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DOUBLE-LAYERED MODELS CAN EXPLAIN MACRO AND MICRO STRUCTURE OF HUMAN SLEEP

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Abstract

The model simulates the activity of three neural populations using a Lotka–Volterra predator–prey system and, based on neuro-anatomical and neuro-physiological recent findings, assumes that a functional thalamo-cortical gate should be crossed by 'queuing' thalamic signals and that a sleep promoting substance acts as a modulator. The resultant activity accounts for the sleep stage transitions. In accordance with sleep cycles timing, the model proves to be able to reproduce the clustering and randomness of those peculiar transient synchronized EEG patterns (TSEP) described in normal human sleep and supposed to be related to the dynamic building up of NREM sleep until its stabilization against perturbations.

Keywords: EEG; sleep; nonlinear analysis; recurrence plot

1. Introduction

Brain activity results from the synchronization and interconnection of a huge number of neuronal assemblies. Such a complex interplay can be captured and detected by different technological tools, among which the most widely diffused and investigated is Electroencephalography (EEG). EEG signals are known to be altered in various neurological and psychiatric disorders, such as Alzheimer's disease, epilepsy and seizures, coma, schizophrenia, attention deficit etc., all such anomalies being related to abnormal cortex functionality or cortical-subcortical connectivity[1–3].

Sleep is an active and complex process usually investigated through the analysis of EEG signal frequencies (EEG rhythms), detected during polysomnographic recordings. The so-called macrostructure of physiological sleep (sleep stages), according to Rechtschaffen and Kales (RK) criteria[4], is characterized by a chain of regular and predictable events (cyclic alternation of NREM and REM sleep, 90–120min intervals among REM sleep periods, progression from stage 1 and stage 2 NREM sleep towards NREM slow wave sleep (SWS), prevalence of REM phases and stage 2 sleep during the second half of normal sleep.

The process, however, shows an intrinsic variability, since, in addition to circadian and homeostatic processes, several factors interfere with sleep induction and maintenance (mental state, acute or chronic disease, pain, muscle efforts, drugs, external environment). In this perspective sleep may be considered a dynamic process which has to finely modulate itself, and therefore the neurophysiological structures involved in this process should not exhibit a rigidly predetermined behavior, but rather maintain the maximum adaptability although preserving sleep macrostructure.

Determinants of such 'macrostructure preservation' are supposed to be a family of neurons distributed in the hypothalamus and brain stem[5–7]. Starting from the pioneering paper[8], which is obsolete on the biological ground but had the merit of suggesting a meaningful phenomenological mathematical approach, the interplay between such neuronal populations can be described by a system of ordinary differential equations in which a variable number of actors were competing with each other according to the classical Lotka–Volterra predator–prey population system.

Modulation of sleep induction and persistence is performed by the interaction between circadian rhythms and homeostatic needs. Sleep homeostasis is thought to be modulated by a number of substances including peptides (tumor necrosis factor alpha (TNF-), insulin and growth hormone (GH)) and small molecules such as nitric oxide and adenosine.

The last one is thought to be the most powerful endogenous (and possibly astrocyte-regulated) sleep promoter[9] against which caffeine is known to be effective.

'Adaptability' and 'stability' of NREM sleep, on the contrary, is related to the so-called EEG sleep microstructure. Among these EEG activities, peculiar transient synchronized EEG patterns (TSEP) are supposed to be the expression of EEG synchronizing mechanisms of cortical neurons (which has been proved to be achievable in high dimensional chaotic neural networks[10]) that accompany the dynamic building up, organization and stabilization of NREM sleep, ensuring flexible adaptation against perturbations. TSEP include: (a) high voltage, low frequency components of the Cycling Alternating Pattern (CAP)[11–13]; (b) high voltage, low frequency component of K-complexes; (c) transient delta bursts. The last two EEG patterns may be encompassed in CAP sequences. During normal sleep TSEP are progressively grouping in recurring clusters, until steady slow wave sleep (SWS), expression of maximal EEG synchrony and deep sleep, is reached.

Although TSEP are detected from the cortex, in addiction to local cortical phenomena[14], various evidences are accumulating about the existence of a generating thalamo-cortical network. The latter has been extensively studied as well[15,16]. In particular Kim *et al.*[17] studied an *in vitro* preparation of sagittal slices of the ferret dorsal lateral geniculate nucleus and showed that spindle waves occurring spontaneously in any part of the preparation were able to collide and therefore produce some sort of synchronization and could propagate through the thalamus exhibiting a relative refractory period between 7 and 14 s. Starting from these results, several other confirmations have been accumulated. According to Astori *et al*.[18] specific neural populations in the nucleus reticularis thalami act as an oscillatory burst

generator or ‘pacemaker’ randomly generating spikes in the low frequency range (4–10Hz) by abundantly expressing CaV 3.3 protein.

Also Crunelli *et al.*[19] showed evidences that the thalamic low-threshold Ca2+ potential generates the slow (< 1Hz) sleep oscillation in the thalamo-cortical network.

A crucial role is then played by the structures which limit, or even disrupt, signal transmission from the periphery to the cortex, where TSEP are actually detected.

The study by Esser *et al.*[20] further investigates such ‘cortical gate’, on the basis of a concept previously suggested by other authors[15], and produced by the hyperpolarization of thalamo-cortical neurons which reduce their firing in response to a prethalamic activation, accounting for many possible mechanisms. They conclude that neuronal connectivity is progressively reduced in Slow Wave Sleep, delaying signal transmission.

Refractory periods in the cortex, supposed to be determined by the thalamic nuclei, have already been shown to play an important role in synchronization[21].

Our study aims at developing a model based on double-layered interacting structures able to reproduce the interaction between sleep macro- and microstructures related to sleep stage transitions and sleep maintenance.

Although we know that such an euristic model cannot exhaust the almost infinite modeling options, we think it may be useful because easily managed with the Recurrence Plot mathematical approach. Further refinements are however required to make it more realistic and better resemble the signals recorded by EEG. The wake–sleep cycle and its regulation are not included in the present model, which exclusively focuses on the different stages of sleep, after sleep onset.

2. A Model Based Description of Sleep Macrostructure

We investigate a system of three ordinary differential equations in which three formal neuronal populations are activated and regulated according to the classical Lotka–Volterra predator–prey system of population theory. These formal populations represent the collective activities of real neuronal populations described in literature[6] and were defined: ‘REM ON’ (corresponding to neuron populations active during REM phases), ‘MnPN’ (corresponding to the median preoptic nucleus, which shows activity at the beginning of NREM sleep, progressive reduction of activity until the end of NREM sleep, increased activity during REMphase concomitantly with REM ON inhibition) and ‘Tal’ (resulting activity of thalamic populations projecting to cortex, during sleep). It reads:

$$\begin{cases} Tal & = Tal(e - sRemOn) \\ RemOn & = RemOn(a - bMnPN + gTal) \\ MnPN & = MnPN(-m + cRemOn), \end{cases} \tag{1}$$

where *a*, *b*, *c*, *e*, *g*, *s* represent biological parameters, suitably chosen so that solutions oscillate and provide five peaks of REM sleep during the eight sleeping hours.

The system stability is given by the eigenvalues of the Jacobian, which reads:

$$J = \begin{vmatrix} e - s * Tal & -s * RemOn & 0 \\ g * RemOn & a - b * MnPN + g * Tal & -b * RemOn \\ 0 & c * MnPN & -m + c * RemOn \end{vmatrix} \quad (2)$$

at the equilibrium points of (2). The latter are the origin P1 = (0, 0, 0, 0) and the point (0, *m/c, a/b*) which are locally unstable resulting in system oscillation.

Their values were selected as:

$a = 8*10^{-4}$, $b = c = 10^{-3}$, $m = 7*10^{-4}$, $g = s = 1.2*10^{-3}$ and $e = 8*10^{-4}$.

Figure 1 shows the oscillatory pattern obtained with the above choice of the parameter values. Green lines correspond to NREM periods, black lines correspond to REM phases.

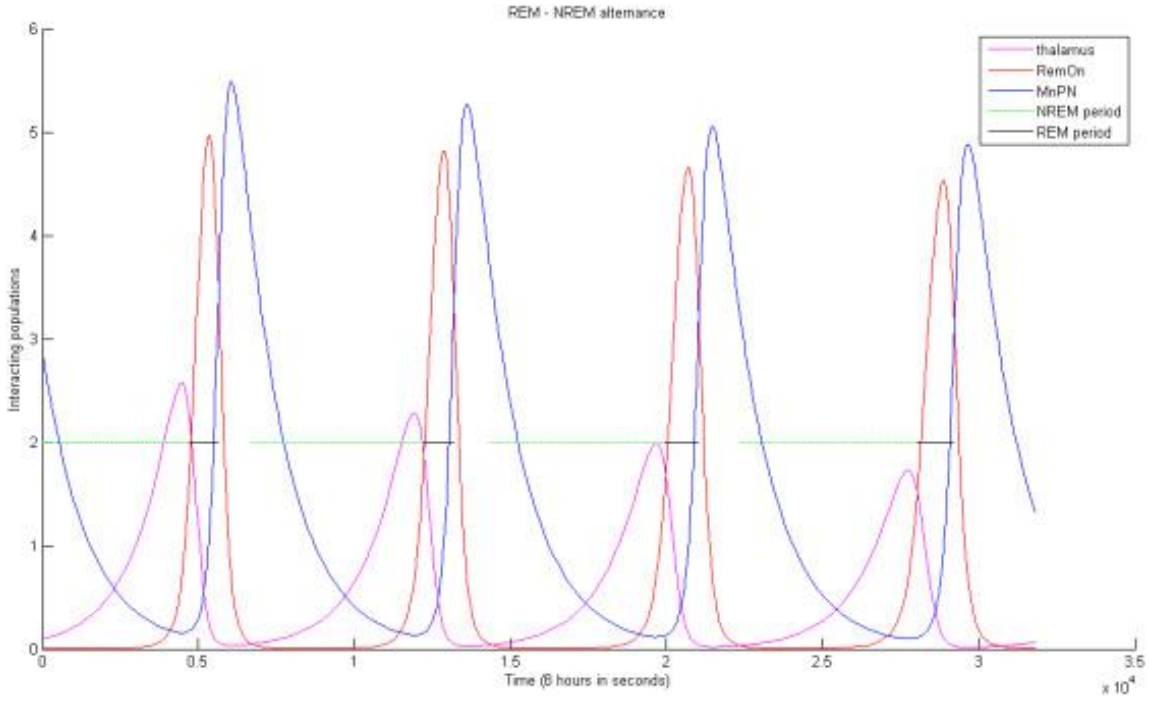


Fig. 1. (Color online) Plot of the temporal oscillations of the state of activation of the three neuronal populations REM ON, MnPN and Tal as solution of Eq. (1).

As it is clearly evidenced, the duration of a single REM period progressively increases proceeding from the first to the later sleep cycles (black lines), while the peak activity of thalamic population slowly decreases.

The above features are observed and characterize healthy human sleep, and it is noteworthy that both derive from the model without any '*ad hoc*' assumption or the imposition of thresholds or boundaries, except the temporal adaptation of five REM peaks during the eight sleeping hours, in order to conform human species.

3. A Model-Based Description of Sleep Microstructure

The microstructure of sleep is related to both the activity of the thalamic pacemaker and the signal modulation occurring at the cortical gate, which can be simulated using different mathematical approaches relying on the idea of 'colliding bumps'[22] or local architectures[23].

Figure 2 describes the scheme simulated by the present model:

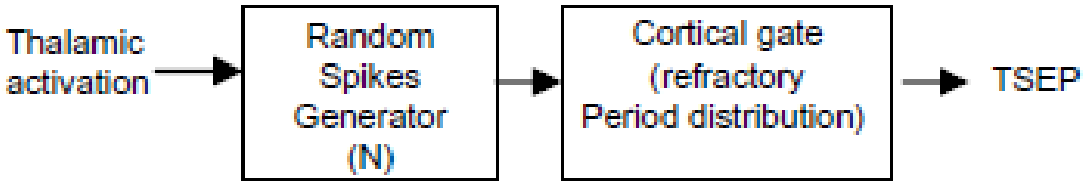


Fig. 2. Sketch of the model simulation of the cortical gate.

The Random Spikes Generator (RSG) activated following the thalamic activation *Tal* (*t*) has been modeled accounting for *N* (from 1 to 7) subpopulations generating spikes at different frequencies. It is well known that information transfer in biological neurons, i.e. via the precise timing of spikes or a sequence of spikes is so efficient that inspired many Artificial Neural Networks (SNNs) computational approaches[24] and even practical applications such as the control of robotic arms[25].

Since in human sleep the clustering capability of TSEP decreases from the first to the last NREM sleep period (i.e. time intervals between two successive TSEP become greater and TSEP appear more randomly distributed), we assume that the thalamiccortical gate is influenced by the progressive inactivation of some sleep-promoting substance (SPS)[6,9].

In particular, our model assumes that SPS concentration exponentially decreases along sleep. Accordingly, the number *N* of randomly oscillating thalamic neuronal subpopulations activated at the beginning of each NREM sleep decreases from 7 (1st phase) to 4 (last phase). Each spike generated by the RSP crosses the cortical gate, therefore producing a cortical TSEP, provided:

I. its magnitude is larger than a given threshold [= 0.6]
II. only NREM periods occur
III. it experiences a delay *m* Δ being *m* the number of signals queuing at the cortical gate (which depends on the number *N* of thalamic subpopulations activated at that time) and Δ(*t*) the delay:

$$\Delta(t) = \frac{\max(Tal(t))}{Tal(t)}. \qquad (3)$$

Tal (*t*) being the level of activation of the thalamus (defined by Eq. (1)) and max (*Tal* (*t*)) being its maximum value in that specific NREM sleep phase).

As an example of the final result, Fig. 3(a) shows a simulation reproducing on the horizontal axis the time in s and on the vertical axis the intervals of two successive cortical TSEP (blue) detected beyond the cortical gate and generated by a number N (N = 5 − 7) of randomly oscillating thalamic neuronal subpopulations.

Figure 3(b) shows the corresponding plot derived from TSEP time series detected in normal human sleep. TSEP clustering (evidenced with arrows), in normal sleep may be temporarily interrupted by arousals or complete awakenings (evidenced with black asterisk), so that the process has to start again. During REMphases (horizontal black lines) sequence of TSEP are not present.

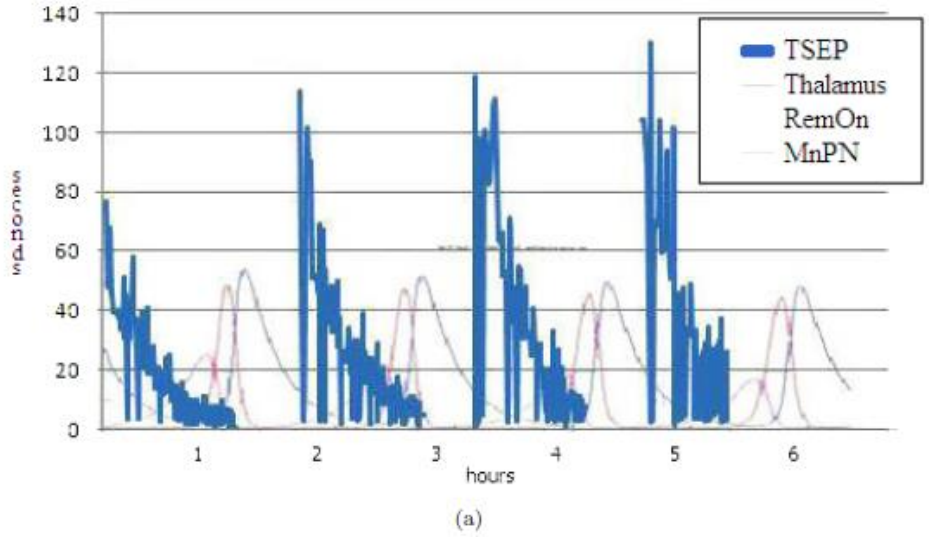


Fig. 3. (Color online) Plot of (a) the prediction of the TSEP detected in the cortex according to Eqs. (1) and (3) and (b) data recorded from a healthy young patient. Each point corresponds to the TSEP–TSEP interval of two consecutive TSEP, expressed in seconds (y-axis), during sleep time (x-axis). Horizontal black lines correspond to REM periods.

4. Multiscale Representation of TSEP Time Series and Comparison with Experimental Data

To produce an effective representation of both the sleep macrostructure and sleep microstructure as generated by the brainstem-hypothalamic neural populations and thalamo-cortical interactions, a 'multiscale' approach is needed. Many nonlinear approaches, as the so-called higher order spectra (HOS), has been proposed so far[26] and proved effective in discriminating normal, interictal, and epileptic EEG segments[27].

The above techniques have already been proposed to analyze EEG signals[28–32] in both the wake and the sleep states, and have been used to evaluate sleep microstructure, i.e. TSEP time series[33]. It also showed useful to effectively classify seizures in epilepsy[34].

Phase-space plots can be produced by reporting the time series given by the successive TSEP–TSEP intervals.

Figure 4a shows the plot obtained by activating the thalamic random spike generator with $N = 7$ different frequencies.

In order to compare them with their experimental counterparts, in Fig. 4(b) the phase portrait of the sleep of a healthy young men is reported[35,36]:

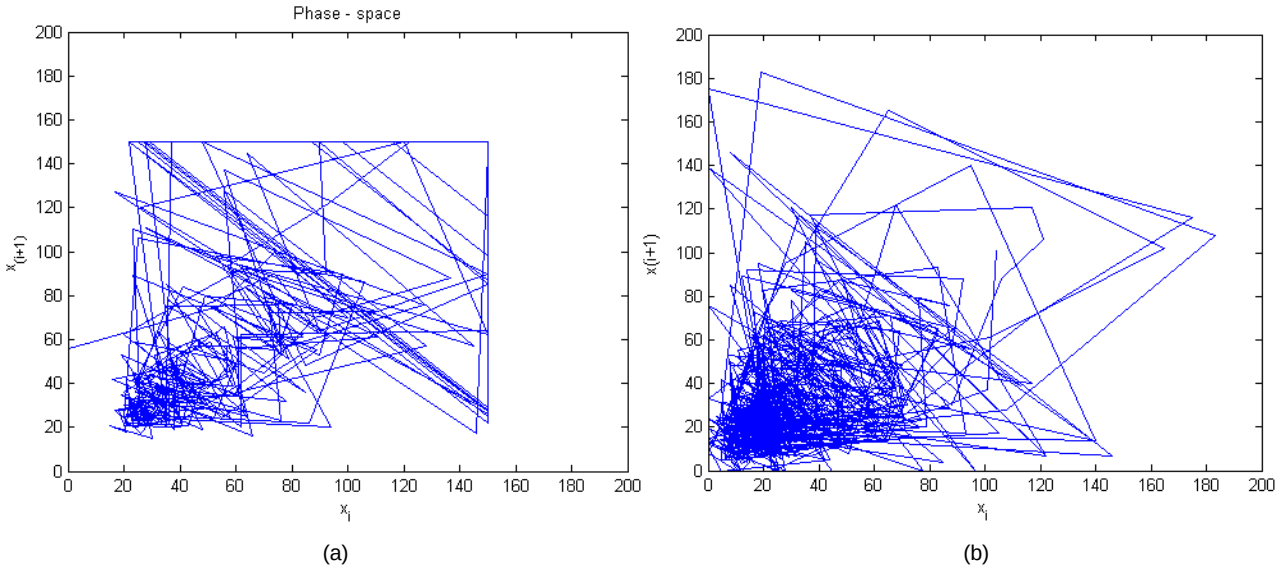


Fig. 4. Phase space plot of the TSEP–TSEP intervals obtained by (a) model simulation and (b) data recorded from a healthy young patient.

An "attractor" corresponding to inter-TSEP intervals of about 20–40 s is present in real data and is reproduced by our model.

Complex phenomena, however, should usually be described using higher-dimensional phases by means of the so-called Recurrence Plot (RP).

Given the discrete time series *ui* = *u*(*i*Δ*t*), where *i* = 1*, . . .,N* and Δ*t* is the sampling rate of the measurement, the phase space can be reconstructed using the time delay (or "delayed coordinate embedding") method,

$$x_i = \sum_{j=1}^{m} u_{i+(j-1)\tau} e_j, \qquad (4)$$

where *m* is the embedding dimension, τ is the time delay and e_j the space eigenvectors, which need to be appropriately chosen. The recurrences of a trajectory $\vec{x}_i \in \mathbb{R}^d$ in phase space are currently visually inspected using RPs. Provided the distances

$$D_{ij} = \|x_i - x_j\| \qquad (5)$$

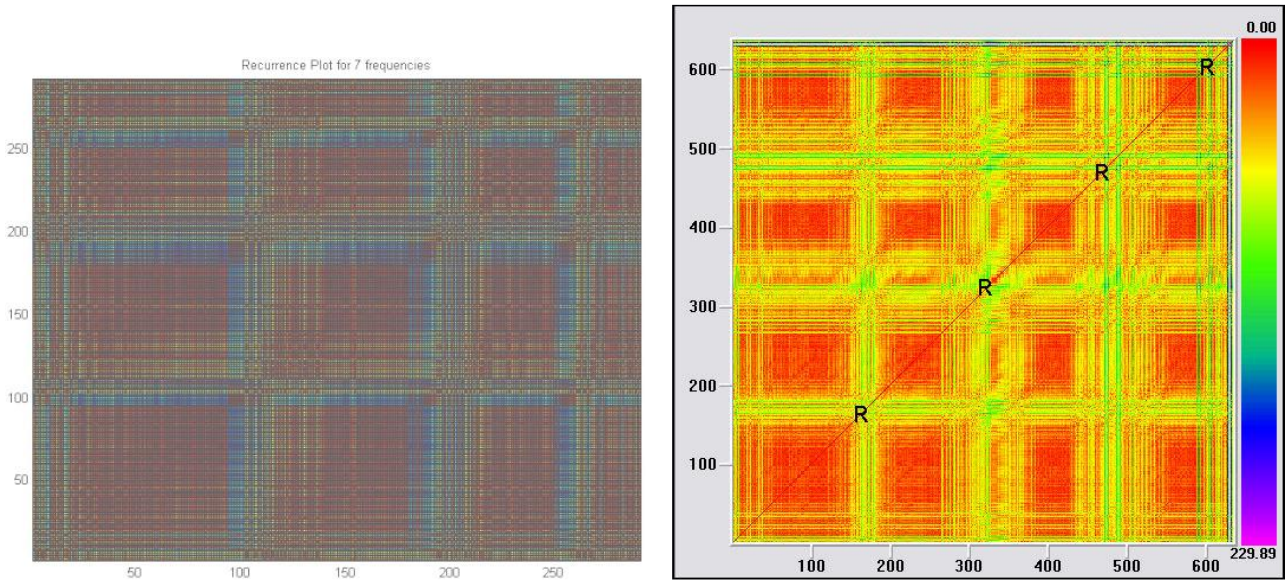
are plotted, the *global recurrence plot* or *unthresholded recurrence plot*[24–32] is obtained.

As a pictorial and qualitative indication of the presence of recurrences in the dataset, the unthresholded RP is plotted, using a representation of colored dots (*i*; *j*), where "hot" colors (red, orange and yellow) mark recurrence points associated with small distances (i.e. the *j*th point *p*(*j*) of the trajectory into the neighborhood of the given *i*th point *p*(*i*)), while "cold" colors (blue, violet) are used to show larger distances. Each point is plotted against itself along the *x* = *y* line, thus the RP is symmetric with respect to this diagonal.With these rules constructed RP corresponds to a two-dimensional colored representation of recurrences occurring in the original time series of inter-TSEP-intervals, thoughout NREM sleep cycles, regardless any *a priori* knowledge of the underlying dynamics. In some specific applications it is also possible to compensate for temporal distortions of repeated measurements in eventrelated potential research[37].

Figure 5(a) shows the RP obtained by the same data of Fig. 4(a). The selected embedded dimension is *m*= 40 and the time delay is equal to 30.

The prevalence of NREM sleep and the thalamocortical activity responsible for the progressive clustering of TSEP is well shown by the short-scale structure in 'hot' colors, which characterizes earlier sleep cycles, while the increase of REM duration and the progressive reduction of TSEP capability to cluster, evidenced by the blue and green color, is mainly present in later sleep cycles.

A similar pattern is shown by the RP produced by the time series of TSEP obtained during human sleep[33,36] (see Fig. 5(b)). In physiological conditions, as explained, TSEP clustering corresponds to a rapid and efficient achievement of deep sleep. The presence of interruptions of red color pattern during NREM sleep, indicating temporary disruption of TSEP clustering, corresponds to movements, arousals or complete awakenings normally present in human sleep.



(a) (b)

Fig. 5. (Color online) Recurrence plot obtained by (a) model simulation, the same time series used for Fig. 3(a) and (b) data recorded from a healthy young patient, the same time series used for Fig. 3(b). REM phases are indicated with 'R'. Dots color ranges from red for smallest inter-point distances in the phase space (shortest TSPE–TSPE intervals), to blue-violet for largest spacing (largest TSEP–TSEP intervals).

5. Discussion and Conclusion

In the present paper we developed a mathematical model based on up-to-date neuro-physiological knowledge. It describes the activity of neural populations using a simple Lotka–Volterra predator–prey system accounting for REMON,MnPN (which sends REM OFF signals) and Tal (thalamic) neuronal populations. Such a model, although simpler with respect to the four-populations model previously proposed[6,30] proves to be able to generate TSEP clustering and randomness comparable to those evidenced in normal human sleep. To our knowledge, this is the first attempt to create a mathematical model of this peculiar aspect of sleep microstructure. In fact it can predict: (a) higher 'strength' of clustering at the beginning of each NREM phase and loss of this capability just before the onset of REM; (b) the prevalence of NREM sleep stages during earlier sleep cycles; (c) the increase of REM duration concomitantly with progressive reduction of TSEP capability to cluster during later cycles, when the need of NREM sleep is almost over.

To predict the appearance and the formation of TSEP clusters, we assume that a functional thalamocortical gate exists and actively modulates cortical activity as documented by EEG signals. Such a hypothesis is very well founded on the basis of neuroanatomical and neuro-physiological recent findings, and is modeled assuming that signals queue to cross the gate and the corresponding delays actually build up TSEP clustering throughout overnight NREM sleep cycles.

A more realistic result is obtained by assuming also that the concentration of a sleep-promoting substance plays a role in modulating the activity of the thalamic neuronal subpopulations actually discharging during sleep.

Effective graphical representation of the different time scales present in the model requires the use of phase-space plots and recurrence plots. The latter is particularly suitable to

evidence recurrences occurring in the original time series of inter-TSEPintervals, also permitting comparison between the model results and the correspondent experimental findings in humans.

At this stage of development our model only refers to event recurrences, regardless of signal morphology. Nevertheless, to our knowledge, this is the first attempt in literature to reproduce the dynamics of real TSEP occurrences, included in a sleep model. In other words the model reproduces the “behavior” of TSEP in the building-up of NREM sleep, not their exact onsets which always differ from one sleep to another, as expected by a typical dynamic process. Further integrations will be directed towards the quantitative analysis, the inclusion of wake and wake-cycle regulation into the model, and the definition of amplitude and duration parameters, in order to characterize signal morphology.

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