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Commentary on the mutual interaction model of McCarley and Massaquoi for REM-NREM cycle

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DAAN, SERGE, AND DOMIEN G. M. BEERSMA. *Commentary on the mutual interaction model of McCarley and Massaquoi for REM-NREM cycle.* Am. J. Physiol. 251 (Regulatory Integrative Comp. Physiol. 20): R1030–R1032, 1986.—McCarley and Massaquoi successfully simulated human REM-NREM cycle characteristics by extending the McCarley-Hobson model with two sets of assumptions, one creating limit cycle behavior, the other introducing two sources of circadian variation. We argue that the limit cycle assumptions, due to freedom in choosing parameter values, suffice to explain variation in REM across the night. Nonmonotonic circadian variation in REM latency requires a circadian cycle dependence only of initial conditions at sleep onset.

mathematical model; sleep; circadian movement

EVER SINCE THE FIRST description of rapid and non–rapid-eye movement (REM and NREM, respectively) sleep by Dement and Kleitman (7), the regular alternation of these sleep states has been the subject of detailed investigation. Yet researchers who have attempted to model the mechanism generating the REM-NREM cycle are remarkably few [Zung et al. (19); McCarley and Hobson (13); Lawder (11)]. This is in conspicuous contrast with the situation in circadian cycles. The circadian literature is replete with physical, electronic, mathematical models, and these theoretical analyses have proved invaluable for our understanding of the basic properties of circadian oscillators. Indeed the models developed serve as guidelines in the physiological analysis of circadian pacemakers that have been localized. Circadian rhythmicity has obvious adaptive meaning and it has long been realized that synchrony with the earth's rotation due to entrainment by the light-dark cycle is a prerequisite for their functional integrity. Circadian models have therefore generally been functional models, which could be formulated independent of physiological detail [e.g., Pavlidis (15); Winfree (18)]. In ultradian rhythmicity, functions are usually far from clear and presumably diverse [Schulz and Lavie (17)]. In particular there is no generally accepted theory as to why organisms should have REM or NREM sleep, let alone why these should alternate in species-specific patterns. There is no general response such as the phase response of circadian systems to light, which can be employed to assay the functional properties of ultradian oscillators. Any ultradian model needs to be rooted firmly in the physiology of the system studied, rather than in the quicksand of its elusive function. The earlier reciprocal interaction model for the REM-NREM cycle in the cat by McCarley and Hobson (13) was indeed closely tied with neurophysiological research. The attractive simplicity of this model was insufficient to simulate the whole human sleep cycle, although it allowed at least a theoretical analysis of REM-latency dependence on initial conditions (Beersma et al., Ref. 3). A number of additional assumptions, some unavoidably with a less firm physiological basis, were required to do this. It is an appropriate and logical consequence that McCarley and Massaquoi have now presented such an expansion of the earlier model. We thoroughly appreciate this enterprise, which will certainly serve as a starting point for much future discussion on precisely which additional properties beyond the simple reciprocal interaction are minimally required for the human REM-NREM cycle to behave as it does.

We are grateful for the opportunity to enter this discussion at an early stage. Before considering the assumptions in the McCarley and Massaquoi model, we make a general comment on strategies in modeling. In our opinion, a useful model is the simplest set of assumptions, which together, explain a complex behavorial phenomenon. Simulation models serve their best purpose in relating hitherto unrelated sets of data, and in generating predictions for new experimental research. In a sense a model is like a statistical null hypothesis, the formulation of which has its greatest merit when it can be rejected. It is only then that we know which particular data set is at variance with the model and which additional assumption is required to also accommodate that data set. It is for this reason that we would have preferred a different presentation of the model, showing where precisely the simplest form is at variance with empirical fact, which is the most logical assumption to accommodate this fact, which other feature of the data then remains unexplained, etc., one step at a time. The McCarley and Massaquoi model contains five new assumptions, all of them physiologically reasonable, and together they account for a variety of data on the human REM-NREM cycle. What remains unclear is whether maybe four of the five would have done the same job, and precisely which data demand which assumption.

The McCarley and Massaquoi approach of the REM-NREM cycle in humans assumes that it is based on an ultradian oscillation that is set in motion at the onset of sleep. This is due to a high value of the excitatory input to Y during wakefulness. The model thus implicitly rejects the old Basic Rest Activity Cycle (BRAC) hypothesis of Kleitman (9), who surmised that an endoge-

nous 90-min oscillation is continuously in motion across the day and night and expresses itself during sleep in the REM-NREM cycle. The BRAC hypothesis has frequently been referred to when a short-term oscillation in physiology or behavior was found, but synchrony, i.e., a consistent phase relationship between such physiological oscillations and with the REM-NREM cycle, has rarely been observed (Kleitman, Ref. 10). We agree with McCarley and Massaquoi that sleep onset initiation of the rhythm is presently better defendable than the BRAC hypothesis. Data on narcoleptic patients recently presented by Schulz (16) show that some of these patients have periodic bouts of spontaneous sleep during wakefulness, timed such that their occurrence can be predicted by extrapolation from the phase of the REM-NREM cycle. A way to reconcile these data with the present model is to surmise that the waking excitatory input to the REM-off cell population is reduced in these narcoleptics, allowing ongoing ultradian oscillation even during wakefulness. Indeed one of the very useful aspects of a model like this is that it may be applied to derive such specific hypotheses.

The new assumptions introduced in the McCarley and Massaquoi model fall in two categories: those changing the original Lotka-Volterra equations into a limit cycle model, and those introducing circadian variation in the system. Assumptions in the first category appear to be reasonable and well inbedded in available neurophysiological evidence. They are moreover mathematically less intrusive than they appear at first glance. The steep limitation functions $b(X)$ and $S_2(Y)$ (further explained in Ref. 14) merely prevent the oscillations from reaching extremely low (X) or high (Y) levels, but exert little effect during major parts of the cycle. The precise location of the limit cycle in the X-Y phase plane is primarily determined by the two new functions, $a(X)$ and $S_1(X)$. Both act on the self-excitation of the REM-on cells, so that actually the previously used constant a is replaced by a single function, $a^*(X) = a(X) \cdot S_1(X)$, maximizing self excitation at intermediate levels of X. The actual shape of this function seems somewhat arbitrary, since it is the product of two arbitrarily scaled sigmoid functions. Since the REM-threshold in X is also arbitrarily chosen, this arbitrariness does not matter for the steady-state oscillation. Choosing a different maximization function $a^*(X)$ is, however, bound to produce a different velocity of approach to the limit cycle. This is relevant for systematic changes in the REM-NREM oscillation in the course of sleep episodes. It would be very useful to explore the effects of varying $a^*(X)$ to see how much of the systematic variation within human sleep may be attributable to the initial approach to the limit cycle.

Taking these assumptions together we find that the McCarley and Massaquoi model presents an elegant physiological explanation for the occurrence of stable REM-NREM cycles during sleep: an explanation that is both simple and a direct consequence of sigmoid limitation of firing rates and neuronal excitability. A further expansion of this model would be the introduction of a source of stochasticity, since the large variability is one of the major characteristics of these cycles, presently not addressed by the model.

In their assumptions on circadian influences on the system, McCarley and Massaquoi appear to be on weaker ground. They introduce two sources of circadian variation in parameters of the system, one modulating the position of the limit cycle in the phase plane as dependent on circadian phase, via d(circ), the other affecting initial conditions at sleep onset. Each one of these oscillations is chosen as a sine wave for simplicity and inevitably specified by at least two free parameters, amplitude and phase.

We feel that the introduction of such circadian effects gives the modeler ample freedom to simulate with considerable accuracy all of the four data sets (entrainment, freerun with early and late sleep with respect to the body temperature rhythm, depression) presently addressed by the model. It would have been worthwhile to have an account of precisely which data on the REM-NREM cycle demand a circadian effect at all. It is true that the duration of the first REM episode is significantly shorter than that of later REM episodes. As the authors admit, there is no solid evidence for further increases after the second REM episode across the night, and their statistical reanalysis of the data by Schulz et al. is equivocal on this point, since it included the first, shorter, REM episode. Likewise, the data of Czeisler et al. (5), quoted on page 22, are irrelevant for this issue, since these show circadian variations in REM duration following repeated 90-min sleep interruptions, not in undisturbed sleep. The short first REM duration in the model is the consequence of the initial approach to the limit cycle. There appears presently to be nothing in the data that demands the assumption that the variable d in the model (representing locus coeruleus/dorsal raphe excitation by REM-on neurons) should vary across the circadian cycle. It is quite possible that a systematic change in REM duration after the first REM episode will be demonstrated empirically, but this could still easily result from a slightly more gradual approach to the limit cycle due, for instance, to a different arbitrary choice of the function $a^*(X) = a(X) \cdot S_1(X)$. The earlier and simpler Karma version of this model (Massaquoi and McCarley, Ref. 12) did not include circadian variation in parameter d. This version may actually be sufficient to simulate variations during sleep episodes. We realize that including d(circ) invokes two extra parameters allowing more easily a close fit with the data, yet we see no evidence really necessitating this extension.

The other circadian modulation is in the initial conditions. It is not fully clear to us exactly how the authors introduced this effect, since it is not explicitly formulated. Simulations at relatively early (entrained) and late (freerun) sleep onsets (Figs. 3, 7 of Ref. 14) start at exactly the same initial X (= 0.2) and Y (= 0.35). Yet some excitatory input to Y persists almost until the first REM episode (Ref. 14). The excitatory input is not specified in the mathematical formulation of the model. This is unfortunate, since it is the major cause of differences in REM latency as dependent on circadian phase, and thus, of the model's main predictive success. The reduced REM latency in depression, generated by reducing the initial Y value, is characteristic also of the simpler McCarley and Hobson model (Beersma et al., Ref. 3) and is therefore no argument in favor of the new circadian assumptions. Nevertheless we agree with the authors that some circadian variation in initial conditions (presumably in Y at sleep onset) is quite likely. Endo et al.

(8) reported short REM latencies in sleep in the morning after one night of total sleep deprivation, and this result suggests that, with monotonic increase in the duration of wakefulness, a nonmonotonic circadian variation of REM latency ensues. The hypothesis of a reduced excitatory input to locus coeruleus/raphe nucleus neurons both during sleep deprivation in healthy subjects and in depression not only nicely explains the short REM latencies found in these conditions, it should also be attractive to psychiatrists interested in circadian changes in arousal and mood especially in depressive patients.

McCarley and Massaquoi imply that the model explains patterns in changing REM-intensity, hypothetically reflected in the density of rapid-eye movements, as well as REM-duration, since neuronal X-activity is positively correlated with the frequency of eye movements. However, the model produces virtually constant peak values of X except for reduced values for the first REM episode of normal sleep. This is in contrast with the gradual increases of REM density during sleep episodes reported by Aserinski (2). In fact these data led Aserinski to postulate that REM density is an indicator of sleep satiety rather than of intensity. On functional grounds, one should expect intensity of a behavior to drop when satiety for the behavior increases. This is consistent with the decrease in REM density following REM sleep deprivation reported by Antonioli et al. (1). Hence it is at least questionable whether REM sleep intensity, if there is such a dimension, is represented by the density of eye movements. Much more firmly established now is an intensity dimension to NREM sleep (Borbély and Neuhaus, Ref. 4), and it should be a challenge to incorporate the current knowledge on NREM sleep regulation in the model.

In fact a next step in the development of a general theory of sleep regulation will be the integration of models of the kind presented by McCarley and Massaquoi addressing the ultradian timing of REM and NREM sleep with models for circadian timing of sleep, which were so far solely concerned with NREM sleep (Daan et al., Ref. 6). Despite the complexity of the whole system it will be important to limit the number of assumptions and parameters to the minimum required by the data. It should then be possible to generate predictions of the kind produced by McCarley and Massaquoi for acetylcholine agonist administration. It is by specifying hypotheses for novel physiological experiments that models serve their best purpose. Such tests should be critical; i.e., if the prediction is not upheld, the test should lead to rejection or modification of the model. The phase-response curve prediction for physostigmine presented by McCarley and Massaquoi is extremely interesting and worthy to be tested. We doubt, however, whether finding a phase-response curve different from that in Fig. 13 would lead to rejection of the model. More likely, the result might be accommodated by adjusting some parameter values, since the phase interference (doubling parameter a for one time unit) is arbitrary, and similar interferences (such as tripling a over 5 time units, etc.) necessarily give rise to a wide variety of phase-response curves. Nevertheless, the prediction of phase responses to a pharmacological agent illustrates one of the important aspects of this elegant model, namely the fact that it is in essence a physiological hypothesis in which each variable and each parameter has a definite, if hypothetical meaning. It is this property that will make the model, if not easily rejectable by its multitude of parameters, a framework for discussion of the sleep cycle for years to come.

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