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Mesothalamic Dopaminergic Activity: Implications in Sleep Alterations in Parkinson's Disease

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1. Introduction

Movement, sleep and cognition: three connected realms enriching to the human life. Three harmed realms limiting parkinsonian patients.

A degenerative process in dopaminergic neurons from the substantia nigra (SN) midbrain nucleus is the basic origin underlying a set of symptoms developed in patients with Parkinson's Disease (PD) (Andrade & Ferraz, 2003). The devastating motor difficulties usually do not appear isolated. Indeed, PD consists of distinct kinds of manifestations involving motor and mental rigidity as well as sleep alterations (Dubois & Pillon, 1996; Rye et al., 2000; De Cock et al., 2008; Arnulf & Leu-Semenescu, 2009).

Even though impairments in other brain nuclei also contribute to the symptoms present in PD (Braak et al., 2000), it is surprising how so distinct brain systems suffer influence of the degenerative alterations in the SN. This phenomenon may be regarded as a simple consequence of the connections between the SN and diverse brain areas. As a matter of fact, it also highlights that distinct behavioral aspects are achieved through the sharing of brain resources. Here, we examine - through a neurocomputational model - relationships between alterations in the mesothalamic dopaminergic activity (MDA) and sleep impairments in PD.

With origins in the SN, the mesothalamic pathway (MP) reaches the thalamic complex, in particular the thalamic reticular nucleus (TRN). Investigations on such dopaminergic pathway, evidenced by Freeman and colleagues (Freeman et al., 2001), have been contributing to a more global comprehension of cognitive processes in the brain. Based on experimental results (Florán et al., 2004), the mathematical model proposed in (Madureira et al., 2010) indicates a way by which the mesothalamic dopamine inhibits neurons in the TRN. And computational simulations of this model suggest that alterations in the MDA lead to inattention symptoms as observed in PD and Attention Deficit Hyperactivity Disorder (ADHD).

Thalamic neurons are able to spike under tonic and burst states (Steriade et al., 1993; Llinás & Steriade, 2006). Whenever in the tonic state, these neurons respond linearly to input stimuli. By this way, they propagate information reliably from perceptual systems to the cerebral cortex, where a more refined processing takes place. This mode of activity is crucial to the thalamocortical filtering of perceptual stimuli that allows attention focusing (Madureira et al., 2007, 2010; Carvalho, 1994).

Conversely, under the burst state thalamic neurons are no more reliable channels through which neural representations from sensorial inputs reach the cerebral cortex. As a matter of fact, this mode of activity underlies the thalamic behavior during sleep (Steriade et al., 1993; Pace-Schott & Hobson, 2002). In this case, the environmental stimuli are not perceived consciously as it occurs throughout wakefulness (Carvalho, 1994). The thalamic burst mode also permeates epileptic episodes during which environmental information is not processed reliably (Jeanmonod et al., 1996; Llinás et al., 1999). The dynamics of the ionic channels under the burst mode are different from the ones underlying the thalamic tonic state. That is why, under the burst mode, thalamic neurons spike quite autonomously, in such a way that their pattern of activity does not represent the input information.

Since the inattention symptoms addressed in (Madureira et al., 2010) concerned awakened people, the model considered the behavior of thalamic neurons under the tonic state. In the present work, we go further with the matter and scrutinize relationships between the MDA and the oscillatory state of neurons in the thalamic complex. Doing so, it becomes possible to widen the investigation to examine a possible MDA contribution to sleep alterations in PD and, to look at attention focusing aspects under a little more detailed point of view.

Clinical evidences indicating a variety of sleep alterations in PD suggest that this class of symptoms should not be considered as a secondary one: on the contrary, sleep problems certainly pertain to the core symptoms that define PD (De Cock et al., 2008; Arnulf & Leu-Semenescu, 2009). Such sleep alterations involve daytime sleepiness, inappropriate intrusion of REM sleep episodes throughout the day, and nocturne movement. In other words, parkinsonism disrupts the control of the sleep-wake cycle (Jancovic, 2002; Arnulf & Leu-Semenescu, 2009).

The question thus that naturally arises concerns the dopaminergic role in the sleep-wake cycle control. Given the clinical evidence from sleep impairments in PD, a disease whose basic neural origins is the dopaminergic neurons degeneration, we tend to conclude that dopamine does participate in the sleep regulation. Is it the case?

Up to recently, the above mentioned clinical observations have been quite disregarded. If, through PD, the dopaminergic participation in the control of the sleep cycle may be inferred (Rye, 2004), there is, on the other hand, a number of neuroscientific studies showing that the variation in the dopaminergic level throughout the sleep-wake cycle is too small to be taken into account (Jancovic, 2002).

A series of experiments undertaken by (Dzirasa et al., 2006), however, illuminated this controversy. They were capable of demonstrating that sleep-wake states are also controlled by dopamine. This seminal work shows the importance of the dopaminergic influence in the sleep regulation – even under small variations. In addition, they emphasize the relationship between dopaminergic alterations and sleep impairments in PD.

Here, we address – through a neurocomputational approach – the interference of SN neurons, particularly the degenerated ones, in the thalamocortical spiking modes. Our goal consists in investigating if the PD dopaminergic disruption alters the typical spiking patterns associated to sleep and wake states, thus compromising the normal sleep-wake cycle in PD.

We now outline the contents of this chapter. In Section 2 we introduce our hypothesis of dopaminergic influence on the control of the sleep-wake cycle, and describe the model. In Section 3, we explain how the computational simulations of the model are designed, and present the computational results. Finally, we conclude by discussing the consequences of our results in terms of sleep alterations in PD, in the context of the neuroscience of sleep.

2. The model

In (Madureira et al., 2010), we proposed a mathematical model indicating how the mesothalamic dopamine influences the thalamocortical loop, through the TRN, and thus modulates the attentional focus formation. In particular, we investigated relationships between alterations in this dopaminergic pathway and attention deficits in PD and ADHD.

Here, we extend this model to address how dopamine influences the emergence of distinct spiking modes in thalamic neurons. Since the thalamic modes of spiking are specifically related to sleep and wake neuron states, our modeling enables us to discuss if and how dopaminergic alterations in PD are related to the sleep problems observed in the disease.

Throughout the sleep-wake cycle, complex chemical and electrical networks of events occur in the thalamocortical neural circuit. They give rise to distinct patterns of neural behavior that underlies the different brain rhythms specifically associated to different sleep phases and also to the wake state (Pace-Schott & Hobson, 2002; Hobson & Pace-Schott, 2002; Diekelmann & Born, 2010).

The variety of brain rhythms extensively studied by the neuroscience of sleep (Steriade et al., 2003; De Gennaro & Ferrara, 2003; Llinás & Steriade, 2006; Steriade, 2006; Pace-Schott & Hobson, 2002; Hobson & Pace-Schott, 2002; Hobson, 2009; Diekelmann & Born, 2010) reflects the behavior of neural groups. Indeed, such brain rhythms, e.g. spindles, slow oscillation and theta activity, are measurements of field potential oscillations captured by EEGs experiments – not by single cell recordings. Therefore, they provide information from a scale above the cellular one.

Our model, on the other hand, addresses the dynamics of ionic and synaptic currents. It thus deals with information at the same level of single cell recordings, in particular, variations in the membrane electric potential.

Under this approach, it is reasonable to examine sleep issues by mathematically modeling neurons in the thalamocortical loop, and computationally simulating the action of neuromodulators throughout this brain area.

As an outcome of our neurocomputational model, we conjecture that the inhibitory action of mesothalamic dopamine in the thalamic reticular nucleus (TRN) (Florán et al., 2004) affects the spiking mode of thalamocortical neurons. This is possible whenever the dopaminergic action leads to a period of neuron hyperpolarization that activates the calcium conductance, thus changing the way by which the neuron behaves (Carvalho, 1994). Next, we present the model and develop such ideas more deeply.

2.1 The neural network

We model a thalamocortical circuit with a dopaminergic projection from SN to the TRN, according to Figure 1. We can note the excitatory and inhibitory connections in the modeled neural network. Thalamocortical and corticothalamic projections are excitatory, mediated by glutamate. Both areas send glutamatergic excitatory collateral axons to the TRN. Conversely, efferent projections from the TRN to thalamus are GABAergic inhibitory (Guillery & Harting, 2003).

With relation to the dopaminergic action, the architecture of the network incorporates results gathered together from Freeman et al. (2001) and Florán et al. (2004), which reveal the inhibitory dopaminergic projection from SN to the TRN, or the mesothalamic dopaminergic pathway. The explanation we suggest for the dopaminergic action in TRN is

that dopamine acts on the calcium dependent potassium channels, possibly by increasing its conductance. By this way, the level of potassium that leaves the cell increases, which consequently inhibits neuron spiking. Thus, the GABA release becomes inhibited – for more details see (Madureira et al., 2010).

Given such a structure, external stimuli X and Y are projected through excitatory pathways to neighboring thalamic regions, T_x and T_y, respectively. Once stimulated, T_x activates TRN_x beyond collaterals of an ascending glutamatergic projection, whose final destiny is the PFC. Since our work does not model the PFC explicitly, such excitatory projection ends up in TRN in the model. Also, through an excitatory glutamatergic descending pathway, the cortical region enhances the activation of T_x, and also sends collateral axons to TRN_x. Thus, once activated, the TRN_x inhibits the thalamic region T_y through a GABAergic inhibitory projection. Summarizing, the thalamocortical circuit activation by an external stimulus X excites a central thalamic region T_x and inhibits its neighborhood, represented by the neuron T_y. As the mesothalamic dopamine inhibits neurons in TRN, a rise in the dopaminergic level contributes to deactivating such cells. This leads to a more active thalamic region T_y. Conversely, a reduction in the dopaminergic level activates TRN, and increases the inhibition of T_y. A symmetrical case involves the T_y and TRN_y neurons, as illustrated in Figure 1.
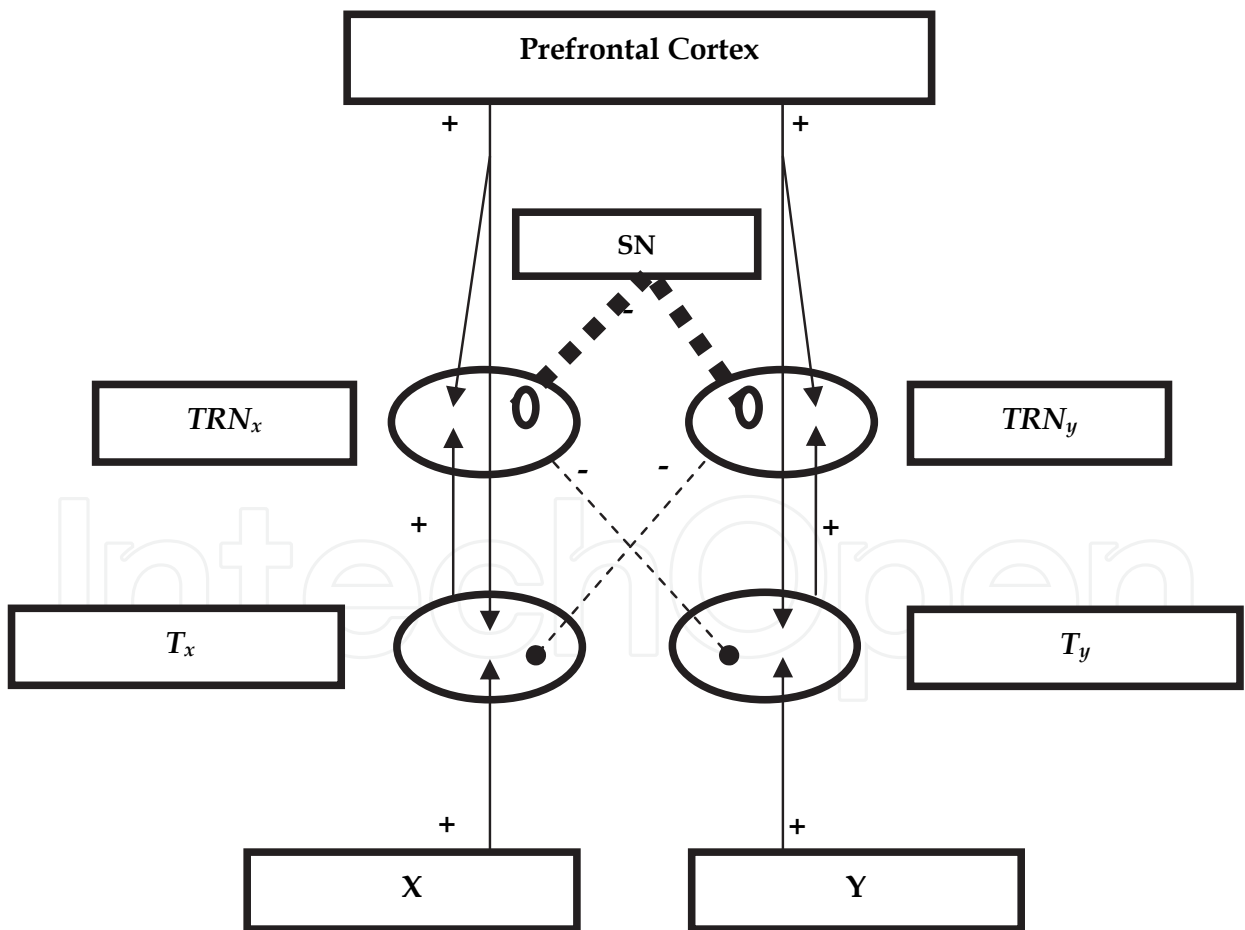

Fig. 1. The modeled thalamocortical network architecture: excitatory glutamatergic synapses (arrows), inhibitory GABAergic synapse (black sphere), inhibitory dopaminergic synapse (white sphere).

In the following, we describe the systems of equations that model the behaviors of T_x, T_y, TRN_x and TRN_y. The neural activities of the SN and the PFC, as well as the excitatory projections from X and Y are codified as temporal sequences representing their respective spiking times. As this work takes further the model presented in (Madureira et al., 2010), throughout the next section we examine specially the particular aspects of this extension.

2.2 Ionic currents

To better investigate alternate thalamic states, this model incorporates physiological features related to the tonic and the bursting modes of thalamic spikes. Thus, we address the neuron spike by considering the sodium, I_{Na}, and the calcium, I_{Ca}, currents, which depolarize the neuron, and the potassium current, I_K, which restores the cellular membrane potential (Kandel, 2000). With relation to the patterns of intervals between spikes, associated to different potassium currents (McCormick et al., 1995), our model incorporates the calcium dependent-potassium current, I_c, particularly, in the TRN neurons: it is a transient current, whose amplitude increases with intracellular calcium concentration, and it suffers dopaminergic influence (Florán et al., 2004; Madureira et al., 2010). Essentially associated to the bursting mode, the I_{ahp}, a current that underlies neural hyperpolarization, is modeled as described below.

The model deals with a network of ionic and synaptic events that leads to a specific mode of spiking. Particularly, under this approach we examine if dopamine is able to influence the spikes of thalamic neurons. In this model we assume that a high inhibitory dopamine action on D4 receptors in TRN neurons hyperpolarizes such cells, thus facilitating the activation of calcium currents. As a consequence, and according to thalamic properties (Carvalho, 1994), even a small membrane depolarization is capable of triggering an action potential, due to the low threshold calcium-currents. Whenever the inflow of Ca^{2+} in the cell, due to spikes, increases the Ca^{2+} concentration above a threshold, then the hyperpolarizing current I_{ahp}, becomes activated, hyperpolarizing the neuron. Therefore, the calcium currents become activate – or remain activated, depending on their previous state – and a cyclic or oscillatory behavior takes place in the TRN neuron. This is the burst thalamic mode of spiking, associated to sleep states (Steriade et al., 1993; Llinás & Steriade, 2006). It may be interrupted due to the calcium currents inactivation, which occurs whenever the neuron does not suffer hyperpolarization for around 100ms.

Based on this model, we speculate another possibility that is directly related to the PD origins: the generation of bursting in thalamic neurons, due to a strong inhibition imposed by TRN neurons. Such situation is plausible to occur in case of mesothalamic hypodopaminergy, which allows the inhibitory TRN neurons to become atypically over stimulated (Madureira et al., 2010, Florán et al., 2004).

Because of the dopaminergic modulation in the TRN, two types of neurons are modeled: the thalamic ones, T_x and T_y, and the TRN neurons. Both are single point spiking and are presented next.

2.2.1 Thalamic neurons

We define a simplified neuron model with a single compartment where dendrites, soma and axons are concentrated, and whose electric potential is V. The neural membrane is modeled according to the equation:

$$C_T \frac{\mathrm{d}V}{\mathrm{d}t} = I_k + I_{ahp} + I_{syn} + I_l \, ,$$

where we recall that I_k represents the potassium current, I_{ahp} the hyperpolarizing current, I_{syn} the dendritic current induced by synaptic action, and I_l the leak current, i.e., currents that are not modeled.

Considering the relation between membrane voltage and ionic currents, as

$$
\begin{aligned}
I_k &= g_k \left(E_k - V \right), \\
I_{ahp} &= g_{ahp} \left(E_k - V \right), \\
I_l &= g_l \left(E_l - V \right), \\
I_{syn} &= g_{syn} \left(E_{syn} - V \right)
\end{aligned}
\tag{1}
$$

where the constants E_k, E_{ahp}, E_l and E_{syn} are reversal potentials for the currents I_k, I_{ahp}, I_l and I_{syn}, respectively, and g_k, g_{ahp}, g_l and g_{syn} represent the conductances corresponding to these currents.

The occurrence of a spike is associated to a step function $s(V)$, whose unitary value indicates the action potential depolarizing phase, depending on the I_{Na} or I_{Ca} currents:

$$
s(V) = \begin{cases} 1, \text{ if } V \geq \theta_{\text{spike}} \\ \\ 0, \text{ if } V < \theta_{\text{spike}}, \end{cases}
$$

where θ_{spike} is a voltage threshold for the channel opening. It is defined as:

$$
\theta_{\text{spike}} = \begin{cases} \theta_{\text{Na}}, \text{ if } I_{Ca} \text{ is inactivated} \\ \\ \theta_{\text{Ca}}, \text{ if } I_{Ca} \text{ is activated}, \end{cases}
$$

where, θ_{Na} is the voltage threshold for the sodium channels opening, and θ_{Ca} for the calcium channels. We have $\theta_{\text{Na}} > \theta_{\text{Ca}}$, and the spikes triggered by the calcium ionic channels are the low threshold spikes (LTS).

During the network activity, the membrane potential, V, is monitored. When strong inhibitory events lead to periods of hyperpolarization, around 100ms, the I_{Ca} currents become activated (Carvalho, 1994). Once in activity, I_{Ca} currents cause the LTS.

Following a spike, the conductance g_k of the restoring current I_k increases rapidly, bringing the neuron back to a resting potential. Such a process is described by

$$\frac{\mathrm{d}g_k}{\mathrm{d}t} = \frac{s\beta_k - g_k}{\tau_k}$$

where the constant β_k represents a variation rate of g_k, and τ_k a time constant associated to the potassium channel.

According to the frequency of spikes, the calcium concentration increases – and decreases due to calcium buffers and pumps (Carvalho & Roitman, 1995). Then, we have:

$$\frac{\mathrm{d}[Ca]}{\mathrm{d}t} = \frac{s\beta_{Ca} - [Ca]}{\tau_{Ca}} \qquad (2)$$

where β_{Ca} represents the rate of calcium concentration variation, and τ_{Ca} a time constant.

If the intracellular calcium concentration reaches a given threshold Θ_{Ca}, the potassium channels related to the hyperpolarizing current are opened. The step function f([Ca]) describes such event as:

$$f([Ca]) = \begin{cases} 1, \text{ if } [Ca] \geq \Theta_{Ca} \\[2ex] 0, \text{ if } [Ca] < \Theta_{Ca}. \end{cases}$$

The following equation describes how its conductance, g_{ahp}, behaves with respect to the I_{ahp} current:

$$\frac{\mathrm{d}g_{ahp}}{\mathrm{d}t} = \frac{f\beta_{ahp} - g_{ahp}}{\tau_{ahp}}$$

where β_{ahp} represents a variation rate of g_{ahp}, and τ_{ahp} a time constant.

Once in the activated state, the I_{Ca} current facilitates the occurrence of LTS, and the consequent increase of the calcium concentration, $[Ca]$. As a result, the conductance g_{ahp} grows, and the neuron suffers a hyperpolarization.

2.2.2 *TRN* neurons

Since TRN and thalamic neurons main properties are similar, the equations for the *TRN* neuron are quite similar to the ones considered in 2.2.1, except for the inclusion of the calcium-dependent potassium current I_c.

We assume the final target of dopaminergic action is the calcium-dependent potassium channel, whose ionic current is I_c (Madureira et al., 2010; Florán et al., 2004). Thus, the membrane equation for the *TRN* neuron incorporates the ionic current I_c as:

$$C_{TRN}\frac{\mathrm{d}V}{\mathrm{d}t} = I_k + I_{ahp} + I_c + I_{syn} + I_l$$

Indeed, $I_c = g_c (E_k - V)$, where E_k represents the potassium reversal potential, and g_c the conductance of ionic current I_c.

The conductance g_c suffers dopaminergic influence, via D4 receptor, and depends on the intracellular calcium concentration. Thus, $g_c = \hat{g}_c D_4^* S([Ca])$, where $\hat{g}_c$ is a constant, D_4^* stands for the dopaminergic action on g_c, and $S([Ca])$ stands for a sigmoid function of the intracellular calcium concentration, which increases by virtue of a neural spiking. We set

$$S([Ca]) = \frac{1}{1 + \exp(-a[Ca])}$$

where the constant a controls the slope of S, and rhe calcium concentration behaves according to the equation (2). Indeed, in (2) the term s raises the calcium concentration

whenever there is a neural spiking. Therefore g_c increases and inhibits the cell, if the cell is excited beyond a threshold.

The dopaminergic action on g_c is modeled by the summation of alpha functions (Carvalho, 1994) representing the rise and the decrease of the dopaminergic level, in each of the N presynaptic spikes that occurred at times t_i, before t, with $1 \leq i \leq N$:

$$D_4{}^* = \hat{g}_{d4} \sum_{i=1}^{N} (t - t_i) \exp[-(t - t_i) / t_{pd}]$$

Here, the constant t_{pd} stands for the peak time for the alpha function, and $\hat{g}_{d4}$ is the conductance constant of the dopaminergic projection. For further details, see ref. (Madureira et al., 2010).

2.3 Synaptic projections

Finally, we present the synaptic modeling (Carvalho, 1994). For the synaptic conductance g_{syn}, appearing in Equation (1), it follows that

$$g_{syn} = \hat{g}_{syn} \sum_{i=1}^{N} (t - t_i) \exp\left[-(t - t_i) / t_p\right]$$

where $\hat{g}_{syn}$ is the maximal conductance, which assumes different values for each particular synapse. In fact, each modeled synapse has a specific associated conductance, reflecting its influence: $\hat{g}_{c\text{-}trn}$ and $\hat{g}_{c\text{-}t}$ for synapses between the cortex and the TRN, and between the cortex and the thalamus, respectively; $\hat{g}_{t\text{-}trn}$ and $\hat{g}_{trn\text{-}t}$ for synapses between the thalamus and the TRN, and vice versa; and $\hat{g}_{e\text{-}t}$ for synapses between somatosensory projections and the thalamus.

The synaptic conductance g_{syn} is also represented by a summation of alpha functions, for each of the N presynaptic spikes that occurred at times t_i before t, for $1 \leq I \leq N$. We denote by t_p the peak time for the alpha function, and it assumes the values t_{pe} and t_{pi} for excitatory and inhibitory synapses respectively.

We used the ANSI C ® programming language to implement the model. The differential equations are integrated by the Euler's method. Ref. (Madureira et al., 2010) and Table 1 present glossaries with all necessary parameter values.

I_{ahp}	Hyperpolarizing potassium current	(μA.cm^{-2})
g_{ahp}	Conductance of I_{ahp}	(m.mhos.cm^{-2})
θ_{Ca}	Threshold for calcium channel's opening	(0 mV)
θ_{Na}	Threshold for sodium channel's opening	(1 mV)
Θ_{Ca}	Intracellular calcium concentration threshold for I_{ahp} activation	(mM)
β_{ahp}	Variation rate of g_{ahp}	(100)
τ_{ahp}	Time constant of g_{ahp}	(2 ms)

Table 1. Glossary of parameters.

3. Computational simulations

Due to a mechanism of inhibitory feedback between thalamic and TRN neurons in the thalamocortical circuit, when a projected stimulus on the central thalamic area T_x is propagated for posterior cortical processing, its neighboring thalamic area T_y suffers inhibition from *TRN*. This property was highly explored in (Madureira et al., 2010), because our major concern was the attentional focus formation.

Here, we explore such inhibitory feedback to inspect how the activity degree in the TRN influences the thalamic excitatory state. Summarizing, our simulations illustrate how dopamine modulates the activation of TRN neurons and, consequently, that of the thalamic cells.

With relation to the dopaminergic action in the TRN, we assume a relationship between the level of mesothalamic dopamine released in the TRN and the nigral spiking frequency. Consequently, we simulate variations in the level of dopamine released in the TRN by varying the SN spiking pattern. We also address the dopamine receptor D4 degree of activity, through the term $\hat{g}_{d4}$ in (3). Indeed, $\hat{g}_{d4}$ model the weight of the connection between the SN and *TRN* neurons. Then, $\hat{g}_{d4}$ tells us how much receptor D4, in the TRN, is affected by the dopamine release due to a nerve impulse from SN, or due to the action of exogenous factors as drugs that alter the dopamine level throughout synaptic clefts.

Overall, throughout these simulations our major concern is the dopaminergic effect on the thalamocortical dynamics. We do not intend to focus our exploration on the consequences of variations in external or cortical stimuli.

3.1 Asymmetrical architecture

In this section, we describe a series of simulations performed using an artificial neural network that presents the architecture illustrated in the Figure 2. Since such network is the one used in (Madureira et al., 2010), we set it as our departure point.
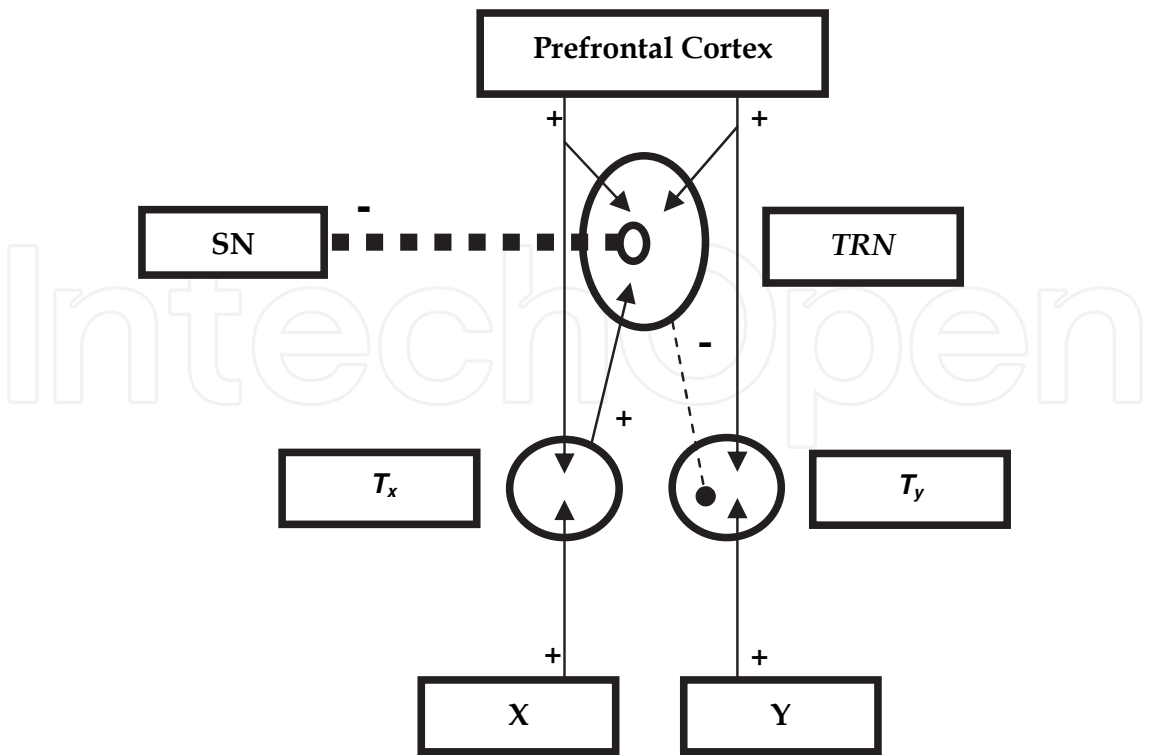

Fig. 2. The asymmetrical network architecture (from (Madureira et al., 2010)).

Here, we investigate if variations in the activity of receptor D4 in the TRN may influence the mode of spiking in neurons of the thalamic complex, along different SN spiking frequencies. We impose a drastic decrease in the nigral dopamine level, reflecting a disturbance in the mesothalamic system, and raise the dopaminergic level afterwards. Through the 500ms-simulations, variations in the dopaminergic receptor activation are modeled by altering the parameter $\hat{g}_{d4}$ after 250ms.

Table 2 describes all simulated variations in the SN spiking frequency, the imposed changes on receptor D4 activation, as well as the characteristic spike modes related to each situation. From these results, we gather that the bursting mode was elicited in two opposing situations: increase of D4 activation under mesothalamic hypoactivity (interval between spikes in SN equals 50 and above) and, decrease of D4 activation under mesothalamic hyperactivity (interval between spikes in SN equals 5).

In the first case, the mesothalamic hypoactivity turns the TRN_x neuron so highly excited, that T_y becomes strongly inhibited, thus activating the calcium current. The posterior increase of the D4 activity, plausibly representing the effect of some dopaminergic agonist, was able to elicit LTSs. Consequently, the calcium concentration reached a threshold value that activated the hyperpolarizing current, promoting the oscillatory pattern in the thalamic cell T_y.

Interval between Spikes in SN (ms)	Changes in the Activity of Dopamine Receptor D4 ($\hat{g}_{d4}$)	Neuron	Spike Mode
100, 150 and 200	1.0 to 1.2	T_y	Tonic to Bursting
50	1.0 to 1.2	T_y	Tonic to Bursting
10	1.0 to 1.2	-	Tonic
5	1.0 to 0.8	TRN	Tonic to Bursting

Table 2. Spiking modes examined through an asymmetrical network.

Conversely, in the second case, the mesothalamic hyperactivity generated the strong inhibition in the TRN neuron, which enabled the calcium currents activation. Then, the imposed decrease of D4 activity was sufficient to diminish the TRN inhibition, thus allowing LTSs and, finally, the bursting mode of spiking.

3.2 Symmetrical architecture

Following the first series of experiments, we extend the network architecture to incorporate the symmetry between neighboring thalamic areas. The symmetrical architecture is represented in the Figure 1.

3.2.1 SN spiking frequency and the attentional focus

We start exploring the extended architecture by addressing the dopaminergic action in neurons under the tonic mode of spiking. Therefore, as a first approximation, we apply the mathematical model developed in (Madureira et al., 2010). In this set of simulations, a weaker stimulus X is presented to the network before the a stronger one, Y. Again, we

initiate with a low SN spike frequency, characterizing the mesothalamic dopamine hypoactivity, and raise the SN activity in successive steps. Table 3 presents our simulations results. Overall, we gather that as the mesothalamic dopaminergic activity decreases, the *TRN* neurons become more excited. Also, T_x becomes be more inhibited than T_y, enlarging thus the difference between the activations of T_x and T_y, as showed in Table 4. Therefore the mesothalamic dopamine hypoactivity forces the attention to focus on the stimulus Y, implying in attentional shifting difficulty and mental rigidity. On the other hand, the almost identical neural activity of T_x and T_y, enhanced by the mesothalamic dopamine hyperactivity, lead to a no-winner competition between stimuli X and Y, which may represent distraction or lack of attentional focus. These results are compatible with the ones provided by our previous model.

Interval between Spikes in SN (ms)	Spikes in 100ms			
	T_x	T_y	TRN_x	TRN_y
	(100ms – 200ms)			
	(400ms – 500ms)			
50	11	0	25	14
	2	14	14	28
30	14	0	23	9
	4	14	16	25
20	12	0	21	10
	7	13	13	21
10	18	0	17	0
	10	15	5	10
5	18	0	0	0
	18	19	0	0

Table 3. SN spiking frequency and the thalamic tonic state.

3.2.2 Receptor D4 activity and the attentional focus

In the next series of experiments, we keep up our focus on the tonic mode of spiking. And, for each imposed SN spike frequency, we examine the effects of changes in the receptor D4 activation. Since the different degrees of D4 activation can be associated to not modeled exogenous or endogenous factors, that are not modeled, this approach makes it possible to speculate plausible outcomes of the dopaminergic agonists (or antagonists) action at the synaptic cleft. The simulations results are summarized in Table 4. First, we may note that the results presented in the column relative to $\hat{g}_{d4}$ = 1.0 agree with the previous set of experiments. It is more interesting, however, to observe that as the receptor D4 activity diminishes, the thalamic neurons become less active, thus reaching a completely inhibited state. Conversely, as the receptor D4 activity increases, thalamic neurons become more active and tend to spike at the same frequency. Finally, we highlight that, except for the baseline case where the interval between spikes in SN equals 10, when $\hat{g}_{d4}$ assumes values lower than 1.0, the differences between T_x and T_y spiking frequencies disappear. So, the mesothalamic hypoactivity does not impose the attention to focus on the stimulus Y anymore.

		Spikes in 100ms					
Interval between Spikes in SN (ms)		Activity of Dopamine Receptor D4 ($\hat{g}_{d4}$)					
		0.4	0.6	0.8	1.0	1.2	1.4
50	T_x	-	0	2	2	11	14
	T_y	-	0	2	14	16	19
	TRN_x	-	46	32	14	9	4
	TRN_y	-	46	32	28	15	6
30	T_x	-	0	4	4	12	15
	T_y	-	0	4	13	17	18
	TRN_x	-	42	30	25	12	2
	TRN_y	-	42	30	25	12	5
20	T_x	-	0	5	7	12	18
	T_y	-	0	5	13	15	18
	TRN_x	-	40	30	13	10	5
	TRN_y	-	40	30	21	12	2
10	T_x	0	0	0	10	16	18
	T_y	0	6	10	15	17	19
	TRN_x	52	30	20	5	5	0
	TRN_y	50	30	30	10	4	0
5	T_x	0	5	15	18	18	-
	T_y	0	5	15	19	19	-
	TRN_x	40	25	10	0	0	-
	TRN_y	40	20	5	0	0	-

Table 4. Receptor D4 activity and the thalamic tonic state.

3.2.3 Dopaminergic activity and the oscillatory state

Next, we simulate the mathematical model described in Section 2 through the extended symmetrical network illustrated in the Figure 1. In this set of experiments, two identical, external stimuli, *X* and *Y*, activate the network simultaneously. As in the previous experiments, we impose different SN spiking frequencies. We observe, in Table 5, that extreme and opposing situations lead to the bursting spiking mode in the thalamic complex: the drastic mesothalamic dopamine hypoactivity caused the oscillatory pattern in the T_x and T_y neurons, whereas the mesothalamic dopamine hyperactivity made the TRN neurons to spike through bursts. With relation to the T_x and T_y neurons, the appearance of the bursting mode comes from the strong inhibition they suffered through the GABAergic projection from the TRN neurons, which were over activated due to the low dopaminergic activity. Conversely, the oscillatory behavior of the TRN_x and TRN_y neurons originated from the inhibition suffered by the TRN due to the high dopaminergic level. The dynamics of the ionic currents involved in such processes are the same described in Subsection 2.2. Figure 3 illustrates the changes in the T_x behavior due to the diminishing of the receptor D4 activation, throughout the dopamine hypoactivity case, described in the first line of Table 5.

Interval between Spikes in SN (ms)	Activity of Dopamine Receptor D_4^* ($\hat{g}_{d4}$)	Neurons	Spike Mode
100	0.8	T_x and T_y	Bursting
	0.9	all	Tonic
	1.0	all	Tonic
50	0.8	all	Tonic
	0.9	all	Tonic
	1.0	all	Tonic
40, 30, 20, 10	1.0	all	Tonic
5	1.0	TRN_x and TRN_y	Bursting

Table 5. Distinct dopaminergic activities in presence of similar stimuli.

3.2.4 Variations in the dopaminergic activity and the oscillatory state

In our last series of simulations, we deepen our investigations on the changes in the spiking mode. Now, we repeat the strategy undertaken in Subsection 3.2.1, where a stimulus *X* is presented to the asymmetrical network before a stronger one, *Y*. Through the extended mathematical model we propose in Section 2, here we look for situations where changes in the dopaminergic action lead to the burst mode in neurons of the thalamic complex. In this set of simulations, we examine only extreme cases of dopaminergic alterations. Such option was because all previous experiments indicated these extreme situations as the more plausible to initiate the ionic events that underlie the burst mode occurrence. Table 6 summarizes our results.
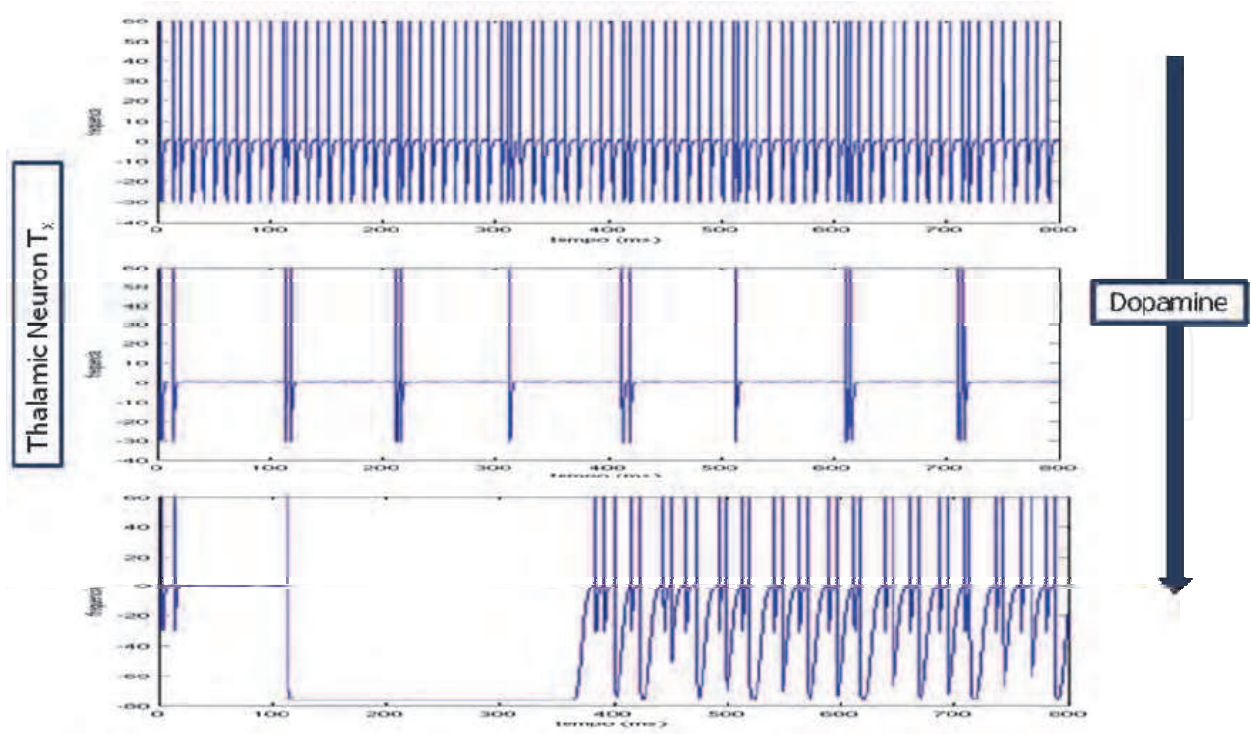
Fig. 3. Decreases in the receptor D4 activation, under mesothalamic dopaminergic hypoactivity, turned the tonic state into the burst one in T_x.

In the case of mesothalamic hypoactivity, where the SN neuron spikes every 150ms, the constant activation of D4 as $\hat{g}_{d4}$ = 0.9 made the T_y neuron to spike through bursts – not T_x one. This occurs because the T_y activation is greater than the T_x one by an amount enough to trigger the LTS - after the hyperpolarization due to the high activity in the TRN. In Figure 4, we can observe the T_x and T_y behaviors. The receptor D4 activations imposed by $\hat{g}_{d4}$ = 1.0 or $\hat{g}_{d4}$ = 1.1 did not allow the TRN neurons to spike highly enough to start the necessary hyperpolarization that activates the calcium currents.

Another case of mesothalamic hypoactivity we simulate by fixing the SN frequency in one spike each 100ms. Compared to the previous experiment, the SN is slightly more active. This time, it is the T_x neuron that presents an oscillatory pattern, when $\hat{g}_{d4}$ = 0.9. In this case, the inhibition from TRN$_x$ was not strong enough to hyperpolarize T_y. However, the less stimulated T_x neuron suffered the necessary inhibition that activated calcium currents, thus facilitating the consolidation of the burst mode of spiking. Figure 5 illustrates the distinct spiking modes of T_x and T_y.

Interval between Spikes in SN (ms)	Activity of Dopamine Receptor D₄* ($\hat{g}_{d4}$)	Neurons	Spike Mode
150	0.9	T_y	Bursting
	1.0	all	Tonic
	1.1	all	Tonic
100	0.8	all	Tonic
	0.9	T_x	Bursting
	0.9 to 1.0	T_x and T_y	Bursting
5	1.1 to 0.8	TRN$_x$ and TRN$_y$	Bursting

Table 6. Distinct dopaminergic activities in presence of different stimuli.
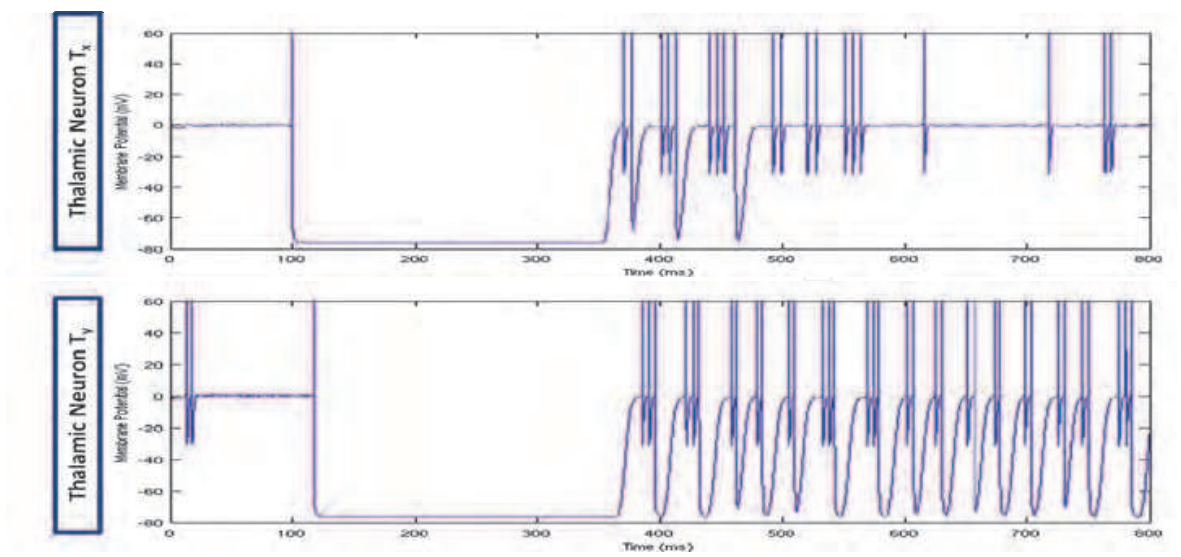

Fig. 4. Behaviors of T_x and T_y. Mesothalamic dopaminergic hypoactivity enables the oscillatory behavior of T_y. SN spikes every 150ms and $\hat{g}_{d4}$ = 0.9.
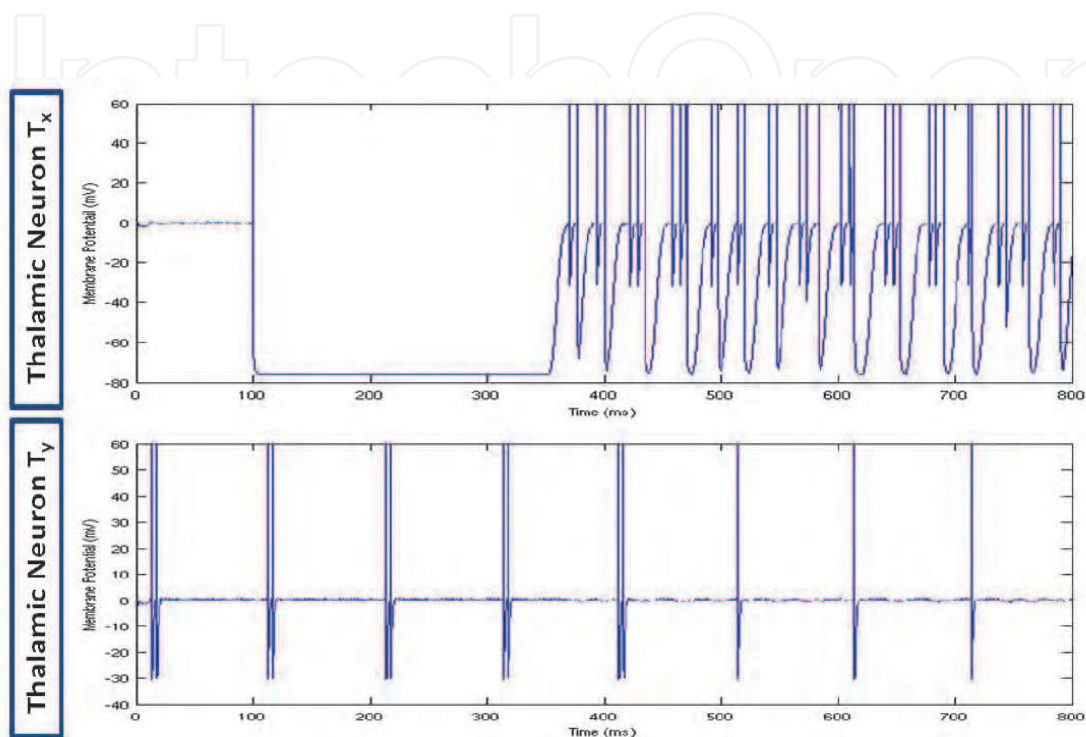
Fig. 5. The distinct spiking modes of T_x and T_y. When SN spikes every 100ms and $\hat{g}_{d4} = 0.9$, T_x presents the burst mode of spiking.

Also with the SN neuron set to spike each 100ms, we started a 800ms-experiment with the parameter $\hat{g}_{d4} = 0.9$. This time, however, we turned $\hat{g}_{d4}$ to 1.0 after 350ms. It is plausible to interpret such alteration in the $\hat{g}_{d4}$ value as a consequence of some increase in the dopaminergic level, due to an exogenous factor. In this case, both T_x and T_y start to oscillate. The last situation presented in Table 6 refers to the extreme case of mesothalamic hyperactivity. During a 800ms-experiment, the interval between spikes in the SN was set to 5ms. In addition, at the beginning we imposed a high activation in receptor D4 with $\hat{g}_{d4} = 1.1$. This dopaminergic context inhibited the TRN neurons, which suffer even a hyperpolarization. It was, however, the imposed decrease of $\hat{g}_{d4}$ to 0.8, after 350ms, that starts the burst mode in both *TRN* neurons. In this case, the lowering in the dopaminergic receptor activity enables the *TRNs* membrane potential to reach a threshold value that triggered LTS in such neurons. Figure 6 illustrates such situation.
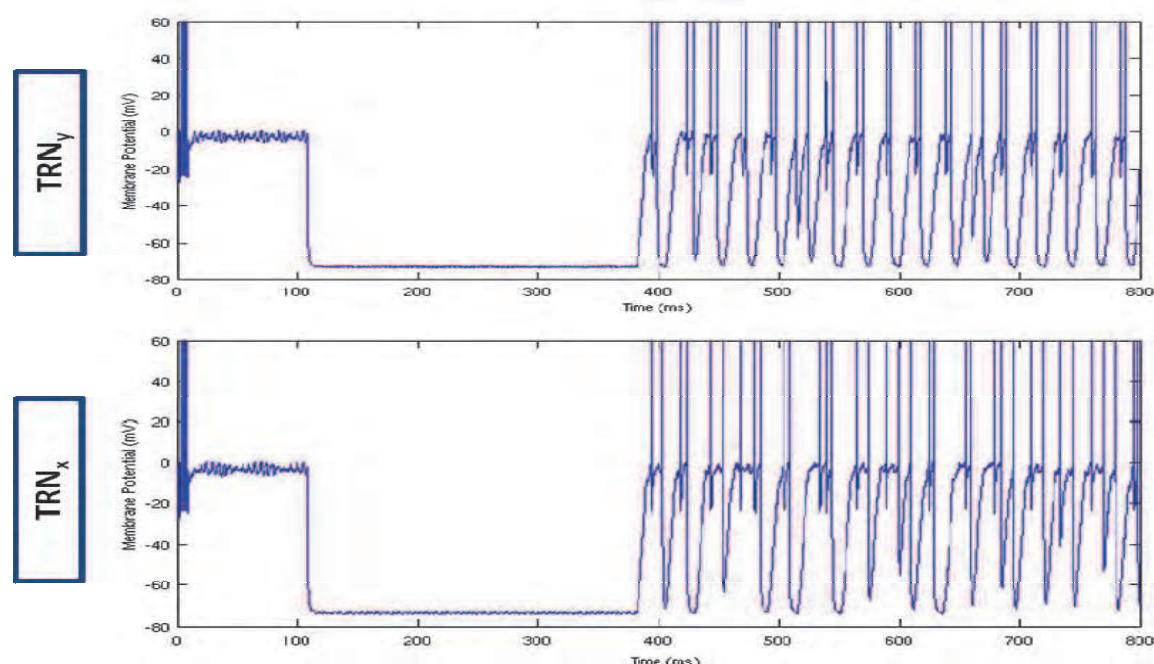
Fig. 6. Decrease in receptor D4 activation, under mesothalamic dopaminergic hyperactivity, originates the burst state in both TRN_x and TRN_y.

4. Discussion

Overall, the current knowledge in neuroscience conducts us through a multiscale world. The understanding of whatever peculiarity the human behavior exhibits requires us to travel throughout our brain's different levels of organization. In particular, this is the case with sleep neuroscience.

Here, we speculate the dopaminergic influence on neuron states associated to sleep and sleep alterations in PD. Our ideas, however, should be considered by keeping in mind the broad cascade of events that underlies the wake-sleep cycle.

Environmental as well as genetic factors trigger networks of intra and inter cellular signals, which promote the specific characteristics associated to wake or sleep states. For instance, due to the light impinging on the retina, signals from circadian oscillators reach specific hypothalamic regions. Such areas regulate the action of distinct brain systems associated to the different responses that an organism presents throughout the sleep-wake cycle. In this sense, the hypothalamus regulates wake-sleep switches through its suprachiasmatic, subparaventricular and dorsomedial nuclei; together with the basal forebrain, it controls ascending arousal systems, through its ventrolateral preopitic, lateral and tuberomammilary nuclei. The hypothalamus also regulates brainstem nuclei, as dorsal raphe and locus ceruleus, which control the cyclic transition between the rapid eye movement (REM) and non-REM (NREM) sleep phases. On the other hand, projections from such brainstem and diencephalon ascending arousal systems reach cortical and thalamic areas, known to be involved in the origin and maintenance of different brain rhythms that specifically underlie some sleep states (Pace-Schott & Hobson, 2002; Hobson & Pace-Schott, 2002).

Brain rhythms reflect the spike mode occurring in groups of neurons. And, as revealed by polysonographic recordings, the wake state as well as the NREM and REM sleep phases, are defined, each one, by characteristic field potential oscillations (Pace-Schott & Hobson, 2002;

Hobson & Pace-Schott, 2002). Accordingly, each behavioral state presents distinct cognitive activities and conscious experiences. Throughout the night, there is a cyclic occurrence of NREM and REM sleep phases, where the NREM stage is composed by the slow wave sleep (SWS) - that includes the sleep stages 3 and 4, besides the lighter sleep stages 1 and 2. In particular, the SWS is characterized by rhythms known as slow oscillations, spindles and sharp wave-ripples (Pace-Schott & Hobson, 2002; Hobson & Pace-Schott, 2002; Hobson, 2009; Diekelmann & Born, 2010).

Thalamocortical systems are highly involved in the achievement of oscillations associated to the SWS, in special, slow oscillations and spindles (Steriade et al., 1993; Steriade, 2006). Whereas slow oscillations originate at the cortex and propagate to the thalamus, the spindles have their origins in the thalamus and propagate to the cortex mediated by the TRN pacemaker (Steriade et al., 1993; Llinás & Steriade, 2006; Steriade, 2006). In both cases, however, the origin of the oscillatory pattern is associated to some strong inhibition leading to a consequent burst mode of spiking. More, according to (Steriade et al., 1993), different types of rhythms may appear depending on the magnitude of such inhibitory event.

Indeed, the cholinergic and noradrenergic neuromodulatory systems are known to regulate the neurophysiologic aspects underlying the brain rhythms in the NREM and REM sleep phases (Diekelmann & Born, 2010). However, the experiments revealing the existence of the mesothalamic dopaminergic pathway (Freeman et al., 2001) made it possible to hypothesize on the dopaminergic influence on neuron states associated to sleep (Pace-Schott & Hobson, 2002).

In this work, we propose that the mesothalamic dopamine action in the thalamocortical circuit is able of generating oscillatory patterns that are typical in sleep states, both in thalamic and TRN neurons, depending on the level of dopaminergic activity. In particular, we consider that the dopaminergic alteration in PD is an essential factor underlying the sleep problems observed in such disease. In this case, both the dopaminergic hypoactivity - due to the SN neurons degeneration -, and the increases in the dopaminergic activity due to the appliance of dopamine-related drugs, would contribute to the appearance of sleep alterations.

Basically, our computational simulations explore two ways by which mesothalamic dopamine may affect the thalamocortical dynamics: the SN activity and the dopamine receptor D4 activation. Overall, we conclude that an extreme dopaminergic mesothalamic hypoactivity favors the appearance of the burst mode in thalamic neurons. Conversely, a high degree of dopaminergic mesothalamic hyperactivity propitiates such an oscillatory rhythm in the TRN neurons. In addition, our simulations hint that, when the SN activity is markedly diminished, a slight factor inducing an increase in the receptor D4 activation triggers the bursting pattern in thalamic neurons. On the other hand, the application of some agent that lowers the D4 activation, under a situation of extreme mesothalamic dopamine hyperactivity, enables the burst mode in the TRN.

In the context of PD, such results point anomalous somnolence as a consequence of the lack of dopamine, due to the SN degeneration. More, neural sleep states may appear as a consequence of drugs administration to increase the dopamine action, when the SN activity is highly disrupted. Another situation we consider important to emphasize refers to the dopaminergic hyperactivity case. Due to the lifelong need of medication for equilibrating the nigral dopaminergic level, PD patients usually present symptoms related to excess of dopamine (March, 2005). We illustrate such situation by increasing the dopaminergic activity. We then observe that a slight diminishing in the receptor D4 activation induces the

burst mode of spiking in the TRN. Since the TRN plays an essential role in the consolidation of brain rhythms associated to sleep states, it is plausible supposing that such unnatural dopaminergic hyperactivity underlies the emergence of some spurious sleep states, via TRN, in PD. On the other hand, with relation to the thalamic neurons, such dopaminergic hyperactivity prevents them from entering into an oscillatory state. It thus suggests that symptoms pointing to lack of sleep may have origins in the abnormal presence of high dopaminergic activity, due to drug administration. This situation would also contribute to the understanding of why, in PD, a night of sleep deprivation is commonly followed by a daytime of high alertness (Rye et al., 2000).

Our results agree with the striking ideas exposed in (Dzirasa et al., 2006), which shows that dopamine does play a role in the control of the sleep-wake cycle. Here, through a neurocomputational model, we indicate possible ways by which sleep-related states should emerge as a consequence of alterations in the mesothalamic dopamine activity.

Altogether, this work proposes a link between sleep neuroscience and PD. Through a mathematical and computational approach, we infer that the dopaminergic alterations in PD reach brain nuclei highly engaged in the control of rhythms that characterize different sleep states. Therefore, the presence of anomalous dopaminergic activities facilitate the appearance of spurious sleep states, not achieved in normal conditions through the brain systems directly associated to the circadian control of the sleep-wake cycle.

5. Acknowledgments

6. References

Andrade LAF, Ferraz HB. Quadro clínico. In: Meneses MS, Teive HA (Eds). Doença de Parkinson. Rio de Janeiro: Guanabara Koogan, 2003:80-90.

Arnulf I and Leu-Semenescu S. Sleepiness in Parkinson's Disease. *Parkinsonism and Related Disorders* 1553, S101-S104 (2009).

Braak H, Rüb U, Sandmann-Keil D, Gai WP, de Vos RA, Jansen Steur EN, Arai K, Braak E. Parkinson's disease: affection of brain stem nuclei controlling premotor and motor neurons of the somatomotor system. *Acta Neuropathol* 99, 5:489-95 (2000).

Carvalho LAV. Modeling the Thalamocortical Loop. *International Journal of Bio-Medical Computing* 35, 267-296 (1994).

Carvalho LAV and Roitman VL. A Computational Model for the Neurobiological Substrates of Visual Attention. *International Journal of Bio-Medical Computing* 38, 33-45 (1995).

De Cock VC, Vidailhet M, Arnulf I. Sleep Disturbances in Patients with Parkinsonism. *Nature Clinical Practice Neurology* 4 (5), 254-266 (2008).

De Gennaro L and Ferrara M. Sleep Spindles: An Overview. *Sleep Medicine Reviews* 7, 5,432-440 (2003).

Diekelmann S and Born J. The Memory Function of Sleep. *Nature Reviews Neuroscience* 11, 114-126 (2010).

Dubois B, Pillon B. Cognitive deficits in Parkinson's disease. J Neurol. 1996;244:2–8.

Dzirasa K, Ribeiro S, Costa R, Santos LM, Lin S-C, Grosmark A, Sotnikova TD, Gainetdinov RR, Caron MG, Nicolelis MAL. Dopaminergic Control of Sleep-Wake States. *The Journal of Neuroscience* 26, 41, 10577-10589 (2006).

Florán B, Florán L, Erlij D, Aceves J. Activation of dopamine D4 receptors modulates [3H]GABA release in slices of the rat thalamic reticular nucleus. Neuropharmacology 2004;46:497-503.

Freeman A, Ciliax B, Bakay R, et al. Nigrostriatal collaterals to thalamus degenerate in parkinsonian animal models. Ann Neurol 2001;50:321-329.

Guillery RW, Harting JK. Structure and connections of the thalamic reticular nucleus: advancing views over half a century. J Comp Neurol 2003;463:360-371.

Hobson JA and Pace-Schott EF. The Cognitive Neuroscience of Sleep: Neuronal Systems, Consciousness and Learning. *Nature Reviews Neuroscience* 3, 679-693 (2002).

Hobson JA. REM Sleep and Dreaming: Towards a Theory of Protoconsciousness. *Nature Reviews Neuroscience* 10, 803-813 (2002).

Jankovic J. Emerging Views of Dopamine in Modulating Sleep/Wake State from an Unlikely Source: PD. *Neurology* 58 (3), 341-346 (2002).

Jeanmonod D, Magnin M, Morel A. Low-threshold Calcium Spike Bursts in the Human Thalamus: Common physiopatology for sensory, motor and limbic positive symptoms. *Brain* 119, 363-375 (1996).

Kandel, E.R., Schwartz, J.H. and Jessel, T.M., 2000, *Principals of neuroscience*. 4ed. International Edition: Mc-Graw Hill.

Llinás RR and Steriade M. Bursting of Thalamic Neurons and States of Vigilance. *Journal of Neurophysiology* 95, 3297-3308 (2006).

Llinás RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical Dysrhythmia: A Neurological and Neuropsychiatric Syndrome Characterized by Magnetoencephalography. *Proceedings of the National Academy of Science* 96, 26, 15222-15227 (1999).

Madureira DQM, Carvalho LAV, Cheniaux E. Attentional Focus Modulated by Mesothalamic Dopamine: Consequences in Parkinson's Disease and Attention Deficit Hyperactivity Disorder. *Cognitive Computation* 2, 1, 31-49. DOI 10.1007/s12559-009-9029-4 (2010).

Madureira DQM, Carvalho LAV, Cheniaux E. Modelagem Neurocomputacional do Circuito Tálamo-cortical: Implicações para Compreensão do Transtorno de Déficit de Atenção e Hiperatividade. *Arq. Neuro-Psiquiatr.* 65, 4a, 1043-1049 (2007).

March L. Psychosis in Parkinson's Disease. *Primary Psychiatry* 12, 7, 56-62 (2005).

McCormick, D.A., Connors, B.W., Lighthall, J.W. and Prince, D.A., 1985, Comparative electrophysiology of pyramidal and sparsely spiny stellate neurons of the neocortex. *Journal of Neurophysiology*, 54, 782-806.

Pace-Schott EF and Hobson JA. The Neurobiology of Sleep: Genetics, Cellular Physiology and Subcortical Networks. *Nature Reviews Neuroscience* 3, 591-605 (2002).

Rye DB, Bliwise DL, Dihenia B, Gurecki P. Daytime Sleepiness in Parkinson's Disease. *Journal of Sleep Research* 9, 63-69 (2000).

Rye DB. Parkinson's Disease and RLS: The Dopaminergic Bridge. *Sleep Medicine* 5, 317-328 (2004).

Steriade M, McCormick DA, Sejnowski TJ. Thalamocortical Oscillations in the Sleeping and Aroused Brain. *Science* 262, 679-685 (1993).

Steriade M. Grouping of Brain Rhythms in Corticothalamic Systems. *Neuroscience* 137, 1087-1106 (2006).
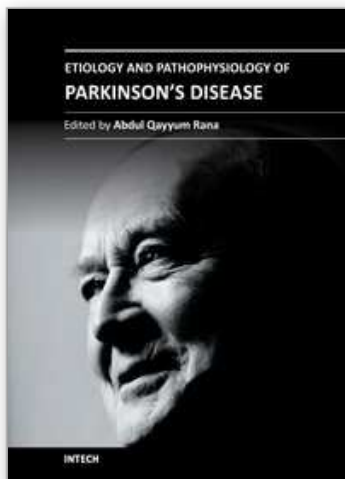
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Edited by Prof. Abdul Qayyum Rana

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