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Modeling the temporal architecture of rat sleep-wake behavior

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Abstract—**The fine architecture of sleep-wake behavior shows a distinct dynamic structure with distributions of rat sleep and wake bout durations displaying qualitatively different profiles. Wake bout durations follow a power-law relation whereas sleep bout durations are exponentially distributed. We show that a physiologically-based sleep-wake regulatory network model with an underlying deterministic structure governing neuronal interactions can generate realistic rat sleep-wake behavior as assessed by both standard summary statistics and survival analysis of bout distributions. Obtaining appropriate bout duration distributions depended on stochastic elements included in the model, the existence of multiple mechanisms for state transitions, and specific relationships among time constants governing state maintenance. This model provides a novel framework for exploring the disruptions of sleep-wake architecture associated with pharmacological, genetic, and disease states.**

I. Introduction

Recent studies quantifying the effects of specific genetic, developmental, and disease states on sleep-wake behavior have highlighted the inadequacy of standard metrics for sleep characteristics, such as percent time spent in wake and sleep states, mean duration of wake and sleep bouts, and the number of bouts, for differentiating experimental conditions or correlating with behavioral measures [1-5]. For example, such standard metrics can only weakly quantify state fragmentation which is the primary sleep pathology in disorders such as sleep apnea and narcolepsy [6, 7].

Survival analysis of state bout durations has emerged as a higher-order metric of sleep patterning that can better distinguish experimental conditions and disease states. Early approaches using survival analysis identified key qualitative differences in the distributions of wake and sleep bout durations: wake bout durations were governed by power-law behavior (proportional to $t^{-\alpha}$) while sleep bout durations were exponentially distributed [8]. Furthermore, these features were shown to persist across species [9], though they may be altered in the presence of disease or genetic mutation [2, 4, 5, 10]. Recent work has suggested that a multi-exponential distribution may accurately capture the power-law-like features of the wake bout distribution [11], but the qualitative difference between wake and sleep bout distributions remains clear.

Although stochastic models have captured the appropriate temporal architecture of wake and sleep bout durations, it is difficult to link stochastic models to underlying physiology [8, 12]. By contrast, physiologically-based mathematical models of the interactions among sleep-wake regulatory neuronal populations in the brainstem and hypothalamus provide a theoretical framework in which to examine proposed neuronal mechanisms of sleep-wake regulation as well as to investigate disruption of these mechanisms as occurs in sleep disorders [13-17]. However, underlying dynamics in these models are based on deterministic interactions among the participating neuronal populations that are reflected in the resulting distributions of wake and sleep bout durations. Therefore, even when these models reproduced standard summary statistics, the fine architecture of simulated sleep-wake behavior failed to realistically simulate the distributions of sleep and wake states. Hence, the question arises whether an inherently deterministic model can simulate a dynamic architecture displaying characteristics of an inherently stochastic system.

To investigate this question, we simulate realistic rat sleep-wake behavior in a physiologically-based model of the sleep-wake regulatory network. Deconstruction of this modeling framework allowed analysis of the source of power-law-like and exponential distributions of wake and sleep bout durations, respectively, and provided insights into the key generative mechanisms of the temporal architecture of sleep-wake behavior.

II. Methods

A. Modeling the sleep-wake regulatory network

The structure of the model sleep-wake regulatory network was based on experimental characterization of the relevant anatomy and physiology (see [18] for review) and has been described previously [14]. The model network includes wake-active, wake- and rapid eye movement (REM) sleep-active, REM sleep-active, and non-REM (NREM) sleep-active neuronal populations and the neurotransmitters they express (Fig 1).

The dynamic interactions between neuronal populations were modeled using a firing rate model formalism that explicitly includes both population firing rates and the concentrations of neurotransmitter released by associated presynaptic populations [14]. Briefly, firing rates of neuronal populations depend on the concentrations of neurotransmitters released by presynaptic populations and evolve dynamically to sigmoidal steady state functions. Neurotransmitter concentrations depend on the firing rate of the associated presynaptic population and evolve to a saturating steady state release function. A simulated

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homeostatic sleep drive *h(t)*, based on the characteristics of the neuromodulator adenosine, increases during wake and decreases during sleep, modulating the activity of the NREM-promoting population VLPO to induce transitions between wake and NREM sleep states.

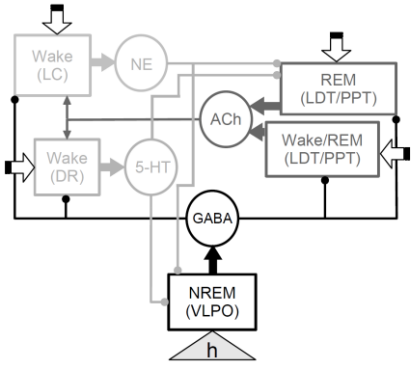

Figure 1: Schematic of model sleep-wake regulatory network showing connectivity among wake- (light gray, locus coeruleus (LC), dorsal raphe (DR)); NREM sleep- (black, ventrolateral preoptic area (VLPO)); and REM sleep-, and wake- and REM sleep- (gray, subpopulations of the laterodorsal tegmental nucleus and the pedunculopontine tegmental nucleus (LDT/PPT)) promoting neuronal populations and their associated neurotransmitters (noradrenaline (NE), serotonin (5-HT), GABA and acetylcholine (ACh), respectively). Large filled arrows indicate neurotransmitter expression by neuronal populations, lines ending in small arrows (circles) indicate excitatory (inhibitory) post-synaptic effects of neurotransmitters, and open striped arrows indicate external excitatory input. The homeostatic sleep drive (triangle) acts on the NREM-promoting VLPO.

B. Stochastic elements in the deterministic model

We identified three key physiological sources of variability to include in our sleep-wake network model: (1) variability in neurotransmitter release, modeled by scaling steady state neurotransmitter release functions by noise factors; (2) variability in the level of the homeostatic sleep drive, modeled by replacing the maximum and minimum thresholds of *h(t)* with normally distributed random numbers (mean h_{max} = 0.6, mean h_{min} = -0.4, SD = 1) that changed values at time points determined by a Poisson process (average rate = 0.01 Hz); and (3) random excitatory inputs from presynaptic populations that are external to the network, modeled by adding excitatory pulses of random amplitude arriving according to a Poisson process to the argument of a population's steady state firing rate function. Variability in neurotransmitter release and in the homeostatic sleep drive are motivated by the stochastic nature of synaptic transmission, while random excitatory inputs simulate activity on excitatory afferents from other brain regions targeting network populations.

As described previously, parameter values were based on or consistent with experimental data when possible, or set to physiologically reasonable values that optimized state-dependent behavior [14]. All equations and parameter values are as given in [14] with the exception of the noisy formulation of the *h*-equation; the inclusion of random excitatory inputs to the REM and Wake/REM-promoting populations with average rate 0.001 Hz, mean amplitude of 10 and SD of 1; an increased rate of 0.004 Hz, mean amplitude of 10 and SD of 2 for the random excitatory inputs to the LC and DR populations; and the values of the following parameters: $g_{G,LC} = g_{G,DR} = 2.7$, $g_{N,R} = g_{S,R} = 3.8$, $g_{A,R} = 3$, $g_{G,R} = 1.65$, $g_{A,WR} = 0.6$, $g_{G,WR} = 1.5$, $\tau_R = 10$s, $\tau_{A(R)} = \tau_{A(WR)} = 50$s, $\beta_{LC} = \beta_{DR} = 1$, $\beta_R = -0.72$, $\alpha_R = 0.28$, $\beta_{WR} = -0.15$, $k_1 = 0.6$, $k_2 = 4$, $\tau_{hw} = 170$s, and $\tau_{hs} = 250$s. Model equations were numerically solved using a modified Euler method with time step 0.005s implemented in XPPAUT (http://www.math.pitt.edu/~bard/xpp/xpp.html).

C. Statistical analyses of results

States of wake, NREM sleep, and REM sleep were scored based on the activity levels of wake-, NREM-, and REM-promoting populations. Data were scored in 10 s epochs according to the dominant state in each epoch. We compared the simulated rat sleep-wake behavior from 10 simulation runs to that reported for nocturnal rats in the light period [19] using a two-sample t-test with 5% significance.

To analyze the fine architecture of the simulated sleep-wake behavior, we computed Kaplan-Meier survival distributions for wake and sleep bout durations (NREM and REM sleep were both scored as "sleep" for this analysis). Statistical distributions of the bouts were determined by plotting data in log-log and semi-log coordinates and fitting by linear regression [5, 20]. We used r^2 values >0.95 to evaluate goodness-of-fit to power-law and exponential distributions. These analyses were performed with MATLAB (The Mathworks Inc., Natick, MA, USA).

III. RESULTS

The model generated realistic rat sleep-wake patterning with standard summary statistics showing no significant difference from those reported for experimental rat sleep recordings in the light period (two-sample t-test, $p<0.05$, Table I). More importantly, distribution profiles of simulated wake and sleep (NREM and REM sleep states combined) bout durations displayed appropriate qualitative features (Fig 2): wake bout durations between 10 and 480 s followed a power-law distribution (fit with $861t^{(-0.837)}$, $r^2=0.9724$, Fig 2A inset), while sleep bout durations followed an exponential distribution (fit with $135.8\exp(-0.0101t)$, $r^2=0.9882$, Fig 2B inset). Fits of either distribution with alternate functions, such as an exponential function for the wake durations or a power-law function for sleep durations, yielded lower r^2 values ($r^2=0.9213$ and $r^2=0.6216$, respectively). The threshold of 480s for power-law behavior of wake bouts is consistent with the range of durations previously reported to show a power-law relation in experimentally recorded rat sleep during the light period [9].

In experimental recordings of rat sleep during the light period, the longest few percent of wake bouts did not follow a power-law relation but instead formed a hump-like tail representing sustained bouts with durations up to 100 min, most likely promoted by environmental stimuli [9]. In our simulations, the longest 4% of wake bouts also deviated from power-law behavior, but maximum durations were

approximately 15 min reflecting the absence in the model of external inputs that would promote very long wake bouts.

Obtaining appropriate distribution profiles of wake and sleep bout durations depended on the stochastic elements included in the model. Generally, when all stochastic elements ((1)-(3) in Sec IIB) are removed from the model, states cycle through wake, NREM, REM, and return to wake, and bout durations are fixed for each state [14].

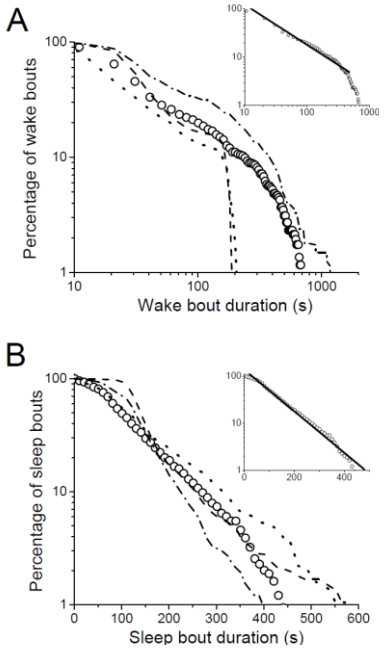

Fig 2: Survivor plots of wake bout (A, log-log) and sleep bout (B, semilog) duration distributions from 10 model simulation runs (open circles). Insets show optimal fits of wake bout distribution to a power-law function (A) and sleep bout distribution to an exponential function (B). Bout distribution profiles depend on stochastic components included in the model: neurotransmitter variability only (dashed curves), neurotransmitter and sleep homeostat *h* variability (dashed-dotted curves), neurotransmitter variability and random excitatory inputs to LC and DR (dotted curves).

To assess the contributions of each stochastic element, we considered the distribution of wake and sleep bout durations in the presence of the following: variability in neurotransmitter levels only; variability in neurotransmitter levels and sleep homeostat thresholds; variability in neurotransmitter levels and the presence of random excitatory inputs to the wake-promoting populations.

Based on the structure of our model network, sustained wake bouts occur at the homeostatically-controlled transitions between NREM sleep and wake, and shorter wake bouts occur at the termination of REM bouts as a result of the reciprocal interactions between the wake-promoting LC and DR populations and the REM-promoting population. For the model parameter values considered here, the addition of neurotransmitter variability causes regular REM cycling to occur during the NREM sleep state with brief wake bouts terminating each REM bout. As a result, the distribution of wake bout durations is bimodal with symmetric peaks centered at approximately 30 s and 180 s (Fig 2A, dashed curve). Adding variability in the homeostatic sleep drive *h* introduces much more variance in the durations of sustained wake bouts (dash-dotted curve) thus preventing the survival curve from falling precipitously around 200 s. Including random excitatory inputs to the wake-promoting populations introduces many short wake bouts that contribute to an initial power-law profile for the shortest bout durations (dotted curve). Transforming the bimodal distribution that results when both homeostatic variability and random excitatory inputs to the wake-promoting populations are removed (dashed curve) to a power-law-like profile (circles) required that, compared to the brief "post-REM" wake bouts, the randomly initiated wake bouts have shorter average duration and the homeostatically initiated wake bouts have longer average durations. Therefore, both the existence of three separate mechanisms with distinct time constants governing wake bout maintenance and the appropriate relationship among the time constants produce power-law-like behavior of wake bout durations.

For sleep bouts, the longest duration bouts (> 200s) followed approximately exponential distributions for every combination of stochastic elements included in the model (Fig 2B, dashed, dash-dotted and dotted curves), reflecting the variable termination of these longer bouts by homeostatically-controlled transitions to sustained wake or brief wake bouts following REM bouts. Obtaining an initial exponential profile for shorter sleep bouts depended on the presence of random excitatory inputs to the wake-promoting populations that introduced higher fragmentation of the NREM state (dotted curve).

TABLE I
COMPARISON OF SUMMARY STATISTICS FOR SIMULATED AND EXPERIMENTALLY RECORDED RAT SLEEP PATTERNING

		Mean (SEM) percent time in state	Mean (SEM) bout duration (min)	Mean (SEM) number of bouts
Model[1]	Wake	31.0 (1.6)	1.5 (0.1)	51.6 (2.0)
	NREM	53.7 (1.5)	2.6 (0.1)	50.1 (2.0)
	REM	14.6 (0.5)	1.4 (0.03)	24.3 (0.8)
Data[2]	Wake	31.0 (1.5)	1.6 (0.2)	47.4 (2.0)
	NREM	55.0 (2.0)	2.8 (0.1)	47.2 (2.0)
	REM	16.0 (1.0)	1.5 (0.05)	25.9 (1.5)

[1]Computed from 10 simulation runs; [2]Sleep recordings from nocturnal rats in the light period under 12:12 light/dark conditions [19].

IV. DISCUSSION

A. Summary and limitations

We have shown that a physiologically-based sleep-wake regulatory network model with an underlying deterministic structure for neuronal interactions and with appropriate stochastic elements can generate realistic rat sleep-wake behavior as assessed by both standard summary statistics and survival analysis of bout distributions. We matched simulated sleep-wake behavior with standard statistics reported for rat light period behavior, and since wake and sleep bout duration distributions were not reported for this data set, we constrained the model to reproduce qualitative features of reported distribution profiles. While these results may not represent an optimal fit of the model to the fine temporal architecture of rat sleep behavior, they do indicate how a deterministic model can more accurately replicate sleep-wake temporal dynamics. Future work will focus on constraining our physiological model with experimental recordings of rat sleep-wake behavior, for which distributions of REM sleep bout durations may also be investigated.

For our model network, the included stochastic elements

contributed to the distributions of bout durations, and removal of any of these elements compromised the qualitative profile of bout distributions. For wake bouts, an appropriate distribution profile depended on the existence of multiple mechanisms for state transitions and a specific relationship among the time constants associated with each of these mechanisms. For sleep bouts, durations were determined by the occurrence of wake bouts and variability in each of the mechanisms initiating wake bouts readily generated an approximately exponential distribution for sleep bout durations.

Despite the important role of stochastic elements in model behavior, the majority of state transitions are controlled by deterministic dynamics inherent to network structure. However, the structure of the mammalian sleep-wake regulatory network, especially mechanisms regulating REM sleep, has not been completely determined. Future work should consider other network structures and the implications of different structures on resulting simulated sleep-wake temporal architecture. In addition, although we have shown that the stochastic elements we included were sufficient to produce appropriate distributions of wake and sleep bouts (and were necessary in this context), we have not shown that they are the only elements that could generate these results. Future work should determine the necessary and sufficient stochastic elements required for generating realistic sleep-wake behavior in a given deterministic model and evaluate the robustness of these elements across different network structures.

B. Qualitative features of sleep-wake architecture

The characterization of power-law behavior for wake bouts and exponential behavior for sleep bouts has been questioned, particularly when these characterizations are only applied to part of a distribution (such as wake bouts < 480 s, see below) [11]. In particular, multi-exponential distribution profiles have been proposed to provide more accurate fits for wake bout durations [2, 3]. Furthermore, even when sophisticated fitting techniques are applied [21], recent work has shown that it can be difficult to distinguish between power-law and multi-exponential behavior [11]. This suggests that our simulation results may also be well fit with a multi-exponential function. The pertinent question, however, may not be which function better fits wake bout distributions, but instead what the characteristics of the distribution imply for the mechanisms underlying bout initiation and maintenance. The presence of dissimilar behavior in wake and sleep bout durations highlights a lack of symmetry between states. However, if simulated sleep-wake behavior is described by regular movement around a hysteresis loop, as occurs in models of a mutually inhibitory flip-flop switch, then the resulting distributions of wake and sleep bout durations will be similar. In our model, disruption of the underlying hysteresis loop by stochastic elements, asymmetries in the site of action of some stochastic elements and the additional wake transition mechanism provided by the reciprocal interaction structure regulating REM sleep allow for the emergence of qualitative differences in distributions of wake and sleep bouts.

REFERENCES

[1] A. J. Gall, B. Joshi, J. Best, V. R. Florang, J. A. Doorn, and M. S. Blumberg, "Developmental emergence of power-law wake behavior depends upon the functional integrity of the locus coeruleus," *Sleep,* vol. 32, pp. 920-6, Jul 1 2009.

[2] M. T. Bianchi, S. S. Cash, J. Mietus, C. K. Peng, and R. Thomas, "Obstructive sleep apnea alters sleep stage transition dynamics," *PLoS One,* vol. 5, p. e11356, 2010.

[3] R. H. Joho, G. A. Marks, and F. Espinosa, "Kv3 potassium channels control the duration of different arousal states by distinct stochastic and clock-like mechanisms," *Eur J Neurosci,* vol. 23, pp. 1567-74, Mar 2006.

[4] R. D. Chervin, J. L. Fetterolf, D. L. Ruzicka, B. J. Thelen, and J. W. Burns, "Sleep stage dynamics differ between children with and without obstructive sleep apnea," *Sleep,* vol. 32, pp. 1325-32, Oct 1 2009.

[5] C. G. Diniz Behn, N. Kopell, E. N. Brown, T. Mochizuki, and T. E. Scammell, "Delayed orexin signaling consolidates wakefulness and sleep: physiology and modeling," *J Neurophysiol,* vol. 99, pp. 3090-103, Jun 2008.

[6] B. J. Swihart, B. Caffo, K. Bandeen-Roche, and N. M. Punjabi, "Characterizing sleep structure using the hypnogram," *J Clin Sleep Med,* vol. 4, pp. 349-55, Aug 15 2008.

[7] Y. Dauvilliers, I. Arnulf, and E. Mignot, "Narcolepsy with cataplexy," *Lancet,* vol. 369, pp. 499-511, Feb 10 2007.

[8] C.-C. Lo, L. A. Nunes Amaral, S. Havlin, P. C. Ivanov, T. Penzel, J.-H. Peter, and H. E. Stanley, "Dynamics of sleep-wake transitions during sleep," *Europhys Lett,* vol. 57, 2002.

[9] C. C. Lo, T. Chou, T. Penzel, T. E. Scammell, R. E. Strecker, H. E. Stanley, and P. Ivanov, "Common scale-invariant patterns of sleep-wake transitions across mammalian species," *Proc Natl Acad Sci U S A,* vol. 101, pp. 17545-8, Dec 14 2004.

[10] M. S. Blumberg, C. M. Coleman, E. D. Johnson, and C. Shaw, "Developmental divergence of sleep-wake patterns in orexin knockout and wild-type mice," *Eur J Neurosci,* vol. 25, pp. 512-8, Jan 2006.

[11] J. Chu-Shore, M. B. Westover, and M. T. Bianchi, "Power law versus exponential state transition dynamics: application to sleep-wake architecture," *PLoS One,* vol. 5, p. e14204, 2010.

[12] G. G. Gregory and R. Cabeza, "A two-state stochastic model of REM sleep architecture in the rat," *J Neurophysiol,* vol. 88, pp. 2589-97, Nov 2002.

[13] 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,* vol. 97, pp. 3828-40, Jun 2007.

[14] C. Diniz Behn and V. Booth, "Simulating microinjection experiments in a novel model of the rat sleep-wake regulatory network," *J Neurophysiol,* vol. 103, pp. 1937-1953, 2010.

[15] M. J. Rempe, J. Best, and D. Terman, "A mathematical model of the sleep/wake cycle," *J Math Biol,* vol. 60, Jun 26 2009.

[16] Y. Tamakawa, A. Karashima, Y. Koyama, N. Katayama, and M. Nakao, "A quartet neural system model orchestrating sleep and wakefulness mechanisms," *J Neurophysiol,* vol. 95, pp. 2055-69, Apr 2006.

[17] A. J. 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,* vol. 22, pp. 167-79, Apr 2007.

[18] C. B. Saper, T. E. Scammell, and J. Lu, "Hypothalamic regulation of sleep and circadian rhythms," *Nature,* vol. 437, pp. 1257-63, Oct 27 2005.

[19] C. Blanco-Centurion, D. Gerashchenko, and P. J. Shiromani, "Effects of saporin-induced lesions of three arousal populations on daily levels of sleep and wake," *J Neurosci,* vol. 27, pp. 14041-8, Dec 19 2007.

[20] M. S. Blumberg, A. M. Seelke, S. B. Lowen, and K. A. Karlsson, "Dynamics of sleep-wake cyclicity in developing rats," *Proc Natl Acad Sci U S A,* vol. 102, pp. 14860-4, Oct 11 2005.

[21] A. Clauset, C. R. Shalizi, and M. E. J. Newman, "Power-Law Distributions in Empirical Data," *SIAM Review,* vol. 51, pp. 661-703, 2009.