Sleep-Awake Switch with Spiking Neural P Systems: A Basic Proposal and New Issues

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Summary. Spiking Neural P Systems are a kind of Membrane Systems developed with the aim of incorporating ideas from biological systems, known as spiking neurons, in the computational field. Initially, these systems were designed to take concepts of the neural science based on action potentials with the purpose of testing its possibilities from a computational point of view and not to be used as neurological models. In this work, a basic approach in the opposite sense is reviewed by means of the application of such systems on a well-known biological phenomenon. This phenomenon refers to the fluctuations among neural circuits which are responsible for swapping between awake-asleep states. This basic approach is analyzed and new issues are exposed.

1 Introduction

Sleep is a highly organized and actively induced cerebral state with different stages [11]. It has been observed two kinds of sleep: REM-sleep and non-REM sleep, each one with a number of specific features. Specifically, non-REM sleep comprises four stages. Each stage is defined according to its activity in the electroencephalogram (EGG). Stage 1 contains alternative periods of alpha activity (8-12Hz), irregular speed activity and theta activity (3.5-7.5Hz). Stage 2 does not show alpha activity in the EGG although in this stage appears a phenomenon called *sleep spindles* (bursts of 12-14Hz sinusoidal waves) and, sometimes, high-voltage biphasic waves called K complexes. Stage 3 consists of delta activity (less than 3.5Hz) during part of its time (20-50%) and stage 4 consists of delta activity during the most time (more than 50%). Approximately 90 minutes after sleep starts human beings fall in non-REM sleep which is characterized by rapid eye movements, unsynchronize EGG, a nearly complete inhibition of skeletal muscle tone (atonia). The brain temperature and metabolic rate are high, equal to or greater than during the waking state and some sexual activity can be present as well.

From a neural point of view, although sleep is controlled by the great part of the encephalon [4], there is a particularly important zone. It is the *ventrolat-*

eral preoptic nucleus (VLPO)which is located rostral to the hypothalamus. Some anatomical studies have shown that VLPO contains neurons that inhibit the system responsible of activating the brainstem and the forebrain. On the other hand, VLPO receives inhibitory afferents from the same regions that it inhibits. As Saper suggested [12] this reciprocal inhibition might be the basis to establish the transition between sleep and wake states. Reciprocal inhibition also is a feature in an electronic circuit called *flip-flop switch*. A flip-flop switch can be either *on* or *off*. According to Saper and collaborators' model, either VLPO is active and inhibits regions which induce wakefulness or regions that induce wakefulness are actives and inhibit VLPO. Like these regions are reciprocally inhibited it would not be possible that they were active at the same time.

There are some models that show how this switch might perform. On one hand, for example, Carlson's model [4] and Saper's model [12] are further schemes that show the information flow among neural groups along the circuits. On the other hand, several mathematical models have been proposed. A good review about these models is presented in [9]. With the aim to include some dynamical and structural aspects of the flip-flop switch a computational model that claim to describe the Saper's model is reviewed and analyzed in this paper. The model is based on *Spiking Neural P Systems* [6]. This type of computational model is part of the *Membrane Computing* [10] and its starting point consists on adding concepts typical of the neuronal computation based on spiking with the goal of testing its possibilities from a computational viewpoint. Nevertheless, this paper shows a Spiking Neural P system oriented in the opposite way. The system describes a specific neurophysiological mechanism called the sleep-wake switch.

The paper is organized as follows. Section 2 describes the neural control of slow waves sleep and the sleep-wake switch. Section 3 reviews a basic model of the sleep-wake switch with Spiking Neural P Systems. Section 4 shows results of the basic model. Finally, section 5 analyzes the proposed basic model and comments new issues to develop in the future.

2 Neural Control of Slow Waves Sleep

2.1 Non-REM stages

In non-REM sleep there is a low neuronal activity and both the metabolic function and the temperature of the brain are on its lowest level [11]. Besides, the sympathetic flow, heart rate and blood pressure decreases. Inversely, parasympathetic activity is increased while the muscle tone and reflexes remain intact.

Non-REM sleep is divided in four stages. Stage 1 represents the transition from wakefulness to sleep state. It lasts several minutes. When an individual is awoken shows an activity in the EGG with low voltage ($10 - 30\mu$V and 16-25Hz). As they relax, individuals show alpha activity around of $20 - 40\mu$V and 10Hz. This stage shows some activity on the muscles but there is no rapid eye movement, rather the sleeper shows slow eye movement and his EGG is characterized by a

low voltage and mixed frequencies. Stage 2 reveals bursts of sinusoidal waves called *sleep spindles* and biphasic waves called *K complexes*. These impulses are presented in an episodic way in front of a continuous activity in the EGG with low voltage. Stage 3 is characterized by a EGG which shows slow delta waves (0.5-2Hz) and high amplitude. Finally, in stage 4 this slow waves are increased and domain the EGG. In human beings stage 3 and stage 4 are known as *slow wave sleep*.

2.2 The sleep switch

The circuits in the brain that are responsible to regulate sleep and to produce wakefulness include cell groups in the brainstem, the hypothalamus and the basal forebrain [13] which are very important to activate the cerebral cortex and the thalamus. Neurons of these groups are inhibited during the sleep by a neural group that produces GABA (gammaminobutiric acid; an inhibitory neurotransmitter that seems to be widely distributed by all the encephalon and the spinal cord. It appears in many synaptic communications). This group corresponds with the *ventrolateral preoptic nucleus*. The reciprocal inhibition between both circuits acts like a switch and defines sleep and awake states. These states are discreet and they have sharp transitions among them.

To understand better how this switch performs it is very useful to look at the awake system and sleep system separately. We cite here the Saper's works [12] [13]. Regarding the first system, several studies carried out in the 70's and 80's showed an ascending activation pathway which induce the wakefulness state. The pathway has two main branches. The first one is an ascending branch directed toward the thalamus and it activates the thalamic relay neurons that are crucial for transmission of information to the cerebral cortex [13]. A mayor input of this thalamic relay neurons comes from a pair of neuron groups that produce acetylcholine (ACh): the *pedunculopontine tegmental nuclei* (PPT) and the *laterodorsal tegmental nuclei* (LDT). Neurons on these groups are more active during wakefulness and REM sleep and much less active during non-REM sleep when cortical activity is decreased. The second branch in the ascending activation system avoids the thalamus and activates neurons in the *lateral hypothalamus* (LHA) and the *basal forebrain* (BF). This second route starts from monoaminergic neurons in the upper brainstem and the caudal hypothalamus including the *locus coeruleus* (LC) which contains noradrenaline (NA), the *dorsal and median raphe nuclei* (DR) which contains serotonin (5-HT), the *ventral periaqueductal grey matter* which contains dopamine (DA) and the *tuberomammillary nucleus* containing histamine (HIS). The input to the cerebral cortex is augmented thanks to the lateral hypothalamic peptidergic neurons containing orexine or hypocretin (ORX), the melanin-concentrating hormone (MCH) and the basal forebrain neurons which contain GABA. Neurons in the monoaminergic nuclei have the property to fire faster during the wakefulness, slowing down during the non-REM sleep and stopping during REM sleep. Figures 1 and 2 show a schematic drawing with the mentioned systems.

During the 80's and 90's several researchers began to show interest for the inputs to the monoaminergic cells and found out that VLPO sent signals toward

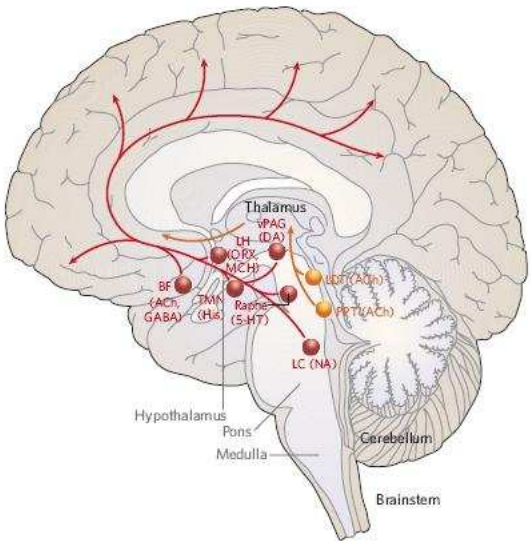


Fig. 1. Scheme with the main items in the Ascending Arousal System (AAS). Please see [13] for details

the main cells of the hypothalamus and the brainstem that are active during the wakefulness. Neurons in the VLPO are mainly active during sleep and they contain inhibitory neurotransmitters like GABA. These neurons form a dense group and a extended part more diffuse. Some of the studies showed that lesions in the dense group disrupted the non-REM sleep and lesions in the extended group did the same with the REM sleep. Experiments also showed that VLPO was innervated by the very monoaminergic systems that it innervates during sleep.

Reciprocal inhibition between sleep system and ascending arousal system acts like a circuit usually known as flip-flop in engineering [12]. A switch can be *on* or *off*. So, either VLPO is active and inhibits regions that induce wakefulness or these regions are actives and inhibit VLPO. This oscillator mechanism tries to avoid intermediate states because it is considered an adaptive advantage whether an animal is either asleep or awake. Saper and collaborators [12] suggested that an important function of hypocretinergic neurons situated in the lateral hypothalamus consist in helping to stabilize the oscillator. When these neurons are actives they induce wakefulness and inhibit sleep. The following schematic drawing in figure 3 shows the model proposed by Saper [13] in order to explain the sleep switch.

2.3 Homeostatic control of sleep

Nowadays is known that hypocretinergic neurons do not receive inhibitory afferents from each part of the oscillator, so that activation of these parts do not affect

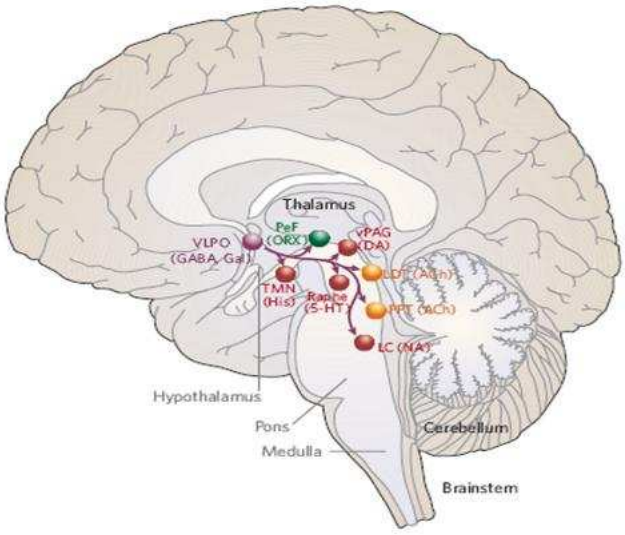


Fig. 2. Scheme with the projections from VLPO to (AAS). Please see [13] for details

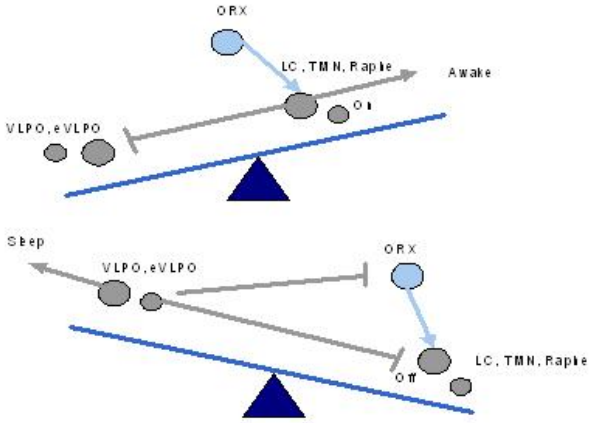


Fig. 3. Schematic drawing of the sleep switch proposed by Saper. Please see [13] for details

them [4]. If these neurons induce wakefulness they would hold the oscillator on. A question arise: how is sleep induced? Benington and cols. [3] suggested that a neurotransmitter called *adenosine* might play an essential role on the sleep control system. Its theory means that when neurons are getting especially actives

adenosine is accumulated. This substance acts like an inhibitory modulator and it produces an effect opposite to wakefulness. As Carlson suggests [4], if the VLPO is a critic region to generate sleep and the accumulated adenosine is a key factor to produce sleepiness it could be possible that this substance activates the VLPO. The proposed hypothesis suggests that adenosine favor sleep because it inhibits the neurons that usually inhibit the VPLO.

2.4 Circadian control of sleep

Several neurophysiological studies have confirmed a strong impact of 24-hour circadian cycle on the sleep control system. As Saper writes [13] "The *suprachiasmatic nucleus* (SCN) serves as the brain's master clock". Neurons in the SCN fire following a 24-hours cycle. The relation between SCN and the sleep control system has been studied [4] and the results show that SCN has projections to the VLPO or neurons containing orexin. However, the most outputs are directed toward the *adjacent subparaventricular zone* (SPZ) and the *dorsomedial nucleus of the hypothalamus* (DMH). The SPZ contains a ventral part (vSPZ) and a dorsal part (dSPZ) and it presents limited projections toward the VLPO, the neurons containing orexin and other elements in the sleep-wake system. Nevertheless, DMH is a main target because that region receives a lots of the afferents from the SPZ. Finally, the DMH is a main source of inputs to the VLPO and neurons containing orexin and it is very important in the sleep-wake regulatory system. The projections from DMH to VLPO comes from neurons containing GABA (therefore, they inhibit the sleep) while the projections toward the LHA are originated in neurons that contain glutamate (they act like exciters). Figure 4 shows the projections between all cited items as was proposed in [4].

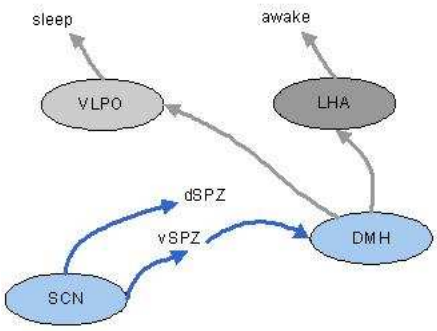


Fig. 4. Relation between the SCN and the sleep-wake regulatory system

3 Sleep-Wake Cycle with Spiking Neural P Systems: A Basic Model

Spiking Neural P Systems (SN P systems) were defined in [6] with the aim of introducing concepts typical of the spiking neurons [7], [5] into membrane computing. The standard model of SN P systems only considered excitatory rules but this configuration is not realistic to model the sleep-wake system because of the inhibitory nature of some synapses between neural groups. Starting from the standard model some variants has been proposed with the aim of modeling different situations. For example, in [1] an SN P system with extended rules was defined. A extended rule considers the possibility to send spikes along the axon with different magnitudes at different moments of time. Another idea about inhibitory connections among cells was slightly described in the same work. Bearing in mind these ideas in [8] an *SN P System with inhibitory rules* is described in the following way.

Definition 1. *A SN P System with inhibitory rules of degree m is a construct*

$$\Pi = (O, \sigma_1, \ldots, \sigma_m, syn, out_1, \ldots, out_n)$$

where

- $O = \{a\}$ *is the alphabet (the object a is called spike);*
- $\sigma_1, \ldots, \sigma_m$ *are neurons such as $\sigma_i = (n_i, R_i)$, with $1 \leq i \leq m$, means:*
  - $n_i \geq 0$ *is the initial number of spikes inside the neuron*
  - R_i *is a finite set of rules with the general form:*

    $$E/a^c \rightarrow a^p; d; t$$

    where E is a regular expression and it only uses the symbol a, $c \geq 1$ and p, $d \geq 0$, with $c \geq p$; besides, if $p = 0$ then $d = 0$. If the rule is excitatory then $t = 1$ and if the rule is inhibitory then $t = -1$
- $syn \subseteq \{1, 2, \ldots, m\} \times \{1, 2, \ldots, m\}$, *with $(i, i) \notin syn$ for $1 \leq i \leq m$, are the synapses*
- $out_1, \ldots, out_n$ *represents output neurons with $1 \leq n \leq m$.*

As is usual in the SN P Systems literature these models can be represented by means of a graph with arcs between nodes. In an SN P System with inhibitory rules we can draw inhibitory rules with discontinuous lines and excitatory rules with continuous lines. Main differences between standard SN P systems and SN P systems with inhibitory rules as they have been defined are: a) the possibility of several output neurons, and b) the definition of inhibitory rules. Excitatory rules act like they do it in a standard SN P system and the inhibitory rules are interpreted in the following way: *if a neuron σ_i has an inhibitory connection with a neuron σ_j then spikes arriving from σ_i close the neuron σ_j during a step of time* (because of $t = -1$ in an inhibitory rule).

In the basic model proposed in [8] there are established the following simplifications:

- The *ascending arousal system* in the brainstem and the forebrain are necessaries to accumulate adenosine as consequence of a long activity of their neurons. This means that when the organism is awoken the adenosine is accumulated. The neural groups which are responsible to accumulate this necessity are called *Accumulator System.*
- The *dorsomedial nucleus of the hypothalamus* (DMH) is the most active part in the *suprachiasmatic nucleus* (SCN) and it is responsible to control sleep-wake transitions following a 24-hour cycle. This neural group is called *DMH System* and its goal is to provide a motivation to awake.
- The *Acumulator System* and the *DMH system* act as activators for the asleep and awake states but once they have activated their neural groups they stop to fire and neurons in the activation system (neurons of the groups LHA, TMN, LC and DR) and neurons in the regulator-VLPO combined system start to fire while the system remains sleeping or awakening.
- Bearing in mind the previous suppositions the DMH system and the LHA are the neural groups that control the awake state and the Acumulator system and the Regulator System are the neural groups that control the asleep state.

Figure 5 shows the possible connections that control sleep-wake switch from a neurological viewpoint. The connections were explained in Section 2.

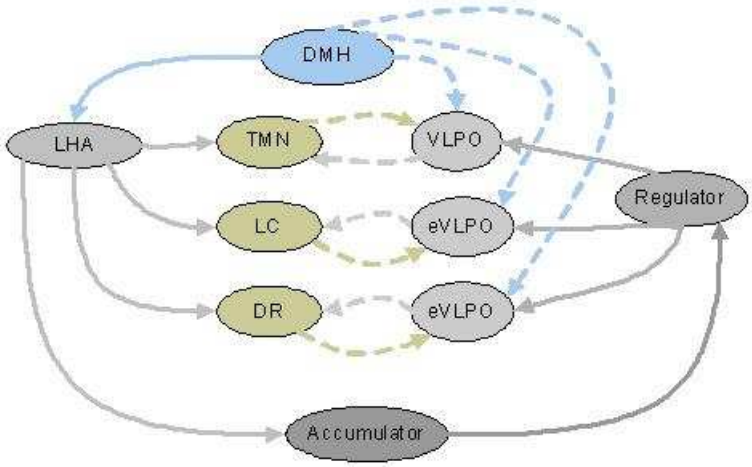


Fig. 5. Schematic drawing of the flip-flop circuit

In Figure 5, *LHA, DMH, TMN, LC, DR, VLPO (VLPO dense group), eVLPO (VLPO extended group)* are neural groups defined previously in section two. *Acumulator* represents the region where the necessity to sleep is accumulated and

Regulator would be a component of the Acumulator and its goal is to feed neurons in the VLPO. Both, *accumulator* and *regulator* groups are suppositions in the model because, from a neural point of view, regions that are responsible of accumulating adenosine are not known.

Starting from the previous figure and the SN P system with inhibitory rules a basic model for sleep-wake system is shown in Figure 6 where the inhibitory rules are represented as discontinuous lines and the excitatory rules as continuous lines.

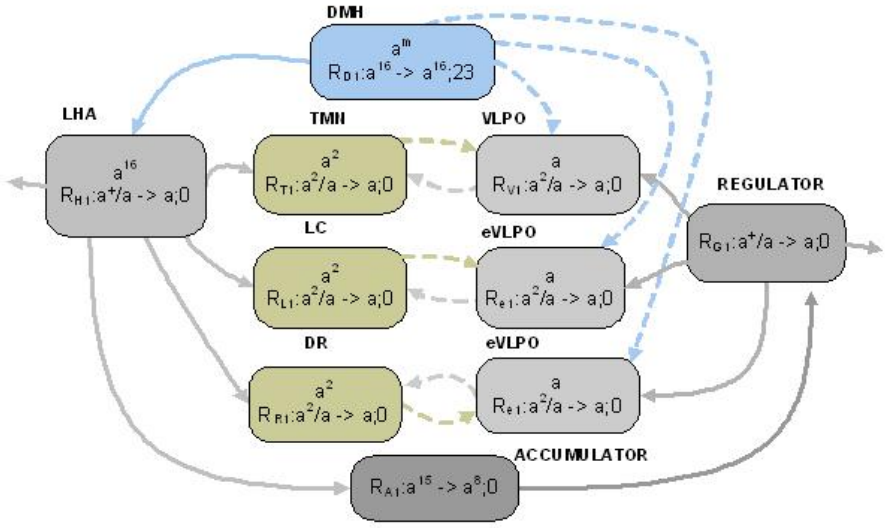


Fig. 6. Sleep-Wake basic switch with a Spiking P System

4 Results of the Basic Model

To analyze conveniently the system several suppositions must be taken into account:

- The system supposes that an individual is awoken during 16 hours and is sleeping during 8 hours. Another configurations, for example, 18 hours awake/6 hours sleep, are possible but always a fixed period is maintained.
- Each step of time in the system represents one hour of real time.

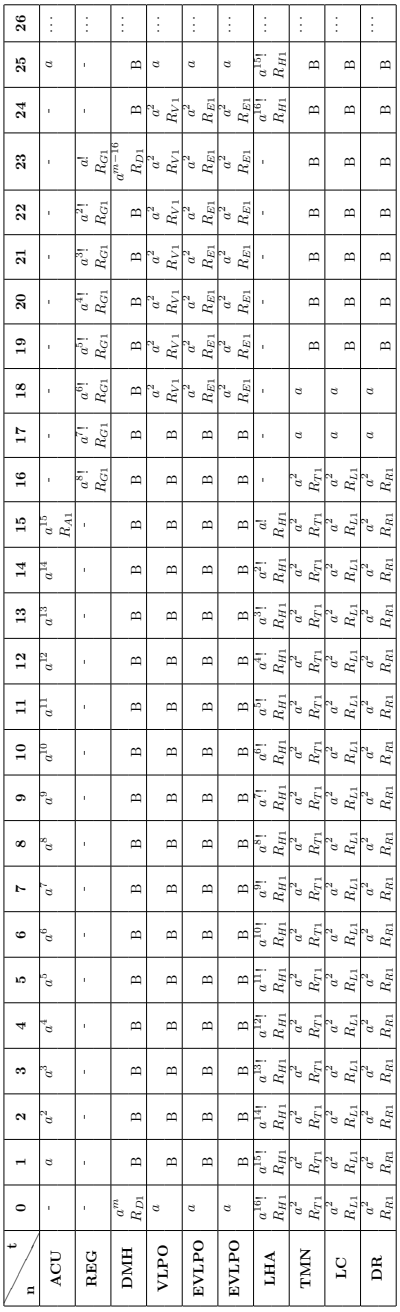
The basic model described previously can be applied starting from an initial configuration. Table 7 shows results when the system starts in awake state. First row on each square shows initial spikes and the second one represents the rule

applied. An exclamation symbol close to spikes means that the spike gets out from the network to the environment and it is useful to identify two states: *on* or *off*. When neurons in the LHA are firing the system represents wakefulness and if neurons in the *regulator system* are actives the system falls asleep. A brief explanation shows these situations. In wakefulness the neurons in the activation system (LHA, TMN, LC and DR) are firing and they select and execute a rule ($a^+/a \rightarrow a; 0$ is selected in LHA and $a^2/a \rightarrow a; 0$ in TMN, LC and DR). The activated rule in LHA, TMN and LC locks during a step of time neurons in the VLPO, both the dense group and the extended group, because of inhibitory rules among them. A lock is shown in the table with the **B** symbol. DMH system acts like the system's clock. In $t = 0$ DMH contains **m** spikes ($m >> 16$ is a necessary supposition if system does not finish) and it applies its only rule ($a^{16} \rightarrow a^{16}; 23$). This rule sends 16 spikes after 23 step of time because a daily cycle lasts 24 hours and the system tries to simulate that situation. This way, a complete cycle in the system lasts 24 steps of time (from 0 to 23). The only rule in DMH serves out to activate neurons in the LHA each 24 hours (steps of time). For its part, neurons in LHA are actives during 16 hours (steps of time). Along this period the necessity of sleep is accumulated in the *accumulator system*. When 15 steps of time have been consumed a state switch is started, the system gets to sleep and the *accumulator system* sends 8 spikes to the *regulator system* (it uses the rule $a^{15} \rightarrow a^8; 0$). To use this rule means that 7 spikes are losts and sleep state only lasts 8 hours (steps of time). Now, the *regulator system* controls sleep state executing its rule $a^+/a \rightarrow a; 0$. Once the system is sleeping, neurons of the dense and extended group are actives and execute the rule $a^2/a \rightarrow a; 0$. Besides, this rule locks neurons in TMN, LC and DR groups during a step of time. When $t = 23$, DMH is open again and it emits 16 spikes to LHA. Then, the system comes back to wakefulness and the process is repeated.

Notation: **n:** neural groups, **t:** steps of time, **ACU:** accumulator system, **REG:** regulator system, **DMH:** dorsomedial nucleus of the hypothalamus, **VPO:** dense group of the ventrolateral preoptic nucleus, **eVLPO:** extended group of the ventrolateral preoptic nucleus, **LHA:** neurons in the lateral hypothalamus, **TMN:** neurons in the tuberomammillary nucleus, **LC:** neurons in the locus coeruleus and **DR:** neurons in the dorsal and median raphe nuclei

5 Comments and New Issues

A computational basic model for sleep-wake switch is examined in this paper. The goal was to model a neurophysiological process by means of a computational device such as Spiking Neural P Systems. Traditionally, this type of computational mechanisms include biological concepts in order to test its possibilities from a computational point of view but this paper tries to apply them in a well-known neural process. In order to apply SN P Systems to this process a new definition of extended rules was necessary and this work proposes a definition for inhibitory rules with the aim of modeling the inhibitory connections among neural groups



n \ t	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
ACU	-	a	a^2	a^3	a^4	a^5	a^6	a^7	a^8	a^9	a^{10}	a^{11}	a^{12}	a^{13}	a^{14}	a^{15} R_{A1}	-	-	-	-	-	-	-	-	-	a	$\cdots$
REG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	$a^8 \mid$ R_{G1}	$a^7 \mid$ R_{G1}	$a^6 \mid$ R_{G1}	$a^5 \mid$ R_{G1}	$a^4 \mid$ R_{G1}	$a^3 \mid$ R_{G1}	$a^2 \mid$ R_{G1}	$a \mid$ R_{G1}	-	-	$\cdots$
DMH	a^m R_{D1}	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	a^{m-16} R_{D1}	B	B	$\cdots$
VLPO	a	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	a^2 R_{V1}	a^2 R_{V1}	a^2 R_{V1}	a^2 R_{V1}	a^2 R_{V1}	a^2 R_{V1}	a^2 R_{V1}	a	$\cdots$
EVLPO	a	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	a^2 R_{E1}	a^2 R_{E1}	a^2 R_{E1}	a^2 R_{E1}	a^2 R_{E1}	a^2 R_{E1}	a^2 R_{E1}	a	$\cdots$
EVLPO	a	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	a^2 R_{E1}	a^2 R_{E1}	a^2 R_{E1}	a^2 R_{E1}	a^2 R_{E1}	a^2 R_{E1}	a^2 R_{E1}	a	$\cdots$
LHA	$a^{161} \mid$ R_{H1}	$a^{151} \mid$ R_{H1}	$a^{141} \mid$ R_{H1}	$a^{131} \mid$ R_{H1}	$a^{121} \mid$ R_{H1}	$a^{111} \mid$ R_{H1}	$a^{101} \mid$ R_{H1}	$a^{91} \mid$ R_{H1}	$a^{81} \mid$ R_{H1}	$a^{71} \mid$ R_{H1}	$a^{61} \mid$ R_{H1}	$a^{51} \mid$ R_{H1}	$a^{41} \mid$ R_{H1}	$a^{31} \mid$ R_{H1}	$a^{21} \mid$ R_{H1}	$a^1 \mid$ R_{H1}	-	-	-	-	-	-	-	$a^{61} \mid$ R_{H1}	$a^{151} \mid$ R_{H1}	$\cdots$
TMN	a^2 R_{T1}	a^2 R_{T1}	a^2 R_{T1}	a^2 R_{T1}	a^2 R_{T1}	a^2 R_{T1}	a^2 R_{T1}	a^2 R_{T1}	a^2 R_{T1}	a^2 R_{T1}	a^2 R_{T1}	a^2 R_{T1}	a^2 R_{T1}	a^2 R_{T1}	a^2 R_{T1}	a^2 R_{T1}	a^2 R_{T1}	a	a	B	B	B	B	B	B	$\cdots$
LC	a^2 R_{L1}	a^2 R_{L1}	a^2 R_{L1}	a^2 R_{L1}	a^2 R_{L1}	a^2 R_{L1}	a^2 R_{L1}	a^2 R_{L1}	a^2 R_{L1}	a^2 R_{L1}	a^2 R_{L1}	a^2 R_{L1}	a^2 R_{L1}	a^2 R_{L1}	a^2 R_{L1}	a^2 R_{L1}	a^2 R_{L1}	a	a	B	B	B	B	B	B	$\cdots$
DR	a^2 R_{R1}	a^2 R_{R1}	a^2 R_{R1}	a^2 R_{R1}	a^2 R_{R1}	a^2 R_{R1}	a^2 R_{R1}	a^2 R_{R1}	a^2 R_{R1}	a^2 R_{R1}	a^2 R_{R1}	a^2 R_{R1}	a^2 R_{R1}	a^2 R_{R1}	a^2 R_{R1}	a^2 R_{R1}	a^2 R_{R1}	a	a	B	B	B	B	B	B	$\cdots$

Fig. 7. Results of SN P System simulating the sleep-awake switch

which are involved in the sleep-awake transitions. Starting from an SN P System with inhibitory rules a basic model is built with two important constraints:

1. the system supposes that an individual is slept or is awoken during fixed periods previously established.
2. the system splits the sleep control in two subsystems: *accumulator* and *regulator*. This supposition produces a delay in transition between states. Specifically, a step of time is lost from sleep to wakefulness and vice versa because accumulator and regulator subsystems can not start to perform at the same time. This is the reason why the rule $a^{15} \rightarrow a^8; 0$ in the accumulator uses 15 as number instead of 16.

In spite of this constraints the system can represent in a clear way a complex biological process and it defines formally such process. This formally definition would let possible implementations once an appropiate software was developed. Clarity of reading is also an advantage feature of SN P Systems in front of other alternatives like mathematical models based on equations, for example.

However, a number of interesting questions arises about the natural process and the basic model that it would be precise to analyze and solve in order to come near the model and the biological reality.

- The sleep and wakefulness states with fixed period are a very simplification because, obviously, neither human beings nor animals maintain along their life an established amount of time on each activity. Moreover, an individual does not sleep at all a day or more if really he or she cannot do it. This kind of flexibility is difficult to implement in the basic model even in SN P Systems as they are currently defined.
- Because the system considers one hour as step of time, the transition between sleep and wakefulness is completed slower than it occurs really in the biological process. Shorter steps can be defined in the model but then the model would be larger and tedious to show results in a table format. A possibility would be implement steps of time with different magnitudes but this question is not considered by currents SN P Systems.
- The inhibitory mechanism proposed by the model has several constraints and their effects are easily visible looking at the table. When a transition sleep-awake is produced either the *regulator system* or the *LHA neuron groups* fires (an exclamation symbol appears close to spikes). That way, the system represents that a state is active but, during one or two steps, the other main neuron groups in the dominant state does not fire because they still are locked by neurons in the opposite control system. For example, when $t = 16$ and $t = 17$, which is a sleep state, neurons in VLPO (dense and extended group) are locked (a B symbol appears in the square) because neurons in TMN, LC and DR are executing their rules yet. A similar situation occurs when $t = 24$ and $t = 25$ for the wakefulness state. This is a problem originated in the definition of the SN P System because a step of time is consumed since a spike gets out of a

neuron and comes in another one. Maybe, a best definition of inhibitory rules should be attended.

- Sleep or wakefulness states in the biological processes are a behavior but in the model they are simulated as firing in neuron groups. The model associates *LHA neurons* and *regulator system* as the output neurons in a way that is different of usual SN P systems. A best approach would be if a special cell or item in the SN P system performed this function.
- SN P systems generally send and receive signals from a state to another one but the system performs like a closed system in the sense that everything must be in the system. This is a drawback in this case because, for example, the *suprachiasmatic nucleus* does not receive only inputs of the considered neurons but other items. The basic model has replaced this fact with the delay property that SN P systems incorporate and the axiom ($m >> 16$) to simulate a non finite execution but better ideas on this matter would be a great contribution.
- SN P systems usually work with individual neurons and the basic model represents neuron groups as a single cell. A complex and interesting question to solve is concerned with how the model would be modified to work with several neurons on each group, for example, several LHA, TMN, LC, DR and VLPO cells.
- Besides the sleep-wake switch another biological process that has been studied from a neurological point of view are the transitions between non-REM and REM sleep. This transition involves practically the same neuron groups but it adds more complexity and connections among items. Contributions about this topic would also be interesting.

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