Influence of nicotine and alcohol on sleep and implications on insomnia: the reward-attention circuit model

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Abstract

Dopamine, a neurotransmitter well known for regulating movement, reward, and learning, is emerging as one of the neuromodulators of wakefulness. Drugs that increase the level of dopamine in the brain (including, but not limited to, nicotine) also increase feelings of wakefulness. Diseases that are characterized by low dopamine levels, like Parkinson’s disease, also are related to sleep disorders.

In this work we investigate the influence that nicotine and alcohol exert on sleep, modeling the coupling of reward and thalamocortical circuits in a reward-attention circuit. Computer simulations of the circuit reflect the spiking behavior of neurons in the network under the presence or absence of nicotine or alcohol.

Each neuron in the reward-attention model represents a population of cells in the circuit, and is described by a coupled system of nonlinear differential equations that replicates essential neurophysiological properties of the population. The computational simulations highlight aspects of clinical insomnia symptoms in Parkinson’s disease, attention deficit hyperactivity disorder and autism spectrum disorder.

Our results imply that nicotine can disrupt sleep, promoting wakefulness. In contrast, alcohol increases sleep latency (time to fall asleep). Also, the simulations suggest that alcohol has a sedative effect in people with insomnia.

Keywords: Nicotine, Alcohol, Dopamine, Sleep, Parkinson’s disease, Autism spectrum disorder, Attention deficit hyperactivity disorder,

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1. Introduction

Besides being the main gateway of sensory information to the cerebral cortex, the thalamus is also the first station at which incoming signals can be blocked by synaptic inhibition during sleep. This mechanism contributes to the shift that the brain undergoes as it changes from an aroused state, open to signals from the outside world, to the closed state of sleep [1, 58].

Growing evidence points to a central role of dopamine in regulating sleep-wake states. Stimulants enhancing dopaminergic tone are among the most potent wake-promoting substances known [2] and their arousing effects are abolished in mice deficient in dopamine signaling [3, 4]. Partial dopamine depletion causes disturbances of REM sleep without affecting motor functions [5]. Humans with reduced levels of dopamine reuptake transporter display altered slow-wave activity following sleep deprivation [6].

In the last decade, morphological evidence showing that the thalamic reticular nucleus (TRN) has significant dopaminergic innervation originating in the substantia nigra pars compacta (SNpc) began to emerge [7, 8].

The TRN plays a central role in the control of attention while attention deficit hyperactivity disorder (ADHD) is associated with genetic abnormalities of dopamine D4 receptors [9, 10]. The results of [7] suggest that abnormal dopaminergic transmission in NRT may generate at least some of the symptoms of ADHD.

Based on this experimental evidence, we proposed a neurocomputational model to investigate the influence that nicotine exerts on attention focusing and its consequences on ADHD [11]. Justified by synaptic projections the nucleus accumbens (NAcc) sends to the substantia nigra (SN) [12], our neurocomputational model investigates the influence of nicotine on attention through the interaction between the reward and thalamocortical circuits. Nicotine and alcohol share many common molecular and cellular targets. Using the same circuits, we next studied [13] the influence that alcohol exerts on the focus of attention and consequences on autism spectrum disorder (ASD). Our approach highlights the importance of subcortical systems in attentional mechanisms, in particular the dopaminergic role in the thalamocortical circuit.

Here, we extend this model to address how nicotine and alcohol influence sleep. More specifically, computational simulations of the model circuit pro-
vide numerical results that describe the spiking activity of the subsystems comprising the network. Each neuron in the model represents the cell population of the corresponding subsystem, and is modeled by a system of coupled differential equations that captures the electrophysiological characteristics of the population, both in the presence or absence of nicotine or alcohol.

Insomnia is defined as the symptom of difficulty in falling asleep, repeated awakenings with difficulty in returning to sleep, or sleep that is nonrestorative or poor in quality, often accompanied by the perception of short overall sleep duration. Moreover, insomnia is the most prevalent sleep disorder in people with Parkinson’s disease [14], ADHD [15] and ASD [16]. In our previous works [11, 13], these disorders were used as an application of our model to observe the focus of attention on individuals affected by them. Here, we will use insomnia as something in common to these diseases.

This article is structured in the following way. Sections 2 and 3 describe, respectively, the neurophysiology of the considered circuit and its modeling. Section 4 explains the design of the computational simulations. The results of the simulations are presented in Section 5, followed by a discussion in Section 6. Finally, the Appendix contains tables describing the acronyms and a glossary of the parameters.

2. Architecture of the reward-attention circuit

The architecture of the reward-attention network is shown in Figure 1. Based on neurophysiological and neurochemical aspects, the reward-attention circuit model addresses the interaction between the reward and thalamocortical circuits.

In our model, the reward circuit [12, 17, 18] is represented by the prefrontal cortex (PFC), and the VTA and NAcc regions. The thalamocortical [19, 20, 21] circuit includes the PFC, thalamus and the thalamic reticular nucleus (TRN). The communication between these circuits is established through the SNpc, which inhibits the TRN and receives inhibitory projections from the NAcc and SNpr. The pedunculopontine nucleus (PPN), in turn, excites the SNpc.

Approximately half of the dopaminergic (DA) neurons in the midbrain are spontaneously active, i.e., they have a current in pacemaker activity that is independent of external stimuli [22]. The dopaminergic neurons (found mainly in the lateral VTA and in the substantia nigra compacta) display
Figure 1: **Architecture of the reward-attention circuit.** Excitatory synapses (continuous lines), inhibitory synapses (dotted lines). (Left) Basic reward-attention circuit. As a consequence of the nicotinic stimulus, the PFC excites the VTA. In the VTA, nicotine and the glutamate that is released by the PFC stimulate the GABAergic interneurons and the dopaminergic neurons to release their respective neurotransmitters. Therefore, the GABAergic cells inhibit the dopaminergic ones, while these keep synaptic connections with the NAcc. In the sequence, the NAcc GABAergic neurons inhibit the dopaminergic neurons at the SN. On the other hand, the stimuli \( x \) and \( y \) excite the neighboring thalamic areas \( T_x \) and \( T_y \), respectively. Excitatory projections from both \( T_x \) and the PFC stimulate the \( TRN_x \), which inhibits the thalamic area \( T_y \). The same happens with \( T_y \), inhibited by \( TRN_y \). The dopaminergic neurons at the SNpc modulate the \( TRN_x \) and \( TRN_y \) activation by inhibiting such area. (Right) Inclusion of alcohol in the circuit. Alcohol stimulates the PFC and the VTA in the reward circuit. As a consequence, the PFC excites the VTA. In the VTA, alcohol and the glutamate that is released by the PFC stimulate the GABAergic interneurons and the dopaminergic neurons to release their respective neurotransmitters. The rest of the circuit is the same as the one on the left.

Various modes of firing activity *in vivo*, including tonic and phasic activation [23, 24]. The tonic activity involves slow irregular patterns of single action potentials, whereas the phasic activity involves short-latency bursts of action potentials. The tonic firing is driven by a pacemaker current, and the transition from one mode to the other has been associated with sensory responses and drug effects [25].

In the reward circuit (Figure 1-Left), the burst activity of dopamine neurons plays an important physiological role. Brief periods (approximately 300
ms) of dopamine neuron bursts are particularly apparent at presentation of primary rewards or their associated cues [26]. Also, it was shown that as regards the functional efficiency of DA neurons, the burst firing increased DA release to a greater degree than firing frequency [27].

In our model, nicotine or alcohol is responsible for activating the reward circuit. The psychopharmacological mechanism involved is the direct action of nicotine on the nicotinic acetylcholine receptors (nAChR). There are two types of nicotinic receptors in the reward circuit, the \( \alpha_7 \) and the \( \alpha_4\beta_2 \), which, for simplicity, we denote by \( \alpha_7^+ \) and \( \alpha_7^- \). Nicotine acts on the axonic terminals of PFC neurons and, as a result, glutamate is released into the VTA [28, 29].

In the VTA, nicotinic and glutamatergic receptors are activated by nicotine and glutamate, respectively, stimulating the GABAergic interneurons and the dopaminergic neurons. The activity of the GABAergic interneurons lasts only a few minutes, due to the \( \alpha_7^- \) receptors, which become inactive faster than the \( \alpha_7^+ \) receptors. Dopaminergic neurons, in turn, continue to receive excitatory inputs from cortical glutamatergic neurons, even after the termination of stimuli from inhibitory GABAergic interneurons.

In the alcohol case (Figure 1-Right), the impacts caused by alcohol consumption are mediated by some target sites in the brain, stimulating transmission at GABAergic synapses, and can inhibit the function of glutamatergic receptors [30, 31]. However, glutamatergic transmission can differ in other brain regions. Acute application of alcohol to VTA brain slices enhances glutamatergic transmission onto DA neurons [32]. Represented by PFC and interneurons in VTA, glutamatergic and GABAergic neurons, respectively, are activated by alcohol in our model. These, in turn, are afferents to the VTA dopaminergic neurons.

NMDAR activation in the VTA is necessary for dopamine neuron burst firing and phasic dopamine release in projection areas that occur in response to rewards or reward-predicting stimuli [33, 34]. Studies report that repeated \textit{in vivo} exposure to nicotine or alcohol causes enhancement of long-term potentiation (LTP) of NMDAR-mediated transmission in VTA dopamine neurons [29, 35]. This form of NMDAR metaplasticity results from an amplification of action potential-evoked Ca\(^{++}\) [36], which amplifies the hyperpolarization phase of the action potential [37]. One of the ions carried by the NMDA current is calcium, which is a major player in long-term neural changes. This ion current is also thought to play a role in maintaining persistent activity required for short-term memory [38].

Moreover, alcohol increases the spontaneous firing frequency of VTA DA
neurons in a concentration-dependent manner [39, 40].

Thus, the interaction between the membrane’s ionic currents and the afferent synaptic inputs contributes to accelerate or decelerate the firing activity of DA neurons, depending on the need to optimize dopamine release. VTA DA neurons project to NAcc GABAergic neurons, the final site currently associated with the pleasure sensation triggered by nicotine or alcohol.

From there, the NAcc and SN connect the reward and the thalamocortical circuits and also inhibit the DA neurons in the SNpc. Neurons in the SNpr provide GABAergic afferents to SNpc DA neurons.

An early in vivo recording study demonstrated that systemic administration of alcohol suppresses the firing of neurons in the SNpr [41].

Let us assume that electrical signals due to two external stimuli, \( x \) and \( y \), are conveyed through excitatory pathways to two neighboring thalamic regions \( T_x \) and \( T_y \), respectively. Once stimulated, \( T_x \) activates the \( TRN_x \) beyond collaterals of an ascending glutamatergic projection, with the PFC as the final destination. Since we do not explicitly model the cortical region related to the thalamocortical circuit, such excitatory projection ends up in the TRN. Also, through an excitatory glutamatergic descending pathway, the cortical region increases the activation of \( T_x \) and also sends collateral axons to the \( TRN_x \).

Once activated, the \( TRN_x \), through its GABAergic projections, inhibits the thalamic region \( T_y \) in the neighborhood of \( T_x \). Our model addresses the \( TRN_x \) area stimulated by the thalamic region \( T_x \) and the PFC. Summarizing, the thalamocortical circuit activation by an external stimulus \( x \) excites a central thalamic region \( T_x \) and inhibits its neighborhood, represented by the region \( T_y \).

Furthermore, the \( TRN_x \) receives dopaminergic inhibitory projections from the SNpc. Accordingly, a rise in the nigral dopamine release contributes to the \( TRN_x \) deactivation, thus leading to a more active thalamic region \( T_y \). Conversely, a reduction in the SNpc dopaminergic level makes the TRN more excited and increases the inhibition on \( T_y \). A symmetric case involves the \( T_y \) and \( TRN_y \) neurons, as illustrated in Figure 1.

Thalamic neurons are able to spike under tonic and burst states [1, 42]. 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 [11, 13, 20].
Conversely, under the burst state thalamic neurons are no longer reliable channels through which neural representations from sensorial inputs reach the cerebral cortex. The burst mode of activity underlies the thalamic behavior during sleep [1, 43]. In this condition, environmental stimuli are not perceived consciously as it occurs during wakefulness. The thalamic burst mode also permeates epileptic episodes during which environmental information is not processed reliably [44]. The dynamics of the ionic channels under the burst mode are different from the ones underlying the thalamic tonic state.

Overall, our working hypothesis is that the NAcc activity influences the SN behavior, which modulates the thalamocortical circuit, and that the presence of nicotine or alcohol is powerful enough to bias the NAcc activation.

Since the inattention symptoms addressed in our previous models [11, 13] concerned wake individuals, the reward-attention model considered the behavior of thalamic neurons under the tonic state. In the present work, we extend our previous studies and scrutinize relationships between the nigral dopaminergic activity and the oscillatory state of neurons in the thalamic complex. Doing so, it becomes possible to widen the investigation to examine a possible mesothalamic dopaminergic activity contribution to sleep alterations in presence of nicotine or alcohol.

In the next section, we present the systems of equations that model the behavior of the neurons described in this section.

3. Mathematical formulation

In Section 2 we presented the architecture of our modeled network, which includes all connections among the 12 areas involved in the reward-attention model. Each modeled area refers to a population of neurons with similar behavior. The model is based on homogenization theory. Such approach replaces differential equations with multiscale features by simpler systems [45, 46, 47]. For a discussion of homogenization in neuroscience, see [48]. In our case, we model a whole region through equations describing a spiking neuron. This approach was previously applied elsewhere [11, 13, 19, 20, 49]. Moreover, each connection depicted in Figure 1 represents a synaptic (excitatory or inhibitory) projection through which an area influences other area. And the currents that operate in each modeled neuron — which represents a homogeneous neural population — are based on the neurochemical aspects also described in Section 2.
From a mathematical point of view, we describe the neurons using the integrate-and-fire formalism [50] according to which a neuron fires when it reaches threshold. This simple neuron model is suitable for network simulations and can be adapted to simulate a broad class of neuronal behavior. We consider single-compartment neurons with membrane potential \( V \) \[51, 52\].

The membrane equation is given by

\[
\begin{align*}
C_i \frac{dV_i}{dt} &= \sum_{j=1}^{J_i} I_i^j + I_{\text{ext}} \quad \text{for } t \in (0, T] \text{ and } V_i < \theta_{\text{Na}}, \\
V_i(0) &= V_i^0,
\end{align*}
\]

where \( i = 1, \ldots, n \) refers to each of the \( n \) neurons in the network, \( C_i \) denotes their capacitances, and \( J_i \) is the number of ionic currents \( I_i^j \) being modeled in the \( i \)th neuron. The external currents \( I_{\text{ext}} \) are due to eventual influences of the synaptic currents and the presence of nicotine or alcohol and will be described further below. Finally, \( \theta_{\text{Na}} \) is a fixed, predefined constant. The currents are defined as \( I_i^j = g_j(V_i)(E_j - V_i) \), where \( g_j \) is the conductance and \( E_j \) is the Nernst potential corresponding to the \( j \)th ion. The physiological characteristics of each neuron are modeled by the conductances \( g_k \)s, which might not only depend on \( t \) explicitly but also on previous values of \( V_i \) itself, through, for instance, additional differential equations.

As an exception, the sodium current is not represented as described above. It is activated by the action of the Heaviside function \( \Theta : \mathbb{R} \to \{0, 1\} \), defined by

\[
\Theta(x) = \begin{cases} 
1 & \text{if } x \geq 0 \\
0 & \text{if } x < 0,
\end{cases}
\]

applied to \((V_i - \theta_{\text{Na}})\), where \( \theta_{\text{Na}} \) is a fixed constant.

After a spike, the conductance \( g_k \) of the restoring current \( I_K \) increases rapidly, bringing the neuron back to the resting potential. This process is described in general by

\[
\frac{dg_k}{dt} = \frac{\beta_K \Theta(V - \theta_{\text{Na}}) - g_k}{\tau_k} \quad \text{for } t \in (0, T], \quad g_k(0) = g_k^0
\]

where the constants \( g_k^0, \beta_K \) and \( \tau_k \) are, respectively, the initial state of \( g_k \), the variation rate of \( g_k \), and the time constant associated with the potassium channel. The above equation actually holds for all neurons, with \( V \) being replaced \( V_i \), \( g_k \) replaced by \( g_{k,j} \), etc.
The external currents $I_{ext}$ acting on the $i$th neuron can be given by synaptic currents of the form $g_{syn}(t)(E_{syn} - V_i)$ and by $alcohol$ (see (3)) due to the presence of alcohol.

The synaptic conductances $g_{syn}$ reflect the level of a neurotransmitter released by the pre-synaptic neuron, being described by

$$g_{sin}(t) = \hat{g}_{sin} \sum_j (t - t_j) \exp \left(-\frac{t - t_j}{t_p}\right) \Theta(t - t_j),$$

where the times $t_j$, with $j = 1, \ldots, N$, are the spiking times of a presynaptic cell, while the constant $\hat{g}_{sin}$ is the maximal conductance. 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.

All the neurons in the network, therefore, present sodium and potassium ionic currents, and synaptic currents. However, each neuron receives distinct neurotransmitters according to its specific afferents. Besides the currents involved in the action potential, there are those associated with particular properties of each neuron. Next, we describe them.

The nicotine or alcohol (at different times) acts on the cortical neuron as an external current. The nicotine operates through the $\alpha_7$ receptors. The variation in the number of activated $\alpha_7^+$ receptors is given by the solution of the equation

$$\frac{d\alpha_7^+}{dt} = k_1 \alpha_7^- n_{ic} - k_2 \alpha_7^+ \quad \text{for} \quad t \in (0, T], \quad \alpha_7^+(0) = \alpha_7^{+,0}, \quad (1)$$

where $\alpha_7^{+,0}$, $\alpha_7^-$, $k_1$ and $k_2$ are constants, and $n_{ic} : (0, T] \rightarrow \mathbb{R}$ is solution to the following differential equation

$$\frac{dn_{ic}}{dt} = -M_1 n_{ic} \quad \text{for} \quad t \in (0, T], \quad n_{ic}(0) = n_{ic}^0, \quad (2)$$

where $M \in n_{ic}^0 \in \mathbb{R}$.

In its turn, the action of alcohol is represented by $alcohol : (0, T] \rightarrow \mathbb{R}$, which is solution to the following differential equation

$$\frac{dalcohol}{dt} = -M_2 alcohol \quad \text{for} \quad t \in (0, T], \quad alcohol(0) = alcohol^0, \quad (3)$$

where $M \in alcohol^0 \in \mathbb{R}$.
The NMDA current in the VTA dopaminergic neurons is triggered by the conductance $g_{\text{NMDA}} = \bar{g}_{\text{NMDA}} h(t) B(V_3)$, where $V_3$ is the voltage of the VTA dopaminergic neuron, and $h(t)$ denotes the fraction of open channels and satisfies

$$\frac{dh}{dt} = a_r (1 - h) \mathcal{T}(V_1) - a_d h \quad \text{for } t \in (0, T], \quad h(0) = h^0.$$ 

The parameters $a_r = 0.072 \text{ mM}^{-1}\text{ms}^{-1}$ and $a_d = 0.0066 \text{ ms}^{-1}$ characterize the rate of increase and decay of the conductance, respectively. The function $\mathcal{T}$ depends on the cortical neuron as follows

$$\mathcal{T}(V_1) = \frac{T_{\text{max}}}{1 + e^{-(V_1 - V_T)/k_p}},$$

where $T_{\text{max}} \in \mathbb{R}$ is the maximum concentration of neurotransmitters in the synaptic cleft, $V_1$ is the voltage of the cortical neuron, $k_p = -5\text{mV}$ is the decay of neurotransmitters and $V_T = -10\text{mV}$ represents the value at which the function is activated.

The term $B(V_3)$ models the blocking of the ion channel by magnesium [53],

$$B(V_3) = \frac{1}{1 + e^{-(V_3 - V_T)/16.13}},$$

where $V_T = 16.13 \ln \left(\frac{[\text{Mg}^{++}]_{3.57}}{3.57}\right)$ is the half activation.

As the NMDA receptors open, calcium ions enter the cell. The calcium conductance $g_c = \bar{g}_c [Ca]$ is proportional to the intracellular calcium, with the constant rate $\bar{g}_c$. The equation describing the concentration of calcium in the cell is given by

$$\frac{d[Ca]}{dt} = \frac{\beta_{[Ca]} \Theta(V_3 - \theta_{\text{Na}}) - [Ca]}{\tau_{[Ca]}} \quad \text{for } t \in (0, T], \quad [Ca](0) = [Ca]^0, \quad (4)$$

where $[Ca]^0$ is the initial condition, and the constants $\beta_{[Ca]}$ and $\tau_{[Ca]}$ represent the rate of the calcium concentration variation and a time constant. The function $\Theta(V_3 - \theta_{[Na]})$ raises the calcium concentration whenever there is a neuronal spike. When the intracellular calcium concentration reaches a threshold value $\theta_{[Ca]}$, the $K^+$ ion channels of the hyperpolarizing current $I_{\text{ahp}}$ open and the conductance $g_{\text{ahp}}$ increases at rate $\beta_{\text{ahp}}$. This is represented by the equation,

$$\frac{dg_{\text{ahp}}}{dt} = \beta_{\text{ahp}} \Theta([Ca] - \theta_{[Ca]}) - g_{\text{ahp}} \quad \text{for } t \in (0, T], \quad g_{\text{ahp}}(0) = g_{\text{ahp}}^0.$$
where $\tau_{ahp}$ is a time constant.

The pacemaker current is described by $I_{pm} = g_{pm}(V_3 - E_{pm})$, where $g_{pm}$ and $E_{pm}$ are constants if there is no alcohol use. In the case that $a_{\text{coho}}^0 \neq 0$, $g_{pm}$ is described by $g_{pm} = g_{pm}^0 + a_{\text{coho}}$, where $a_{\text{coho}}$ is as in (3).

Dopamine inhibits the $TRN_x$ and $TRN_y$ neurons, and we assume that the final target of the dopaminergic action is the calcium-dependent potassium channel \[7\]. Its conductance $g_{k-c} = \hat{g}_c D_4^* S([Ca])$ suffers the dopaminergic influence through the receptor $D_4^*$ and depends on the intracellular calcium concentration. In the above formula, $\hat{g}_c$ is a proportionality constant and the sigmoid function $S([Ca])$ describes the increase in intracellular calcium concentration due to the neuronal spike,

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

where the constant $\alpha$ controls the slope of $S$.

The calcium concentration is described as in (4), with $V_3$ being replaced by $V_{10}$. Note that $g_{k-c}$ increases and inhibits the cell if the cell is excited beyond a threshold. The dopaminergic action on the $D_4^*$ receptor represents the ups and downs of the dopaminergic level according to the equation

$$D_4^*(t) = \hat{g}_{d4} \sum_j (t - t_j) \exp \left( -\frac{t - t_j}{t_{pd}} \right) \Theta(t - t_j),$$

where $t_{pd}$ stands for the peak time and $\hat{g}_{d4}$ is the conductance constant of the dopaminergic projection.

The differential equations are discretized in time using the Euler’s method. In the Appendix A, Table 1 presents a glossary of all parameters with their respective values.

4. Simulation methods

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 previously by us \[11, 13\], because our major concern was the influence of the nicotine/alcohol on attentional focus formation.
Here, we explore this inhibitory feedback to inspect how the degree of TRN activity influences the excitatory state of the thalamus. In summary, our simulations illustrate how dopamine from SNpc modulates the activation of TRN neurons and, consequently, of thalamic cells. The SN, in turn, receives projection from the reward circuit.

During sleep, there is a cyclic occurrence of rapid eye movement (REM) and non-REM (NREM) sleep phases, where the NREM stage is composed by the slow wave sleep (SWS) phase, which includes the sleep stages 3 and 4, and the lighter sleep stages 1 and 2.

Here, we consider that in the waking state the thalamic neurons fire in tonic mode and when falling asleep in burst mode.

Prior to conducting experiments to address the network behavior, we calibrate each neuron separately, according to their specific neurophysiological properties [11, 13], before they are included in the network.

4.1. Baseline case

In this section, we describe a series of simulations performed using an artificial neural network that presents the architecture illustrated in Figure 2. Since such network is the one used earlier by us [11, 13], we set it as our departure point.

Initially, our simulations consider a “healthy” brain, and set the physiological parameters in the “normal” range [11, 13, 19, 20], an essential step to establish benchmark results. By healthy, we mean an individual with no pathology, whose brain has not been exposed to nicotine \( n_{ic}^0 = 0 \) in (2) or alcohol \( alc_{ohol}^0 = 0 \) in (2) and without sleep disorders.

In this work, we consider that at the baseline case the reward system remains almost inactive in the absence of nicotine or alcohol. Therefore, the cortical neuron — in the reward circuit — and the VTA GABAergic neurons present no spikes. On the contrary, the VTA dopaminergic neuron runs a pacemaker activity, delivering to the NAcc a basal level of dopamine.

The SNpc receives excitatory inputs from the PPN and GABAergic inputs from the SNpr. The mesothalamic dopamine from the SNpc modulates the degree by which the \( TRN_x \) and \( TRN_y \) inhibits \( T_y \) and \( T_x \), respectively.

Furthermore, during a 500 milliseconds simulation, the PPN and SNpr behaviors, the excitatory inputs \( x, y \) and the PFC projection in the thalamocortical circuit are represented by time-periodic sequences of 1 spike per millisecond.
4.2. Exposure to nicotine

Next, we designed an experiment addressing the case involving exposition to nicotine. Starting from the baseline case, nicotine is added to the system by imposing \( n_{ic}^0 \neq 0 \) in (2). All other parameters are the same as in the baseline case.

Accordingly, both the cortical and the VTA GABAergic neurons become active due to the consumption of nicotine. It is important to remark that, in our model, the influence of alcohol on the VTA GABAergic neuron occurs because of the increased cortical excitatory stimulation triggered by nicotine.

4.3. Exposure to alcohol

In the same way as in the previous case, we designed an experiment addressing the exposition to alcohol. Starting from the baseline case, alcohol is added to the system by imposing \( a_l^0 \neq 0 \) in (3). Here also all other parameters are the same as in the baseline case.

The cortical and the VTA GABAergic neurons become active due to the consumption of alcohol.

4.4. Applications in the case of insomnia

Lesion studies have been traditionally used to assess roles of different brain areas in sleep regulation. Insomnia and hyperactivity were observed after lesions in SNpc and SNpr [54, 55].

Concerning the SNpc firing rate in the baseline experiment, it is important to note that low SNpc spiking rates are associated with mesothalamic dopaminergic hypoactivity, whereas the opposite case is associated with mesothalamic dopaminergic hyperactivity. Furthermore, the dopaminergic hypoactivity is associated with the mental rigidity observed in both Parkinson’s disease, ADHD and ASD, while the dopaminergic hyperactivity underlies the defocusing symptoms in ADHD [20, 11].

Thus, variations in the SNpc spiking frequencies are simulated through changes in the firing rate of SNpr. All other parameters are the same as in the baseline case. Departing from the simulation of an insomnia-like pathological state, nicotine or alcohol is added to the system.

5. Numerical results

5.1. Results for the baseline case

Our first results refer to the case of normal awake state without nicotine or alcohol. In Figures 2a–f, we show the voltage behavior of the VTA
dopaminergic, SNpc, TRN$_x$, TRN$_y$, $T_x$ and $T_y$ neurons.

The pacemaker current acting on the VTA dopaminergic neuron induces a tonic spiking mode, thus sending a basal level of dopamine to the NAcc (see Figure 2a). In turn, the dopaminergic neurons of the SNpc keep TRN$_x$ and TRN$_y$ under inhibitory control.

This experiment provides a baseline reference for our further simulations concerning nicotine, alcohol and insomnia.

5.2. Results for exposure to nicotine

Next, we show our results for an individual whose brain is exposed to nicotine. So, starting from the baseline case, nicotine is added to the system. Consequently, the VTA dopaminergic neuron starts to receive cortical glutamatergic and VTA GABAergic stimuli. In comparison with the baseline case, shown in Figure 2a, it becomes more excited, thus increasing the level of dopamine that is released into the NAcc, as one can observe in Figure 3a. It is important to note that such mechanism results in a reward sensation.

With the cessation of the GABAergic inhibition and the ensuing continuity of cortical excitatory glutamatergic stimulation on the VTA dopaminergic neuron, long term potentiation plausibly occurs. As a consequence, there occurs a change in the spiking mode of the VTA neurons, which start to fire in bursts. This happens due to the activation of the NMDA receptors, the calcium current and the hyperpolarizing current. Figures 3b–d depict the behavior of the SNpc, NRT$_x$, NRT$_y$, $T_x$ and $T_y$ neurons.

Due to the strong inhibition of the SNpc (see Figure 3b), coming from the NAcc projection and the subsequent low level of dopamine released by the SNpc that excites the TRN$_x$ and TRN$_y$, thalamic neurons exit burst firing mode. Therefore, the use of nicotine is able to promote dopaminergic hypoactivity in SNpc, which causes the thalamic neurons to spike in tonic mode, corresponding to wakefulness.

5.3. Results for exposure to alcohol

In the sequel, our results concern an individual whose brain is exposed to alcohol. As in the previous case, we start from the baseline case and alcohol is added to the system. The VTA dopaminergic neuron starts to receive cortical glutamatergic and VTA GABAergic stimuli, and there is an increase in the pacemaker current.

As a consequence of LTP and due to the activation of NMDA receptors, VTA DA neurons start to fire in bursts (Figure 4a). Alcohol, on the other
Figure 2: Healthy wakeful behavior, without nicotine or alcohol: (a) VTA dopaminergic neuron under a pacemaker activity; (b) Behavior of SNpc; (c) Behavior of $NRT_x$; (d) Behavior of $NRT_y$; (e) Behavior of $T_x$; (f) Behavior of $T_y$. 
Figure 3: Awake behavior with exposure to nicotine: (a) VTA dopaminergic neuron spikes in bursts; (b) Behavior of SNpc; (c) Behavior of $NRT_x$; (d) Behavior of $NRT_y$; (e) Behavior of $T_x$; (f) Behavior of $T_y$. 
hand, suppresses the SNpr spiking, which provides GABAergic afferents for SNpc. Although under strong inhibition from NAcc projection, SNpc becomes more active due to the inhibition of SNpr neurons by alcohol. Figures 4b–d show the behavior of the SNpc, NRTx, NRTy, Tx and Ty neurons.

Note that in this case, due to the dopaminergic hyperactivity, T_x and T_y do not change their spiking modes. This implies that alcohol does not cause wakefulness. On the contrary, the spikes of T_x and T_y start before \( \approx 100 \text{ ms} \) (Figures 4e–f) in comparison to baseline, when firing starts later at \( \approx 190 \text{ ms} \) (Figures 2e–f).

5.4. Results for insomnia

In order to simulate insomnia from the baseline case, we simulate nigral dopaminergic hypoactivity (Figure 5b). As the nigral dopaminergic activity decreases, the TRNx and TRNy (Figures 5c–d) neurons become more excited. Consequently, T_x and T_y (Figures 5e–f) remain firing in tonic mode as in an awake state.

Starting from the simulation of insomnia, alcohol was added to the system (Figures 6a–f). In this case, as alcohol suppresses SNpr spiking, this allows the SNpc to become more active, resulting in T_x and T_y firing as in sleep state.

6. Discussion

This work presents a neurocomputational model that couples the reward and thalamocortical circuits to investigate how the action of nicotine and alcohol influences and modulates the asleep processing. Also, it explores relationships between changes in mesothalamic dopaminergic activity and symptoms of asleep deficits in patients with insomnia and addresses possible effects of alcohol consumption.

Through mathematical modeling, we provide a description of the inhibitory role that mesothalamic dopamine plays in the TRN. Although there is experimental evidence for this, the corresponding mechanism has not been extensively explored. Here, we use our model with the dopaminergic modulation of the thalamocortical loop, in particular, explicitly modeling the effect of mesothalamic dopamine on TRN firing, to study the effect of nicotine and alcohol on sleep.

Our computational simulations suggest that variations in the mesothalamic dopamine level alter the sleep mechanism in the thalamocortical loop.
Figure 4: Awake behavior with exposure to alcohol: (a) VTA dopaminergic neuron spikes in bursts; (b) Behavior of SNpc; (c) Behavior of $NRT_x$; (d) Behavior of $NRT_y$; (e) Behavior of $T_x$; (f) Behavior of $T_y$. 
Figure 5: Insomnia without alcohol exposure: (a) VTA dopaminergic neuron spikes in bursts; (b) Behavior of SNpc; (c) Behavior of $NRT_x$; (d) Behavior of $NRT_y$; (e) Behavior of $T_x$; (f) Behavior of $T_y$. 
Figure 6: Insomnia with alcohol exposure: (a) VTA dopaminergic neuron spikes in bursts; (b) Behavior of SNpc; (c) Behavior of $NRT_x$; (d) Behavior of $NRT_y$; (e) Behavior of $T_x$; (f) Behavior of $T_y$.
Our results with attention focus had applications in ADHD and ASD [11, 13]. Since this circuit involves brain areas related to sleep disturbs (in particular, insomnia) in PD, ADHD and ASD, the activity alterations indicated by our simulations can also be present in these disorders.

Nicotine replacement therapy affects the sleep of non-smokers and previous smokers in the same manner, inducing sleep suppression [56]. On the other hand, in low to moderate doses, alcohol initially promotes sleep. However, scientific consensus maintains that chronic use ultimately disrupts sleep-related physiology [57].

Starting from a circuit with a dynamics that provides a predefined normal sleep state, we simulate the influence of nicotine and alcohol in the reward-thalamo-cortical system. Our results indicate that nicotine can disrupt sleep, promoting wakefulness. On the other hand, alcohol can have a stimulating effect that increases sleep latency (time to fall asleep). Therefore, they corroborate some clinical trials that highlight the role of nicotine and alcohol on sleep [56, 57].

Decrease in the level of mesothalamic dopamine leads to exaggeration in attention focus consolidation and a consequent lack of cognitive flexibility [20, 11, 13] in PD, ADHD and ASD. Besides, insomnia and hyperactivity were observed after lesions in SNpc and SNpr [54, 55]. Starting from this point, we simulated the insomnia condition and added alcohol to the system. Our results show that alcohol can have a sedating effect that induces sleep.

Our results agree with ideas proposed elsewhere [5], according to which dopamine plays a role in the control of the sleep-wake cycle. Here, through a neurocomputational model, we indicate possible ways by which sleep-related states could emerge as a consequence of alterations in the mesothalamic dopamine activity.

Summarizing, by exploring the interaction between the reward and thalamocortical circuits via SN, we studied the interference of nicotine and alcohol on subcortical sleep mechanisms through their action on the reward system. Overall, our results stress the distributed processing that underlies brain functionalities, in particular, the influence of nicotine and alcohol on sleep. Additionally, our work delineates relationships between alterations in dopamine activity and insomnia symptoms, and also suggests a neuronal mechanism underlying sleep deficits in PD, ADHD and ASD.
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Appendix A

Table 1 presents a glossary of the parameters used in the reward-attention circuit model.

References

References

[1] M. Steriade, D. A. McCormick and T. J. Sejnowski, Thalamocortical oscillations in the sleeping and aroused brain, Science, vol. 262:(5134), 679–685, (1993)

[2] B. Boutrel and G. F. Koob, What Keeps Us Awake: the Neuropharmacology of Stimulants and Wakefulness Promoting Medications, Sleep, vol. 27:(6), 1181–1194, (2004)

[3] J. P. Wisor, S. Nishino, I. Sora, G. H. Uhl, E. Mignot and D. M. Edgar, Dopaminergic Role in Stimulant-Induced Wakefulness, Journal of Neuroscience, vol. 21:(5), 1787–1794, (2001)

[4] W-M. Qu, Z-L. Huang, X-H. Xu, N. Matsumoto and Y. Urade, Dopaminergic D1 and D2 Receptors Are Essential for the Arousal Effect of Modafinil, Journal of Neuroscience, vol. 28:(34), 8462–8469, (2008)

[5] K. Dzirasa, S. Ribeiro, R. Costa, L. M. Santos, S-C. Lin, A. Grosmark, T. D. Sotnikova, R. R. Gainetdinov, M. G. Caron and M. A. L. Nicolelis, Dopaminergic Control of Sleep–Wake States, Journal of Neuroscience, vol. 26:(41), 10577–10589, (2006)

[6] S. C. Holst, A. Bersaglieri, V. Bachmann, W. Berger, P. Achermann and H-P. Landolt, Dopaminergic Role in Regulating Neurophysiological Markers of Sleep Homeostasis in Humans, Journal of Neuroscience, vol. 34:(2), 566–573, (2014)
[7] B. Floran and L. Floran and D. Erlij and J. Aceves, Activation of dopamine D4 receptors modulates [3H]GABA release in slices of the rat thalamic reticular nucleus, Neuropharmacology, vol. 46, 497–503, (2004)

[8] Freeman, A., Ciliax, B., Bakay, R., Nigrostriatal Collaterals to Thalamus Degenerate in Parkinsonian Animal Models. Annals of Neurology, v. 50, 321–329, (2001)

[9] LaHoste, G.J. and Swanson, J.M. and Wigal, S.B. and Glabe, C. and Wigal, T. and King, N. and Kennedy, J.L., Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. Molecular Psychiatry, vol. 1:(2), 121–124, (1996)

[10] Faraone, S.V. and Doyle, A.E. and Mick, E. and Biederman, J., Meta-analysis of the association between the 7-repeat allele of the dopamine D4 receptor gene and attention deficit hyperactivity disorder. American Journal of Psychiatry, vol. 158:(7), 1052–1057, (2001)

[11] K. Guimarães, D. Q. M. Madureira and A. L. Madureira, The Reward-Attention Circuit Model: Nicotines Influence on Attentional Focus and Consequences on Attention Deficit Hyperactivity Disorder, Neurocomputing, vol. 242, 140–149, (2017)

[12] R. A. Wise, Brain Reward Circuitry: Insights from Unsensed Incentives, Neuron, vol. 36:(2), 229–240, (2002)

[13] K. Guimarães, Extension of Reward-Attention Circuit Model: Alcohol’s Influence on Attentional Focus and Consequences on Autism Spectrum Disorder, Neurocomputing, vol. 325, 242–253, (2018)

[14] G. Loddo, G. Calandra-Buonaura, L. Sambati, G. Giannini, A. Cecere, P. Cortelli and F. Provini, The Treatment of Sleep Disorders in Parkinsons Disease: From Research to Clinical Practice, Frontiers in Neurology, vol. 8, 42, (2017)

[15] D. Bijlenga, E. J. W. Van Someren, R. Gruber, T. I. Bron, I. F Kruithof, E. C. A. Spanbroek and J. J. S. Kooij, Body temperature, activity and melatonin profiles in adults with attention-deficit/hyperactivity disorder and delayed sleep: a case-control study, Journal of Sleep Research, vol. 22:(6), 607–616, (2013)
[16] P. Tani, N. Lindberg, T. Nieminen-von Wendt, L. von Wendt, L. Alanko, B. Appelberg and T. Porkka-Heiskanen, Insomnia is a frequent finding in adults with Asperger syndrome, BMC Psychiatry, vol. 3, 12–12, (2003)

[17] J. Olds and P. Milner, Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain, Journal of Comparative and Physiological Psychology, vol. 47:(6), 419–427, (1954)

[18] S. N. Haber and B. Knutson, The Reward Circuit: Linking Primate Anatomy and Human Imaging, Neuropsychopharmacology, vol. 35:(1), 4–26, (2009)

[19] L. A. V. de Carvalho, Modeling the thalamocortical loop, International Journal of Bio–Medical Computing, vol. 35, 267–296, (1994)

[20] D. Q. M. Madureira, L. A. V. de Carvalho and E. Cheniaux, Attentional focus modulated by mesothalamic dopamine: consequences in parkinson’s disease and attention deficit hyperactivity disorder, Cognitive Computation, vol. 2, 31–49, (2010)

[21] E. G. Jones, Some aspects of the organization of the thalamic reticular complex, The Journal of Comparative Neurology, vol. 162:(3), 285–308, (1975)

[22] L. A. Chiodo, Dopamine-containing neurons in the mammalian central nervous system: Electrophysiology and pharmacology, Neuroscience & Biobehavioral Reviews, vol. 12:(1), 49 – 91, (1988)

[23] A.A. Grace, Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: A hypothesis for the etiology of schizophrenia, Neuroscience, vol. 41:(1), 1 – 24, (1991)

[24] B. I. Hyland, J. N. J. Reynolds, J. Hay, C. G. Perk and R. Mille, Firing modes of midbrain dopamine cells in the freely moving rat, Neuroscience, vol. 114:(2), 475–492, (2002)

[25] W. Schlitz and R. Romo, Dopamine neurons of the monkey midbrain: contingencies of responses to stimuli eliciting immediate behavioral reactions, J. Neurophysiol., vol. 63, 607 – 624, (1990)
[26] W. Schultz, Predictive reward signal of dopamine neurons, J. Neurophys. vol. 80, 1–27 (1998)

[27] F. G. Gonon, Nonlinear relationship between impulse flow and dopamine released by rat midbrain dopaminergic neurons as studied by in vivo electrochemistry, Neuroscience, vol. 24:(1), 19–28, (1988)

[28] H. D. Mansvelder and D. S. McGehee, Cellular and synaptic mechanisms of nicotine addiction, Journal of Neurobiology, vol. 53, 606–617, (2002)

[29] H. D. Mansvelder and D. S. McGehee, Long–Term Potentiation of Excitatory Inputs to Brain Reward Areas by Nicotine, Neuron, vol. 27:(2), 349–357, (2000)

[30] R. E. Maldve, T. A. Zhang, K. Ferrani-Kile, S. S. Schreiber, M. J. Lippmann, G. L Snyder, A. A. Feinberg, S. W. Leslie, R. A. Gonzales and R. A. Morissett, DARPP-32 and regulation of the ethanol sensitivity of NMDA receptors in the nucleus accumbens, Nat Neurosci, vol. 5:(7), 641–648, (2002)

[31] A. M. Dopico and D. M. Lovinger, Acute Alcohol Action and Desensitization of Ligand-Gated Ion Channels, Pharmacological Reviews, vol. 61:(1), 98–114, (2009)

[32] C. Xiao, X. M. Shao, M. F. Olive, W. C. Griffin, K-Y. Li, K. Krnjević, C. Zhou and J-H. Ye, Ethanol Facilitates Glutamatergic Transmission to Dopamine Neurons in the Ventral Tegmental Area, Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, vol. 34:(2), 307–318, (2009)

[33] L. A. Sombers, M. Beyene, R. M. Carelli and R. Mark Wightman, Synaptic Overflow of Dopamine in the Nucleus Accumbens Arises from Neuronal Activity in the Ventral Tegmental Area, Journal of Neuroscience, vol. 29:(6), 1735–1742, (2009)

[34] L. S. Zweifel, J. G. Parker, C. J. Lobb, A. Rainwater, V. Z. Wall, J. P. Fadok, M. Darvas, M. J. Kim, S. J. Y. Mizumori, C. A. Paladini, P. E. M. Phillips and R. D. Palmiter, Disruption of NMDAR-dependent burst firing by dopamine neurons provides selective assessment of phasic dopamine-dependent behavior, Proceedings of the National Academy of Sciences, vol. 106:(18), 7281-7288, (2009)
[35] B. E. Bernier, L. R. Whitaker and H. Morikawa, Previous Ethanol Experience Enhances Synaptic Plasticity of NMDA Receptors in the Ventral Tegmental Area, Journal of Neuroscience, vol. 31:(14), 5205–5212, (2011)

[36] G. Cui, B. E. Bernier, M. T. Harnett and H. Morikawa, Differential Regulation of Action Potential- and Metabotropic Glutamate Receptor-Induced Ca$^{2+}$ Signals by Inositol 1,4,5-Trisphosphate in Dopaminergic Neurons, Journal of Neuroscience, vol. 27:(17), 4776–4785, (2007)

[37] M. Foddai, G. Dosia, S. Spiga, M. and Diana, Acetaldehyde Increases Dopaminergic Neuronal Activity in the VTA, Neuropsychopharmacology, vol. 29:(3), 530–536, (2003)

[38] J. E. Lisman and J. M. Fellous and X. J. Wang, A role for NMDA-receptor channels in working memory, Nature Neuroscience, vol. 1, 273–275, (1998)

[39] M. S. Brodie, S. A. Shefner and T. V. Dunwiddie, Ethanol increases the firing rate of dopamine neurons of the rat ventral tegmental area in vitro, Brain Research, vol. 508:(1), 65 – 69, (1990)

[40] T. Okamoto, M.T. Harnett and H. Morikawa, Hyperpolarization-Activated Cation Current ($I_h$) Is an Ethanol Target in Midbrain Dopamine Neurons of Mice, Journal of neurophysiology, vol. 95:(2), 619–626, (2006)

[41] G. Mereu and G. L. Gessa, Low doses of ethanol inhibit the firing of neurons in the substantia nigra, pars reticulata: a {GABAergic} effect?, Brain Research, vol. 360, 325 – 330, (1985)

[42] R. R. Llinás and M. Steriade, Bursting of Thalamic Neurons and States of Vigilance, Journal of Neurophysiology, vol. 95:(6), 3297–3308, (2006)

[43] E. F. Pace-Schott and J. A. Hobson, The Neurobiology of Sleep: Genetics, cellular physiology and subcortical networks, Nat Rev Neurosci, vol. 3:(8), 591–605, (2002)

[44] D. Jeanmonod and M. Magnin and A. Morel, Low-threshold calcium spike bursts in the human thalamus, Brain, vol. 119:(2), 363–375, (1996)
[45] D. Cioranescu and P. Donato, An Introduction to Homogenization, Oxford Lecture Series in Mathematics and Its Applications, Oxford University Press, 1 edition, (2000)

[46] A. Bensoussan, J. L. Lions and G. Papanicolaou, Asymptotic Analysis for Periodic Structures, AMS Chelsea Publishing, American Mathematical Society, (2011)

[47] A. L. Madureira, Numerical Methods and Analysis of Multiscale Problems, Springer Briefs in Mathematics, (2017)

[48] P. C. Bressloff, Waves in Neural Media: From Single Neurons to Neural Fields, Lectures Notes on Mathematical Modelling in the Life Sciences, (2014)

[49] L. A. V. Carvalho and V. L. Roitman, A computational model for the neurobiological substrates of visual attention, International Journal of Bio-Medical Computing, v. 38, 33–45, (1995)

[50] W. Gerstner and W. M. Kistler, Spiking neuron models: single neurons, populations, plasticity, Cambridge UK: Cambridge University Press, 94–105, (2002)

[51] R. J. MacGregor, Neural and brain modeling, San Diego: Academic Press Incorporation, (1987)

[52] R. J. MacGregor and R. M. Oliver, A model for repetitive firing in neurons, Biol Cybern, vol. 16, 53–64, (1974)

[53] C. E. Jahr and C. F. Stevens, A quantitative description of NMDA receptor-channel kinetic behavior, J. Neuroscience, vol. 10, 1830–1877, (1990)

[54] Y. Y. Lai, T. Shalita, T. Hajnik, J.-P. Wu, J.-S. Kuo, L.-G. Chia and J.M. Siegel, Neurotoxic N-methyl-D-aspartate lesion of the ventral midbrain and mesopontine junction alters sleep-wake organization, Neuroscience, vol. 90:(2), 469-483, (1999)

[55] D. Gerashchenko, C. A. Blanco-Centurion, J. D. Miller and P. J. Shihomani, Insomnia following hypocretin2-saporin lesions of the substantia nigra, Neuroscience, vol. 137:(1), 29 –36, (2006)
[56] A. Jaehne, B. Loessl, Z. Barksai, D. Riemann and M. Hornyak, Effects of nicotine on sleep during consumption, withdrawal and replacement therapy, Sleep Medicine Reviews, vol. 13:(5),363–377, (2009)

[57] M. D. Stein and P. D. Friedmann, Disturbed sleep and its relationship to alcohol use, Substance abuse : official publication of the Association for Medical Education and Research in Substance Abuse, vol. 26:(1), 1–13, (2005)

[58] T. J. Sejnowski and A. Destexhe, Why do we sleep?, Brain Research, vol. 886, 208–223, (2000)
| Parameter  | Description                                         | Value/Unit                   |
|-----------|-----------------------------------------------------|------------------------------|
| $C_i$     | Membrane’s capacitance                              | $1 \, \mu\text{F.cm}^{-2}$  |
| $E_K$     | Reversal potential of $K^+$                         | $-80 \, \text{mV}$          |
| $E_L$     | Reversal potential of $I_L$                         | $0 \, \text{mV}$            |
| $\beta_K$ | Increase rate of $g_K$                              | $150$                        |
| $\tau_K$  | Time constant of $g_K$                              | $1.5 \, \text{ms}$          |
| $g_L$     | Conductance of $I_L$                                | $10 \, \text{mhos.cm}^{-2}$ |
| $\theta$  | Threshold for sodium channel’s opening              | $1 \, \text{mV}$            |
| $M_1$     | Nicotine decay rate                                 | $0.0001$                     |
| $M_2$     | Alcohol decay rate                                  | $0.001$                      |
| $T_{max}$ | Maximum concentration of neurotransmitters in the synaptic cleft | $1 \, \text{mM}$            |
| $E_{\text{NMDA}}$ | Reversal potential of $I_{\text{NMDA}}$ | $0 \, \text{mV}$          |
| $E_c$     | Reversal potential of Ca$^{++}$                     | $70 \, \text{mV}$           |
| $g_c$     | Increase rate $g_c$                                 | $1$                          |
| $\beta_{\text{Ca}^2+}$ | Variation rate of calcium concentration | $100$                      |
| $\tau_{\text{Ca}^2+}$ | Time constant of calcium’s pump | $500 \, \text{ms}$      |
| $\theta_{\text{Ca}^2+}$ | Threshold to activate $I_{\text{ahp}}$ | $0.4 \, \text{mV}$      |
| $\beta_{\text{ahp}}$ | Increase rate of $g_{\text{ahp}}$ | $100$                      |
| $\tau_{\text{ahp}}$ | Time constant of $g_{\text{ahp}}$ | $2 \, \text{ms}$          |
| $g_{\text{pm}}$ | Conductance of pacemaker current | $0.29 \, \text{mhos.cm}^{-2}$ |
| $E_{\text{sin}}$ | Reversal potential of excitatory synapses | $40 \, \text{mV}$      |
| $E_{\text{sin}}^+$ | Reversal potential of inhibitory synapses | $-40 \, \text{mV}$    |
| $g_{\text{c-gvta}}$ | Maximal conductance of the synaptic projection cortex-gvta | $0.18 \, \text{mhos.cm}^{-2}$ |
| $g_{\text{c-dvta}}$ | Maximal conductance of the synaptic projection cortex-dvta | $1.3 \, \text{mhos.cm}^{-2}$ |
| $g_{\text{gvt-a-dvta}}$ | Maximal conductance of the synaptic projection gtva-dvta | $0.3 \, \text{mhos.cm}^{-2}$ |
| $g_{\text{dtva-nacc}}$ | Maximal conductance of the synaptic projection dtva-nacc | $0.5 \, \text{mhos.cm}^{-2}$ |
| $g_{\text{nacc-snc}}$ | Maximal conductance of the synaptic projection nacc-snc | $0.3 \, \text{mhos.cm}^{-2}$ |
| $g_{\text{ppn-snc}}$ | Maximal conductance of the synaptic projection ppn-snc | $0.2 \, \text{mhos.cm}^{-2}$ |
| $g_{\text{srn-snc}}$ | Maximal conductance of the synaptic projection srn-snc | $0.2 \, \text{mhos.cm}^{-2}$ |
| $g_{\text{ct-nrt}}$ | Maximal conductance of the synaptic projection cortex-thalamus | $0.1 \, \text{mhos.cm}^{-2}$ |
| $g_{\text{trn-t}}$ | Maximal conductance of the synaptic projection thalamus-trn | $1.3 \, \text{mhos.cm}^{-2}$ |
| $g_{\text{tc-t}}$ | Maximal conductance of the synaptic projection cortex-thalamus | $1.3 \, \text{mhos.cm}^{-2}$ |
| $g_{\text{tc-nrt}}$ | Maximal conductance of the synaptic projection cortex-nrt | $0.1 \, \text{mhos.cm}^{-2}$ |
| $g_{\text{t-pe}}$ | Maximal conductance of the synaptic projection stimulus-thalamus | $0.1 \, \text{mhos.cm}^{-2}$ |
| $g_{\text{t-pe}}$ | Peak time of excitatory synaptic alpha function | $1.5 \, \text{ms}$        |
| $g_{\text{t-psi}}$ | Peak time of excitatory synaptic alpha function | $1.5 \, \text{ms}$        |
| $g_c$     | Constant regulating increase $g_{\mu-c}$           | $0.4$                        |
| $\alpha$  | Constant regulating the sigmoid inclination        | $1$                          |
| $g_{\text{d4}}$ | Proportion constant of dopaminergic projection | $1 \, \text{mhos.cm}^{-2}$ |
| $t_{pd}$  | Peak time of D$_4$ receptor’s                      | $2 \, \text{ms}$            |

Table 1: Glossary of parameters