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An Integrated Model of Sleep Regulation

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Abstract: We present a new model of sleep regulation which integrates the two process model and the limit cycle reciprocal interaction model. In the two process model the interaction of a homeostatic process (S signal) and of a circadian process determines the timing of sleep and waking. In the limit cycle model, the NREM - REM sleep cycle is generated by the reciprocal interaction of two coupled cell population. The present model integrates the two considered models introducing the trigger REM - NREM generated by the REM-ON signal and activated when REM-ON overcomes the S signal.

1. Introduction

The main clinical features of narcolepsy are frequent sleep periods during the day. The main criterion for the diagnosis of narcolepsy is the presence of multiple REM phase sleep episodes. It has been suggested that narcolepsy may derive from a disturbance in sleep organization due to alterations, circadian and ultradian regulation processes in patients with narcolepsy could be regarded as so strong as to interfere with circadian regulation systems. Several models have been proposed representing interactions among homeostatic, circadian and ultradian processes, which can be used to validate different possible assumptions on the interactions among these processes. The available models of sleep regulation attains to the sleep timing or to the intrasleep NREM-REM alternation. We propose an integration model which seem to be adequate to describe sleep architecture both in physiological and in pathological conditions where the position and the duration of REM sleep can be abnormal.

2. Previous models

2.1. Two process model

In this model [1, 2, 3, 4] the sleep propensity in humans is determined by a homeostatic process S and a circadian process C. The interaction of S and C determines the timing of sleep and wakefulness. The time course of S is derived from EEG slow wave activity; the phase position and shape (skewed sine wave) of C is derived from sleep duration data obtained at various times of the 24-h cycle.

With this model the following data simulation can be obtained:

- timing of sleep:
  - after sleep deprivation
  - during prolonged bedrest
- internal desynchronization during free run
- variations of sleep on set and sleep termination
- level and time course of slow-wave activity in sleep
  - after total sleep deprivation
  - after repeated partial sleep deprivation
  - after daytime naps
- variations of sleep latency.

The neurobiological bases of sleep homeostat are still unknown, possible bases can be singled out from EEG slow wave activity [5] and this absence of physiological bases makes it indispensable an artificial signal (REM-trigger) to cause the decrease of the S signal.

2.2. Limit cycle reciprocal interaction model

In this model [6, 7] the NonREM-REM sleep cycle is generated by the reciprocal interaction of two coupled cell population in the brain stem. This model retains the main features of a previous model [8] mainly about the self-excitatory and self-inhibitory connections of the cell populations; but the assumption of a stable limit cycle oscillation that is independent of initial conditions is rejected. In this system a circadian term is introduced to determine the mode of approach to the limit cycle.

With this model the following data simulation can be obtained:

- REM sleep latency and REM sleep episode durations in normal humans under various experimental conditions and in depressives;
- prediction of an ultradian phase response curve to a cholinergic agent;
- effect of forced waking on the dynamics of non-REM/REM sleep cycle by an exogenous excitatory input.

This model does not explain the differences of the REM-ON cycles caused by the sleep pressure arising for a long waking period before sleep.

2.3. An integrated proposal

In order to overcome these limitations, an extended version of the previous model was proposed by Massaquoi and McCarley [9] in which the non-REM/REM sleep cycle, generated by the reciprocal interaction of the two coupled brain cell populations, is integrated by the sleep homeostasis signal and arousal events. This model is based on the assumption of first-order decay dynamics for the arousal system and allows a qualitative simulation of ultradian slow-wave activity pattern.

The time course of the S signal is taken from the two process model. Whereas the REM-trigger is absent as the REM-ON cells produce a strong antagonistic signal of the S signal, which is used to trigger the REM events with the fast decreasing of the S signal. The hypothesis is that a REM episode begins when the REM-ON signal overcomes a predefined threshold.

The simulation carried out using the parameter values indicated in [9] produces less REM episodes than the ones which are present in a healthy young person. Changing, even to a small amount these parameters, the output changes its behaviour, as in chaotic-

deterministic systems. Moreover, experimental data on healthy young people show that the length of the REM episodes increases during sleep and that the first NREM phase is shorter than the following ones, but this model doesn't reflect these aspects.

3. The new integrated model

The present model aims to overcome the problem of the integrated model described above which, however, remains the most physiological one. In our model we maintain the idea that the ultradian oscillator, specifically the REM-ON signal, causes the REM-NREM triggering, and the idea to integrate the two process model and the limit cycle model.

The main difference with the previous model is in the determination of the triggering threshold over which the REM-ON signal causes the beginning of a REM episode. We chose to take the S signal as a variable threshold (after a specific scale correction).

4. Results

Fig. 1 represents a complete output of the model after a simulation which uses the parameters values indicated in the previous models. The X-axis represent time (in minutes) and Y-axis represent the signals in legend with scale corrections to make the result comparable. In the figure is clear that the decreasing profile of the S signal causes the decrease of the intersection level with the REM-ON signal. This decrease causes a progressive increase of REM episode length.

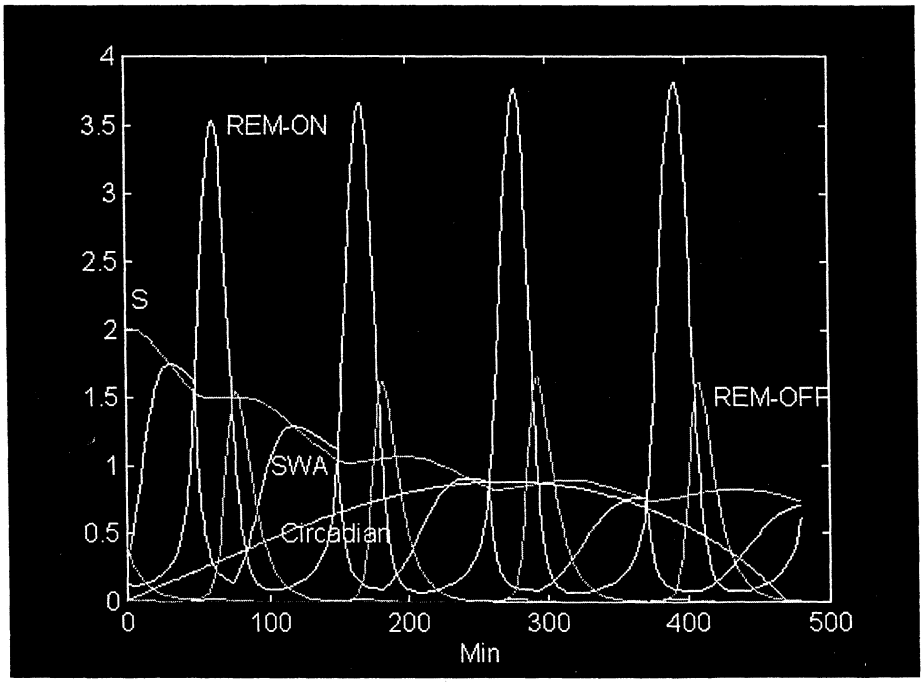

Fig. 1: The following signals are shown: REM-ON, S, SWA, REM-OFF, circadian process. These signals are obtained as outputs of the integrated model.

The shortness of the first NREM episode is also obtained with this model, and this is more evident in fig. 2, which is a simplified version of the previous graph, where only the S and the SWA signal are shown. This has been done to make NREM episodes easy to be detected visually. According to the proposed model a NREM episode results from the fact that the SWA signal is greater or equal to the S signal.

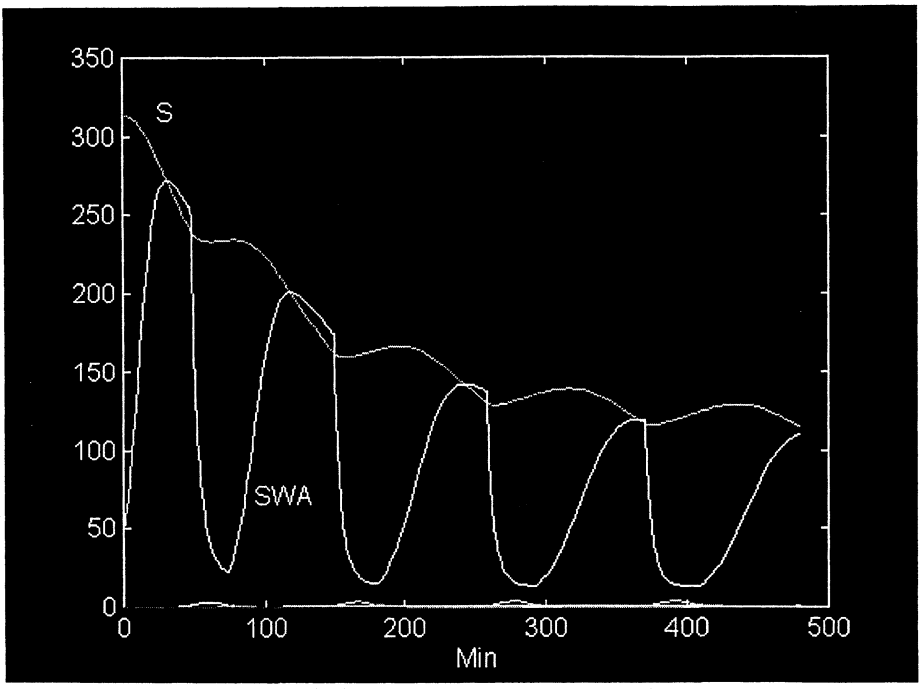

Fig. 2 S signal and SWA signal shown in fig. 1

5. Conclusions

The simulations with the presented model obtain behaviours of the system which are both nearer to the behaviours observed in healthy young people (fig. 3) and more stable than the behaviours obtained with all previous models.

Future work will be in the direction of clinical use of this model in the study of narcolepsy, where the patient has to sleep more frequently than a healthy person, begins to sleep directly in a REM phase, and has longer REM episodes. We think that these features can derive from alterations of the REM-ON signal.

We need further work to determine both correct values for many model parameter, and a deep evaluation of the sensitivity of model behaviour to their variations.

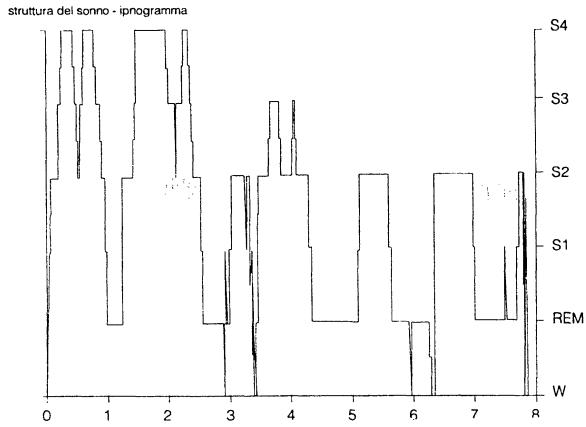

Fig. 3: Stages and phase of sleep in one night sleep in a young, healthy subject. From F. Ferrillo: "Struttura del sonno", in "Manuale medicina del sonno" (G. Coccagna, S. Smirne Eds.), UTET, 1993, Milano.

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