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Sleep and wakefulness neurophysiology: A behavioural neuroscience-related model for the sleep-wake 2D NREM-REM alternation system cycle

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ABSTRACT

In this study, we try to give fundaments to neurophysiologic patterns of a two-phase model of the sleep-wake cycle through implementation of a closed-loop biological system. Some biological assumption are taken into account, mainly different neuron groups different discharge profiles, firing rates and inhibit sleep-promoting behaviours during NREM and REM sleep.

KEYWORDS

Sleep-wake cycle;
Neurophysiologic patterns;
NREM sleep;
REM sleep.

INTRODUCTION

Most of the available sleep-wake models are based on the seminal two-process models of sleep regulation, which were conjointly developed by Daan *et al*.[1] and Borbély[2]. Such models state that sleep and wakefulness dynamics are governed by two basic mechanisms: a circadian process that modulates time-dependent sleep pressure[3] and a homeostatic process that builds and dissipates pressure for sleep during wakefulness and sleep periods, respectively[4].

The past three decades have brought meaningful progress in identifying the neural fundaments of sleep regulation[5-10]. The present model is based on a selective choice of relevant neuron groups involved in a hypothalamic sleep-wake switch along with the concept of the arithmetical difference. This concept states that waking neurobehavioral functions can be predicted through arithmetical differences between the sleep-related and wakefulness-related respective homeostatic and circadian pressures. The resolution of the enhanced governing equations system has been carried out using an experimented and widely discussed polynomial scheme.

MATERIALS AND METHODS

The works of Boissard *et al*.[7], Phillips *et al*.[8] and Plazzi, *et al*.[9] stressed that five groups of neurons have the determinant roles in the NREM-REM alternation scheme. Basal forebrain GABAergic neurons, VLPO (GABA,GAL) i. e., are assumed to be sleep-promoting neurons according to their discharge profiles, while neurons in LC/DR, and PPT/LDT seem to have similar and relevant discharge features and important regulating roles according to their loci and neurotransmitter nature[11-13]. The main neuronal groups interaction scheme is presented in Figure 1.

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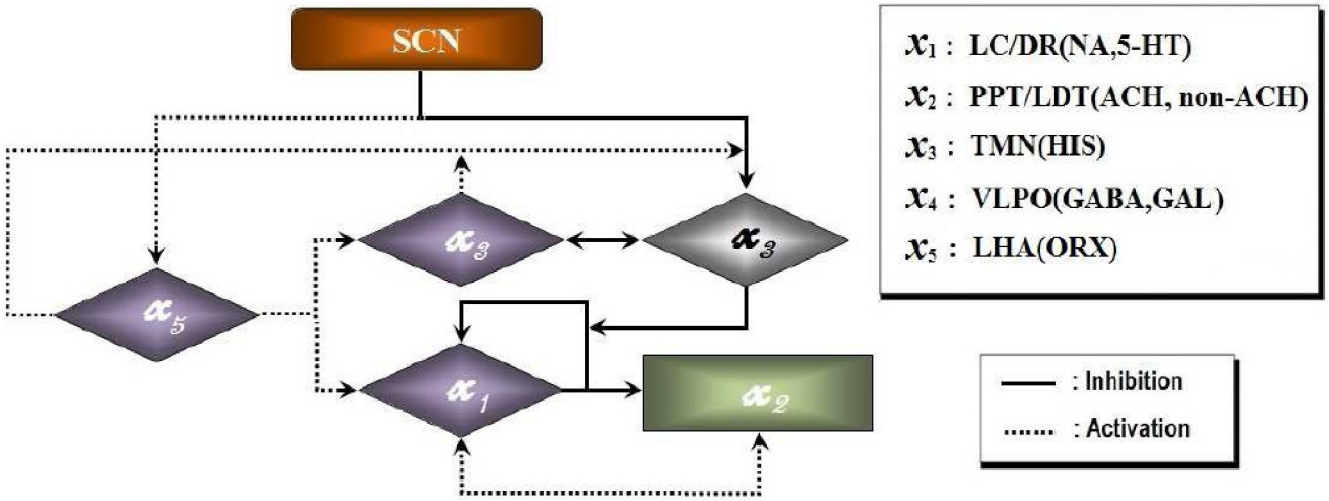

Figure 1 : System global scheme

The presented model lies on an ODF system:

$$\begin{cases} \frac{dx_1}{dt} = a_1 x_1^{\varepsilon_{11}} x_2^{\varepsilon_{12}} x_4^{\varepsilon_{14}} - b_1 x_1 \\ \frac{dx_2}{dt} = a_2 x_1^{\varepsilon_{21}} x_2^{\varepsilon_{12}} - b_2 x_2 \\ \frac{dx_3}{dt} = a_3 x_4^{\varepsilon_{34}} x_5^{\varepsilon_{35}} - b_3 x_3 \\ \frac{dx_4}{dt} = a_4 x_1^{\varepsilon_{41}} x_3^{\varepsilon_{43}} - b_4 x_4 \\ \frac{dx_5}{dt} = a_5 - b_5 x_5 \\ \text{with :} \begin{cases} x_1 : \text{ratio in the group LC/DR(NA,5-HT)} \\ x_2 : \text{ratio in the group PPT/LDT(ACH, non-ACH)} \\ x_3 : \text{ratio in the group TMN(HIS)} \\ x_4 : \text{ratio in the group VLPO(GABA,GAL)} \\ x_5 : \text{ratio in the group LHA(ORX)} \end{cases} \end{cases} \quad (1)$$

where $a_i|_{i=1..5}$ and $b_i|_{i=1..5}$ are model's constants and $x_i|_{i=1..5}$ represent the average firing activity (Figure 2)

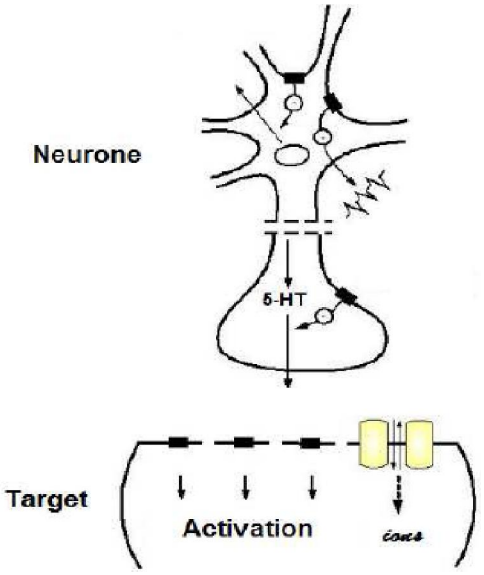

Figure 2 : Neurone firing scheme example

inside a of one neuron group, or ratio of activated neurons (Figure 1) among a given neuronal group ($0 \le x_i \le 1$).

According to the biological meanings of $\varepsilon_{ij}|_{i=1..4, j=1..5}$, the condition $\varepsilon_{ij} = 0|$ is equivalent to a situation of no-projection between neurones with ratios x_i and x_j. The overall biological conditions on these coefficients are gathered in TABLE 1.

TABLE 1 : Biological conditions for coefficients $\varepsilon_{ij}|_{i=1..4, j=1..5}$, $a_i|_{i=1..5}$ and $b_i|_{i=1..5}$

Parameter	ε_{11}	ε_{12}	ε_{14}	ε_{15}	ε_{21}	ε_{22}	ε_{34}	ε_{35}	ε_{41}	ε_{43}	a_i	b_i
Condition	<0	>0	<0	>0	<0	>0	<0	>0	<0	<0	>0	>0

INVESTIGATIONS AND RESULTS

For given values of the coefficients $\varepsilon_{ij}|_{i=1..4, j=1..5}$, $a_i|_{i=1..5}$ and $b_i|_{i=1..5}$, the resolution of Eq. (1) is carried out using the Boubaker polynomials Expansion Scheme BPES.

The BPES[14-33] is applied through setting the expressions:

$$x_i(t) = \frac{1}{2N_0} \sum_{k=1}^{N_0} \lambda_{k,i} \times B_{4k}(r_k t) \quad (2)$$

where B_{4k} are the *4k*-order Boubaker polynomials, t is the normalized time, r_k are B_{4k} minimal positive roots, N_0 is a prefixed integer, $\lambda_{k,i}|_{\substack{k=1..N_0 \\ i=1..5}}$ are unknown pondering real coefficients. Consequently, it comes for Eq. (1) that:

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$$\begin{cases}
\sum_{k=1}^{N_0}\lambda_{k,1}\times r_k\dfrac{dB_{4k}(r_k t)}{dt}= \\
\quad \dfrac{1}{4N_0^2}a_1\left(\sum_{k=1}^{N_0}\lambda_{k,2}B_{4k}(r_k t)\right)^{\varepsilon 11}\left(\sum_{k=1}^{N_0}\lambda_{k,1}B_{4k}(r_k t)\right)^{\varepsilon 12}\left(\sum_{k=1}^{N_0}\lambda_{k,4}B_{4k}(r_k t)\right)^{\varepsilon 14}-b_1\left(\sum_{k=1}^{N_0}\lambda_{k,1}B_{4k}(r_k t)\right) \\
\sum_{k=1}^{N_0}\lambda_{k,2}\times r_k\dfrac{dB_{4k}(r_k t)}{dt}=\dfrac{1}{2N_0}a_2\left(\sum_{k=1}^{N_0}\lambda_{k,1}B_{4k}(r_k t)\right)^{\varepsilon 21}\left(\sum_{k=1}^{N_0}\lambda_{k,2}B_{4k}(r_k t)\right)^{\varepsilon 12}-b_2\left(\sum_{k=1}^{N_0}\lambda_{k,2}B_{4k}(r_k t)\right) \\
\sum_{k=1}^{N_0}\lambda_{k,3}\times r_k\dfrac{dB_{4k}(r_k t)}{dt}=\dfrac{1}{2N_0}a_3\left(\sum_{k=1}^{N_0}\lambda_{k,4}B_{4k}(r_k t)\right)^{\varepsilon 34}\left(\sum_{k=1}^{N_0}\lambda_{k,5}B_{4k}(r_k t)\right)^{\varepsilon 35}-b_3\left(\sum_{k=1}^{N_0}\lambda_{k,3}B_{4k}(r_k t)\right) \\
\sum_{k=1}^{N_0}\lambda_{k,4}\times r_k\dfrac{dB_{4k}(r_k t)}{dt}=\dfrac{1}{2N_0}a_4\left(\sum_{k=1}^{N_0}\lambda_{k,1}B_{4k}(r_k t)\right)^{\varepsilon 41}\left(\sum_{k=1}^{N_0}\lambda_{k,3}B_{4k}(r_k t)\right)^{\varepsilon 43}-b_4\left(\sum_{k=1}^{N_0}\lambda_{k,4}B_{4k}(r_k t)\right) \\
\sum_{k=1}^{N_0}\lambda_{k,5}\times r_k\dfrac{dB_{4k}(r_k t)}{dt}=2N_0a_5-b_5\left(\sum_{k=1}^{N_0}\lambda_{k,5}B_{4k}(r_k t)\right)
\end{cases} \quad (3)$$

The BPES protocol ensures the validity of the related boundary conditions expressed through biological conditions, regardless main equation features. In fact, thanks to Boubaker polynomials first derivatives properties:

$$\begin{cases}\sum_{q=1}^{N}B_{4q}(x)\Big|_{x=0}=-2N\neq 0; \\ \sum_{q=1}^{N}B_{4q}(x)\Big|_{x=r_q}=0;\end{cases} \quad (4)$$

and:

$$\begin{cases}\sum_{q=1}^{N}\dfrac{dB_{4q}(x)}{dx}\Big|_{x=0}=0 \\ \sum_{q=1}^{N}\dfrac{dB_{4q}(x)}{dx}\Big|_{x=r_q}=\sum_{q=1}^{N}H_q\end{cases} \quad (5)$$

$$\text{with : } H_n=B'_{4n}(r_n)=\left(\frac{4r_n[2-r_n^2]\times\sum_{q=1}^{n}B_{4q}^2(r_n)}{B_{4(n+1)}(r_n)}+4r_n^3\right)$$

boundary conditions are inherently verified.

The BPES solution is obtained through four steps:

- ✓ Integrating, for a given value of N_0, the whole expressions given by Eq. (3) along time domain.
- ✓ Setting the subsequent five systems (for i=1… 5):

$$\begin{cases}\begin{pmatrix}\theta_{1;1} & .. & .. & \theta_{1;N_0}\\ .. & \theta_{2;2} & .. & .. \\ .. & .. & .. & .. \\ \theta_{N_0;1} & .. & .. & \theta_{N_0;N_0}\end{pmatrix}\begin{pmatrix}\lambda_{1,i}\\ \lambda_{2,i}\\ ..\\ \lambda_{N_0,i}\end{pmatrix}=\begin{pmatrix}\beta_1\\ \beta_2\\ ..\\ \beta_{N_0}\end{pmatrix}\end{cases} \quad (6)$$

with the matrix standard form:

$$\begin{cases}[\Theta]\times[\lambda]_i=[B] \\ \text{with : }[\Theta]=\begin{pmatrix}\theta_{1;1} & .. & .. & \theta_{1;N_0}\\ .. & \theta_{2;2} & .. & .. \\ .. & .. & .. & .. \\ \theta_{N_0;1} & .. & .. & \theta_{N_0;N_0}\end{pmatrix}; \\ [\lambda]_i=\begin{pmatrix}\lambda_{1,i}\\ \lambda_{2,i}\\ ..\\ \lambda_{N_0,i}\end{pmatrix};\qquad [B]=\begin{pmatrix}\beta_1\\ \beta_2\\ ..\\ \beta_{N_0}\end{pmatrix}\end{cases} \quad (7)$$

The system (7) is solved using Householder[34-36] algorithm, detailed in APPENDIX.

- ✓ Incrementing N_0.
- ✓ Testing the convergence of the coefficients $\lambda_{k,i}^{(Sol.)}\Big|_{\substack{k=1..N_0\\ i=1..5}}$.

The final result is hence (for N_0 = 79):

$$x_i(t)=\frac{1}{2N_0}\sum_{k=1}^{N_0}\lambda_{k,i}^{(Sol.)}B_{4k}(r_k t) \quad (8)$$

DISCUSSION

In this work, the first assumption consisted of considering the circadian rhythm as a 24-hour periodic external signal for NREM-REM alternations. The circadian signal, which is originated in the supra-chiasmatic nucleus (SCN), serves as the brain's master clock (Figure 1), as it establishes the 24-hour rhythm for all other physiological rhythms in the organism[37-39].

For reaching a full understanding of the neuronal

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activity profiles, the five neurons groups have been distinctively characterized. Noradrenaline (NA) neurons are localized in the locus ceruleus (LC) of the pons and they have the highest firing rate during wakefulness, decrease their firing rate in NREM sleep and almost cease firing in REM sleep[38]. They do not only act as wake-promoters, but also take part in the system permitting REM sleep by suppressing the cholinergic REM-ON neurons in brainstem. Serotonin (5HT) neurons are located in the dorsal raphe nucleus (DR) and are more active during wakefulness than sleep. PPT/LDT group gathers REM-ON acetylcholinergic and monoaminergic REM-OFF neurons with several subtypes of neurons having different discharge profiles and which reciprocally interact resulting in the ultradian alternation of mammalian REM and NREM sleep. Histamine (HIS) neurons are located in the tubero-mammillary nucleus (TMN) of the posterior hypothalamus. They play a major role in maintenance of wakefulness and turn off during REM sleep. VLPO neurons are situated in the hypothalamic preoptic area (POA) and are strongly activated in response to increasing sleep amount. Finally, Orexin neurons are distributed in a restricted region of perifornical region of the lateral hypothalamus. They are responsible of activating, during the entire wake period, a panoply of ascending aminergic transmitter systems implicated in the regulation of arousal, including serotonergic, noradrenergic, cholinergic, histaminergic and dopaminergic systems[40].

Plots of the solution obtained with the present method are presented in Figures 3 and 4.

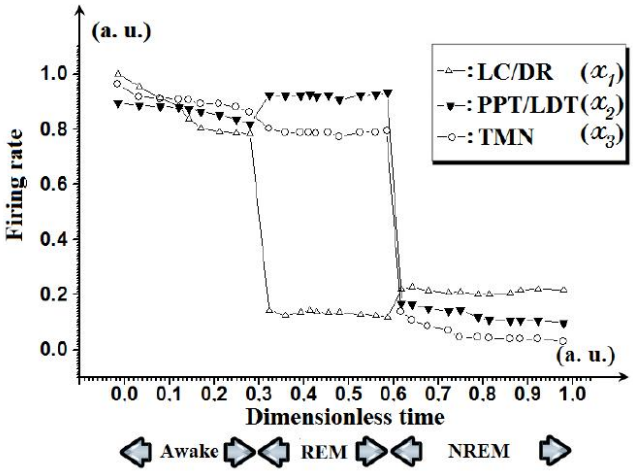

Figure 3 : Solution plots: Neurone firing rate during a whole period (x_1, x_2 and x_3)

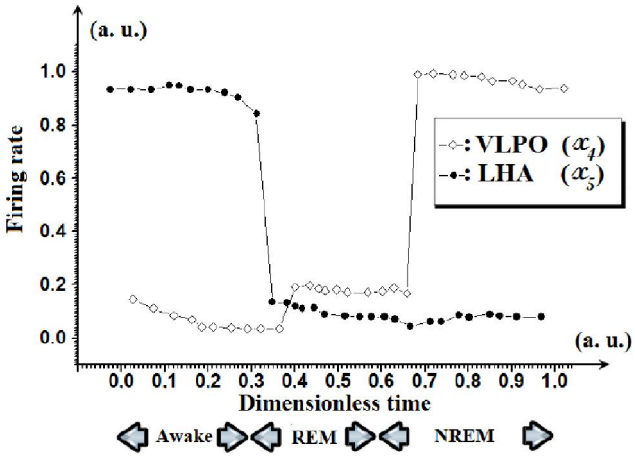

Figure 4 : Solution plots: Neurone firing rate during a whole period (x_4 and x_5)

It can be noticed that the activity of neurons in VLPO, which doesn't maintain a constant value, is at its apogee during NREM phase (Figure 4). This first feature is in good agreement with the results of Massimini *et al*.[37] and Tononi *et al*.[38,39] who recorded that there was a reciprocal inhibition between neurons in VLPO and LC/DR, the oscillations of REM-OFF (LC/DR) and REM-ON neurons affect the activity of VLPO and cause it to oscillate slightly (Figure 3, 4). A gradual decrease of the VLPO neurons activity during sleep has been also recorded.

A second noticeable feature is the duality between the Noradrenaline (NA) group and the 5HT- GABA groups. In fact, Nitz *et al*.[40] stated that NA neurons can be excited by ORX, ACH and HIS neurons and inhibited by 5HT and GABA in preoptic area. In the same context, Siegel[41] noted that Serotonin (5HT)

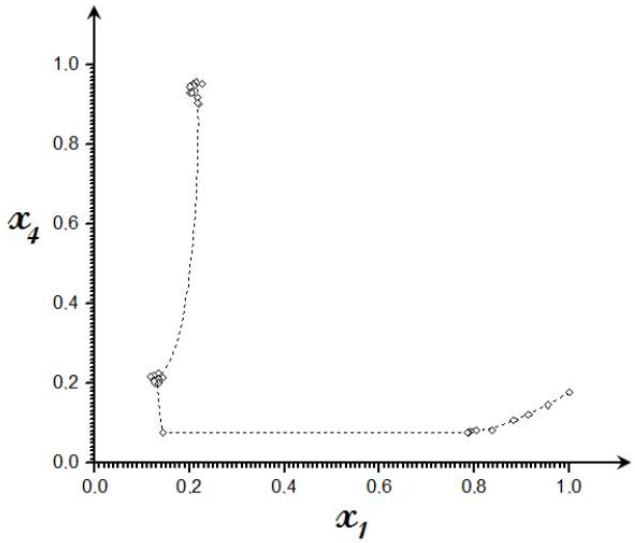

Figure 5 : Solution plots: Conjoint firing rate < represented in (x_1,x_4)-plane >

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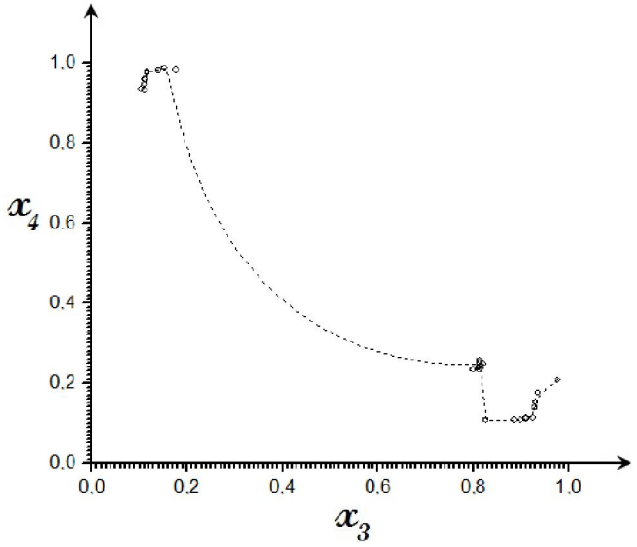

Figure 6 : Solution plots: Conjoint firing rate < represented in (x_3,x_4)-plane >

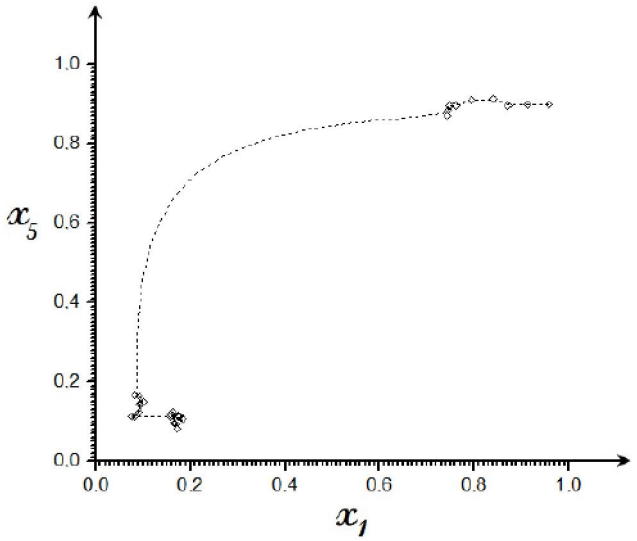

Figure 7 : Solution plots: Conjoint firing rate < represented in (x_1,x_5)-plane >

neurons can be excited by ORX, monoamine-containing neurons, such as HIS and NA and inhibited by GABA in brainstem and the preoptic area. For illustrating these patterns, additional binary diagrams have been performed, respectively, in (x_1,x_4), (x_3,x_4) and (x_1,x_5)-planes: (Figures 5, 6 and 7).

APPENDIX

Householder [algorithm consists of establishing a serial of orthogonal square arrays $[H]_\nu\big|_{\nu=1..M_0}$ defined, at a stage ν, by relation (A.1).

$$[H]_\nu = I_\nu - 2[U][U]^T = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & .. & 0 \\ 0 & .. & .. & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} - 2\begin{pmatrix} u_1 \\ u_2 \\ u_3 \\ .. \end{pmatrix}(u_1, u_2, u_3, ..) \quad \textbf{(A1)}$$

$$\text{with } [\Theta] = \overbrace{[H]_1[H]_2[H]_3...[H]_\nu}^{[\Omega]_\nu}[R], [U] = \frac{[\Theta]-[\Omega]_\nu}{\|[\Theta]-[\Omega]_\nu\|}, \text{and} \sqrt{\sum_{k=1}^{n} u_k^2} = 1$$

According to Householder algorithm, the array [H]ν verifies the triangulating relation:

$$[H]_\nu = \begin{pmatrix} \sqrt{\sum_{k=1}^{n} a_{k,1}^2} & a'_{12} & a'_{13} & .. \\ 0 & a'_{22} & a'_{23} & .. \\ 0 & a'_{32} & a'_{33} & .. \\ 0 & .. & .. & .. \end{pmatrix} \quad \textbf{(A2)}$$

Applying the same method to minor order remaining array [A]':

$$[A]' = \begin{pmatrix} a'_{22} & a'_{23} & .. \\ a'_{32} & a'_{33} & .. \\ .. & .. & .. \end{pmatrix} \quad \textbf{(A3)}$$

and to next minors leads to the final equation (A.4):

$$[A] = \overbrace{[H]_1[H]_2...[H]_\nu...[H]_{M_0}}^{[\Omega]_{M_0}}[R] = [\Omega]_{M_0}[R] \quad \textbf{(A4)}$$

with *** orthogonal and [R] upper triangle;

Equation (11) is easily solved by stepping back procedure since array [R] is upper triangular:

$$[\beta]_{sol} = [R]^{-1}[\Omega]^{-1}[B] = [R]^{-1}[\Omega][B] \quad \textbf{(A5)}$$

The convergence test is performed using the Minimum Square Method (MSM). This method consists of stopping iterations when the functional amount (A.6) is inferior to a preset standard value ε_0.

$$\| [A]\times[\beta]_{sol} - [B] \| \le \varepsilon_0 \quad \textbf{(A6)}$$

CONCLUSION

In this work we have tried to give to give fundaments to neurophysiologic patterns of a two-phase model of the sleep-wake cycle through implementation of a closed-loop biological system. Some biological assumption have been taken into account, mainly different neuron groups different discharge profiles, firing rates and inhibit sleep-promoting behaviors during NREM and REM sleep. Further studies should focus on the analysis of specific roles of each kind of neuron group in NREM-REM alterations with more comprehensive model structures.

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