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A simple model for the origin of quasiperiodic ultradian rhythms in sleep-wake state in the rat

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In a recent study,[1] ultradian rhythms of rat sleep-wake behavior were found, using several methods of time series analysis, to be "quasiperiodic." That is, ultradian period varied apparently randomly around a mean of approximately 4 h, with no relationship between ultradian period and time of day. Here it is proposed that a simple two-oscillator model can explain the quasiperiodic characteristic of these rhythms. Specifically, in this model a periodic oscillator interacts with a stochastic oscillator to generate a behavioral pattern in which the period and amplitude of the simulated ultradian waves vary randomly around an average value. Preliminary simulations support the plausibility of the model; simulated waveforms were closely similar to behavior patterns observed in adult male rats. It is hypothesized that ultradian rhythms in sleep-wake behavior may arise from a periodic feedback loop (e.g., the sleep-wake homeostat) coupled to a stochastic sleep-wake "flip-flop" switch.

Ultradian rhythms are clearly evident in recordings of sleep-wake behavior and rest-activity cycles, especially in species such as rats that exhibit so-called "polyphasic" patterns of behavior. However, such rhythms are not well characterized and little is known about their underlying physiological mechanisms. Moreover, few attempts have been made to incorporate ultradian rhythmicity into models of sleep-wake regulation. Ultradian rhythms in sleep-wake patterns have been assumed to be combinations of periodic waves[2] or a periodic wave with noisy amplitude.[3,4] Recently, we have shown that these assumptions are not entirely accurate. By using autocorrelation and maximum entropy spectral analysis (MESA), together with wave-by-wave analyses, we have confirmed that ultradian rhythms in sleep-wake behavior have a dominant period at approximately 4 h and that amplitudes of the waves vary randomly over time. However, we have also found that the period of the waves varied randomly, and substantially, around the mean such that the number of ultradian waves varied from 4 to 8 per day. This characteristic of randomly varying period is called "quasiperiodicity" (not to be confused with mathematical quasiperiodic and almost-periodic functions) and may hold clues as to the nature of the physiological mechanisms underlying dynamic patterns of sleep-wake behavior. Here I propose a conceptual model for the origin of quasiperiodic ultradian rhythms in sleep-wake state and establish its plausibility (but not necessarily its verity) using computer simulations.

In essence, this simple model consists of a deterministic oscillator that (in part) determines the mean period of the ultradian cycle, interacting with a stochastic oscillator that gives rise to variability in the cycle duration. Here I reduce the model to its essential elements and conduct a preliminary "proof of principle" study. Detailed description, sensitivity analysis and elaboration of the model will be the subject of future work.

The key simplifying assumptions of the model are as follows: (1) That there are two states of wakefulness and sleep (i.e., NREM and REM are treated as a combined state); (2) that the regulated variable is cumulative time awake; (3) that the deterministic oscillator is a feedback loop that acts to limit the accumulation of time spent awake; this is analogous to the sleep-wake homeostat;[5] (4) that a stochastic oscillator mediates the transitions between the states of wakefulness and sleep; this is analogous to the well-known "flip-flop" sleep-wake switch;[6] (5) that WAKE bout duration is subject to probabilistic modulation by the action of the feedback loop; (6) that the stochastic oscillator occupies one of two distinct probability states dependent upon the phase of the deterministic oscillator; (7) that the phase of the deterministic oscillator is defined by a threshold; (8) that the feedback threshold exhibits a significant hysteresis (i.e., functions as a dual threshold).

In simple terms, above an upper threshold of cumulative WAKE, the stochastic oscillator has relatively high probability of sleep onset (a wake to sleep transition; P_{ws}) and relatively low probability of arousal (a sleep to wake transition; P_{sw}). Conversely, below a lower threshold of cumulative WAKE, P_{ws} is relatively low and P_{sw} is relatively high. Thus, the state of the system cycles between intervals of high WAKE probability/low SLEEP probability and intervals of low WAKE probability/high SLEEP probability. The mean period of the cycle is determined by the magnitude of the hysteresis and by the ratio of the values of P_{ws} and P_{sw}.

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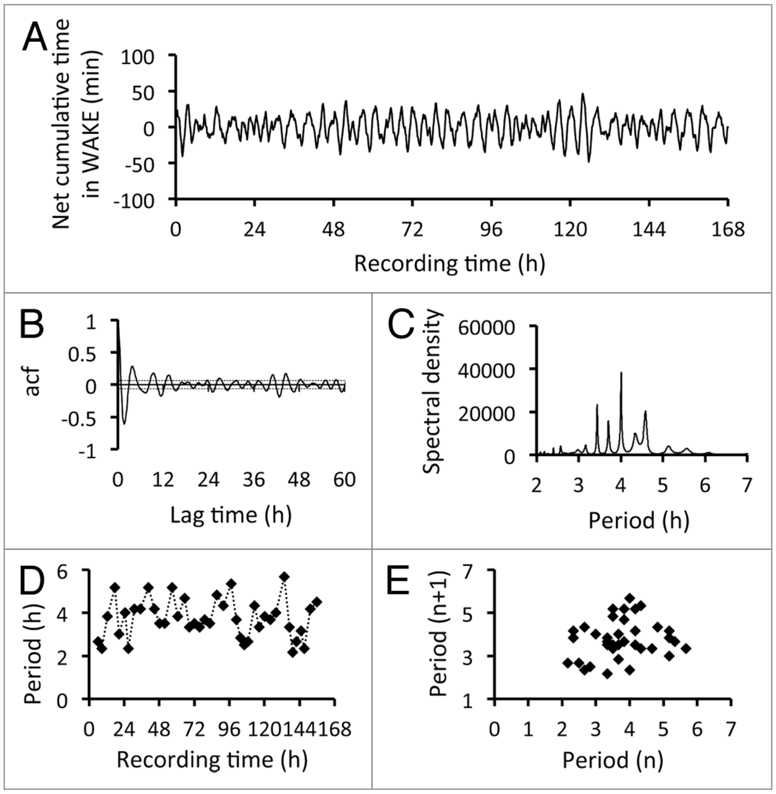

Figure 1. Example of a time series analysis of simulated data generated by a simple two-oscillator model. Simulated data were processed in exactly the same manner as recorded data (see ref. 1 for details). (**A**) Simulated time series generated by the model. (**B**) Autocorrelation analysis of the waveform shown in (**A**), showing primary lag at 3.83 h. (**C**) Spectral analysis, using MESA, of the waveform shown in (**A**). Primary peak is at 4 h and multiple additional peaks in the range 3–6 h. (**D**) Wave-by-wave analysis shows that instantaneous period varies randomly over time. (**E**) First return map indicating unstructured cloud suggesting random variation of period over time. These analyses demonstrate that the simulated waveform captures the major dynamic features of rat WAKE ultradian rhythms.

The model was implemented in worksheet format (Excel v. 2011, Microsoft Corp.). Simulations were computed at a temporal resolution of 5 sec to reflect the epoch duration of animal recordings.[1] A total of 120960 iterations were generated to simulate a week of data. Simulated data were then expressed as detrended net cumulative WAKE and the time series were binned, filtered and analyzed exactly as described for rat data.[1] Digital filters, autocorrelation analysis and maximum entropy spectral analysis (MESA) were performed using analysis programs custom-written in FORTRAN and implemented in DOS-executable form, as described in detail elsewhere.[7]

Exploratory simulations were conducted with a range of parameter values but the following is intended only to establish the general plausibility of the approach. Here I report a preliminary simulation conducted using the following parameter values: threshold hysteresis, 30 min; supra- and sub-threshold P_{sw}, 0.02062; suprathreshold P_{ws}, initial 0.11715, final 0.00554; subthreshold P_{ws}, initial 0.11593, final 0.00416. The threshold hysteresis is an arbitrary value. P_{ws} and P_{sw} are the probability of state transition within any given 5 sec epoch. P_{sw} is constant [as dictated by simplifying assumption (2), above] and corresponds to an arbitrary mean sleep bout duration of 4 min. P_{ws} determines mean WAKE duration and varies in two ways; as a function of time awake (to account for the reported power law or multi-exponential distribution of WAKE bout durations),[8,9] and as a function of threshold status. The P_{ws} values used here yield highly variable simulated WAKE bout durations (as intended) with overall mean durations of approximately 5–10 min (subthreshold) and 2–4 min (suprathreshold).

Model computations produced simulated time series that closely resembled those described for rats in LL. An example of a simulated time series and corresponding analysis are illustrated in **Figure 1** and can be directly compared with rat data shown in Figures 2, 4 and 5 in our recent paper.[1] Detrended simulated waveforms exhibit random variability of period and amplitude. MESA spectra feature multiple peaks between 3–6 h, with a prominent peak at 4 h. The autocorrelogram also indicates a significant primary lag at 4 h that diminishes over subsequent repeats. It is notable that the autocorrelogram of model output differs from rats in that there is no evidence of long-range correlation in the simulated data, reflecting the fact that the daily interaction (entrainment) between ultradian and circadian rhythms that was seen in rats[1] was not included in this preliminary version of the model. This minor difference notwithstanding, it is stressed here that this model can reproduce the quasiperiodic pattern of ultradian rhythms in sleep and wakefulness, when using values of P_{ws} and P_{sw} calculated from mean bout duration data in the literature,[10] assuming multi-exponential state transition dynamics[9] and an assumed threshold hysteresis of 0.5 h.

This simple model consists of a periodic oscillator interacting with a stochastic oscillator to produce cycles of variable duration. Such a mechanism was suggested previously[11] to explain infradian (multi-day) rhythms in sleep-like quiescence in the mollusk *Lymnaea stagnalis*. Although the sleep patterns of snails and rats may seem to be very different, the present study suggests that these differences are superficial since both species display behavioral dynamics that can be explained by the same conceptual model, albeit with different time constants applied. Thus the present analysis supports the suggestion that fundamental mechanisms of sleep-wake regulation may be evolutionarily conserved.[12,13] In this context it is tempting to speculate that the deterministic oscillator can be conceptualized as the sleep-wake homeostat which itself is modeled as a simple feedback loop. Moreover, the stochastic oscillator is analogous to the "flip-flop" switch model that has been proposed[6] to describe the executive neural control mechanism regulating transitions between behavioral states in mammals.

The proposed model is undoubtedly overly simplistic in its present form but the basic principle is of interest because it represents a plausible and parsimonious explanation for the origin of quasiperiodic ultradian rhythms. The model does not rely on an unidentified "ultradian pacemaker" structure but instead posits that ultradian rhythms arise from the dynamic interactions of known (albeit, incompletely understood) mechanisms—the sleep-wake homeostat and the flip-flop switch. Thus, in contrast to circadian rhythms, which arise from a clock-like mechanism and are highly periodic, ultradian rhythms may arise from a system-level "network" mechanism. If the ultradian rhythms represent the output of the sleep-wake homeostat, then by extension, quantitative analysis of ultradian rhythms may provide a novel approach to the study of sleep-wake homeostasis and lead to new insights into the underlying mechanism. This study has shown that ultradian rhythms represent more than "noise" and may hold clues to the dynamic interplay between mechanisms regulating sleep-wake state in mammals. This highlights a need for further research into the dynamics and underlying mechanisms of ultradian rhythms in sleep-wake state.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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