic neurons in the median preoptic area, thus functioning differently from our rs and rf variables. Although the quartet model is consistent with general measures of sleep–wake behavior, such as mean duration and percentage of time in each state, additional work was needed to develop a modeling framework that could describe the fine architecture of sleep–wake behavior.

By specifying an oscillatory regime for the equations associated with wake-active neuronal populations, our model includes a mechanism for wake bouts with durations that are governed by intrinsic properties of the population rather than homeostatic sleep drive. Thus simulated sleep–wake behavior reflects the structure and organization of mouse sleep–wake behavior; in particular, distributions of bout durations and the distinction between brief and sustained wake bouts are reproduced by the model. The absence of environmentally induced brief awakenings in our model may be responsible for the slightly lower number of brief awakenings in the simulated behavior compared with the experimental data.

Fine architecture of sleep–wake behavior

FIG. 9. Distributions of wake (A), NREM sleep (B), and REM sleep (C) bout durations in simulated wake–sleep behavior capture the features of the distributions of bout durations in experimental data.
Concurrent activity in wake- and sleep-active populations

By implementing the mutual inhibition of the flip-flop switch in the context of coupled relaxation oscillators, our approach captures the key feature of a sleep–wake switch—two stable states with minimal time spent in intermediate states (Saper et al. 2001). A pure flip-flop switch mechanism is subject to inappropriate transitions in the presence of noise; in behaving animals, such inappropriate transitions would translate to potentially dangerous switches between wake and sleep. Our model also includes time courses associated with inhibition onset that maintain the robustness and stability necessary in a physiological system.

In our model there are certain conditions under which concurrent activity in wake- and sleep-active populations can occur. In particular, simulated brief awakenings occur when \( W \) becomes active for a short time during an extended sleep bout, but high homeostatic sleep drive prevents a transition into sustained wake. This theoretical mechanism for brief awakenings predicts that wake-promoting and VLPO neurons may be active concurrently during brief awakenings in mice.

Unfortunately, existing experimental data do not address the issue of concurrent activity in wake- and sleep-active populations. Unit recordings (Szymusiak et al. 1998) and fos immunostaining (Sherin et al. 1996) established that VLPO neurons are active during sleep, although the long half-life of fos cannot resolve VLPO activity during brief awakenings and unit recordings have been analyzed only during stable wake. Thus VLPO neurons may remain active during brief awakenings and additional experiments are needed to test this prediction.

A NREM–REM flip-flop switch?

Lu and colleagues (2006) recently proposed a conceptual model for NREM–REM alternation involving mutual inhibition between GABAergic REM-on (sublaterodorsal nucleus) and REM-off (ventrolateral part of the periaqueductal gray matter and the lateral pontine tegmentum) populations. In this framework, increased activity in eVLPO inhibits monoaminergic populations, thereby removing excitation from REM-off populations. The resulting decrease of activity in REM-off populations results in disinhibition (and activation) of REM-on populations.

Our approach to NREM–REM alternation during a sleep cycle is based on the classical view of interacting (REM-off) monoaminergic populations (\( W \) and REM-on cholinergic populations (\( R \)) (McCarley and Hobson 1975). However, our implementation is consistent with the theory that increased activity in the eVLPO results in disinhibition of REM-on neurons because we model increased inhibition of \( W \) over the course of the sleep cycle as a result of increased eVLPO activity.

In contrast to the idea of the NREM–REM flip-flop switch, the disinhibition of \( R \) in our model is not mediated through REM-off neurons. Although the intermediate REM-off population is not necessary for modeling normal sleep–wake behavior, REM-off neurons may be involved in other regulatory aspects of REM phenomena (Lu et al. 2006). Therefore we may need to extend our model to include a REM-off intermediary population in future work.

Technical considerations and future directions

By using relaxation oscillator equations to model each population, we imposed an assumption of fast transitions between high- and low-activity levels as demarcated by the knees of the cubic nullclines associated with \( v \)-variables. Although the model predicts some gradual changes in activity, such as the slow increase in activity of VLPO neurons preceding a transition to NREM sleep, it does not capture the timescales of changes on the level of single- or multiunit firing rates. As additional experiments establish time courses of activity for every population in the sleep–wake network, future models of the network could incorporate these refinements. By describing the time courses of transitions, such models would represent increasingly complex network dynamics and may offer an important framework for exploring the relative dynamics and causal implications of firing rate changes among these populations.

The period of relaxation oscillations is relatively robust to noise, so the durations of simulated brief awakenings and REM bouts tend to be normally distributed around the characteristic period of the oscillations associated with the \( W \) and \( R \) equations, respectively. In experimental data, the durations of brief awakenings and REM bouts follow power law and exponential distributions, respectively. Therefore although our simple implementation of noise was sufficient to reproduce the major statistical features of mouse sleep–wake behavior, relaxation oscillator formalism limits our ability to fully capture all the properties of the distributions of bout durations. Formal analysis of the implementation of noise—including an assessment of the type of noise used and the placement of stochastic terms in the model equations—might improve some of these statistical features of the simulated data.

The interaction between the circadian system and sleep–wake behavior has been studied extensively and recent experiments established some of the neural circuitry involved in this interaction. Our model does not yet capture circadian effects, such as hourly variations in the amounts of wake and sleep, extended wake bouts at the onset of the dark period, and nonuniform distribution of REM sleep (Mochizuki et al. 2004). Future studies will integrate circadian effects into this model and should provide an excellent opportunity to explore how the circadian system modulates sleep–wake dynamics.

Our model provides a novel framework for understanding dynamics observed in altered sleep–wake behavior, especially when physiologic observations have analogs in the model parameters. For example, disruption of sleep with aging may be linked to a loss of VLPO neurons (Gaus et al. 2002). In our model, this would correspond to a decrease in the parameter \( g_{5, \text{max}} \), \( S \), and we find that decreasing \( g_{5, \text{max}} \) increases the number of brief awakenings in simulations. As another example, it remains unclear how a loss of orexin signaling causes the behavioral state instability associated with narcolepsy (Mochizuki et al. 2004). Because narcolepsy is essentially a disorder of sleep–wake dynamics, our model framework is well suited for investigating the functional role of orexin neurons. A full theoretical understanding of the dynamic effects of changes in the model may suggest mechanisms of age- and orexin-related changes in sleep–wake behavior.

In summary, we have shown that a model of three coupled relaxation oscillators can generate the network dynamics associated with behavioral state control to realistically simulate mouse sleep–wake behavior. By directly addressing the dynamics of the sleep–wake network, this modeling approach
may provide predictions and insights that improve our understanding of normal and pathologic sleep–wake behavior and its underlying physiology.

APPENDIX

The activity of each population is modeled by modified Morris–Lecar equations. Morris–Lecar equations are a lower-dimensional form of conductance-based Hodgkin–Huxley-type single-cell models (Hodgkin and Huxley 1952). A single gating variable on the potassium current yields a two-dimensional system of equations in the standard notation

\[
\frac{dv}{dt} = I_i - g_l(v) - g_{Ca}m_s(v)(v - E_C) - g_K\theta(v - E_K)
\]

\[
\frac{du}{dt} = \Phi[u_s(v) - u]/\tau_s(v)
\]

where \( I_i, g_L, E_L, g_{Ca}, E_{Ca}, g_K, E_K, \) and \( \Phi \) are constant parameters (Morris and Lecar 1981) and \( m, u, \) and \( \tau_s \) are functions defined below. Because we are describing population activity rather than membrane voltage, we rescaled these equations with the affine transformation \( A(v) = (v + 65)/130 = \hat{v} \). Then \( \hat{v} \) assumes values between 0 and 1, and

\[
\hat{v} = \frac{1}{130} v
\]

By rescaling parameters, grouping terms appropriately, and adding coupling terms \( c_i \), we obtain the following expressions

\[
\frac{dv}{dt} = \hat{I} - [\alpha + \beta m_s(\hat{v})]\hat{v} + \left( \frac{\beta}{2} + \eta \right) m_s(\hat{v}) - (\sigma_s - 0.5\sigma - \zeta)\theta + c,
\]

\[
\frac{du}{dt} = \Phi[u_s(\hat{v}) - \hat{u}]/\tau_s(\hat{v})
\]

where \( \hat{I}, \alpha, \beta, \eta, \sigma_s, \zeta, \) and \( \Phi \) are constant parameters (parameter values are listed in Table A1); the coupling terms \( c_i \) are given in the text; and the functions \( u_s(\cdot) \) and \( \tau_s(\cdot) \) are defined below. For convenience, we will suppress the “hat” notation, thereby letting \( v_i \) and \( u_i \) denote the rescaled variables.

As previously described, we chose Morris–Lecar relaxation oscillation equations for the geometry of the nullclines associated with \( v_i \) and \( u_i \) for \( i = W, S, R \). Because these equations are usually associated with single-cell activity rather than population activity, the timescales associated with our modified relaxation oscillator equations are much slower than the timescales involved in the original Morris–Lecar equations.

The saturating functions describing the onset of inhibition from \( S \) and \( W \), respectively, are given by the following equations

\[
g_s(t) = g_{S\max}\tanh(\rho_S t)
\]

\[
g_w(t) = g_{W\max}\tanh(\rho_W t)
\]

with constant parameters \( g_{S\max}, g_{W\max}, \rho_S, \) and \( \rho_W \). The variables \( t_s \) and \( t_w \) measure time elapsed since the onset of the current wake or sleep bout and are governed by

\[
\frac{dt_s}{dt} = \begin{cases} 1 & \text{during sleep} \\ 0 & \text{during wake} \end{cases}
\]

\[
\frac{dt_w}{dt} = \begin{cases} 1 & \text{during wake} \\ 0 & \text{during sleep} \end{cases}
\]

The saturating function describing the onset of orexinergic effects is given by

\[
g_{OXS}(t_s) = O_X[\tanh(OX_{OXT})(0.75) + 2[\tanh(OX_{OXT})]^{-1}]
\]

with constant parameters \( O_X \) and \( OX_{OXT} \). The important element of this functional form is a change of concavity that allows \( g_{OXS}(t_s) \) to remain very low for the first minute of activation.

The equations for \( m_s(v_i), u_s(v_i), \) and \( \tau_s(v_i) \) are given, respectively, by

\[
m_s(v) = \{1 + \exp(-(-\lambda v - \theta_s)\psi_m)\}^{-1}
\]

\[
 u_s(v) = \xi_{u(m,w)}[1 + \exp(-(-\lambda v - \theta_{u(m,w)}))\psi_{u(m,w)}]^{-1}
\]

\[
 \tau_s(v) = \{\cosh((\lambda v - \theta_{u(m,w)})/(2\psi_{u(m,w)})\}^{-1}
\]

with constant parameters \( \xi_{u(m,w)}, \theta_{u(m,w)}, \) and \( \psi_{u(m,w)} \).

The state-dependent equations for \( h, r_f, r_s, \) and \( \epsilon_f \) were given in the main text. The parameter values used to generate simulated behavioral data are listed in Tables A1 and A2.

### Table A1. Parameters associated with the wake-, sleep-, REM-active neuronal populations (W, S, and R) and typical parameter values as adapted and rescaled from Morris–Lecar formalism

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Parameter</th>
<th>Value</th>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( I_i )</td>
<td>3.4</td>
<td>( I_w )</td>
<td>4.16</td>
<td>( I_R )</td>
<td>3.6</td>
</tr>
<tr>
<td>( \alpha_s )</td>
<td>4.0</td>
<td>( \alpha_w )</td>
<td>4.0</td>
<td>( \alpha_R )</td>
<td>4.0</td>
</tr>
<tr>
<td>( \beta_s )</td>
<td>8.0</td>
<td>( \beta_w )</td>
<td>8.0</td>
<td>( \beta_R )</td>
<td>8.0</td>
</tr>
<tr>
<td>( \eta_s )</td>
<td>7.385</td>
<td>( \eta_w )</td>
<td>13.539</td>
<td>( \eta_R )</td>
<td>7.385</td>
</tr>
<tr>
<td>( \sigma_s )</td>
<td>8.0</td>
<td>( \sigma_w )</td>
<td>8.3</td>
<td>( \sigma_R )</td>
<td>8.0</td>
</tr>
<tr>
<td>( \zeta_s )</td>
<td>-5.169</td>
<td>( \zeta_w )</td>
<td>-5.491</td>
<td>( \zeta_R )</td>
<td>-5.169</td>
</tr>
<tr>
<td>( \phi_s )</td>
<td>1.2</td>
<td>( \phi_w )</td>
<td>0.85</td>
<td>( \phi_R )</td>
<td>0.045</td>
</tr>
</tbody>
</table>

*Parameters associated with \( m_s, u_s, \) and \( \tau_s \) are given as follows:*

\[
\theta_{\theta_{m,w}} = 63.8 \quad \lambda = 130.0 \quad \psi_m = 7.0
\]

\[
\theta_{\theta_{u,m,w}} = 1.0 \quad \epsilon_m = 2.0 \quad \psi_u = 4.0
\]

\[
\theta_{\theta_{u,m,w}} = 55.0 \quad \theta_{u,m,w} = 57.8 \quad \psi_{u,m,w} = 7.0
\]

*Parameter values from Morris and Lecar (1981).*

### Table A2. Parameters and typical parameter values associated with coupling between wake-, sleep-, and REM-active populations (W, S, and R) and homeostatic sleep drives

<table>
<thead>
<tr>
<th>Coupling</th>
<th>Homeostatic Sleep Drives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role</td>
<td>Parameter</td>
</tr>
<tr>
<td>Maximal strength</td>
<td>( g_{max} )</td>
</tr>
<tr>
<td>( g_{max} )</td>
<td>2.69</td>
</tr>
<tr>
<td>( g_{L,C} )</td>
<td>1.92</td>
</tr>
<tr>
<td>( g_{L,C} )</td>
<td>0.538</td>
</tr>
<tr>
<td>( g_{L,C} )</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*Direction of effect \( a_{L,C} \)

- Slow REM | \( r_{up} \) | 800.0 |

*Rate of activation \( \rho_S \)

- 6.0 | \( \rho_W \) | 3.0 |

*Orexin \( OX \)

- 0.033 | \( OX_{m} \) | 0.7 |
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REFERENCES


