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Victoria Booth

Cecilia G. Diniz Behn
Gettysburg College

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Abstract

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Keywords

firing rate model, bifurcation analysis, bursting, hysteresis, limit cycle, bistability

Disciplines

Mathematics | Other Mathematics

A Fast-Slow Analysis of the Dynamics of REM Sleep*

Cecilia G. Diniz Behn[†] and Victoria Booth[‡]

Abstract. Waking and sleep states are regulated by the coordinated activity of a number of neuronal populations in the brainstem and hypothalamus whose synaptic interactions compose a sleep-wake regulatory network. Physiologically based mathematical models of the sleep-wake regulatory network contain mechanisms operating on multiple time scales including relatively fast synaptic-based interactions between neuronal populations, and much slower homeostatic and circadian processes that modulate sleep-wake temporal patterning. In this study, we exploit the naturally arising slow time scale of the homeostatic sleep drive in a reduced sleep-wake regulatory network model to utilize fast-slow analysis to investigate the dynamics of rapid eye movement (REM) sleep regulation. The network model consists of a reduced number of wake-, non-REM (NREM) sleep-, and REM sleep-promoting neuronal populations with synaptic interactions reflecting the mutually inhibitory flip-flop conceptual model for sleep-wake regulation and the reciprocal interaction model for REM sleep regulation. Network dynamics regularly alternate between wake and sleep states as governed by the slow homeostatic sleep drive. By varying a parameter associated with the activation of the REM-promoting population, we cause REM dynamics during sleep episodes to vary from suppression to single activations to regular REM-NREM cycling, corresponding to changes in REM patterning induced by circadian modulation and observed in different mammalian species. We also utilize fast-slow analysis to explain complex effects on sleep-wake patterning of simulated experiments in which agonists and antagonists of different neurotransmitters are microinjected into specific neuronal populations participating in the sleep-wake regulatory network.

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1. Introduction. Wakefulness and sleep states are produced by coordinated activity of neuronal populations distributed in different brain areas, primarily the brainstem and hypothalamus. The temporal patterns of activation of these populations, and thus wake and sleep behavior, are modulated by circadian and homeostatic processes: the circadian process drives the 24-hour (24-h) rhythms of sleep-wake behavior across the day, and the homeostatic process maintains an appropriate balance of sleep-wake behavior by increasing sleepiness and recovery sleep time as a function of prior wakefulness. Compared to the millisecond time scale of individual neuronal activity, the time scales associated with the circadian and homeostatic drives represent naturally arising slow variables in the sleep-wake regulatory system.

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[†]Department of Mathematics, University of Michigan, 530 Church Street, Ann Arbor, MI 48109. Current address: Department of Mathematics, Campus Box 0402, Gettysburg College, Gettysburg, PA 17325 (cdinizbe@gettysburg.edu).

[‡]Departments of Mathematics and Anesthesiology, University of Michigan, East Hall Rm. 4075, 530 Church Street, Ann Arbor, MI 48109 (vbooth@umich.edu).

Early phenomenologically motivated mathematical models of sleep-wake behavior focused exclusively on the interactions between circadian and homeostatic systems [4, 18]. However, recent physiologically based mathematical modeling approaches have necessarily adopted the multiple time scales that are indicated by the underlying biology [50, 14, 35, 12, 39]. All these models describe sleep-wake behavior in terms of firing rates in neuronal populations whose activity is correlated with states of wake, rapid eye movement (REM) sleep, and non-REM (NREM) sleep. Transitions in firing activity of these populations result from synaptic interactions among the populations, which define the sleep-wake regulatory network, as well as slow modulation by circadian and homeostatic drives. While some of these models omit the effects of circadian modulation, by considering sleep-wake behavior averaged over the 24-h day or focusing on a specific circadian phase, in all of these models the homeostatic sleep drive plays a fundamental role in driving transitions between wake and sleep states.

The existence of a natural slow time scale provided by the homeostatic sleep drive in physiologically based models of sleep-wake regulation allows for the use of fast-slow decomposition techniques [40, 16, 23] to analyze dynamics. In particular, one can identify model mechanisms governing transitions in population activity levels by examining the bifurcation structure of the system with respect to the homeostatic sleep drive. Previous modeling studies have exploited separation of time scales to investigate transition dynamics among wake and sleep states [35, 14, 39]. Here, we show how fast-slow analysis can provide insight into the dynamics of REM sleep regulation. REM sleep dynamics vary significantly across different mammalian species, with robust, approximately periodic cycling between NREM and REM sleep observed in humans, and more sporadic REM sleep timing occurring in rodents [6, 25, 45]. However, the structure of the neuronal sleep-wake regulatory network is thought to be maintained across these species [47]. In addition, REM sleep dynamics are tightly controlled by the circadian process such that over the 24-h day an animal will transition between regimes in which REM sleep occurs sparsely (e.g., the dark period for a nocturnal rodent) to regimes in which REM sleep commonly occurs (e.g., the light period for a nocturnal rodent) [54]. Our fast-slow analysis shows how the single network structure of our sleep-wake regulatory network can generate a range of REM sleep dynamics similar to differences observed across species and across the 24-h day.

Experimental investigation of the dynamic interactions within the neuronal sleep-wake regulatory network is hampered by current limitations in technology for recording neuronal activity from multiple, distributed locations deep in the brains of a behaving animal. In order to probe the contributions of wake- and sleep-promoting populations to the regulation of a behavioral state, experimentalists rely on pharmacological manipulation of the activity of a targeted population through microinjection or microdialysis and analysis of the subsequent changes in sleep-wake behavior (e.g., [51], reviewed in [2]). Generally, when activity of an isolated neuronal population is manipulated by separate application of an agonist and antagonist of a neurotransmitter known to affect its properties, one expects the agonist and antagonist to produce opposite effects. When applying neurotransmitter agonists and antagonists to populations involved in the sleep-wake regulatory network in the behaving animal, their effects will be highly dependent on the endogenous neurotransmitter milieu, which is continuously changing with behavioral state. Specifically, the effects of a neurotransmitter antagonist can be expected to influence the behavioral state in which the neurotransmitter has a high concen-

tration, for example noradrenaline during waking or GABA during sleep states. On the other hand, the effects of infusing a neurotransmitter agonist may be more difficult to predict since it will introduce actions of that neurotransmitter during states in which it is normally not present, for example, GABA during waking or noradrenaline during sleep states. To understand these effects of manipulation of individual populations within the sleep-wake network, we apply fast-slow analysis to the reduced sleep-wake regulatory network and analyze how the changes to the underlying bifurcation structure of the system affect model dynamics.

Including this Introduction, this work is divided into five sections. Section 2 introduces a reduced version of our previously developed, physiologically based model of the sleep-wake regulatory network [12]. We also describe the decomposition of the reduced model into a fast subsystem and a slow variable representing the homeostatic sleep drive, as well as the simulation of microinjection of neurotransmitter agonists and antagonists into neuronal populations of the model network. Section 3 investigates REM sleep dynamics by applying fast-slow analysis to the reduced model. In addition, we address how feedback from the network dynamics onto the slow homeostatic sleep drive can modulate network behavior. Section 4 applies the fast-slow analytical framework to compare the effects of simulated microinjection of neurotransmitter agonist/antagonist pairs on network behavior. Section 5 summarizes our results and discusses the broader mathematical and physiological implications of our analyses.

2. Model and methods.

2.1. Network structure. Sleep-wake regulation is governed by the interactions among a number of different neuronal populations in the brainstem and hypothalamus including wake-promoting populations (locus coeruleus (LC), dorsal raphe (DR) nucleus, and tuberomammillary nucleus (TMN)) and sleep-promoting populations (ventrolateral preoptic nucleus (VLPO)). While there is broad consensus that mutually inhibitory synaptic projections between the sleep-promoting VLPO and the wake-promoting LC, DR, and TMN constitute a flip-flop switch for the regulation of transitions between wake and NREM sleep [42], the populations involved in the regulation of REM sleep and their synaptic interactions are much debated [31, 5, 44, 9, 27]. One hypothesis for REM sleep regulation proposes a causal role for acetylcholine release from REM-active subpopulations of the laterodorsal tegmental nucleus (LDT) and pedunculopontine tegmental nucleus (PPT) in promoting REM sleep. The interaction between these putative REM-promoting populations and the wake-promoting LC and DR forms the basis for the classic reciprocal interaction model for REM-on/REM-off cycling during sleep [31, 30]. Although other mechanisms for REM sleep regulation have been proposed [27, 28], we will constrain our model by assuming a reciprocal interaction network structure.

To facilitate the analysis of the underlying network dynamics, we consider a minimal sleep-wake regulatory network consisting of single wake-, sleep-, and REM-promoting populations (Figure 1). Synaptic interactions between populations reflect the mutually inhibitory flip-flop switch between the wake (W) and NREM sleep (N) populations, and reciprocal excitatory-inhibitory interactions between the W and REM sleep (R) populations. Our original sleep-wake regulatory network model had the same general structure, but it contained two wake-promoting populations corresponding to the LC and the DR, and a wake- and REM-promoting population corresponding to a distinct subpopulation of the LDT and PPT, for a total of five

Figure 1. Schematic for the reduced sleep-wake regulatory network. For neuronal coupling, circles denote inhibition, and arrows denote excitation.

coupled neuronal populations [12].

2.2. Population modeling formalism. We use a population firing rate model formalism to model the neurotransmitter-mediated interaction between neuronal populations. In the original formalism, the mean firing rate of a presynaptic population, $F_Y(t)$, induces expression of neurotransmitter concentration, $C_i(t)$, which drives the mean postsynaptic firing rate, $F_X(t)$ [12]. In this reduced model, we further decrease the dimension of the system by taking neurotransmitter release to be instantaneous and replacing $C_i(t)$ with the value predicted by its steady-state release function, $C_{i\infty}(F_Y)$. The implied assumption that $F'_X \ll C'_i$ is a reduction in the complexity of the model and is not meant to represent physiological characteristics of the system. Thus, the mean firing rate $F_X(t)$ for each population (in Hz, $X = W, N$, or R) is modeled by the following equation:

$$(2.1) \quad F'_X = \frac{F_{X\infty}(\sum_i g_{i,X} C_{i\infty}(F_{Y_i})) - F_X}{\tau_X},$$

where $F_{X\infty}(\cdot)$ is the steady-state firing rate response function; its argument consists of the sum of neurotransmitter concentrations released to population X , $C_{i\infty}(F_{Y_i})$, which reflect the mean firing rate of the associated presynaptic population, $F_{Y_i}(t)$; and the variable $F_X(t)$ evolves to its steady-state value with time constant τ_X . Each presynaptic population F_{Y_i} is associated with a neurotransmitter concentration $C_{i\infty}$. For $i = E$ (noradrenaline), $F_{YE} = F_W$; for $i = G$ (GABA), $F_{YG} = F_N$; and for $i = A$ (acetylcholine), $F_{YA} = F_R$. The concentrations $C_{i\infty}(\cdot)$ of each neurotransmitter i released to postsynaptic population X are weighted by the constant parameter $g_{i,X}$, where the sign of each $g_{i,X}$ distinguishes between an excitatory ($g_{i,X} > 0$) or an inhibitory ($g_{i,X} < 0$) effect of the neurotransmitter. Neurotransmitter concentrations are normalized between 0 and 1, so $C_{i\infty}$ is unitless, with units of concentration being absorbed by the constant $g_{i,X}$.

The steady-state neurotransmitter release function has a saturating profile given by $C_{i\infty}(f) = \tanh(f/\gamma_i)$, where the parameter γ_i controls the sensitivity of release as a function of presynaptic firing rate f .

The steady-state firing rate response function has the sigmoidal profile utilized in standard firing rate models [53] (see reviews in [15, 10, 11]) that saturates for high levels of neurotransmitter concentration c :

$$F_{X\infty}(c) = X_{max}(0.5(1 + \tanh((c - \beta_X)/\alpha_X))).$$

The parameters X_{max} , α_X , and β_X represent the maximum firing rate, sensitivity of response, and half-activation threshold, respectively.

2.3. Modeling the homeostatic sleep drive. The sleep-wake network is modulated by a homeostatic sleep drive, $h(t)$, which represents the phenomenon that the propensity for sleep increases as a function of wakefulness. A comprehensive physiological substrate for the homeostatic sleep drive has not been established, although several relevant mechanisms have been identified. Our implementation of $h(t)$ is based on current theories involving adenosine, a somnogenic chemical whose levels increase during wakefulness and decrease during sleep [49, 7, 38, 46]. The model homeostatic sleep drive, $h(t)$, mimics adenosine dynamics by increasing towards a maximum value, H_{max} , during wakefulness and decreasing towards 0 during sleep states with time scales τ_{hw} and τ_{hs} , respectively:

$$(2.2) \quad h' = \frac{(H_{max} - h)}{\tau_{hw}} H[F_W - \theta_W] - \frac{h}{\tau_{hs}} H[\theta_W - F_W],$$

where $H[z]$ is the Heaviside function defined as $H[z] = 0$ if $z < 0$ and $H[z] = 1$ if $z \geq 0$, and the state dependence of homeostatic activity is gated by the firing rate of the W population, F_W .

Adenosine is thought to act in part by disinhibiting the sleep-promoting VLPO [7, 34, 21]. In the model, $h(t)$ modulates the activation threshold of the N population:

$$(2.3) \quad F_{N\infty}(c) = N_{max}[0.5(1 + \tanh((c - \beta_N(h))/\alpha_N))],$$

where $\beta_N(h) = -kh$ for constant k . During wakefulness, as h increases, the N activation threshold decreases to permit activation of the N population and a transition to NREM sleep. On the other hand, when h decreases during sleep states, the N activation threshold increases and causes the N population to inactivate, thereby transitioning the network back to the wake state. This mechanism mimics the effects of adenosine on the VLPO.

2.4. Simulated sleep-wake behavior. In numerical simulations of our network model, we interpret the behavioral state of the model by the population with the highest firing rate, where the REM state is defined by high activity in both F_N and F_R . The reduced sleep-wake regulatory network model displays solutions similar to those of our full 5-population network model under deterministic conditions. Specifically, our full network model contains stochastic components, such as randomly varying multiplicative scaling factors in the steady state neurotransmitter release functions $C_{i\infty}(f)$ and randomly occurring brief excitatory stimuli to the wake-promoting populations, that produced high variability in sleep-wake transitions, consistent with observed rodent behavior [12]. When these stochastic components were removed, the dynamics of the resulting deterministic full network model showed periodic cycling from wake to NREM sleep to REM sleep and back to wake, with NREM bouts having longer durations than wake bouts. The reduced network model can replicate these deterministic dynamics of the full network model (compare our Figure 2(A) to Figure 5B in [12]). By varying parameters in the reduced network model, we can generate sleep-wake patterning more similar to that observed in humans (Figure 2(B)). This parameter regime results in a periodic solution of an ~ 16 h wake bout followed by an ~ 8 h sleep bout during which REM bouts occur regularly

Figure 2. Time traces of population firing rates simulating deterministic sleep-wake behavior similar to (A) rodent sleep as modeled in [12], and to (B) human sleep (F_W = green curve, F_N = red curve, F_R = blue curve, homeostatic sleep drive h = orange curve). Wake is defined when F_W is greater than $\theta_W = 2\text{Hz}$; NREM is defined when $F_W < \theta_W$ and F_N is high; and REM is defined when $F_W < \theta_W$ and both F_N and F_R are high.

with an $\sim 90\text{min}$ period. Since our reduced sleep-wake model is minimal and deterministic, it is not able to exactly replicate all characteristics of experimentally recorded rodent or human sleep, such as the high variability in bout durations and transitions observed in rodent sleep [26], the progressive increase in REM bout duration during the night in human sleep [6], and the fragmentation of human REM sleep by brief interruptions of NREM and wake states [33]. However, these results show that the basic network structure of our reduced model is capable of generating a range of sleep-wake patterning similar to the differences observed across species. In addition, as we have shown for rodent sleep [12, 13], this basic network framework, with the inclusion of neurotransmitter dynamics and appropriate stochastic components, is capable of generating sleep-wake patterning that more closely replicates experimental sleep recordings.

In this paper, we focus on understanding the model mechanisms generating changes in REM sleep dynamics; thus we consider a model parameter regime that generates generic transitions between wake and NREM states and allows a sufficiently long sleep stage to accommodate the model's full spectrum of REM sleep dynamics. In this regime, parameter values are as follows: maximum firing rates $W_{max} = 6.5\text{ Hz}$, $N_{max} = 5\text{ Hz}$, and $R_{max} = 5\text{ Hz}$; weights for post-synaptic effects of neurotransmitter concentrations are $g_{G,W} = -2$, $g_{A,W} = 1.2$, $g_{E,N} = -2$, $g_{E,R} = -4$, $g_{G,R} = -1.4$, $g_{A,R} = 1.5$; time constants for firing rate response dynamics are $\tau_W = 25\text{s}$, $\tau_N = 10\text{s}$, $\tau_R = 1\text{s}$; parameters characterizing the steady-state functions for firing rate and neurotransmitter concentration release are $\alpha_W = 0.5$, $\beta_W = -0.3$, $\gamma_E = 5$, $\alpha_N = 0.25$, $\gamma_G = 4$, $\alpha_R = 0.25$, $\gamma_A = 3$; and parameters governing the homeostatic sleep drive are $H_{max} = 1$, $\theta_W = 2\text{Hz}$, $\tau_{hw} = 600\text{s}$, $\tau_{hs} = 700\text{s}$, and $k = 1.5$. The half-activation threshold of the REM-promoting population, β_R , is varied with parameter values specified in the figure captions. To obtain the rodent-like sleep dynamics shown in Figure 2(A), the following parameters were changed: $g_{E,R} = -2.1$, $g_{G,R} = -1.3$, $\beta_W = -0.23$, $\beta_R = -0.6$, $\tau_{hs} = 380\text{s}$, and $k = 2.5$. To obtain the human-like sleep dynamics shown in Figure 2(B), model time units were defined as minutes, and the following parameters were changed: $g_{G,W} = -1.68$, $g_{A,W} = 1$, $g_{G,R} = -1.3$, $g_{A,R} = 1.6$, $\beta_W = -0.4$, $\alpha_N = 0.175$, $\alpha_R = 0.13$, $\beta_R = -0.9$, $\gamma_A = 2$, $\tau_{hw} = 580.5\text{min}$, and $\tau_{hs} = 510\text{min}$. The time scales for the homeostatic sleep drive

represented key species-dependent parameters; interestingly, they fell within the ranges predicted in recent work by Phillips and colleagues [37]. Numerical simulations of each model were computed with a modified Euler integration method with a time step of 0.005s and were implemented with the software XPPAUT, developed by G. B. Ermentrout and available at <ftp://ftp.math.pitt.edu/pub/bardware>.

2.5. Fast-slow analysis of the model. Since the homeostat h acts on a slow time scale compared to the rest of the variables in the network, we can decompose our model into a fast subsystem, consisting of the equations governing firing rates in each population, and the slow variable h :

$$(2.4) \quad F'_W = \frac{F_{W\infty}(g_{G,W}C_{G\infty}(F_N) + g_{A,W}C_{A\infty}(F_R)) - F_W}{\tau_W} = \Phi_W(F_W, F_N, F_R),$$

$$(2.5) \quad F'_N = \frac{F_{N\infty}(g_{E,N}C_{E\infty}(F_W)) - F_N}{\tau_N} = \Phi_N(F_W, F_N, h),$$

$$(2.6) \quad F'_R = \frac{F_{R\infty}(g_{E,R}C_{E\infty}(F_W) + g_{G,R}C_{G\infty}(F_N) + g_{A,R}C_{A\infty}(F_R)) - F_R}{\tau_R} \\ = \Phi_R(F_W, F_N, F_R, \beta_R),$$

$$(2.7) \quad h' = \epsilon \left[\frac{(H_{max} - h)}{\tau_{hw\epsilon}} H[F_W - \theta_W] - \frac{h}{\tau_{hs\epsilon}} H[\theta_W - F_W] \right].$$

Coupling of the fast subsystem (F_W , F_N , and F_R) and the slow variable (h) occurs in the dependence of $F_{N\infty}$ on h . The separation of time scales fails when $F_W = \theta_W$, and h' changes instantaneously. Away from this transition, the dynamics of h can be considered to be $O(\epsilon)$ for $\epsilon \ll 1$. Following standard methods of fast-slow analysis [40, 16, 23], we consider the limit $\epsilon \rightarrow 0$ in which the slow variable becomes a constant. In this limit, we investigate the structure of solutions to the fast subsystem as a function of the parameter h in bifurcation diagrams where the bifurcation parameter h ranges over values from 0 to $H_{max} = 1$. To understand solutions of the 3-dimensional fast subsystem, we compute bifurcation diagrams of solutions to the fast subsystem in terms of F_W and F_R . The bifurcation diagrams with respect to F_N are qualitatively similar to those with respect to F_W except for a reversal in the firing rates associated with steady-state solutions (see below). Dynamics of the full 4-dimensional model, in which h is slowly varying, are interpreted as being governed by the stable solutions of the fast subsystem computed at instantaneous values of h .

The range of dynamic patterns of transitions between wake, NREM, and REM sleep states that are possible in the model are investigated by varying the half-activation threshold of the steady-state firing rate response function for the REM population, β_R . To understand changes in the solution structure of the fast subsystem with respect to the slow variable h as β_R is varied, we additionally compute bifurcation diagrams of the fast subsystem with respect to β_R for fixed values of h . Bifurcation diagrams were computed numerically using the software AUTO through its interface with XPPAUT.

2.6. Modeling microinjection of neurotransmitter agonists and antagonists. To model the microinjection of a neurotransmitter agonist and antagonist in a specific population in the reduced model, we use an approach similar to that in our original model [12], except

that we consider fixed levels of the agents instead of a dynamic variation reflecting dissipation and uptake of the agents. Concentration levels of an agonist and antagonist are represented by parameters P_i and Q_i , respectively, where i denotes the affected neurotransmitter. Microinjection of agonists introduces a persistent effect of the neurotransmitter in the postsynaptic population and is modeled by replacing the neurotransmitter concentration $C_{i\infty}(F_{Yi})$ in the argument of the steady-state firing rate function of the postsynaptic population with $C_{i\infty}(F_{Yi}) + P_i$. Microinjection of an antagonist causes a decrease in the effects of the endogenous neurotransmitter on the postsynaptic population and is modeled by scaling neurotransmitter concentration $C_{i\infty}(F_{Yi})$ in the argument of the steady-state firing rate function of the postsynaptic population as $(1 - Q_i)C_{i\infty}(F_{Yi})$. Here, we simulate microinjection of GABAergic and cholinergic agonists and antagonists into the W population, so the appropriate modification of $C_{i\infty}(F_{Yi})$ for $i = G$ or A appears in the argument of $F_{W\infty}$. Values of P_i and Q_i are given in the figure captions.

3. Fast-slow analysis of the reduced sleep-wake network and implications for REM sleep. We consider the sensitivity of model behavior to the parameter associated with the activation threshold of the REM-promoting population in our network, β_R . By varying this parameter, the network generates a range of REM sleep patterning that is similar to REM sleep behaviors observed in different species and across circadian phases. In summary, by decreasing the activation threshold of the REM-promoting population, the network transitions from regimes in which REM sleep is sparse (e.g., the dark period for a nocturnal rodent) to regimes in which REM sleep commonly occurs (e.g., the light period for a nocturnal rodent). Additionally, for low values of β_R , robust cycling between NREM and REM sleep occurs, as seen in humans and some other species [6, 48, 24, 22]. Interestingly, the alternation between quiescence in the REM-promoting population during wake and cyclic activation of this population during sleep can be linked to a bifurcation structure similar to that underlying bursting electrical activity in neuronal models [8].

Numerical simulations of the reduced sleep-wake network model show these different activation patterns of the wake, NREM, and REM populations based on the value of the activation threshold for F_R , the parameter β_R (Figure 3). When $\beta_R = 0$, the model alternates periodically between wake and NREM states, and the REM population is completely suppressed. As β_R decreases, the REM population activates at the transition from the NREM state to the wake state, and there is a progression from a single REM bout at this transition to multiple NREM/REM oscillations during the sleep period. REM bouts are followed by brief activations of the wake population. Since F_W does not increase above the threshold separating wake and sleep (θ_W) during these activations, they do not constitute wake bouts. However, in other parameter ranges, they may be interpreted as brief, post-REM wake bouts and can influence model dynamics by introducing feedback of the fast subsystem on the slow variable (see section 3.3).

Intuitively, we can understand the dependence of sleep-wake behavior on β_R since decreased β_R values allow increased participation of the REM population in model dynamics. The neurotransmitters targeting the REM population, noradrenaline (E) and GABA (G), both have inhibitory effects, so β_R must be negative for the REM population to activate. Decreasing β_R values permits REM activation at higher levels of inhibition. We note that

Figure 3. Time traces of population firing rates (in Hz) show dependence of population activation patterns, and thus simulated sleep-wake state, on β_R , the half-activation threshold of the REM population (F_W = green curve, F_N = red curve, F_R = blue curve, homeostatic sleep drive h = orange curve). (A) For $\beta_R \geq 0$, the model alternates between the wake state (high F_W) and the NREM sleep state (high F_N). F_R never activates, and REM sleep is completely suppressed. (B) As β_R decreases to -0.55 , a single REM bout occurs at the transition from the NREM sleep state to the wake state. (C) As β_R continues to decrease to -0.72 , multiple alternations between NREM and REM sleep emerge after an initial NREM period during the sleep state. (D) For $\beta_R = -0.75$, the network begins cyclic alternations between NREM and REM sleep immediately upon transition out of sustained wakefulness.

similar changes in network dynamics can be obtained when β_R is fixed and the strength of the GABAergic inhibition from the NREM-promoting population to the REM-promoting population, $g_{G,R}$, is varied. In this case, the inhibitory inputs to the REM-promoting population are regulating its activation dynamics, instead of its intrinsic excitability properties governed by β_R . In this section, we more quantitatively analyze the effects of variation in β_R and the resulting variation in the participation of the REM population in model dynamics by applying fast-slow analysis that exploits the slowly varying homeostatic sleep drive h .

3.1. Fast-slow analysis of the reduced sleep-wake network. To track this β_R -dependent behavioral progression, we applied a fast-slow analysis to the model by exploiting the natural slow time scale of the homeostatic sleep drive h . By considering h to be a parameter, we analyze bifurcation diagrams of the fast subsystem (i.e., (2.4)–(2.6)) with respect to h for different values of β_R . For each value of β_R , we simultaneously consider fast subsystem solutions in terms of F_W and F_R .

Figure 4. Bifurcation diagrams of the fast subsystem (i.e., (2.4)–(2.6)) when the slow variable h is taken as a parameter reveal the basis for the β_R -dependent changes in model dynamics shown in Figure 3. Steady-state solutions form a Z-shaped curve in F_W (A),(C), F_N (not shown), and F_R (B),(D), defining the stable wake (green) and NREM sleep (red) states and the unstable steady state separating them (dashed gray). As h slowly varies in the full model, the trajectory (cyan curve) moves around this Z-shaped curve in a hysteresis loop with the direction (clockwise in (A),(C); counterclockwise in (B),(D)) dictated by whether F_W is above (h increasing) or below (h decreasing) θ_W (dotted horizontal line). Transitions from wake-to-NREM and NREM-to-wake occur when the trajectory reaches the high h and low h saddle-node points, respectively, terminating the stable branches. As β_R is decreased from 0 (A),(B) to -0.55 (C),(D), the Z-shaped steady-state solution curve remains unchanged in terms of F_W (A),(C) but F_R amplitudes at the low h saddle-node point terminating the NREM branch increase (B),(D), providing for transient F_R activation in the full fast-slow model as the trajectory moves through this saddle-node point.

When $\beta_R = 0$, steady state solutions of the fast subsystem form a Z-shaped curve with respect to h . The Z-shaped structure is most readily apparent in the F_W - h diagram (Figure 4(A)), but it also exists in the F_R - h diagram and defines small differences in the low values of F_R associated with the wake and NREM sleep states. The upper and lower branches of the Z are stable and represent the wake (green, high F_W , low F_N , low F_R) and NREM sleep (red, low F_W , high F_N , low F_R) states, respectively. The middle branch is an unstable steady state demarcating the basins of attraction for the stable steady states (gray dashed curve). The substantial overlap between the h values associated with the existence of stable wake and NREM sleep states represents a region of bistability. The bifurcation diagram in terms of

F_N (not shown) is similar to the F_W diagram, except that the wake state corresponds to the lower stable branch of the Z (low F_N) and the NREM sleep state to the high stable branch (high F_N). In the full fast-slow model, as h slowly varies, the trajectory (cyan curve) moves around the hysteresis loop defined by the Z-shaped structure. The variable h increases when the trajectory is in the wake state (F_W above $\theta_W = 2$, dotted line), and decreases when it is in the sleep state (F_W below θ_W). Thus, the trajectory moves around the hysteresis loop clockwise in the F_W - h diagram (Figure 4(A)) and counterclockwise in the F_R diagram (Figure 4(B)). Transitions from wake to NREM sleep occur when the trajectory reaches the high h saddle-node point terminating the wake (green) solution branch, and transitions from NREM sleep to wake occur when it reaches the low h saddle-node point terminating the NREM sleep (red) solution branch.

In the F_R - h -plane, the solution branches lie close together at low values of F_R , but F_R magnitudes increase near the low h saddle-node point that terminates the NREM branch. For $\beta_R = 0$, this rise in the NREM solution branch results in a small activation of F_R in the fast-slow model at the transition from NREM sleep to wake (Figure 4(B)). As β_R decreases, F_R amplitudes at the low h saddle-node point of the NREM branch increase, thereby resulting in larger activation levels of F_R at the NREM-to-wake transition in the full model as the trajectory tracks along this solution branch. For $\beta_R = -0.55$, the rise in F_R amplitude at the low h saddle-node point of the NREM branch leads the trajectory sufficiently far away from the basin of attraction of the stable wake solution to cause F_R to make a large amplitude excursion before approaching the low amplitude wake branch (Figure 4(D)). This transient excursion in F_R corresponds to the single REM bouts that occur at the NREM-wake transition for this value of β_R . Intuitively, we can understand why amplitudes of the F_R steady-state solutions would increase at low but not high values of h , by considering the levels of inhibitory input the REM population receives for different h values. At the high h termination of the wake solution branch, F_W is fully activated and thus is fully inhibiting the REM population. Deactivation of F_W occurs as a result of inhibition by an increasingly active F_N , which also inhibits the REM population. Thus, net inhibition levels to the REM population do not decrease sufficiently at this transition to allow F_R activation. By contrast, at the low h termination of the NREM solution branch, F_W is low and F_N is decreasing; this reduces levels of inhibition to the REM population and thus allows F_R activation.

While the decrease in β_R from 0 to -0.55 does not perturb the Z-shaped steady-state solution curve of the fast subsystem with respect to F_W (Figure 4(A) and (C)), further decreases in this parameter introduce changes affecting the unstable solution branch. As shown for $\beta_R = -0.72$ (Figure 5(A) and (B)), the Z curve is broken apart near the low h saddle-node point, and two new unstable steady-state branches, extending to very large values of h , appear. The separation of the unstable solution branch occurs for β_R values less than -0.595 , and the unstable branches do not change qualitatively until β_R decreases below -0.725 . When the unstable branch first breaks apart, the dynamics of the full fast-slow model are not disrupted: the pattern of wake-NREM-REM cycling continues with a single REM bout at the transition between NREM sleep and wake. For lower values of β_R , the appearance of multiple REM bouts at the NREM-wake transition coincides with the introduction of a branch of stable periodic solutions extending over a short h interval just below the low h saddle-node point of the NREM stable branch (Figure 5(A) and (B), $\beta_R = -0.72$, blue circles). These periodic

Figure 5. Bifurcation diagrams of the fast subsystem (i.e., (2.4)–(2.6)) when the slow variable h is taken as a parameter for lower values of β_R . (A)–(D) For $\beta_R < -0.595$, the Z-shaped curve of steady solutions is broken apart, and two unstable steady-state solution branches (gray dashed curves) exist for very large values of h . (A),(B) As β_R nears -0.725 , a branch of stable periodic solutions (blue circles) appears over short h intervals just below the low h saddle-node point termination of the branch of stable steady solutions corresponding to the NREM state. These periodic solutions correspond to large amplitude oscillations in F_R and small amplitude oscillations in F_W . In the full fast-slow system, the trajectory (cyan) transitions from the NREM solution branch to the periodic branch and then to the wake solution branch as h decreases, representing the introduction of multiple REM cycles during the NREM state. (C)–(F) For $\beta_R < -0.725$, the branch of stable periodic solutions (blue circles) replaces the steady-state solution branch corresponding to the NREM state. The trajectory of the fast-slow model (cyan) transitions between the stable wake solution branch and the stable branch of periodic solutions as h increases and decreases. (E),(F) For $\beta_R < -0.976$, a Hopf bifurcation point is introduced. This Hopf point terminates the stable periodic branch at high h values and stabilizes the high F_R steady-state solution branch for high h values (pink curve).

solutions correspond to REM-NREM cycling with small post-REM F_W activation. During its progression around the hysteresis loop, the trajectory (cyan curve) transitions from the NREM branch to this branch of periodic solutions and then to the wake branch.

As β_R decreases below -0.725 , a bifurcation occurs and changes the NREM branch of steady solutions to a branch of stable periodic solutions that exists over a large interval of h values (Figure 5(C) and (D), $\beta_R = -0.75$). The fast subsystem still defines a hysteresis loop, but now the trajectory alternates between the branch of the stable steady solution corresponding to the wake state (green) and a branch of stable periodic solutions corresponding to NREM-REM cycling (blue circles). The trajectory in this case resembles that of classic neural models of bursting: activity in F_R alternates between periods of silence and oscillation just as the voltage of a bursting neuron alternates between quiescence and spiking. Additionally, the underlying bifurcation structure of the fast subsystem is similar to neuronal bursting models exhibiting square-wave bursting [3, 16] or, equivalently, fold-homoclinic bursting [23] (see section 5).

When β_R falls below -0.976 , a Hopf bifurcation point appears on the unstable steady-state branch connected to the stable wake solution branch. This Hopf point provides a high h termination point for the stable periodic branch (Figure 5(E) and (F), $\beta_R = -0.99$) and causes a stability change on the steady solution branch: a new stable steady state with high F_N and F_R values, and low F_W amplitude, is introduced (pink). This solution represents steady concurrent activation of the REM- and NREM-promoting populations and does not correspond to a known physiological state; we will refer to it as the NREM & REM state. When h dynamics are included, increasing h will cause the trajectory to jump from the wake state to the NREM & REM state, thereby causing an extended initial REM bout during the sleep stage; as h continues to decrease below the Hopf point, the trajectory will transition to the periodic solution branch and initiate REM cycling.

To summarize the dependence of the solution structure of the fast subsystem on the parameter β_R , we constructed a 2-dimensional bifurcation diagram that depicts the regions of β_R - h parameter space in which different solutions are stable (Figure 6). Each region is labeled with its associated model behavior, and the colors correspond to those of the stable solution branches in Figures 4 and 5. The stable steady solutions corresponding to the wake (green) and NREM sleep (red) states dominate the top half of the parameter space. The boundaries of these regions are determined by the saddle-node points of the Z-shaped steady-state curve and are denoted by yellow lines. The high h saddle-node point terminating the wake solution branch has no β_R dependence and appears as a straight vertical line near $h \approx 0.69$. Bistability between the wake and other states is indicated by the green hatching. The low h saddle-node point terminating the NREM solution appears to move to very large h values for β_R near -0.725 , at the bifurcation where the stable NREM steady state disappears and the stable REM-NREM periodic solution (blue) is introduced. The region of stable REM-NREM cycling is bounded above by this limit point and below by a Hopf point (cyan curve) that defines the parameter region where the steady NREM and REM state is stable (pink). For larger values of h , this Hopf point is subcritical, with the periodic solution gaining stability at a fold point of periodic solutions (purple curve) and forming a small region of bistability between REM-NREM cycling and the high NREM & REM state. For low values of h , the Hopf point and fold point of periodics move farther apart and fail to overlap. This introduces a small region (gray)

Figure 6. A 2-dimensional bifurcation diagram with respect to h and β_R summarizes the stable solutions of the fast subsystem (2.4)–(2.6) observed in different regions of β_R - h parameter space. Each region is labeled with its associated model behavior, and the colors correspond to those associated with stable solution branches in the bifurcation diagrams of Figures 4 and 5. Regions of bistability between the stable wake state (green) and other states is indicated by green hatching. Specific bifurcation points determine most of the boundaries of the regions: saddle-node point (yellow curves), Hopf bifurcation point (cyan curve), fold point of periodic solutions (purple curve), and homoclinic bifurcation point (black curve).

where complex, multimodal oscillations occur. We note that these complex oscillations are not apparent in the trajectory of the full fast-slow model for $\beta_R < -1$ since h moves relatively quickly through this small region. The low h termination of the REM-NREM cycling region (black line) is associated with a homoclinic bifurcation (see below).

Our fast-slow analysis of the reduced sleep-wake regulatory network with respect to the slow variable h provides explanations for several of the changes in network dynamics as the REM population threshold β_R is decreased. These include the characterization of alternation between wake and NREM states as progression around a hysteresis loop and the appearance of REM bouts at the transition from NREM sleep to wake but not at the wake-to-NREM transition. However, viewing the solution structure of the fast subsystem as a function of h is not sufficient to reveal the complete bifurcation structure of the full network. In particular, this perspective did not provide explanations for the breaking apart of the Z-shaped steady-state solution curve that occurs for $\beta_R < -0.595$ or the bifurcation associated with the disappearance of the stable steady NREM solution branch and the appearance of the stable

branch of periodic REM-NREM oscillations for $\beta_R < -0.725$. To investigate the sources of these bifurcations, we consider the solution structure of the fast subsystem as a function of β_R .

3.2. Bifurcation analysis of the fast subsystem with respect to β_R . We begin by considering the breaking apart of the Z-shaped steady-state solution curve of the fast subsystem as a function of h . As β_R decreases below -0.595 , the single unstable steady-state branch connecting the stable wake and NREM solution branches abruptly breaks into two unstable branches that extend to very large values of h (seemingly to $h \rightarrow \infty$). In the bifurcation diagram of the fast subsystem as a function of β_R , for h small (Figure 7(A); $h = 0.07$, corresponding to a vertical cut across Figure 6 at $h = 0.07$), the stable wake state (green) exists for all values of β_R , and the stable NREM state (red) is present for β_R sufficiently large. The saddle-node point terminating the stable NREM solution corresponds to the low h saddle-node point of the Z-shaped curve in the bifurcation diagrams computed with respect to h . For larger values of h (Figure 7(B), vertical cut across Figure 6 at $h = 0.15$), two additional fold points appear on the unstable steady-state curve, thereby introducing an interval near $\beta_R = -0.6$ over which three unstable steady-state solutions exist. This interval exists for all values of $h \geq 0.15$. Thus, the abrupt breaking of the Z-shaped steady-state curve defined with respect to h corresponds to crossing into the β_R interval defined by the right-most and left-most fold points of the unstable solution branch that exists with respect to β_R .

Figure 7. Bifurcation diagrams for the fast subsystem (2.4)–(2.6) with respect to parameter β_R for fixed values of h , corresponding to vertical cuts across Figure 6 at $h = 0.07$ (A) and $h = 0.15$ (B). The wake (green) and NREM (red) solution branches correspond to the wake and NREM stable steady-state solution branches of the Z-shaped steady-state curve in the bifurcation diagram computed with respect to h (Figure 4). The introduction of two fold points on the unstable steady state solution branch (gray dashed curves) results in a β_R interval with three unstable steady-state solutions.

The bifurcations associated with the initiation and termination of the stable REM-NREM periodic solution are also more easily understood by considering bifurcation diagrams of the fast subsystem with respect to β_R for fixed values of h . For $h = 1.0$ (Figure 8(A), vertical

cut across Figure 6 at $h = 1.0$), steady-state solutions form a Z-like curve with the stable upper branch (pink), corresponding to the steady NREM and REM state losing stability at a subcritical Hopf bifurcation point (cyan curve in Figure 6). The stable REM-NREM periodic solution branch (blue circles) extends for larger β_R values and terminates in a saddle-node on an invariant circle (SNIC) bifurcation at the saddle-node point of the NREM state solution branch (red). Thus, the disappearance of the stable NREM solution branch and appearance of the stable REM-NREM periodic branch that occurs as β_R decreases below -0.725 can be understood as crossing over this SNIC bifurcation in β_R .

The β_R - h bifurcation diagram (Figure 6) illustrates that the lower boundary of the stability region for the REM-NREM periodic solution consists of Hopf bifurcation points that can be crossed as either h varies (as in Figure 4(E),(F)) or β_R varies (Figure 8(A)). In the bifurcation diagram of the fast subsystem with respect to β_R at $h = 0.61$ (vertical cut across Figure 6 at $h = 0.61$), both of these Hopf bifurcation points appear (Figure 8(B)). At this value of h , the stable wake solution branch exists for all β_R values (green). Both Hopf bifurcation points appear on a branch of unstable steady-state solutions that emanates from a saddle-node point with the stable NREM state (red). The high NREM and REM state is stable between the Hopf points (pink). The stable REM-NREM periodic solution associated with the high β_R Hopf point extends for larger β_R values and terminates in a SNIC bifurcation with the saddle-node point on the NREM state solution branch (red). The stable REM-NREM periodic solution associated with the low β_R Hopf point extends for lower β_R values, and the reason for its termination (corresponding to the black line in Figure 6) is not apparent in the F_W - β_R plane.

For h near 0.6, the two Hopf bifurcation points bounding the stability region of the REM-NREM periodic solution coalesce. For lower h values, the periodic solution remains stable without being grounded by a Hopf bifurcation in the β_R direction (Figure 8(C),(D), vertical cut across Figure 6 at $h = 0.25$), similar to the isolated stable REM-NREM periodic branch in the bifurcation diagrams with respect to h (Figure 5(A)–(D)). The β_R bifurcation diagram clarifies both the high and low β_R terminations of the stable REM-NREM periodic solution branch. As above in Figures 8(A) and (B), the high β_R termination point is a SNIC bifurcation at the saddle-node point of the stable NREM solution, which is apparent when solutions are displayed with respect to F_W or F_N (Figure 8(C),(D)). While the F_W - β_R diagram offers no explanation for the low β_R termination of the periodic branch (Figure 8(C)), in the F_N - β_R diagram (Figure 8(D)) a homoclinic bifurcation with the branch of unstable steady-state solutions is apparent. This type of bifurcation has been called a saddle-loop bifurcation [3] or a saddle homoclinic orbit bifurcation [23]. In the fast subsystem, as either β_R or h varies between the SNIC and saddle-loop bifurcation points (as in Figure 5(A),(B) or Figure 8(C),(D)), the frequency of oscillations decreases as either bifurcation is approached, due to a lengthening of the interval between F_R activations. The oscillation profiles, however, change differently. Near the SNIC bifurcation, the post-REM F_W activations remain brief, and the interval between F_W peaks increases. Near the saddle-loop bifurcation, on the other hand, the durations of post-REM F_W activations lengthen. These differences can be traced to the location of the saddle point solutions in each bifurcation: at the SNIC bifurcation the saddle point is at the minimum amplitude of the F_W oscillations; at the saddle-loop bifurcation, the saddle point is near the maximum amplitude of the F_W oscillations or, equivalently, the minimum amplitude of the F_N oscillations.

Figure 8. Bifurcation diagrams of the fast subsystem (2.3)–(2.5) with respect to parameter β_R for fixed values of h reveal the bifurcations that initiate and terminate the stability region of the REM-NREM periodic solution. Diagrams correspond to vertical cuts through the β_R - h bifurcation diagram (Figure 6) at $h = 1$ (A), 0.61 (B), and 0.25 (C), (D). (A) For $h = 1.0$, the stable NREM & REM state (pink) loses stability in a subcritical Hopf bifurcation, and the stable REM-NREM periodic solution branch born at this Hopf point (blue circles) is terminated at a SNIC bifurcation at the saddle-node point of the NREM steady-state solution branch (red). (B) Taking $h = 0.61$ reveals a regime in which the stable NREM & REM state (pink) is terminated above and below by Hopf points. (C), (D) For $h = 0.25$, the F_W - β_R and F_N - β_R bifurcation diagrams, respectively, show the termination of the stable REM-NREM periodic solution (blue circles) in homoclinic bifurcations with the branch of unstable steady-state solutions.

3.3. Effect of feedback from the fast system to the slow variable. In our model, the homeostatic sleep drive h exhibits clear state-dependent behavior in which it increases monotonically during wake and decreases monotonically during sleep. States of wake and sleep are determined by the activation level of F_W , so F_W activity relative to the threshold separating wake and sleep, θ_W , determines the sign of dh/dt . This raises the consideration of the threshold dependence of wakefulness in the model. For the previous results, the threshold $\theta_W = 2\text{Hz}$ prevented the small, post-REM activations of F_W from affecting the h dynamics.

Figure 9. The dynamics of the fast subsystem feed back to the slow variable when the threshold separating wake and sleep, θ_W , is lowered to 1 Hz ($\beta_R = -0.75$). (A),(B) Bifurcation diagrams of F_W and F_R , respectively, with respect to h are unchanged by altering θ_W (horizontal dotted line). However, when $\theta_W = 1$ Hz, the network trajectory (cyan) does not complete the expected hysteresis loop. (C) The time traces of the network populations reveal that the network is participating in a stable oscillation resulting in balanced increases and decreases in h as F_W moves back and forth across θ_W (horizontal dotted line).

If θ_W is lowered, then h can increase during these small activations of F_W , thereby disrupting the monotonic decay in h during sleep and allowing the fast subsystem to feed back on the slow variable. Although the bifurcation structure of the fast subsystem is maintained under these conditions, this feedback can disrupt the large scale movement of the network trajectory around the hysteresis loop. As shown in Figure 9 for $\beta_R = -0.75$ and $\theta_W = 1$ Hz, the network enters a stable NREM-REM oscillatory regime with brief post-REM wake bouts that cause small amplitude oscillations in h ; h increases when F_W rises above θ_W , and h decreases when F_W falls below θ_W . This transition in network dynamics due to increasing feedback from the fast subsystem onto the slow variable is similar to the transition from bursting to continuous

spiking analyzed in models of neuron membrane dynamics (see section 5).

The conditions for the fast-slow network dynamics to display this stable REM-NREM oscillatory solution do not depend on a specific value of θ_W , but instead depend on the relationship among θ_W and the time scales of h dynamics, τ_{hw} and τ_{hs} . We can understand the required relationship among these parameters by noting that for the network dynamics to remain on the branch of stable REM-NREM periodic solutions of the fast subsystem, the increase of h during the post-REM F_W activation must be exactly balanced by the decrease of h during the interval between F_W activations. We achieved this balance of h dynamics when $\theta_W = 1$ Hz with $\tau_{hw} = 600$ s and $\tau_{hs} = 700$ s. But progression of network dynamics around the hysteresis loop can be reinstated if τ_{hw} is increased, thus reducing the h increase during the F_W activation, or if τ_{hs} is decreased, thus causing a larger decrease in h between F_W activations. The contribution of θ_W to this parameter relationship is to modulate the time during which h is increasing or decreasing due to the oscillations in F_W . Additionally, the values of these three parameters that result in stable REM-NREM oscillations will depend on the parameters governing the time dynamics of F_W during its post-REM activations. Therefore, this stable oscillatory solution is sensitive to a multitude of parameters, and it is not restricted to occurring over specific values of h . Instead, the appropriate parameter value combination could trap network dynamics near any point on the REM-NREM periodic solution branch of the fast subsystem.

4. Analyzing bifurcation structures associated with agonist/antagonist pairs. Using our original, 5-population sleep-wake regulatory network model, we simulated microinjection of GABA and acetylcholine (ACh) agonists and antagonists into the wake-promoting population LC to investigate their effects on REM sleep behavior [12]. While model results replicated experimentally observed effects on REM sleep [29], the simulated microinjections had more complex effects on the patterning of wake and NREM sleep states. In addition to comparing the actions of agonists and antagonists of a given neurotransmitter, we compared the actions of pairs of agents that exert parallel effects. For example, a GABA agonist and an ACh antagonist would both be expected to inhibit activity in the LC. Model results showed that, in general, agonist and antagonist pairs did not exert opposing effects on behavioral states, and parallel agent pairs did not always invoke parallel effects. Here, we simulate similar microinjection experiments in the reduced model and apply fast-slow analysis to investigate the complex effects that manipulation of one population in the network can have on all wake and sleep states. Specifically, as in our original study, we focus on simulated microinjection of GABA and ACh agonists and antagonists into the wake-promoting population of our reduced model.

In the reduced model, we found that agents that are expected to exert similar inhibitory effects on the activity of the wake-promoting population, namely a GABA agonist and an ACh antagonist, induce similar effects on REM sleep but nonparallel effects on wake and NREM sleep states. We consider the model in the regime where dynamics display homeostatically regulated cycling of wake to NREM sleep to REM sleep to wake ($\beta_R = -0.6$, dynamics similar to those in Figure 3(B) and Figure 4(C),(D)). Simulating microinjection of either a GABA agonist or an ACh antagonist in the W population did not qualitatively perturb this cycling pattern, but each agent increased REM bout durations in a dose-dependent manner (Figure

10(A)). The GABA agonist decreased both wake and NREM bout durations, whereas the ACh antagonist had very little effect on wake and NREM sleep (Figure 10(B)). For the β_R value used in these simulations, REM bouts occur at the NREM sleep-to-wake transition, and their duration is governed by the transient dynamics of F_R and F_W . REM bout durations are extended because simulated microinjection of a GABA agonist into the W population introduces a persistent increase in GABA effects which inhibits the F_W response to changes in excitatory ACh (released from the R population), thus extending the F_R activation. Similarly, simulated microinjection of ACh antagonist into the W population decreases the excitatory effect of ACh released from the R population, thereby decreasing the F_W response and allowing an extension of the transient REM bout.

These changes in the transient dynamics governing REM bout durations with simulated GABA agonist or ACh antagonist in the W population cannot be explained by changes to the bifurcation structure of the fast subsystem (Figure 10(C)–(F)). However, consideration of the bifurcation structure can explain the effects of the simulated microinjections on wake and NREM bout durations. In the absence of simulated agonist or antagonist microinjection (with $\beta_R = -0.6$), steady-state solutions of F_W form a broken Z-shaped curve as a function of the slow variable h , with the upper branch corresponding to the wake state and the lower branch to the NREM state (Figure 10(C) and (D), heavy curves). Simulated GABA agonist in the W population lowers the F_W value in the wake state and moves the high h saddle-node point, which determines the transition from wake to NREM sleep, to lower h values. Simulated GABA agonist has very little effect on the low h saddle-node point (Figure 10(C) inset), moving it to only slightly higher h values. Thus, the overall effect of simulated GABA agonist in the W population is to shrink the hysteresis loop over h that governs wake and NREM bout durations: increased GABA agonist levels lead to smaller h intervals over which the model trajectory travels during the homeostatically regulated cycle of wake to NREM to REM sleep to wake, and thereby decreases wake and NREM bout durations. Simulated ACh antagonist in the W population, on the other hand, has only minor effects on the steady-state solutions of F_W and the broken Z-shaped curve of solutions as a function of h (Figure 10(D)). Model dynamics reflect this lack of effect in the essentially constant wake and NREM sleep bout durations observed when levels of ACh antagonist in W are increased.

While not affecting the mechanism for REM bout generation in the fast-slow model, simulated GABA agonist or ACh antagonist in the W population induces significant effects on the steady solutions of F_R as a function of h (Figure 10(E),(F)). Simulated GABA agonist microinjection increases the amplitude of the unstable solution branch emanating from the high h saddle-node point that terminates the wake state and introduces a saddle-node point at which the NREM & REM state becomes stable (Figure 10(C),(E), pink curves). Thus, there is an h interval of multistability among the wake state, NREM state, and the NREM & REM state. However, for most choices of initial conditions, model dynamics are not attracted to the NREM & REM state: generally, the trajectory will remain on the low F_R solution branches corresponding to the wake and NREM states; the only point at which F_R increases (during the transient REM bout) occurs when h values are near the low h saddle-node point terminating the NREM state, and thus below the h interval over which the NREM & REM state is stable. Furthermore, during the F_R activation, h is decreasing; thus the trajectory is attracted to the low F_R solution branch corresponding to the wake state. Simulated ACh antagonist in the W

Figure 10. Effects of simulated microinjection of a GABA agonist and an ACh antagonist into the W population of the reduced model (with $\beta_R = -0.6$). Both agents increase REM bout durations (A) but do not have parallel effects on wake and NREM bout durations (B). Level of simulated GABA agonist (P_G) and ACh antagonist (Q_A) is shown on the x-axis. (C)–(F) Changes in wake and NREM bout durations can be explained by effects on the bifurcation structure of the steady-state solutions of the fast subsystem as a function of the slow variable h (thick curves: $P_G = 0, Q_A = 0$; multiple thin curves are solution branches at P_G and Q_A values shown in (A) and (B)). Increasing levels of simulated GABA agonist, P_G , reduces the F_W amplitude of the wake state solutions ((C), green curves), while the ACh antagonist has little effect on F_W steady state solutions (D); both agents introduce a saddle-node bifurcation at which the NREM & REM steady solution becomes stable (pink curves).

population has similar effects on the amplitude and stability of this unstable solution (Figure 10(F)).

When we simulated microinjection of a GABA antagonist or an ACh agonist in the W population, we again found similar effects on REM sleep but different effects on wake and NREM sleep (Figure 11(A)). Both the GABA antagonist and ACh agonist, which are predicted to excite activity in the W population, acted to suppress activation of F_R at the NREM-to-wake transition, thereby abolishing REM bouts. In contrast to the results involving the GABA agonist and the ACh antagonist, the effects of the GABA antagonist and the ACh agonist on the transient REM bouts are predicted by changes to the bifurcation structure of the fast subsystem. Increasing levels of both of these agents decreased the amplitude of the F_R solution branch at the low h saddle-node point at which the NREM state is terminated (Figure 11(D),(E)). This eliminated the impetus for transient F_R activation, and the resulting REM bout, as the trajectory reached this saddle-node point, and instead it promoted a direct transition from NREM sleep to wake.

Both the GABA antagonist and the ACh agonist exerted opposite effects on NREM and wake bout durations: NREM bout durations were decreased, whereas wake bout durations were increased, albeit only slightly for the GABA antagonist (Figure 11(A)). This differential effect on wake and NREM bout durations is incongruous with the underlying bifurcation structure of the fast subsystem which dictates that wake and NREM states are defined by two branches of a bistable hysteresis loop. With such a structure, both the wake and NREM states are generated as the slow variable h passes over the same interval but in different directions. Therefore, changes to the hysteresis loop should have similar effects on both wake and NREM bout durations. These results highlight how model dynamics may not be completely predicted from the bifurcation structure of the fast subsystem, and, instead, are influenced by the dynamics of the slow variable. In this case, saturation of the exponential increase and decrease of h near its maximum and minimum threshold values, respectively, leads to dissimilar time dynamics of the model's trajectory on the two branches of the wake-NREM sleep hysteresis loop.

Increasing levels of simulated GABA antagonist in the W population acted to shift the position of the low h saddle-node point that terminates the NREM state to higher h values and slightly increased the h value of the high h saddle-node point that terminates the wake state (Figure 11(B)). Overall, these shifts shortened the wake-NREM hysteresis loop; such an effect would be expected to decrease both wake and NREM bout durations. However, the shifts in the saddle-node points also moved the h interval over which the hysteresis loop is defined to higher values, closer to the maximum threshold for h at 1 and farther away from its minimum threshold at 0. Given its exponential dynamics, when h evolves over this new interval, it moves more slowly towards its maximum threshold when the model trajectory is on the upper branch of the hysteresis loop corresponding to the wake state, and it moves more quickly towards its minimum threshold when the model trajectory is on the loop's lower branch corresponding to the NREM state. These differences in h dynamics cause slight increases in wake durations and decreases in NREM bout durations, respectively.

Increasing levels of simulated ACh agonist in the W population also shifted both the high h and low h saddle-node points to higher h values, with an overall effect of lengthening the wake-NREM hysteresis loop (Figure 11(C)). While the resultant increases in wake bout durations

Figure 11. Effects of simulated microinjection of a GABA antagonist and an ACh agonist into the W population of the reduced model (with $\beta_R = -0.6$). (A) Both agents suppress REM bout activation and have opposite effects on wake and NREM bout durations. Level of simulated GABA antagonist (Q_G) and ACh agonist (P_A) is shown on the x-axis. (B)–(E) Effects induced by these agents on the bifurcation structure of the steady-state solutions of the fast subsystem as a function of the slow variable h do not completely explain effects on bout durations (thick curves: $Q_G = 0$ and $P_A = 0$; multiple thin curves are solution branches at Q_G and P_A values given in (A),(B)). The GABA antagonist shortened the wake-NREM hysteresis loop (B), while the ACh agonist lengthened it (C). However, the effect on bout durations caused by shifting of the h interval of the hysteresis loop with respect to its maximum value at 1 dominated the effect of altering the hysteresis loop. Both agents decreased F_R amplitudes at the low h saddle-node point (D),(E), which inhibited F_R activation at the NREM-to-wake transition.

are consistent with a lengthening hysteresis loop, they are accentuated by increasingly slower h evolution along the upper wake branch as the high h saddle-node point approaches the h maximum threshold at 1. The decreases in NREM bout durations are entirely due to the faster h evolution along the lower NREM branch as the low h saddle-node point moves farther away from the minimum h threshold at 0. To investigate the dependence of these changes in bout durations on h dynamics, we varied the maximum and minimum thresholds for h and were able to recover wake and NREM bout durations that more accurately reflected the changes in the underlying hysteresis loop defined by the fast subsystem (results not shown).

5. Discussion. In physiologically based models of sleep-wake behavior, the homeostatic sleep drive and the circadian drive arise as natural slow variables. Their effects occur over much longer time scales, on the order of wake and sleep bout durations for the sleep homeostat and on the order of several hours for the circadian clock, than the neuronal interactions governing transitions between sleep and wake states or the fast behavioral transitions between sleep and wake states. In this study, we exploited the slow time scale of the homeostatic sleep drive to apply fast-slow decomposition to a reduced model of the sleep-wake regulatory network in order to understand the dynamics of REM sleep generation. Previous modeling studies have applied similar fast-slow decomposition to a model of the sleep-wake flip-flop that did not incorporate REM sleep generating mechanisms [35] and to network models that implemented REM generation with different assumptions about network structure or different intrinsic properties of REM-producing populations [14, 39]. In this study, by varying the activation threshold of the REM sleep-promoting population, we analyzed variation in REM sleep dynamics similar to changes induced by the circadian drive or observed in different mammalian species. In addition, we utilized fast-slow analysis to explain complex effects on sleep-wake patterning of simulated experiments in which agonists and antagonists of different neurotransmitters are microinjected into specific neuronal populations participating in the sleep-wake regulatory network.

5.1. Mathematical implications of model REM sleep dynamics. In all of the recent physiologically based mathematical models of the sleep-wake regulatory network [50, 14, 35, 12, 39], transitions between NREM sleep and wake states are controlled by mutually inhibitory projections between wake-promoting populations and NREM-promoting populations, reflecting the broad support for the flip-flop switch conceptual model of sleep control. Since these mathematical models do not assume intrinsically oscillatory dynamics for the wake- and NREM-promoting populations, state transitions are initiated by the slow variation of the homeostatic sleep drive, possibly in interaction with a slow circadian drive. Although the specific mechanism of action of the homeostatic sleep drive varies among models, the separation in time scales is uniformly preserved. Furthermore, the common mathematical structure underlying these models of the sleep-wake flip-flop switch is a hysteresis loop. Modeling studies have shown that such hysteresis loop dynamics can account for a number of phenomena observed in human sleep-wake dynamics, including recovery from sleep deprivation, arousal responses to external stimuli, and subjective fatigue following sleep deprivation [36, 19, 20, 39].

The network mechanisms regulating REM sleep, on the other hand, are a topic of current debate in the sleep research field, with the classic reciprocal-interaction hypothesis competing with several hypotheses of a REM sleep mutually inhibitory flip-flop switch [27, 28]. The

structure of the model proposed by Rempe and colleagues included a REM flip-flop mechanism that generated different network dynamics compared to the reciprocal-interaction hypothesis [39]. However, in other physiologically based sleep-wake regulatory network models that incorporate reciprocal-interaction-like mechanisms for REM sleep control [50, 14, 12], as in the original mathematical model for the reciprocal-interaction hypothesis [32], the excitatory-inhibitory interactions between REM-promoting and REM-off populations can generate a stable limit cycle solution for REM sleep cycling. Dynamic properties of the limit cycle solution are an important feature of these models and are consistent with data such as the observed changes in REM sleep dynamics in humans with depression [32].

Thus, mathematically, the structure of our reduced sleep-wake regulatory network model represents a hysteresis loop, defined by the interactions of W and N, coupled to a limit cycle, defined by the interactions of W and R. By decreasing the parameter β_R , which allows the REM population to activate in the presence of inhibitory inputs, we are integrating the limit cycle dynamics into the dynamics of the hysteresis loop. The progress of this integration is apparent in the dynamics as they transition from a basic hysteresis loop between two steady states to a hysteresis loop between a steady state and a limit cycle. We have shown that the different levels of integration of limit cycle dynamics into the hysteresis loop dynamics can generate different temporal patterns of REM sleep activation similar to those observed under circadian modulation and in different species. Future work investigating the ability of this general structure of a hysteresis loop coupled to a limit cycle to replicate other dynamic properties of sleep-wake patterning will indicate whether it is a physiologically accurate model for REM sleep regulation and provide a strong basis for contrast to dynamics arising from other network structures.

5.2. Physiological implications of model REM sleep dynamics. The timing of REM sleep is under strong circadian control. Even in animals with polyphasic sleep-wake behavior, REM sleep is generally limited to specific times of day. In our network, different values of β_R differentially promote REM suppression and REM activation (including single and multiple REM bouts). Therefore, our network structure suggests that circadian timing of REM sleep could be achieved by circadian modulation of β_R . Physiologically, such modulation could occur through direct or indirect projections from the circadian pacemaker in the suprachiasmatic nucleus to REM-promoting neuronal populations or through network effects via circadian modulation of wake- or NREM-promoting populations. Such indirect projections have been demonstrated for LDT and PPT (reviewed in [1, 43]). Although the interactions between circadian and homeostatic systems have been explored in several previous models of human sleep [36, 39], our recent work incorporating both feedforward and feedback elements of these interactions in the context of rat sleep-wake dynamics [17] has highlighted some important features of the interaction that are less obvious in human sleep-wake behavior. This work emphasizes the contribution of both network dynamics and direct circadian modulation to the resultant behavior, and more investigation is necessary to understand the relationship between these contributions and a parameter such as β_R .

In addition to circadian modulation, prior behavioral state also affects the occurrence of REM sleep. In normal, adult mammalian sleep-wake behavior, direct transitions from wake to REM sleep are rare. In humans, there is typically a progression through multiple stages

of NREM sleep before REM sleep can occur. However, NREM sleep need not occur during a transition from REM sleep to wake: REM sleep is often followed directly by an awakening. Though these awakenings are typically brief, they represent a full return to a waking state. This asymmetrical feature of sleep-wake patterning is preserved in our model, and our analysis of the dynamic structure of the network provides an explanation for the occurrence of REM sleep at the transition from NREM sleep to wake but not at the opposite transition. In contrast to models of sleep-wake regulation based on other network structures for REM regulation [39], this ordered progression from NREM to REM sleep arises naturally in our network.

Experiments have shown that much of the anatomy and physiology of sleep-wake regulation is preserved across mammalian species [47, 43]. However, the patterning of sleep-wake behavior can vary widely. One major qualitative distinction pertains to the timing of REM sleep. In animals with strongly polyphasic sleep-wake behavior, REM sleep is concentrated at particular times in the 24-h circadian cycle, but there is no discernible ultradian rhythm governing it. By contrast, humans and other animals with longer periods of consolidated sleep have a regular ultradian cycle of NREM/REM alternation [6, 48, 24, 22].

By analyzing the dynamic structure underlying the generation of REM sleep in our reduced sleep-wake regulatory network model, we find that for different values of β_R this fixed network structure admits a parameter-dependent shift between a region of bistability between two stable steady states and a region of bistability between a stable steady state and a stable periodic orbit. The single REM bouts that can occur in the first case are similar to the REM sleep observed in animals with polyphasic sleep-wake behavior, whereas the birth of the stable periodic branches represents a qualitative change that can produce regular, cyclic REM behavior similar to that seen in human sleep. Thus, our model suggests that this network structure is flexible enough to account for a range of qualitative REM sleep behaviors.

The existence of the stable periodic orbit representing REM cycling behavior is robust in large ranges of values of parameters, other than β_R , associated with the REM- and wake-promoting populations. However, obtaining F_R oscillations of sufficiently high maximal amplitude and sufficiently low minimal amplitude to interpret the activity as a distinct REM bout is sensitive to the relative values of the time constants governing REM- and wake-promoting population activity, namely τ_R and τ_W . Specifically, τ_R should be smaller than τ_W to obtain realistic REM cycling behavior. In the parameter sets presented here, $\tau_R = 1\text{s}$ is considerably less than $\tau_W = 25\text{s}$, but such a large difference is not necessary; the stable periodic solution corresponds to realistic REM cycling for values of τ_R up to 20s, when τ_W is fixed at 25s. When $\tau_R \geq \tau_W$, a smaller amplitude of F_R oscillations and a nonzero minimum F_R level make an interpretation of distinct REM bouts less obvious.

This constraint on the relative values of the time constants governing activity of the REM-promoting and wake-promoting populations suggests a prediction of the model network structure. In particular, generating robust REM cycling behavior in a reciprocal interaction-based network for REM sleep generation requires that the feedback inhibition from the wake-promoting populations to the REM-promoting populations occur on a slower time scale than the population response of the REM-promoting populations. While in our reduced network model, time dynamics of population responses are collapsed down to a single governing parameter, τ_X , population responses in the physiological system may depend on multiple factors, such as intrinsic neuronal response properties, postsynaptic transmitter receptor dynamics,

presynaptic transmitter release dynamics, and modulation of these dynamics by additional mechanisms. Thus, the brain may have various ways to implement the predicted differences in time scales. These model results, however, may suggest targets for further experimental investigations.

5.3. Relationship to bursting in neuronal models. Fast-slow analysis was originally developed to analyze bursting dynamics in neuronal models, during which membrane voltage alternates periodically between a quiescent phase and an active phase of rapid oscillatory spiking [40]. In these models, the fast subsystem usually consists of the current balance equation for voltage dynamics and ionic conductance gating variables with fast time scales, while the slow variable can be the gating of a slowly activating ionic conductance or slow accumulation of an ion concentration. Different types of bursting patterns have been observed experimentally in different types of neurons, and formal mathematical modeling of these examples has allowed the classification of bursting dynamics based on the underlying bifurcation structure of the fast subsystem [41, 3, 23]. The dynamics of our reduced sleep-wake regulatory network most resemble neuronal bursting dynamics when β_R is between -0.725 and -1 , when dynamics alternate between the stable wake state and the stable REM-NREM periodic solutions of the fast subsystem. In this parameter regime, the activity of F_R shows the alternations between quiescence near a low amplitude steady solution and large amplitude periodic oscillations characteristic of neuronal bursting. The bifurcation structure of the fast subsystem supporting these bursting-like dynamics (Figure 5(C),(D)) corresponds to that of a square-wave burster [16] or, equivalently, a fold-homoclinic burster [23]. In this bursting category, the transition from the quiescent (wake) state to the spiking (REM-NREM cycling) state occurs at a saddle-node bifurcation (high h saddle-node terminating the stable wake branch), and the transition from the spiking state to the quiescent state occurs at a saddle-loop or saddle homoclinic orbit bifurcation (apparent in the F_N - h plane as in Figure 8(D)).

A general feature of square-wave bursting in standard neuronal models is a monotonic decrease in the frequency of spiking during the active phase of the burst, with the interspike interval progressively lengthening as the trajectory approaches the saddle-loop bifurcation of the fast subsystem [3]. In contrast, in our model, while the frequency of REM-NREM cycling decreases during the active phase of the burst, more complex changes occur to the oscillation profiles of the different variables. In particular, the duration of F_R activations slightly decreases due to the higher peaks of the F_W oscillations, which act to prematurely inhibit F_R . On the other hand, the durations of F_W activation increase as the trajectory approaches the saddle-loop bifurcation. The unstable saddle point of this bifurcation occurs at the minimum amplitude of the F_N oscillation and thus near the maximum amplitude of the F_W oscillation.

In neuronal models of square-wave bursting, varying parameters associated with the slow variable equation can transition dynamics from bursting to continuous spiking [8, 52]. During this transition, dynamics move from regular bursting patterns to irregular, chaotic spiking patterns, and as the transition progresses, higher-order periodic firing is observed before dynamics settle into a regular, periodic firing pattern. In our model, in the β_R interval between -0.725 and -1 , a similar transition from bursting-like solutions to continuous oscillatory solutions occurs as the threshold parameter separating wake and sleep states, θ_W , is decreased,

with a progression through irregular and higher-order periodic firing patterns occurring over small intervals of θ_W . Analysis of this transition in neuronal square-wave bursting models has shown that it occurs as the nullcline curve of the slow variable intersects the saddle-loop bifurcation that terminates the periodic solution of the fast subsystem. Further, the interval of values of the parameter driving the change in the slow variable nullcline over which irregular and higher-order periodic solutions appear depends on the time scale of the slow variable [52]. In contrast, in our model, the transition does not depend on a relationship between θ_W and a specific bifurcation of the fast subsystem, other than θ_W lying below the maximum amplitude of the F_W periodic solution. Instead, either bursting-like or stable REM-NREM firing can occur for any value of θ_W depending on the relative values of the time constants for h dynamics, τ_{hw} and τ_{hs} . For stable REM-NREM firing to occur, the increase in h while F_W is above θ_W during its post-REM activation must be matched by the decrease in h between F_W activations. However, similar to neuronal square-wave bursting models, as the time scale of the slow variable h decreases, the θ_W interval over which irregular oscillatory solutions occur shrinks, and for very slow h time scales, bursting-like solutions transition smoothly to continuous REM-NREM periodic solutions.

5.4. Analysis of simulated microinjection of neurotransmitter agonists and antagonists. The majority of experimental studies probing the contribution of specific neuronal populations to the regulation of sleep and wake states in intact animals utilize microinjection or microdialysis of pharmacological agents that manipulate the actions of neurotransmitters in the population. However, the targeted population is embedded within an extended network of synaptically coupled populations, and the levels of neurotransmitters acting on a given population change dynamically with behavioral state. Thus, effects of the manipulation may be state-dependent and, in addition, may propagate through the network, thereby affecting activation and transition dynamics in complex ways. Simulation of these experiments in physiologically based mathematical models of the sleep-wake regulatory network can provide insight into the complex effects on behavioral state. In our original modeling study utilizing our 5-population sleep-wake regulatory network model, some of the complex effects on state transitions of simulated microinjection experiments were due to the stochastic elements included in the model. Here, using a reduced model with no stochastic components, fast-slow analysis revealed changes to the underlying bifurcation structure of the solutions to the fast subsystem that could, in some cases, completely explain the observed changes in behavioral state dynamics.

In other cases, the h dynamics played a key role in the action of the neurotransmitter agonist or antagonist. This is illustrated by the effects induced by simulation of the actions of a GABA antagonist or an ACh agonist on the W population. In these simulations, behavioral state dynamics depended more sensitively on changes to dynamics of the slow variable than on the solution structure of the fast subsystem. Namely, when the interval over which the slow variable h varies was moved closer to its maximum threshold of 1, the assumed exponential dynamics of h strongly influenced state bout durations: longer wake bouts occurred as increasing h evolution slowed down, and shorter NREM bouts reflected the acceleration of decreasing h evolution. It is interesting to speculate whether these effects reflect an idiosyncrasy of our model or reveal constraints on the underlying physiology.

The slow variable h models the homeostatic sleep drive. Phenomenologically, the sleep homeostat is correlated with the power of slow-wave activity in EEG recordings during sleep, which has been shown to increase and decrease with exponential time courses [4]. A leading physiological candidate for the homeostatic sleep drive is the accumulation of adenosine, which is released during cellular activity and may be assumed to eventually saturate, as most physiological processes do over extended periods of time. Thus, our model assumption of a saturating threshold for the sleep homeostat and the resulting decrease in time dynamics due to the homeostat approaching this saturation level exponentially may not be physiologically unreasonable. However, verification of any model of the homeostatic sleep drive requires further experimental work establishing the physiological basis of the homeostatic sleep drive and investigating its influence on sleep-wake behavior under different conditions.

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REFERENCES

- [1] G. ASTON-JONES, S. CHEN, Y. ZHU, AND M. L. OSHINSKY, *A neural circuit for circadian regulation of arousal*, *Nature Neurosci.*, 4 (2001), pp. 732–738.
- [2] H. A. BAGHDOYAN AND R. LYDIC, *Neurotransmitters and neuromodulators regulating sleep*, in *Sleep and Epilepsy: The Clinical Spectrum*, C. Bazil, B. Malow, and M. Sammaritano, eds., Elsevier Science, New York, 2002, pp. 17–44.
- [3] R. BERTRAM, M. J. BUTTE, T. KIEMEL, AND A. SHERMAN, *Topological and phenomenological classification of bursting oscillations*, *Bull. Math. Biol.*, 57 (1995), pp. 413–439.
- [4] A. A. BORBELY, *A two process model of sleep regulation*, *Hum. Neurobiol.*, 1 (1982), pp. 195–204.
- [5] R. E. BROWN, J. T. MCKENNA, S. WINSTON, R. BASHEER, Y. YANAGAWA, M. M. THAKKAR, AND R. W. MCCARLEY, *Characterization of GABAergic neurons in rapid-eye-movement sleep controlling regions of the brainstem reticular formation in GAD67-green fluorescent protein knock-in mice*, *Eur. J. Neurosci.*, 27 (2008), pp. 352–363.
- [6] M. A. CARSKADON AND W. C. DEMENT, *Normal human sleep: An overview*, in *Principles and Practice of Sleep Medicine*, M. H. Kryger, T. Roth, and W. C. Dement, eds., Elsevier Saunders, New York, 2011, pp. 16–26.
- [7] N. L. CHAMBERLIN, E. ARRIGONI, T. C. CHOU, T. E. SCAMMELL, R. W. GREENE, AND C. B. SAPER, *Effects of adenosine on GABAergic synaptic inputs to identified ventrolateral preoptic neurons*, *Neuroscience*, 119 (2003), pp. 913–918.
- [8] T. R. CHAY AND J. RINZEL, *Bursting, beating, and chaos in an excitable membrane model*, *Biophys. J.*, 47 (1985), pp. 357–366.
- [9] S. DATTA AND R. R. MACLEAN, *Neurobiological mechanisms for the regulation of mammalian sleep-wake behavior: Reinterpretation of historical evidence and inclusion of contemporary cellular and molecular evidence*, *Neurosci. Biobehav. Rev.*, 31 (2007), pp. 775–824.
- [10] P. DAYAN AND L. F. ABBOTT, *Theoretical Neuroscience: Computational and Mathematical Modeling of Neural Systems*, MIT Press, Cambridge, MA, 2001.
- [11] G. DECO, V. K. JIRSA, P. A. ROBINSON, M. BREAKSPEAR, AND K. FRISTON, *The dynamic brain: From spiking neurons to neural masses and cortical fields*, *PLoS Comput. Biol.*, 4 (2008), e1000092.
- [12] C. G. DINIZ BEHN AND V. BOOTH, *Simulating microinjection experiments in a novel model of the rat sleep-wake regulatory network*, *J. Neurophysiol.*, 103 (2010), pp. 1937–1953.
- [13] C. G. DINIZ BEHN AND V. BOOTH, *Modeling the temporal architecture of rat sleep-wake behavior*, in *Proceedings of the 33rd International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC'11)*, Boston, 2011, pp. 4713–4716.
- [14] C. G. DINIZ BEHN, E. N. BROWN, T. E. SCAMMELL, AND N. J. KOPELL, *A mathematical model of network dynamics governing mouse sleep-wake behavior*, *J. Neurophysiol.*, 97 (2007), pp. 3828–3840.

- [15] G. B. ERMENTROUT, *Neural networks as spatio-temporal pattern-forming systems*, Rep. Progr. Phys., 61 (1998), pp. 353–430.
- [16] G. B. ERMENTROUT AND D. H. TERMAN, *Mathematical Foundations of Neuroscience*, Springer, New York, 2010.
- [17] M. FLESHNER, V. BOOTH, D. B. FORGER, AND C. G. DINIZ BEHN, *Circadian regulation of sleep-wake behavior in nocturnal rats requires multiple signals from suprachiasmatic nucleus*, Phil. Trans. R. Soc. A, 369 (2011), pp. 3855–3883.
- [18] D. B. FORGER, M. E. JEWETT, AND R. E. KRONAUER, *A simpler model of the human circadian pacemaker*, J. Biol. Rhythms, 14 (1999), pp. 532–537.
- [19] B. D. FULCHER, A. J. K. PHILLIPS, AND P. A. ROBINSON, *Modeling the impact of impulsive stimuli on sleep-wake dynamics*, Phys. Rev. E, 78 (2008), 051920.
- [20] B. D. FULCHER, A. J. K. PHILLIPS, AND P. A. ROBINSON, *Quantitative physiologically based modeling of subjective fatigue during sleep deprivation*, J. Theoret. Biol., 264 (2010), pp. 407–419.
- [21] T. GALLOPIN, P. H. LUPPI, B. CAULI, Y. URADE, J. ROSSIER, O. HAYAISHI, B. LAMBOLEZ, AND P. FORT, *The endogenous somnogen adenosine excites a subset of sleep-promoting neurons via A2a receptors in the ventrolateral preoptic nucleus*, Neuroscience, 134 (2005), pp. 1377–1390.
- [22] K.-C. HSIEH, E. L. ROBINSON, AND C. A. FULLER, *Sleep architecture in unrestrained rhesus monkeys (macaca mulatta) synchronized to 24-hour light-dark cycles*, Sleep, 31 (2008), pp. 1239–1250.
- [23] E. IZHIKEVICH, *Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting*, MIT Press, Cambridge, MA, 2007.
- [24] L. LEINONEN AND D. STENBERG, *Sleep in macaca arctoides and the effects of prazosin*, Physiol. Behav., 37 (1986), pp. 199–202.
- [25] J. A. LESKU, T. C. ROTH II, C. J. AMLANER, AND S. L. LIMA, *A phylogenetic analysis of sleep architecture in mammals: The integration of anatomy, physiology, and ecology*, Am. Nat., 168 (2006), pp. 441–453.
- [26] C.-C. LO, T. CHOU, T. PENZEL, T. E. SCAMMELL, R. E. STRECKER, H. E. STANLEY, AND P. CH. IVANOV, *Common scale-invariant patterns of sleep-wake transitions across mammalian species*, Proc. Natl. Acad. Sci. USA, 101 (2004), pp. 17545–17548.
- [27] J. LU, D. SHERMAN, M. DEVOR, AND C. B. SAPER, *A putative flip-flop switch for control of REM sleep*, Nature, 441 (2006), pp. 589–594.
- [28] P. H. LUPPI, D. GERVASONI, L. VERRET, R. GOUTAGNY, C. PEYRON, D. SALVERT, L. LEGER, AND P. FORT, *Paradoxical (REM) sleep genesis: The switch from an aminergic-cholinergic to a GABAergic-glutamatergic hypothesis*, J. Physiol. Paris, 100 (2006), pp. 271–283.
- [29] B. N. MALICK, S. KAUR, AND R. N. SAXENA, *Interactions between cholinergic and GABAergic neurotransmitters in and around the locus coeruleus for the induction and maintenance of rapid eye movement sleep in rats*, Neuroscience, 104 (2001), pp. 467–485.
- [30] S. G. MASSAQUOI AND R. W. MCCARLEY, *Extension of the limit cycle reciprocal interaction model of REM cycle control. An integrated sleep control model*, J. Sleep Res., 1 (1992), pp. 138–143.
- [31] R. W. MCCARLEY AND J. A. HOBSON, *Neuronal excitability modulation over the sleep cycle: A structural and mathematical model*, Science, 189 (1975), pp. 58–60.
- [32] R. W. MCCARLEY AND S. G. MASSAQUOI, *A limit cycle mathematical model of the REM sleep oscillator system*, Am. J. Physiol., 251 (1986), pp. R1011–R1029.
- [33] H. MERICA AND J.-M. GAILLARD, *A study of the interrupted REM episode*, Physiol. Behav., 50 (1991), pp. 1153–1159.
- [34] S. MORAIRTY, D. RAINNIE, R. MCCARLEY, AND R. GREENE, *Disinhibition of ventrolateral preoptic area sleep-active neurons by adenosine: A new mechanism for sleep promotion*, Neuroscience, 123 (2004), pp. 451–457.
- [35] A. J. K. PHILLIPS AND P. A. ROBINSON, *A quantitative model of sleep-wake dynamics based on the physiology of the brainstem ascending arousal system*, J. Biol. Rhythms, 22 (2007), pp. 167–179.
- [36] A. J. K. PHILLIPS AND P. A. ROBINSON, *Sleep deprivation in a quantitative physiologically based model of the ascending arousal system*, J. Theoret. Biol., 255 (2008), pp. 413–423.
- [37] A. J. K. PHILLIPS, P. A. ROBINSON, D. J. KEDZIORA, AND R. G. ABEYSURIYAL, *Mammalian sleep dynamics: How diverse features arise from a common physiological framework*, PLOS Comput. Biol., 6 (2010), e1000826.

- [38] T. PORKKA-HEISKANEN, R. E. STRECKER, AND R. W. MCCARLEY, *Brain site-specificity of extracellular adenosine concentration changes during sleep deprivation and spontaneous sleep: An in vivo microdialysis study*, Neuroscience, 99 (2000), pp. 507–517.
- [39] M. J. REMPE, J. BEST, AND D. TERMAN, *A mathematical model of the sleep/wake cycle*, J. Math. Biol., 60 (2010), pp. 615–644.
- [40] J. RINZEL, *Bursting oscillations in an excitable membrane model*, in Ordinary and Partial Differential Equations; Proceedings of the 8th Dundee Conference, Lecture Notes in Math. 1151, B. D. Sleeman and R. J. Jarvis, eds., Springer, New York, 1985, pp. 304–316.
- [41] J. RINZEL, *A formal classification of bursting mechanisms in excitable systems*, in Mathematical Topics in Population Biology, Morphogenesis and Neurosciences, Lecture Notes in Biomath. 71, E. Teramoto and M. Yamaguti, eds., Springer, New York, 1987, pp. 1578–1593.
- [42] C. B. SAPER, T. C. CHOU, AND T. E. SCAMMELL, *The sleep switch: Hypothalamic control of sleep and wakefulness*, Trends Neurosci., 24 (2001), pp. 726–731.
- [43] C. B. SAPER, T. E. SCAMMELL, AND J. LU, *Hypothalamic regulation of sleep and circadian rhythms*, Nature, 437 (2005), pp. 1257–1263.
- [44] E. SAPIN, D. LAPRAY, A. BEROD, R. GOUTAGNY, L. LEGER, P. RAVASSARD, O. CLEMENT, L. HANRIOT, P. FORT, AND P. H. LUPPI, *Localization of the brainstem GABAergic neurons controlling paradoxical (REM) sleep*, PLoS One, 4 (2009), e4272.
- [45] V. M. SAVAGE AND G. B. WEST, *A quantitative, theoretical framework for understanding mammalian sleep*, Proc. Natl. Acad. Sci. USA, 104 (2007), pp. 1051–1056.
- [46] T. E. SCAMMELL, D. Y. GERASHCHENKO, T. MOCHIZUKI, M. T. MCCARTHY, I. V. ESTABROOKE, C. A. SEARS, C. B. SAPER, Y. URADE, AND O. HAYAISHI, *An adenosine A2a agonist increases sleep and induces fos in ventrolateral preoptic neurons*, Neuroscience, 107 (2001), pp. 653–663.
- [47] J. SIEGEL, *Clues to the functions of mammalian sleep*, Nature, 437 (2005), pp. 1264–1271.
- [48] M. B. STERMAN, E. A. LUCAS, AND L. R. MACDONALD, *Periodicity within sleep and operant performance in the cat*, Brain Res., 38 (1972), pp. 327–341.
- [49] R. E. STRECKER, S. MORAIRTY, M. M. THAKKAR, T. PORKKA-HEISKANEN, R. BASHEER, L. J. DAUPHIN, D. G. RAINNIE, C. M. PORTAS, R. W. GREENE, AND R. W. MCCARLEY, *Adenosinergic modulation of basal forebrain and preoptic/anterior hypothalamic neuronal activity in the control of behavioral state*, Behav. Brain Res., 115 (2000), pp. 183–204.
- [50] Y. TAMAKAWA, A. KARASHIMA, Y. KOYAMA, N. KATAYAMA, AND M. NAKAO, *A quartet neural system model orchestrating sleep and wakefulness mechanisms*, J. Neurophysiol., 95 (2006), pp. 2055–2069.
- [51] D. TANASE, H. A. BAGHDOYAN, AND R. LYDIC, *Dialysis delivery of an adenosine A1 receptor agonist to the pontine reticular formation decreases acetylcholine release and increases anesthesia recovery time*, Anesthesiology, 98 (2003), pp. 912–920.
- [52] D. TERMAN, *The transition from bursting to continuous spiking in excitable membrane models*, J. Nonlinear Sci., 2 (1992), pp. 135–182.
- [53] H. R. WILSON AND J. D. COWAN, *Excitatory and inhibitory interactions in localized populations of model neurons*, Biophys. J., 12 (1972), pp. 1–24.
- [54] S. W. WURTS AND D. M. EDGAR, *Circadian and homeostatic control of rapid eye movement (REM) sleep: Promotion of REM tendency by the suprachiasmatic nucleus*, J. Neurosci., 20 (2000), pp. 4300–4310.